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L-Piperazine-2-carboxylic Acid Derived *N*-Formamide as a Highly Enantioselective Lewis Basic Catalyst for Hydrosilylation of *N*-Aryl Imines with an Unprecedented Substrate Profile

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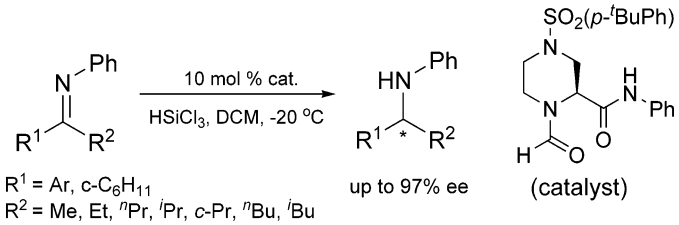
ABSTRACT



L-Piperazine-2-carboxylic acid derived *N*-formamides have been developed as highly enantioselective Lewis basic catalysts for the hydrosilylation of *N*-aryl imines with trichlorosilane. The arene sulfonyl group on N4 was found to be critical for the high enantioselectivity of the catalyst. High isolated yields (up to 99%) and enantioselectivities (up to 97%) were obtained for a broad range of substrates, including aromatic and aliphatic ketimines, particularly those with R^2 as relatively bulky alkyl groups.

Asymmetric Lewis base catalysis has proven to be a powerful and viable asymmetric synthetic method, of which the most successful applications have been in allylations and aldol reactions using trichlorosilylated reagents.[1] Recently, asymmetric reduction of imines, a useful but challenging reaction for the production of chiral amines,[2,3] was also effected by Lewis base catalysis.[4] Matsumura first disclosed that L-proline derived Lewis basic *N*-formamide **1** (Figure 1) catalyzed the reduction of *N*-aryl ketimines with trichlorosilane ($HSiCl_3$) in modest enantioselectivity (up to 66% ee).[4a] Later, Malkov and Kocovsky reported that L-valine derived catalyst **2** significantly improved the enantioselectivity (up to 92% ee).[4b,c,5] In our recent publication, we presented a L-pipecolinic acid derived Lewis basic catalyst (**3**) that afforded the highest level of enantioselectivities (up to 96% ee) with an exceptional substrate spectrum.[6] Encouraged by these results, we continued to search for new highly efficient

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(2) For recent reviews, 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) Kobayshi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

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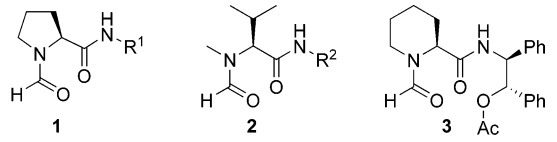


Figure 1. Structures of the catalysts reported previously.

and enantioselective Lewis basic *N*-formamide catalysts with structural diversity. Herein, we report our discovery of the L-piperazine-2-carboxylic acid (PCA) derived new catalyst **4e** (Figure 2) that has a relatively simple structure and

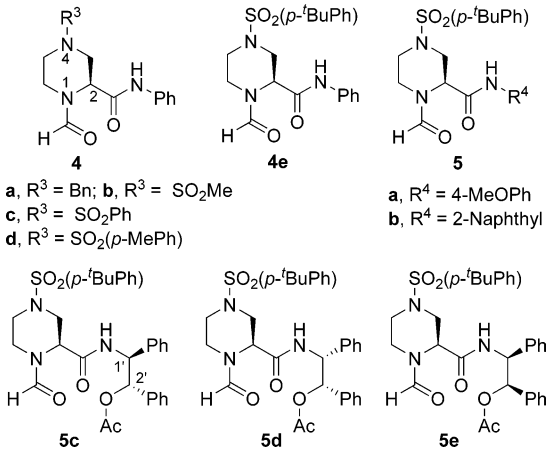


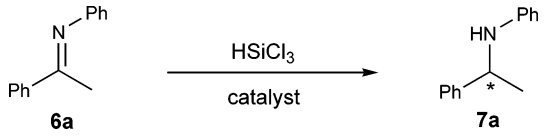
Figure 2. Structures of the catalysts evaluated in this study.

exhibits high enantioselectivity in the hydrosilylation of *N*-aryl ketimines with an unprecedented substrate profile.

Given the outstanding performance of **3**,[6] we were interested to design new catalysts bearing analogous six-membered cyclic backbones. We envisioned that the piperazinyl backbone could be a good replacement of the piperidinyl backbone of **3** considering that the secondary amino group on the 4-position (N4) of the former should provide an excellent open site for introducing diversity elements and thus fine tuning the catalytic properties. On the other hand, it should be interesting to see if the chiral 2-acetoxy-1,2-diphenylethyl amide group of **3**, which was shown to be critical for the high enantioselectivity,[6] is still favorable in the PCA-based new catalyst system. Thus, we prepared a set of new *N*-formamide catalysts (**4a**−**e** and **5a**−**e**, Figure 2) starting from the commercially available L-PCA (see Supporting Information) and tested their catalytic effects in the model reaction of **6a** with $HSiCl_3$ in the presence of 10 mol % of catalyst in CH_2Cl_2 at 0 °C.

