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Catalytic activation of trichlorosilane for efficient and stereoselective reduction of ketones

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Abstract

Some kinds of *N*-formyl cyclic amine derivatives were found to be effective activators for trichlorosilane to reduce ketones. Namely, a catalytic amount of these activators were sufficient to complete the reduction of ketones with trichlorosilane, and the reduction of ketones by trichlorosilane with optically active activators gave enantiomerically enriched *sec*-alcohols in some extent of optical yields (up to 51% ee). © 1999 Elsevier Science Ltd. All rights reserved.

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It is very worthwhile in organic synthesis to exploit new reagents which make it possible to reduce ketones with high selectivities in a preparative scale under mild conditions. Trichlorosilane[1] (Cl_3SiH) may be one of the candidates since it is cheap and easy to handle and has already been used in a large scale for the reduction of easily reducible compounds as exemplified by transforming phosphine oxide[2] to phosphine (BINAP) and *N*-acyliminium ion[3] to *N*-acylamine (herbicide). However, its use for the reduction of ketones is rather limited because of the low reactivity toward ketones.[4–6] An appropriate activator has been expected to improve the reactivity of Cl_3SiH to reduce ketones. In this respect, Kobayashi et al. recently reported that *N*,*N*-dimethylformamide (DMF) worked as an activator for Cl_3SiH to reduce aldehydes and ketones, while an excess amount of DMF was used.[7,8]

We report herein new findings that *N*-formylated pyrrolidine derivatives **1** are efficient catalysts for the activation of Cl_3SiH to reduce ketones, and also that enantiomerically enriched *sec*-alcohols can be formed with up to 51% ee when optically active **1** was used (Eq. 1).

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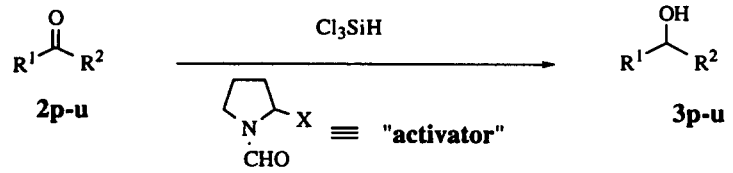
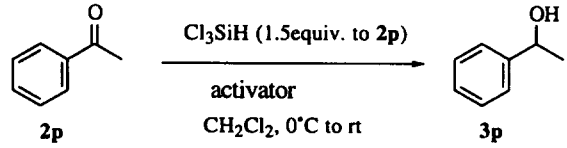


a; X=H
b; X=CONHPh
c; X=CONH-1-Naph
d; X=CONHCHPh$_2$
e; X=CONH-*n*-C$_6$H$_{14}$
f; X=CONH-*t*-Bu
g; X=COOPh
h; X=COOMe
i; X=COO*t*-Bu
j; X=CH$_2$OBn

p; R^1=Ph, R^2=Me
q; R^1=Ph, R^2=Et
r; R^1=4-ClPh, R^2=Me
s; R^1=Ph, R^2=Bn
t; R^1=Ph, R^2=*i*-Bu
u; R^1=CH$_2$CH$_2$Ph, R^2=Me

(1)

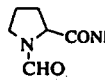
In view of our aim to find out suitable activators for Cl_3SiH to reduce ketones, we first surveyed a variety of *N*-substituted amino compounds such as *N*-formylpyrrolidine (**1a**), *N*-formylproline benzamide (**1b**), *N*-formylpiperidine (**4**), *N*-formylhexamethyleneimine (**5**), *N*-methylformamide (**6**), *N*-methoxycarbonylpyrrolidine (**7**), and *N,N*-dimethylacetamide (**8**) in a reduction of acetophenone (**2p**) with Cl_3SiH (1.5 equiv. to **2p**) (Eq. 2). The amount of the *N*-substituted amino compounds was 1.5–0.1 equiv. to **2p**, and the reactions were carried out in CH_2Cl_2 at 0°C to rt for 12 h or 24 h.[9]



(2)

The yields of the reduction product, 1-phenylethanol (**3p**), are summarized in Table 1 (entries 3–12) which also includes the results using DMF as a reference (entries 1 and 2).

