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First chemo- and stereoselective reduction of imines using trichlorosilane activated with *N*-formylpyrrolidine derivatives

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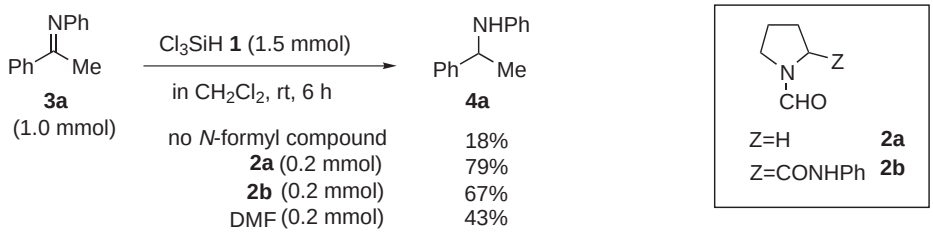
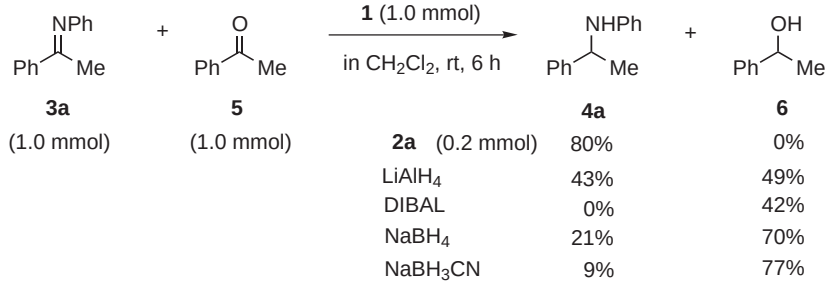
Abstract—Trichlorosilane activated with *N*-formylpyrrolidine derivatives was found to be an effective reagent for reduction of imines to amines. The reagent showed much higher selectivity toward imino groups than carbonyl groups. The reduction of imines using trichlorosilane activated with optically active *N*-formylproline derivatives gave enantiomerically enriched amines in moderate optical yields (up to 66% ee).

Chemo- and stereoselective reduction of imines is very useful for the preparation of functionalized amino compounds. Although there have been a variety of solid reducing reagents,[1] most of them prefer the reduction of a carbonyl group to that of an imino group due to the lower electrophilicity of an imino group.[2] Recently developed dibutylchlorotin hydride[3] and trichlorosilane (**1**)[4,5] can also reduce an imino group. The former reducing reagent is not suitable from the viewpoint of green chemistry because of its non-catalytic nature, as well as the requirement of HMPA as a ligand, while the latter liquid reagent might be useful for industrial use because of the relatively easy handling in operation and low cost.[6] However, there has been little information on selectivity of the reagent **1** toward an imino group.[7] In our continuing exploration of the versatility of **1** activated with *N*-formylpyrrolidine derivatives,[8] we have found the first chemo-, stereo-, and enantioselective reduction of imino compounds using **1** activated with a catalytic amount of *N*-formylpyrrolidines **2a**,**b**.



(1)



(2)

Keywords: amines; imines; reduction; silicon halides.

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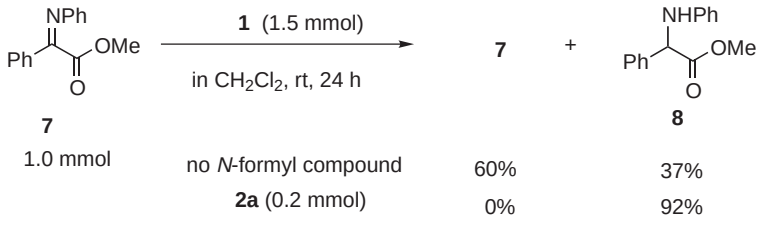

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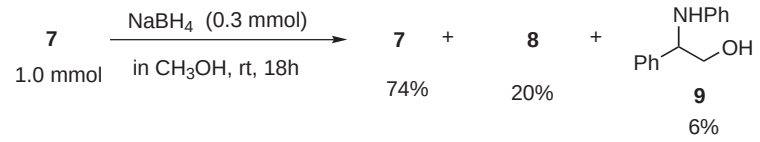


(4)

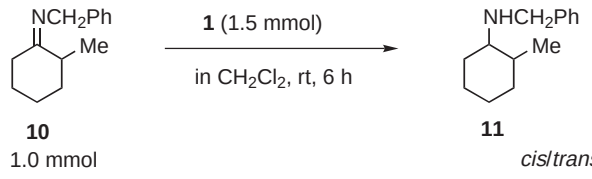
A typical reaction is exemplified by the reduction of imine **3a** (Eq. (1)). Although **3a** was reduced in low yields by **1** in the absence of *N*-formylpyrrolidines **2a**,**b**, the reduction was found to become much more effective in the presence of a catalytic amount of **2a**,**b**, suggesting that **2a**,**b** played the role of efficient activators for **1**. DMF[5] was less effective than **2a**,**b**.