As shown in Table 1, catalyst **4a** with an alkyl group (Bn) on N4 gave only a moderate yield and ee value (entry 1).

Table 1. Asymmetric Hydrosilylation of Ketimine **6a**[a]



entry	catalyst	temp (°C)	yield (%)[b]	ee (%)[c]
1	**4a**	0	65	40
2	**4b**	0	64	<5
3	**4c**	0	77	74
4	**4d**	0	82	77
5	**4e**	0	97	80
6	**5a**	0	92	73
7	**5b**	0	68	56
8	**5c**	0	80	36
9	**5d**	0	71	5
10	**5e**	0	63	71
11	**4e**	−20	95	89
12	**4e**	−40	30	89
13[d]	**4e**	−20	30	88

[a] Unless specified otherwise, reactions were carried out with 10 mol % of catalyst and 2.0 equiv of $HSiCl_3$ on a 0.2 mmol scale in 1.0 mL of CH_2Cl_2 for 48 h. [b] Isolated yield based on the imine. [c] The ee values were determined using chiral HPLC. [d] 5 mol % of catalyst was used.

Surprisingly, when this group was changed to methanesulfonyl, the resulted catalyst **4b** totally lost the selectivity (entry 2). It seems plausible to ascribe this to the competitive nonstereoselective binding of the sulfonyl oxygen with the central silicon atom of $HSiCl_3$. However, the switch of the aliphatic methanesulfonyl group to the aromatic benzenesulfonyl group enables catalyst **4c** to recover the selectivity (74% ee, entry 3). Moreover, the addition of an alkyl group to the para position of the benzene ring was found to be beneficial to both the reactivity and the selectivity. **4d** with a *para*-methyl gave 82% yield and 77% ee (entry 4), and **4e** with a bulky *para*-*tert*-butyl resulted in 97% yield and 80% ee (entry 5).

(3) For selected recent examples, see: (a) Lipshutz, B. H.; Frieman, B. A.; Tomaso, A. E., Jr. *Angew. Chem., Int. Ed.* **2006**, *45*, 1259. (b) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84. (c) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424. (d) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781. (e) Moessner, C.; Bolm, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 7564. (f) Nolin, K. A.; Ahn, R. W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 12462. (g) Trifonova, A.; Diesen, J. S.; Chapman, C. J.; Andersson, P. G. *Org. Lett.* **2004**, *6*, 3825. (h) Lipshutz, B. H.; Shimizu, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 2228. (i) Kadyrov, R.; Riermeier, T. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5472. (j) Chi, Y.; Zhou, Y.; Zhang, X. *J. Org. Chem.* **2003**, *68*, 4120. (k) Xiao, D.; Zhang, X. *Angew. Chem., Int. Ed.* **2001**, *40*, 3425. (l) Hansen, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 713.

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(5) (a) Very recently, modest to high ee values were also achieved with chiral Brønsted basic organocatalysts; see: (a) Malkov, A. V.; Liddon, A.; Ramirez-Lopez, P.; Bendova, L.; Haigh, D.; Kocovsky, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 1432. (b) Onomura, O.; Kouchi, Y.; Iwasaki, F.; Matsumura, Y. *Tetrahedron Lett.* **2006**, *47*, 3751.

(6) Wang, Z.; Ye, X.; Wei, S.; Wu, P.; Zhang, A.; Sun, J. *Org. Lett.* **2006**, *8*, 999.

As observed with the previously reported *N*-formamide catalysts,[4,6] the amide group also has profound impacts on both the reactivity and selectivity of this series of PCA-based new catalysts. Although catalyst **5a** bearing a *para*-methoxyphenyl amide group led to a slightly lowered yield and ee value, a significantly decreased yield and ee value were achieved with **5b** bearing a 2-naphthyl amide group. Moreover, the (1*S*,2*S*)-2-acetoxy-1,2-diphenylethyl amide group, a critical structural motif of **3**,[6] was found to be unfavorable in this catalyst system. **5c** catalyzed the reaction with only 36% ee (entry 8). To check if the absolute stereochemistries in this amide group could make any big difference, the diastereomers **5d** and **5e** were examined. In agreement with the observation in the case of **3**, an (*S*)-configuration is distinctly preferred for C1′ (see **5c** for labeling). **5d** with an (*R*)-C1′ afforded a nearly racemic product (entry 9). Interestingly, although the absolute configuration of C2′ has marginal influence on the selectivity of **3**, **5e** with an (*R*)-C2′ exhibited much higher selectivity than **5d** with an (*S*)-C2′ (entries 9 and 10). Thus, catalyst **5e** with the (1*S*,2*R*)-2-acetoxy-1,2-diphenylethyl amide group has the best-match stereochemistries. Nevertheless, the performance of **5e** is still not as good as that of **4e** (entries 5 and 10). Hence, catalyst **4e** was selected for further studies.

