Evolution of chiral Lewis basic *N*-formamide as highly effective organocatalyst for asymmetric reduction of both ketones and ketimines with an unprecedented substrate scope†

Li Zhou,[ac] Zhouyu Wang,[abc] Siyu Wei[a] and Jian Sun*[a]

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L-Pipecolinic acid derived Lewis basic *N*-formamide 5e has been developed as a first highly effective catalyst for the asymmetric reduction of aromatic and aliphatic ketones as well as aromatic and aliphatic ketimines in good to high enantioselectivity.

Catalytic asymmetric reductions of prochiral ketones and imines have been among the central topics in asymmetric synthesis over the past few decades. A number of highly efficient and enantioselective catalytic methods have been developed for the reduction of either ketones or imines.[1] However, there have been only a few examples of catalytic methods that allow for highly enantioselective reductions of both ketones and imines.[2–5] The currently available methods mainly use transition metal complexes as catalysts and all have narrow substrate scopes.[2] Matsumura and co-workers reported the first organocatalytic enantioselective reduction method applicable to both ketone and imines, which employed a chiral organic Lewis base as the catalyst and trichlorosilane ($HSiCl_3$) as the reducing agent, affording low to moderate enantioselectivities.[4] Recently, Malkov, Kocovsky and co-workers disclosed that significantly improved enantioselectivies could be obtained for this method with the newly designed catalyst **1**.[5] The substrates were, however, limited to aromatic ketones and ketimines. We report here a first catalytic system that allows for efficient reduction of aliphatic and aromatic ketones as well as aliphatic and aromatic ketimines with $HSiCl_3$ in good to high enantioselectivity.[6–8]

We previously reported that chiral Lewis bases **2**,[9a] **3**,[9b] **4**[9c] and **5a**[9c] (Fig. 1) all catalyzed the reduction of ketimines with $HSiCl_3$ with high efficiency and enantioselectivity. We were interested in testing the efficacies of these catalytic systems in the reduction of ketones. Thus these catalysts were examined in the reduction of *para*-trifluoromethylphenyl methyl ketone **6a** with $HSiCl_3$ at 0 °C with toluene as the solvent. To our surprise, extremely low reactivity was observed with **2** and **3** (<5% yield, entries 1 and 2, Table 1). In contrast, the L-pipecolinic acid derived catalyst **4** and its diastereomer **5a** both exhibited good reactivity and enantioselectivity (entries 3 and 4).

Catalyst **4** was previously observed to be slightly more enantioselective than its diastereomer **5a** in the reduction of ketimines.[9c] In contrast, in the reduction of ketone **6a**, the latter was found to be more enantioselective (entry 4 *vs.* 3). Thus our attention was next directed to fine-tuning the structure of **5a** in hope of achieving high efficiency and enantioselectivity for the reduction of ketones.

Analogous catalysts **5b–h** bearing different R groups were easily prepared (see ESI† for experimental details) and examined in the reduction of **6a**. Catalysts **5e–g** with R as alkyl groups turned out to be more enantioselective than the other analogues (entries 4–11). Catalyst **5e** bearing the smallest alkyl group (R = Me) displayed the best overall efficacy, affording the product in 99% yield and 89% ee (entry 8).

We thus selected catalyst **5e** for further studies. To optimize the reaction conditions, the temperature and solvent effects were examined (entries 12–17, Table 1). When the reaction temperature was lowered from 0 to −20 °C, the enantioselectivity was lifted from 89 to 92% whereas the high reactivity was almost unaffected (entry 12 *vs.* 8). Further lowering the temperature to −40 °C caused a substantial decrease in enantioselectivity and an unacceptable loss of reactivity (entry 13). A survey of solvents proved toluene to be the best choice (entries 12 and 14–17).

Having established the optimal reaction conditions, we next examined other ketones to expand the substrate scope of catalyst **5e**. Various ketones were reduced by $HSiCl_3$ in the presence of 10 mol% **5e** in toluene at −20 °C. As shown in Table 2, high yields (92–98%) and enantioselectivities (82–93%) were obtained for typical electron-deficient and electron-rich aromatic ketones **6a–j** (entries 1–10). Remarkably, the notoriously difficult aliphatic

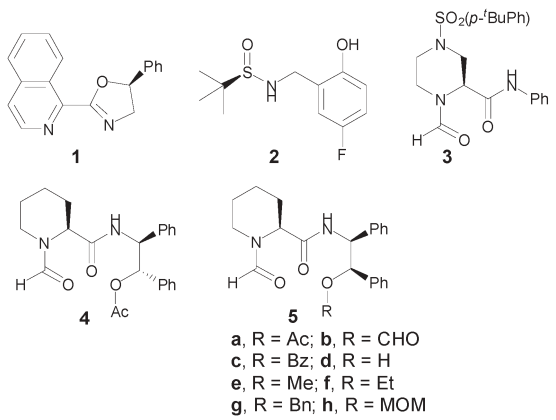

Fig. 1 Structures of the catalysts.