A reducing reagent **1** activated with *N*-formylpyrrolidine **2a** also presented high imino-selectivity in a competitive reduction between **3a** and a ketone **5** (Eq. (2)).[9] A comparison of the selectivity with those using conventional reducing reagents[3] makes the characteristic of **1** activated with **2a** as an imino-selective reducing reagent much clearer.

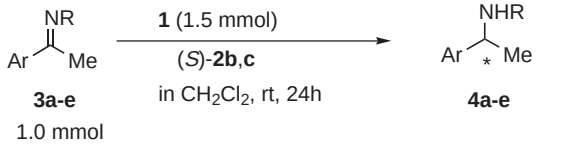
Furthermore, **1** activated with **2a** was used in a selective reduction of imino ester **7** to give amino ester **8** in high yield (Eq. (3)), while the reduction of **7** by $NaBH_4$ resulted in a recovery of **7** with a small amount of **8** contaminated with amino alcohol **9** (Eq. (4)).

Excellent stereoselectivity in the reduction of imine **10** using **1** activated with **2a** was also observed (Eq. (5)).[10] The high *cis*-selectivity in the reduction was comparable to that of superhydride and is much higher than the results obtained using other reducing reagents.[11]

Finally, our system was applied to a preparation of optically active amines. The reduction of aromatic imines **3a**–**e** by **1** was carried out in the presence of optically active *N*-formyl-L-proline aromatic amides



(5)



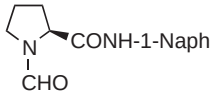
(6)

(*S*)-**2b**,**c** as activators (Eq. (6)). The enantio ratios (ees) of the product **4a**–**e** were moderate, as shown in Table 1.[12]

The fact that (*S*)-**2b**,**c** gave (*R*)-enriched amines (*R*)-**4a**,**b** (entries 1, 2, and 6) suggested that the reduction predominantly proceeds through a pathway involving a transition state **A** rather than the other transition state **B** (Fig. 1). Although the ees of product **4** were still moderate in most cases, a relatively high ee (66% ee) was obtained in a case using 1-naphthylamides (*S*)-**2c** (entry 6).[13]

In summary, we have presented a new finding that trichlorosilane (**1**) activated with *N*-formylpyrrolidine

Table 1. Asymmetric reduction of **3** with optically active **2** as activators

Entry	Activator (mmol)	Substrate	Ar	R	Yield of **4** (%)		% Ee[a]	*R* or *S*
1	(*S*)-**2b** (0.1)	**3a**	Ph	Ph	**4a**	91	55	*R*
2	(*S*)-**2b** (0.1)	**3b**	Ph	Bn	**4b**	97	55	*R*
3	(*S*)-**2b** (0.2)	**3c**	4-NO_2Ph	Ph	**4c**	>99	49	–[b]
4	(*S*)-**2b** (0.2)	**3d**	4-ClPh	Ph	**4d**	95	54	–[b]
5	(*S*)-**2b** (0.2)	**3e**	2-Naph	Ph	**4e**	56	49	–[b]
6	 (*S*)-**2c** (0.1)	**3a**	Ph	Ph	**4a**	52	66	*R*

[a] Determined by Chiralcel OD.
[b] Not determined.

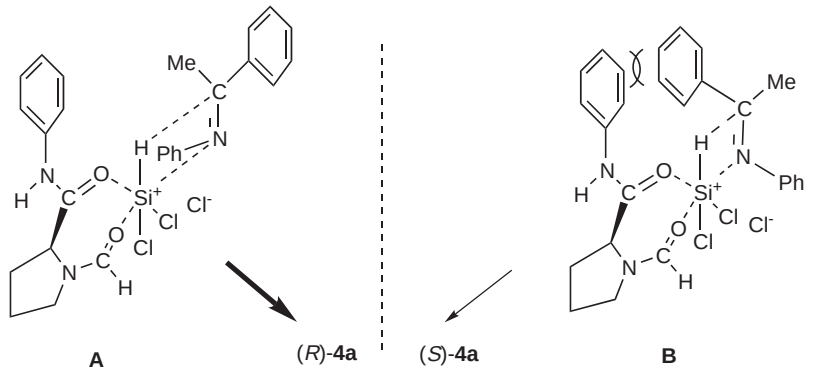


Figure 1. Working hypothesis for asymmetric reduction of **3a** by Cl_3SiH (**1**) activated with (*S*)-**2b**.

derivatives **2** is an effective reagent for the reduction of imines which was not affected by the presence of carbonyl groups. In addition, we qualified this method using **1** with optically active *N*-formylproline derivatives **2b**,**c** as a new enantioselective reduction method of imines. Further study on the mechanistic aspect and the improvement of the ees is currently under way.