Table 1
Reduction of **2p** with a variety of amino compounds as activators

entry	activator	activator equiv.[a]	reaction time (h)	yield (%)[b] of **3p**
1	DMF	1.5	12	52
2	DMF	0.1	24	28
3	 **1a**	1.5	12	90
4	**1a**	0.1	24	59
5	 **1b**	1.5	12	95
6	**1b**	0.1	24	90
7	 **4**	1.5	12	72
8	**4**	0.1	24	46
9	 **5**	0.1	24	27
10	MeNHCHO **6**	1.5	12	26
11	 **7**	1.5	12	0
12	Me_2NAc **8**	1.5	12	0

[a] Equiv. to **2p**. [b] Determined by HPLC.

The results shown in Table 1 indicate the following characteristics: (1) *N*-formylpyrrolidines (**1a,b**) and *N*-formylpiperidine (**4**) were preferable to DMF as activators for Cl_3SiH (entries 3–8); (2) *N*-

formylhexamethyleneimine (**5**) was comparable to DMF (entry 9), and *N*-methylformamide (**6**) was less effective than DMF (entry 10); (3) the protecting groups (methoxycarbonyl and acetyl groups) other than formyl group did not work as a functionality to activate Cl_3SiH (entries 11 and 12); and (4) *N*-formylproline derivative **1b** was much more efficient than *N*-formylpyrrolidine (**1a**) (compare entries 3, 4 with entries 5, 6).

Among (1)–(4), the characteristic (4) seemed to be interesting from a synthetic viewpoint since one tenth of the amount of **1b** also gave a good yield of **3p** (entry 6), which might allow us the method to apply to an asymmetric reduction of ketones using optically active proline derivatives. Thus, we carried out the reduction of **2p** with Cl_3SiH in the presence of various optically active *N*-formylproline derivatives (*S*)-**1b–j** and (*R*)-**1b** as activators in order to clarify the effect of 2-substituent of *N*-formylpyrrolidine ring on the yields and/or enantio ratios (ees) of the product **3p**. The yields and ees of **3p** are summarized in Table 2. The results are as follows. (*S*)-Activator gives (*R*)-enriched alcohols (entry 1, Table 2), while (*R*)-activator gives (*S*)-enriched alcohol (entry 2).

Table 2
Asymmetric reduction of **2p** with optically active **1** as activators[a]

entry	X	1[b]	yield (%)[c] of 3p	*R/S* (%ee)[c]	entry	X	1[b]	yield (%)[c] of 3p	*R/S* (%ee)[c]
1	CONHPh	(*S*)-**1b**	90	65/35 (31)	6	CONH-*t*-Bu	(*S*)-**1f**	80	55/45 (11)
2	CONHPh	(*R*)-**1b**	93	36/64 (27)	7	COOPh	(*S*)-**1g**	53	61/40 (21)
3	CONH-1-Naph	(*S*)-**1c**	78	71/29 (43)	8	$COOCH_3$	(*S*)-**1h**	39	57/43 (14)
4	$CONHCHPh_2$	(*S*)-**1d**	69	61/39 (20)	9	COO-*t*-Bu	(*S*)-**1i**	88	55/45 (11)
5	CONH-*n*-C_6H_{14}	(*S*)-**1e**	82	54/46 (8)	10	CH_2OBn	(*S*)-**1j**	29	56/44 (13)

[a] The reactions were carried out in CH_2Cl_2 at 0°C to rt for 24h. [b] 0.1Equiv. to **2p**. [c] Determined by Chiralcel OB.

