



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

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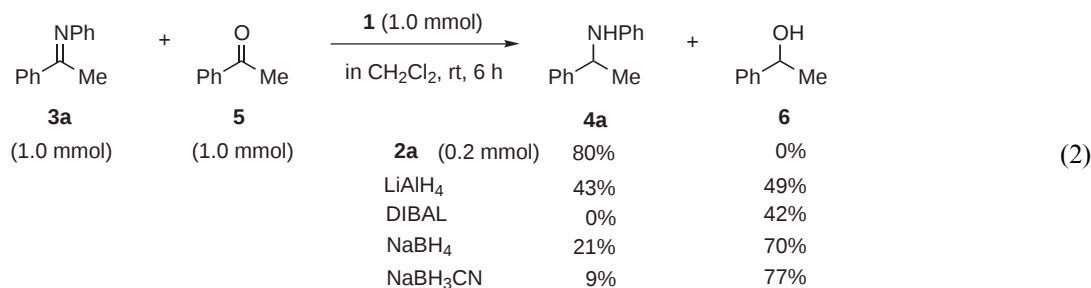
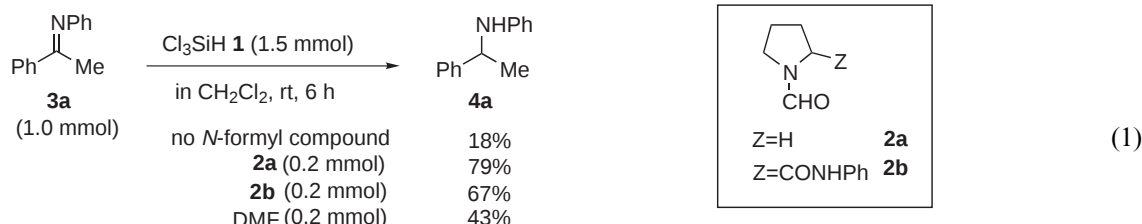
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Abstract—Trichlorosilane activated with *N*-formylpyrrolidine derivatives was found to be an effective reagent for reduction of imines to amines. The reagent showed much higher selectivity toward imino groups than carbonyl groups. The reduction of imines using trichlorosilane activated with optically active *N*-formylproline derivatives gave enantiomerically enriched amines in moderate optical yields (up to 66% ee). © 2001 Elsevier Science Ltd. All rights reserved.

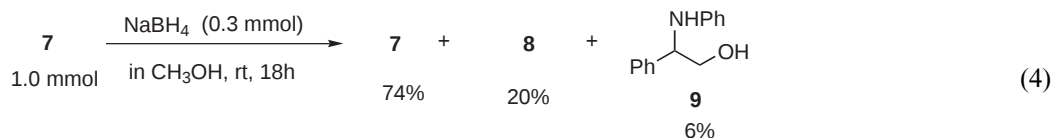
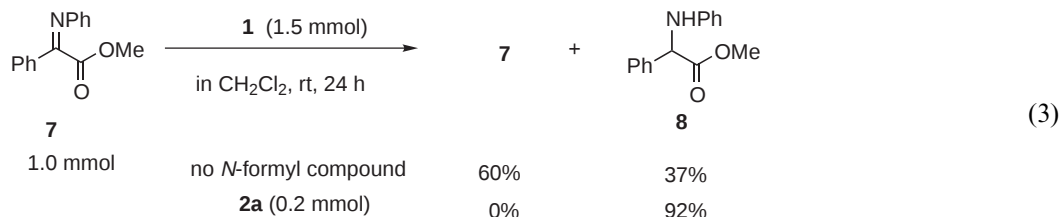
Chemo- and stereoselective reduction of imines is very useful for the preparation of functionalized amino compounds. Although there have been a variety of solid reducing reagents,¹ most of them prefer the reduction of a carbonyl group to that of an imino group due to the lower electrophilicity of an imino group.² Recently developed dibutylchlorotin hydride³ 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**.



Keywords: amines; imines; reduction; silicon halides.