Acknowledgements

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References

1. Hutchins, R. O. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Ed.; Pergamon Press: Oxford, 1991; Vol. 8, Chapter 1.2.
2. Alcaide, B.; López-Mardomingo, C.; Pérez-Ossorio, R.; Plumet, J. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1649–1653.
3. Shibata, I.; Moriuti-Kawakami, T.; Tanizawa, D.; Suwa, T.; Sugiyama, E.; Matsuda, H.; Baba, A. *J. Org. Chem.* **1998**, *63*, 383–385.
4. Benkeser, R. A.; Snyder, D. C. *J. Organomet. Chem.* **1982**, *225*, 107–115.
5. A combination of **1** and a large excess of DMF was an efficient reducing reagent for imines: Kobayashi, S.; Yasuda, M.; Hachiya, I. *Chem. Lett.* **1996**, 407–408.
6. Zulehner, W.; Neure, B.; Rau, G. *Ullmann's Encyclopedia of Industrial Chemistry*; VCH: Weinheim, 1993; Vol. A23, 721–741.
7. The hypervalent silicate reagent ($[(MeO)_4SiH]^-$ from $(MeO)_3SiH$ with OMe^-) was effective for the reduction of carbonyl compounds, while the reagent did not reduce imines except tosylimine. See: (a) Hosomi, A.; Hayashida, H.; Kohra, S.; Tominaga, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 1411–1412; (b) Hojo, M.; Murakami, C.; Fujii, A.; Hosomi, A. *Tetrahedron Lett.* **1999**, *40*, 911–914.
8. This reducing reagent was highly effective for the reduction of ketones to alcohol. See: Iwasaki, F.; Onomura, O.; Mishima, K.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **1999**, *40*, 7507–7511.
9. Similar high imino-selectivity has been observed in alkylation of imines in the presence of aldehydes. Allylation: Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6641–6647. Enolate addition: Kobayashi, S.; Nagayama, S. *J. Org. Chem.* **1997**, *62*, 232–233.
10. The reduction of **10** by **1** without any activator afforded **11** in good yields. This phenomenon can be explained in terms of the difference in reactivity between aromatic imine **3a** and aliphatic imine **10**. The details will be published as a full paper.
11. Wrobel, J. E.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 3447–3450.
12. A typical experimental procedure for the reduction of **3**: To **3a** (1.0 mmol) and (*S*)-**2b** (0.1 mmol) in CH_2Cl_2 (5 mL) was added **1** (1.5 mmol) in CH_2Cl_2 (1 mL) at 0°C. The mixture was stirred for 24 h at rt, and the resulting mixture was poured into saturated aqueous $NaHCO_3$ (10 mL). Generated insoluble materials were removed by filtration. The organic layer was separated and concentrated in vacuo. The residue was chromatographed on silica gel (*n*-hexane:AcOEt = 1:20) to afford (*R*)-**4a** in 91% yield with 55% ee [Daicel Chiralcel OD (4.6 mmϕ, 25 cm×2), *n*-hexane:2-propanol = 15:1 (containing 0.1% diethylamine), detected at 254 nm, flow rate: 0.5 mL/min, retention time: 24 min for the (*S*)-isomer, 29 min for the (*R*)-isomer].
13. Concerning an active species in these reactions, the ^{29}Si NMR spectra of **1**–**2a** and **1**–**2b** in CD_2Cl_2 showed the presence of hypervalent silicates (Ref. 14). **1**: −9.4 ppm; **1**–**2a** (1:1): −41.5 and −185.4 ppm; **1**–**2a** (1:2): −185.3 ppm. **1**–**2b** (1:1): −9.4 and −18.8 ppm; **1**–**2b** (1:2): −18.8, −181.3, and −184.1 ppm.
14. Williams, E. A. In *The Chemistry of Organic Silicon Compounds*; Patai, S.; Rappoport, Z., Ed.; John Wiley & Sons: New York, 1989; Chapter 8.