New Organic Activators for the Enantioselective Reduction of Aromatic Imines with Trichlorosilane

Osamu Onomura,[a] Yoshimi Kouchi,[a] Fumiaki Iwasaki,[b]
and Yoshihiro Matsumura [a,*]

[a]*Graduate School of Biomedical Sciences, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan*

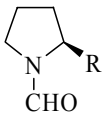
[b]*Tsukuba Research Laboratory, Tokuyama Corporation, 40 Wadai, Tsukuba 300-4247, Japan.*

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. This is 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.

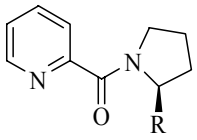
Enantioselective reduction of ketones[1] and imines[2] has been one of recent topics in asymmetric synthesis.[3] A variety of reducing reagents have been used in the reductions but it is still worthwhile to exploit new methods which can be carried out using inexpensive reducing reagents under mild conditions. 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. 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.[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). This is the first data showing that *N*-formyl group is not always essential in the structure of organic activators for Cl_3SiH.[10,11]

Key words: Organocatalysis; Asymmetric reduction; Imines; Optically active amines

* Corresponding author, Tel +81-95-819-2429, Fax +81-95-819-2476, E-mail matumura@net.nagasaki-u.ac.jp (Y. Matsumura).



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

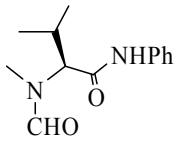


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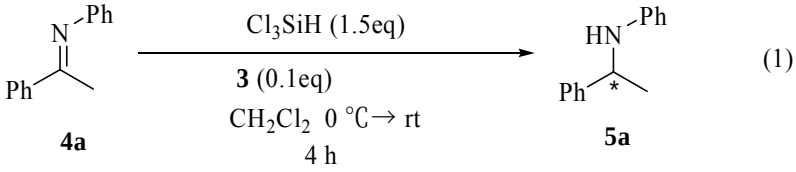
Figure 2. Chiral organic activator for reduction of imines by Cl_3SiH



(1)

A typical reaction was carried out as follows. Cl_3SiH (0.45mmol) was added into a solution of **4a** (0.3mmol) and **3a** (0.03mmol) in CH_2Cl_2 (1.5mL), 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 **3a-f** as activators are summarized in Table 1, which also shows the results using **1a-e** for comparison.

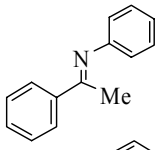
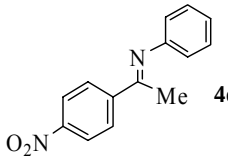
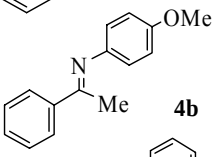
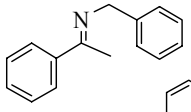
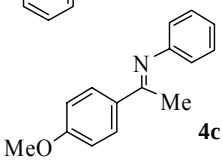
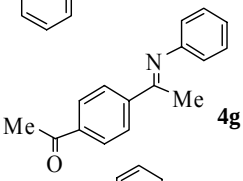
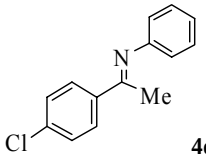
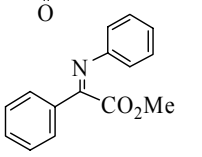
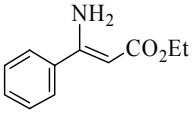
Table 1. Asymmetric reduction of imine **4a** with Cl_3SiH in the presence of **1** and **3**

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*

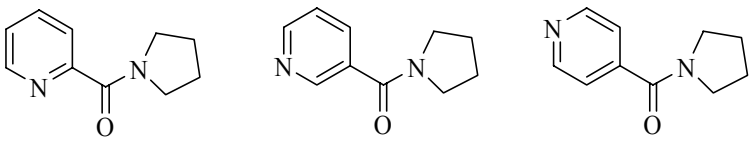
[a] Determined by HPLC. [b] Identified by comparison of the HPLC data with literature data. [c.] Literature data, see ref. 7.

Although the yield of **5a** in the absence of activators was low (entry 1), the reduction became more efficient by 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-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.

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

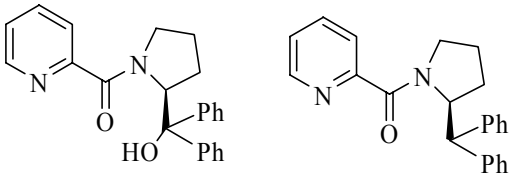
aromatic imines	Yield %	%ee	config.	aromatic imines	Yield %	%ee	config.
 **4a**	86	73	*S*	 **4e**	84	73	*S*
 **4b**	90	75	*S*	 **4f**	67	80	*S*
 **4c**	90	71	*S*	 **4g**	24[a]	67	—[b]
 **4d**	73	71	*S*	 **4h**	80	45	*R*
				 **4i**	65	41	*S*

[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**

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]

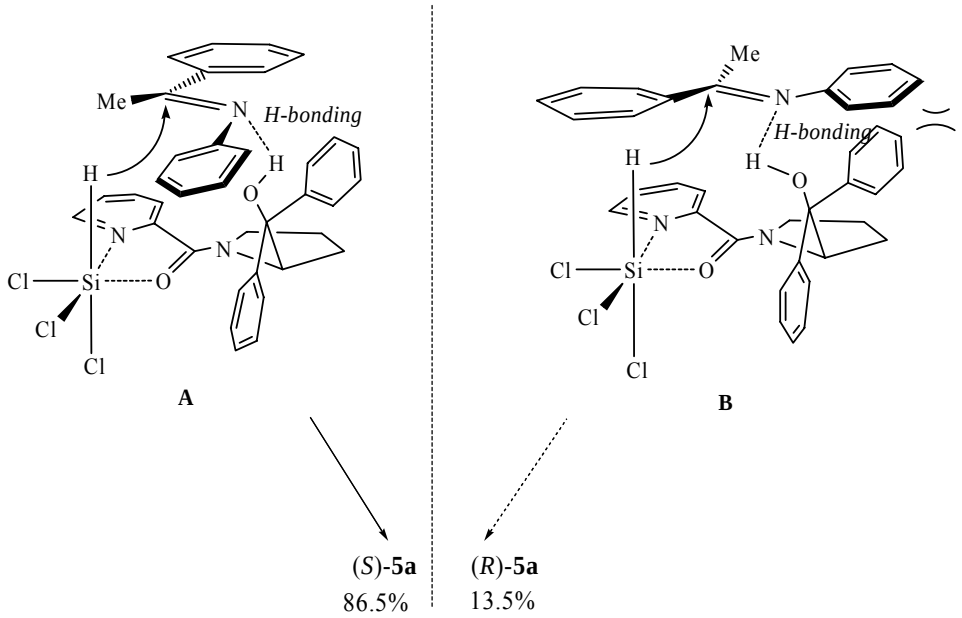


Figure 5. A plausible reaction mechanism for redution of **4a** with **3e**

Acknowledgement

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Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc*. **1998**, *120*, 13529-13530. (j) Ohkuma, T.; Sandoval, C. A.; Srinivasan, R.; Lin, Q.; Wei, Y.; Muniz, K.; Noyori, R. *J. Am. Chem. Soc*. **2005**, *127*, 8288-8289.

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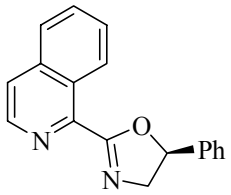

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