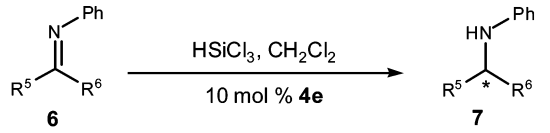
We next examined the influences of some other reaction parameters on the performance of **4e** in the hydrosilylation of **6a**. When the reaction temperature was lowered from 0 to −20 °C, the ee value of product **7a** was lifted to 89% and the yield was almost unchanged (entries 5 and 11). Further lowering the temperature to −40 °C had no effect on the selectivity but caused an unacceptable loss of reactivity (entry 12). When the catalyst loading was reduced from 10 to 5 mol %, the ee value of the product remained in the same level, whereas only 30% yield was obtained because of low conversion (entry 13).

Having established the optimal reaction conditions, we next explored the application scope of **4e**. A broad range of *N*-phenyl ketimines (**6a**−**s**) were reduced with $HSiCl_3$ in the presence of 10 mol % of catalyst in CH_2Cl_2 at −20 °C. As illustrated in Table 2, regular electron-rich and electron-deficient aromatic methyl ketimines **6a**−**f** (R^6 = Me) reacted well to give the desired products **7a**−**f** in high yield and enantioselectivity (63−99% yield, 85−90% ee, entries 1−6). The hydrosilylation of the aliphatic cyclohexyl methyl ketimine **6g** also proceeded well with 86% yield and 82% ee (entry 7). More significantly, ketimines **6h**−**s** with a relatively bulky R^6, including Et, ^{n}Pr, ^{i}Pr, *c*-Pr, ^{n}Bu, and ^{i}Bu, were all found to be good substrates for catalyst **4e**, affording high yields (75−92%) and excellent enantioselectivities (84−97%, mostly 90−97%). Furthermore, consistently higher ee values were obtained for these ketimines bearing a relatively bulky R^6 than the corresponding methyl ketimines (84−97% vs 82−90% ee, entries 8−19 vs 1−7). To the best of our knowledge, such a substrate profile has not been previously reported for the asymmetric reduction of *N*-aryl ketimines. As a matter of fact, when **3** was used as the catalyst, a dramatically different scenario was observed: whereas **6a**−**g** were previously shown to afford excellent ee values (90−95%),[6] only low to moderate enantioselectivities (entries 8, 9, and 15−19; data in parentheses) were attained for **6h**, **6i**, and **6o**−**s**, with only one exception of 92% ee for **6q** with R^6 as cyclopropanyl (entry 17).

We also investigated some other ketimines with different N-substituents (Scheme 1). Unfortunately, with the catalysis of **4e**, the ketimines with a substituted *N*-phenyl group were found to give significantly lowered ee values compared with the corresponding *N*-phenyl ketimines. The *N*-benzyl ketimines were also proven to be unsuitable substrates for the catalyst.

In summary, we have developed the first L-pipecolinic acid based chiral Lewis basic *N*-formamide catalyst (**4e**) that

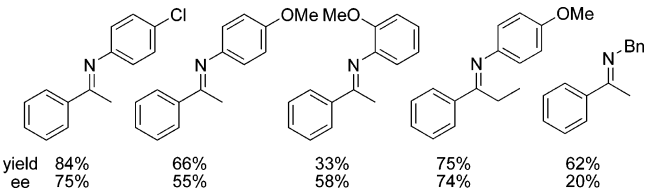
Table 2. Asymmetric Hydrosilylation of Ketimines **6** with Catalyst **4e**[a]



entry	imine		X =	yield (%)[b]	ee (%)[c]
1		**6a**	H	95	89
2		**6b**	*p*-NO_2	99	90
3		**6c**	*p*-Br	81	89
4		**6d**	*p*-Me	71	85
5		**6e**	H	63	88
6		**6f**	OMe	64	85
7		**6g**	Me	86	82
8		**6h**	Et	84	84 (65)
9		**6i**	H	92	94 (67)
10		**6j**	*p*-F	87	95
11		**6k**	*p*-Cl	83	94
12		**6l**	*p*-Br	89	95
13		**6m**	*p*-Me	87	88
14		**6n**	*p*-OMe	83	90
15		**6o**	^{n}Pr	88	90 (45)
16		**6p**	^{i}Pr	75	92 (50)
17		**6q**	*c*-Pr	85	97 (92)
18		**6r**	^{n}Bu	84	89 (29)
19		**6s**	^{i}Bu	86	91 (7)

[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 −20 °C for 48 h. [b] Isolated yield based on the imine. [c] The ee values were determined using chiral HPLC; the data in parentheses are for catalyst **3**.

Scheme 1



promotes the enantioselective reduction of *N*-aryl ketimines with trichlorosilane in high yield and enantioselectivity. Compared with the L-pipecolinic acid based catalyst **3** that we previously developed, the most remarkable features of this catalyst include (a) its structural simplicity given that the bulky and costly chiral amide fragment needed in **3** for ensuring high enantioselectivity is not needed, (b) its high enantioselectivity for both methyl ketimines and ketimines with a relative bulky R^6, and (c) its consistently higher enantioselectivity for the latter substrates than for the former, which is so far unprecedented in organocatalytic asymmetric reduction of imines. The mechanistic aspects of the special substrate profile and the full application scope of this catalyst system are currently under investigation. The results will be reported in due course.

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

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