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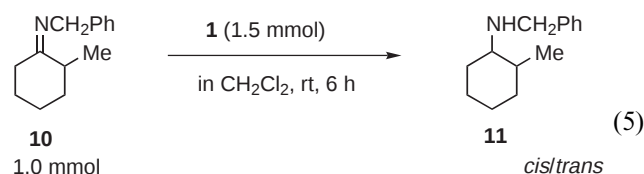
A typical reaction is exemplified by the reduction of imine **3a** (Eq. (1)). Although **3a** was reduced in low yields by **1** in the absence of *N*-formylpyrrolidines **2a,b**, the reduction was found to become much more effective in the presence of a catalytic amount of **2a,b**, suggesting that **2a,b** played the role of efficient activators for **1**. DMF⁵ 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 reagents³ makes the characteristic of **1** activated with **2a** as an imino-selective reducing reagent much clearer.

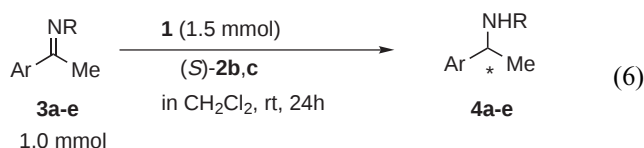
Furthermore, **1** activated with **2a** was used in a selective reduction of imino ester **7** to give amino ester **8** in high yield (Eq. (3)), while the reduction of **7** by NaBH₄ resulted in a recovery of **7** with a small amount of **8** contaminated with amino alcohol **9** (Eq. (4)).

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



2a (0.2 mmol)	85%	98/2
NaBH ₃ CN	82%	64/36
9-BBN	70%	83/17
Superhydride	84%	97/3

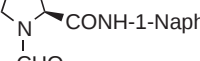


(*S*)-**2b,c** as activators (Eq. (6)). The enantio ratios (ees) of the product **4a–e** were moderate, as shown in Table 1.¹²

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	<i>R</i> or <i>S</i>	
1	(<i>S</i>)- 2b (0.1)	3a	Ph	Ph	4a	91	55	<i>R</i>
2	(<i>S</i>)- 2b (0.1)	3b	Ph	Bn	4b	97	55	<i>R</i>
3	(<i>S</i>)- 2b (0.2)	3c	4-NO ₂ Ph	Ph	4c	>99	49	— ^b
4	(<i>S</i>)- 2b (0.2)	3d	4-ClPh	Ph	4d	95	54	— ^b
5	(<i>S</i>)- 2b (0.2)	3e	2-Naph	Ph	4e	56	49	— ^b
6	 (<i>S</i>)-2c (0.1)	3a	Ph	Ph	4a	52	66	<i>R</i>

^a Determined by Chiralcel OD.

^b Not determined.

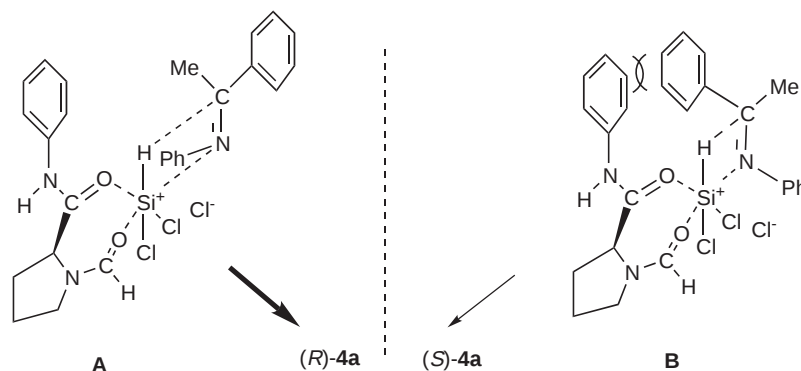


Figure 1. Working hypothesis for asymmetric reduction of **3a** by Cl_3SiH (**1**) activated with (*S*)-**2b**.

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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- 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.
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