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# New organic activators for the enantioselective reduction of aromatic imines with trichlorosilane

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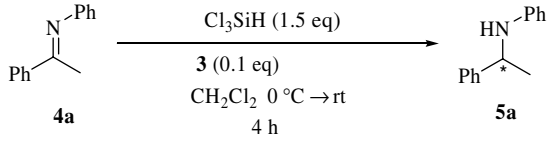
**Abstract**—*N*-Picolinoyl-(2*S*)-(diphenylhydroxymethyl)pyrrolidine was found to work as an organic activator in the reduction of aromatic imines to the corresponding amines by $Cl_3SiH$. The highest selectivity was 80% ee. These are the first data showing that *N*-formyl group is not always essential as N-protecting group of pyrrolidine derivatives for the reduction of imines by $Cl_3SiH$.


Enantioselective reduction of ketones[1] and imines[2] has been one of the recent topics in asymmetric synthesis.[3] A variety of reducing reagents have been used in the reductions but it is still worthwhile to exploit new methods, which can be carried out using inexpensive reducing reagents under mild conditions. One of such reagents may be trichlorosilane ($Cl_3SiH$), a liquid material easily available from silicon industry,[4] though some activator is necessary for $Cl_3SiH$ to efficiently reduce ketones and imines.[5] We already reported chiral *N*-formylpyrrolidine derivatives **1** as organic activators in the enantioselective reduction of ketones[6] and imines[7] with $Cl_3SiH$ (Fig. 1). The reduction proceeds smoothly at room temperature with good yields and enantioselectivity of up to 43% ee for the reduction of ketones and 66% ee for the reduction of imines. Recently, a new activator **2** for $Cl_3SiH$ in reducing imines with high enantioselectivity (up to 92% ee) was reported (Fig. 2).[8] The noticeable point in those reductions was that the presence of *N*-formyl substituent was essential for those reductions. In our continuing effort to exploit new chiral organic compounds in place of **1** to activate $Cl_3SiH$,[9] we found *N*-picolinoylpyrrolidine derivatives **3a**–**f** to also work as organic activators in the reduction of aromatic imine **4** to amine **5** (Eq. 1). These are the first data showing that *N*-formyl group is not always essential in the structure of organic activators for $Cl_3SiH$.[10,11]



(1)

A typical reaction was carried out as follows. $Cl_3SiH$ (0.45 mmol) was added into a solution of **4a** (0.3 mmol) and **3a** (0.03 mmol) in $CH_2Cl_2$ (1.5 mL), and the resulting solution was stirred at room temperature for 4 h. Then, after usual workup, the products were isolated by column chromatography. The results obtained using

**Table 1.** Asymmetric reduction of imine **4a** with $Cl_3SiH$ in the presence of **1** and **3**

| Entry | Organic activator | R | Yield (%) | ee (%)[a] | Config.[b] |
|---|---|---|---|---|---|
| 1[c] | — | — | 18 | — | — |
| 2[c] | **1a** | H | 79 | — | — |
| 3 | **1b** | $CO_2Me$ | 59 | 12 | *R* |
| 4[c] | **1c** | CONHPh | 91 | 55 | *R* |
| 5[c] | **1d** | CONHNaph-1 | 52 | 66 | *R* |
| 6 | **1e** | $CPh_2OH$ | 84 | 5 | *S* |
| 7 | **3a** | H | 83 | — | — |
| 8 | **3b** | $CO_2Me$ | 85 | 20 | *R* |
| 9 | **3c** | CONHPh | 76 | 18 | *S* |
| 10 | **3d** | CONHNaph-1 | 96 | 25 | *R* |
| 11 | **3e** | $CPh_2OH$ | 86 | 73 | *S* |
| 12 | **3f** | $CHPh_2$ | 75 | 13 | *R* |

[a] Determined by HPLC.
[b] Identified by comparison of the HPLC data with the literature data.
[c] Literature data, see Ref. 7.

*Keywords*: Organocatalysis; Asymmetric reduction; Imines; Optically active amines.
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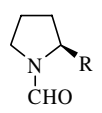
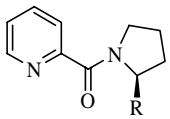


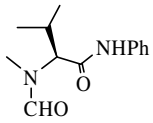
**1a-e**



**3a-f**

**a**; R=H
**b**; R=$CO_2Me$
**c**; R=CONHPh
**d**; R=CONHNaph-1
**e**; R=$CPh_2OH$
**f**; R=$CHPh_2$

**Figure 1.** Chiral organic activators for $Cl_3SiH$.



**2**

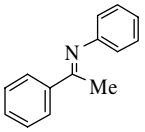
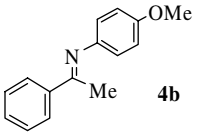
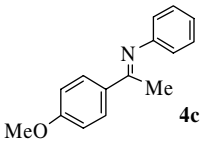
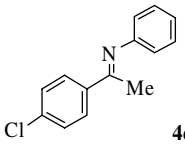
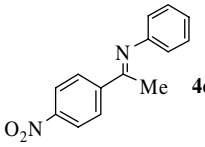
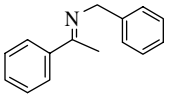
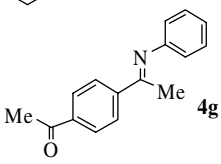
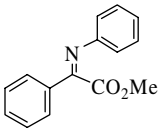
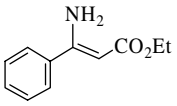
**Figure 2.** Chiral organic activator for reduction of imines by $Cl_3SiH$.