[a]*Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu, 610041, China. E-mail: sunjian@cib.ac.cn; Fax: +86-28-85222753; Tel: +86-28-85211220*
[b]*Department of Chemistry, Xihua University, Chengdu, 610039, China*
[c]*Graduate School of Chinese Academy of Sciences, Beijing, China*
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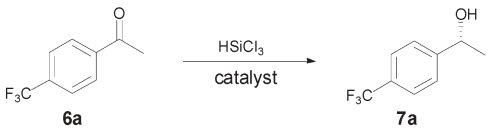
Table 1 Asymmetric reduction of ketone **6a**[a]



6a **7a**

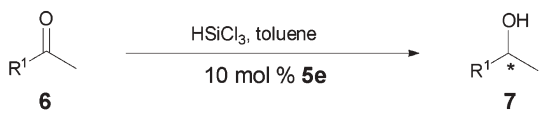
Entry	Catalyst	Solvent	T/°C	Yield[b] (%)	ee (%)[c,d]
1	**2**	Toluene	0	<5	—
2	**3**	Toluene	0	<5	—
3	**4**	Toluene	0	86	74
4	**5a**	Toluene	0	87	80
5	**5b**	Toluene	0	89	78
6	**5c**	Toluene	0	90	71
7	**5d**	Toluene	0	91	80
8	**5e**	Toluene	0	99	89
9	**5f**	Toluene	0	85	89
10	**5g**	Toluene	0	89	85
11	**5h**	Toluene	0	89	83
12	**5e**	Toluene	−20	92	92
13	**5e**	Toluene	−40	20	80
14	**5e**	CH_2Cl_2	−20	77	86
15	**5e**	$ClCH_2CH_2Cl$	−20	82	84
16	**5e**	$CHCl_3$	−20	75	79
17	**5e**	CH_3CN	−20	36	33

[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 ketone. [c] The ee values were determined using chiral HPLC. [d] Product **7a** was *R* configured in all cases, as revealed by comparison of the optical rotation with the literature data.

ketones **6k–m** also reacted well to produce the desired alcohol in high yields (81–99%) with moderate to good enantioselectivities (53–88%, entries 11–13).[10]

To check if catalyst **5e** still retains the high efficiency and enantioselectivity of the original catalyst **4** for the reduction of ketimines, **8a** was reduced in the presence of 10 mol% **5e** under the optimal conditions for **4**, namely at 0 °C with dichloromethane as the solvent.[9c] Delightfully, high yield of 94% and ee value of 90% were obtained (entry 1, Table 3). The enantioselectivity was enhanced to 93% when the reaction temperature was lowered to −20 °C (entry 2). Further survey of solvents revealed that the overall performance of **5e** in toluene is slightly better than in dichloromethane (entries 3 and 4 *vs.* 1 and 2).

Table 2 Asymmetric reduction of ketones **6** with catalyst **5e**[a]

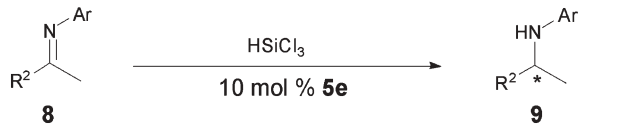


6 **7**

Entry	Ketone	R^1	Yield[b] (%)	ee (%)[c]
1	**6a**	4-$CF_3C_6H_4$	92	92 (*R*)
2	**6b**	4-$NO_2C_6H_4$	92	91 (*R*)
3	**6c**	3-$NO_2C_6H_4$	95	93 (*R*)
4	**6d**	4-ClC_6H_4	95	88 (*R*)
5	**6e**	3-ClC_6H_4	94	87 (*R*)
6	**6f**	4-BrC_6H_4	96	88 (*R*)
7	**6g**	3-BrC_6H_4	96	87 (*R*)
8	**6h**	Ph	94	81 (*R*)
9	**6i**	4-MeC_6H_4	95	87 (*R*)
10	**6j**	2-Naphthyl	98	82 (*R*)
11[d]	**6k**	*c*-C_6H_{11}	90	88 (*R*)
12	**6l**	2-$PhCH_2CH_2$	99	76 (*R*)
13[d]	**6m**	*i*-Pr	81	53 (*R*)

[a] Unless specified otherwise, reactions were carried out with 2.0 equiv. of $HSiCl_3$ on a 0.2 mmol scale at −20 °C for 16 h. [b] Isolated yield based on the ketone. [c] The ee values were determined using chiral HPLC. [d] The product was converted to its *para*-nitrobenzoate for ee determination due to its inefficient visibility for UV detection of HPLC.