**3a**–**f** as activators are summarized in Table 1, which also shows the results using **1a**–**e** for comparison (Fig. 1).

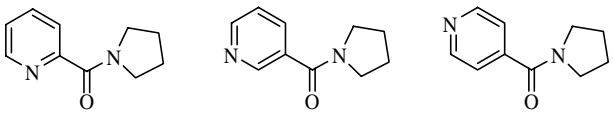
Although the yield of **5a** in the absence of activators was low (entry 1), the reduction became more efficient by the addition of a catalytic amount of *N*-formylpyrrolidines **1a**–**e** (entries 2–6). Similarly, compounds **3a**–**f** were found to work as activators for $Cl_3SiH$ (entries 7–12). Also, it was found that the highest enantioselectivity (entry 11) in **3a**–**f** was better than that in **1a**–**e** (entry 5). The catalytic activity of **3e** was also checked in the reduction of a variety of imines **4b**–**h** and enamine **4i** with almost similar stereoselectivity to that in the reduction of **4a** (Table 2). On the other hand, *N*-nicotinoylpyrrolidine (**3h**) and *N*-(4-pyridylcarbonyl)pyrrolidine (**3i**) did not activate $Cl_3SiH$ (Fig. 3), suggesting an important role of a complex in which Si atom coordinates with both a nitrogen atom of picolinoyl group and a carbonyl oxygen. Little difference of % ee between **3b** and **d** (entries 8–10) also suggests that Si atom does not coordinate with the carbonyl group of proline ester **3b** and amides **3c**,**d**, but with both the nitrogen atom of picolinoyl group and the carbonyl oxygen. Furthermore, the fact that **3e** afforded better result than **3f** (Fig. 4) suggests an important role of hydroxyl group of **3e** to coordinate with the Si atom of $Cl_3SiH$.

On the basis of these facts, we propose a mechanism shown in Figure 5, in which **3e** coordinates with both **4a** and $Cl_3SiH$, the transition state **A** being more likely than transition state **B**, though the mechanism is a working hypothesis.[12]

**Table 2.** Reduction of a variety of imines **4a**–**h** by $Cl_3SiH$ in the presence of **3e**

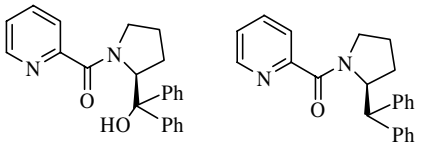
| Aromatic imines | Yield (%) | % ee | Config. |
|---|---|---|---|
|  **4a** | 86 | 73 | *S* |
|  **4b** | 90 | 75 | *S* |
|  **4c** | 90 | 71 | *S* |
|  **4d** | 73 | 71 | *S* |
|  **4e** | 84 | 73 | *S* |
|  **4f** | 67 | 80 | *S* |
|  **4g** | 24[a] | 67 | —[b] |
|  **4h** | 80 | 45 | *R* |
|  **4i** | 65 | 41 | *S* |

[a] *N*-Phenyl-1-(*p*-acetylphenyl)ethylamine.
[b] Not determined.



**3a** 83%　**3h** 12%　**3i** 21%

**Figure 3.** Reduction of **4a** with **3a**,**h**,**i**.



**3e** 73%ee ((*S*)-**5a**)　**3f** 13%ee ((*R*)-**5a**)

**Figure 4.** Reduction of **4a** with **3e**,**f**.

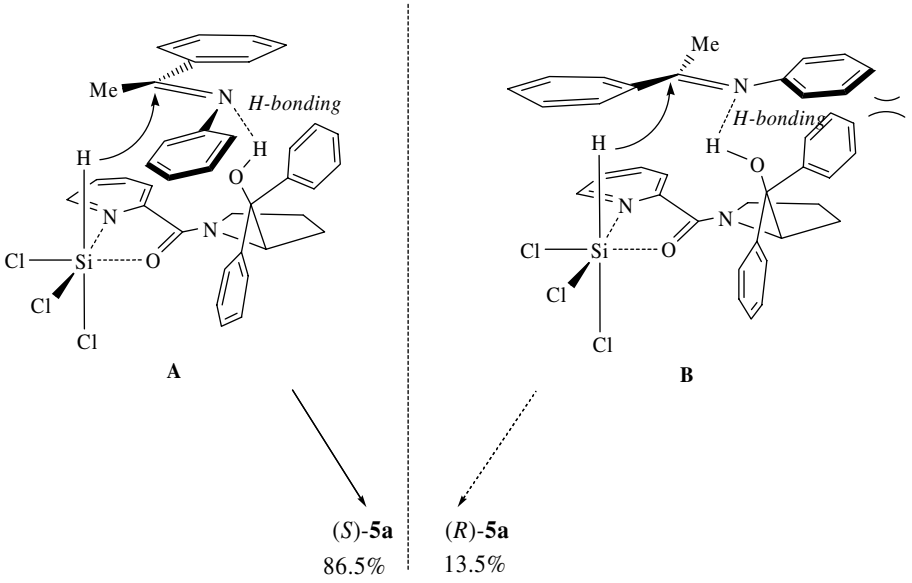



**Figure 5.** A plausible reaction mechanism for reduction of **4a** with **3e**.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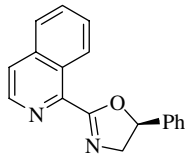


**6**

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