Table 3 Asymmetric reduction of ketimines **8** with catalyst **5e**[a]



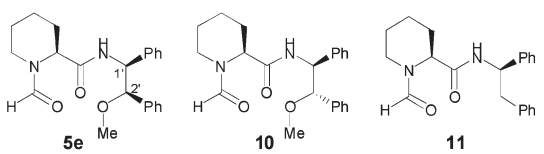
8 **9**

Entry	Ketimine	R^2, Ar	Yield[b] (%)	ee[c] (%)
1[d]	**8a**	Ph, Ph	94	90 (*R*)
2[e]	**8a**	Ph, Ph	85	93 (*R*)
3[f]	**8a**	Ph, Ph	93	91 (*R*)
4	**8a**	Ph, Ph	94	93 (*R*)
5	**8b**	Ph, PMP	93	89 (*R*)
6	**8c**	4-$MeOC_6H_4$, Ph	96	93 (*R*)
7	**8d**	4-$CF_3C_6H_4$, Ph	98	88 (*R*)
8	**8e**	2-Naphthyl, Ph	92	89 (*R*)
9	**8f**	6-MeO-2-naphthyl, Ph	86	90 (*R*)
10[g]	**8g**	*c*-C_6H_{11}, Ph	93	92 (*R*)
11[h]	**8h**	*i*-Pr, Ph	93	89 (*R*)
12[h]	**8i**	*i*-Pr, PMP	88	83 (*R*)

[a] Unless specified otherwise, reactions were carried out with 2.0 of equiv. of $HSiCl_3$ on a 0.2 mmol scale in 1.0 mL of toluene at −20 °C for 24 h. [b] Isolated yield based on the imine. [c] The ee values were determined using chiral HPLC. [d] The reaction was carried out in CH_2Cl_2 at 0 °C. [e] The reaction was carried out in CH_2Cl_2 at −20 °C. [f] The reaction was carried out in toluene at 0 °C. [g] The imine is a 10 : 1 (*E*/*Z*) mixture. [h] The imine is a 6 : 1 (*E*/*Z*) mixture.

To examine the substrate scope of **5e** for the reduction of ketimines, a variety of ketimines were reduced under the optimal conditions. As illustrated in Table 3 (entries 4–9), all the typical aromatic ketimines **8a–f** gave high yields (86–98%) and ee values (88–93%). Moreover, the difficult aliphatic ketimines **8g–i** that exist as *E*/*Z* isomeric mixtures also reacted well to afford high yields (88–93%) and ee values (83–92%, entries 10–12).[6,9,11]

Thus, the present catalyst system represents the most general one for the asymmetric reduction of both aromatic and aliphatic ketones and ketimines known to date. To rationalize the exceptional efficacy of this catalyst system, the methoxy group on C2′ (see **5e** in Scheme 1 for labeling) seems to be an important factor to take into account. It has been shown that replacement of this group with either a bigger alkoxy group (**5f** and **5g** in Fig. 1) or a group with a less electron-rich 2′-oxygen atom (**5a**, **5b**, and **5d**) led to decreased reactivity and/or enantioselectivity of the catalyst for the reduction of ketone **6a** (*vide supra*). Further reversing the stereochemistry of C2′ (**10**) that bears this group or removing it



Scheme 1

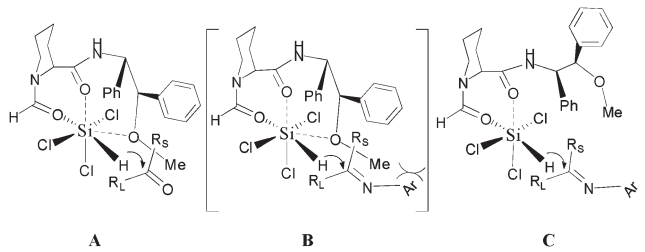


Fig. 2 Proposed transition states.

(**11**) resulted in a significant decrease in both reactivity and enantioselectivity (Scheme 1). Although detailed structural and mechanistic studies remain to be carried out, on the basis of these results we propose that catalyst **5e** could work as a tridentate activator and promote the hydrosilylation of ketones through the heptacoordinate silicon transition structure **A** (Fig. 2).[12] For the hydrosilylation of ketimines, similar transition structure **B** should not be favorable due to the steric repulsion between the *N*-Ar group and the methoxyl group, and the hexacoordinate silicon structure **C** should be preferred, which is justified by the observation that both the diastereomer **10** and the C2′-deoxygenated analogue **11** displayed the same high level of reactivity and enantioselectivity as **5e** for the reduction of ketimine **8a** (Scheme 1).[13]

In summary, we have developed the L-pipecolinic acid derived *N*-formamide (**5e**) as a highly effective Lewis basic organocatalyst for the enantioselective reduction of both ketones and ketimines with an unprecedented substrate scope. The methoxy group on C2′ has proven to be critical for the high efficacy of this catalyst for the reduction of ketones, but not indispensable for the reduction of ketimines. A heptacoordinate silicon transition structure and a hexacoordinate one were proposed for the reduction of ketones and ketimines, respectively.

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