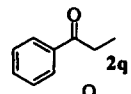
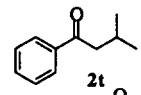
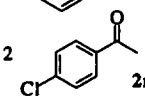
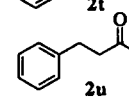
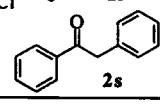
The use of amides (*S*)-**1b–f** as activators gave **3p** in relatively high yields (entries 1–6) and the yields of **3p** were moderate or low in the cases using esters (*S*)-**1g,h** (entries 7, 8) and ether (*S*)-**1j** (entries 10) as activators, while a bulky alkyl ester (*S*)-**1i** gave a good yield of product (entry 9). Those results suggest that the 2-carbonyl group of *N*-formylpyrrolidine derivatives plays an important role as activator for Cl_3SiH to reduce **2p**.

In respect to the ees of **3p**, they were still low in most cases, while moderate ees (31% ee[10,11] and 43% ee) were obtained in the cases using *N*-formyl-(*S*)-proline aromatic amides (*S*)-**1b,c**, respectively (entries 1 and 3).

The reduction by Cl_3SiH was applicable to the other ketones **2q–u**. The results using (*S*)-**1b,c** as activators are shown in Table 3. Although we could not obtain **3** with high ee, the fact that dehydrobenzoin **3s** was reduced with 51% ee (entry 3, Table 3) suggests a potential possibility of the reduction by Cl_3SiH as an asymmetric reduction method.

Although it is not clear yet why the reduction of ketones **2** using Cl_3SiH-(*S*)-**1** affords (*R*)-enriched alcohols **3**, we present a plausible mechanism as exemplified by the reduction of **2p** with (*S*)-**1c**. That is, intermediates **A** or **B** may be formed by *Si*-face or *Re*-face attack of a silylhydride reducing agent in which the Si atom coordinates with a carbonyl oxygen atom of carboxamide function. Possibly **A** giving (*R*)-**3p** may be more stable than **B** giving (*S*)-**3p** because of a severe steric repulsion between naphthyl and phenyl groups in **B** (Fig. 1).

Table 3
Asymmetric reduction of some ketones **2q–u**

entry	substrate	activator[a]	yield (%)[b,c] of 3	R/S (%ee) of 3	entry	substrate	activator[a]	yield (%)[b,c] of 3	R/S (%ee) of 3
1	 2q	(*S*)-1b	3q 47	61/39 (22)[d]	4	 2t	(*S*)-1c	3t 21	68/32 (35)[e]
2	 2r	(*S*)-1b	3r 87	64/36 (29)[d]	5	 2u	(*S*)-1c	3u 76	54/46 (8)[e]
3	 2s	(*S*)-1c	3s 27	75/25 (51)[d]					

[a] 0.1Equiv to 2. [b] The reactions were carried out in CH_2Cl_2 at 0°C to rt for 24h. [c] Isolated yield. [d] Determined by Chiralcel OB. [e] Determined by Chiralcel OD.

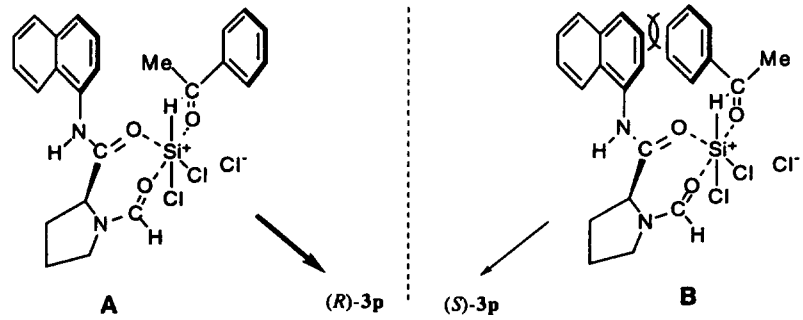


Figure 1. The working hypothesis for asymmetric reduction of **2p** with Cl_3SiH-**1c**

In summary, we have presented a new finding that Cl_3SiH can reduce ketones provided that a catalytic amount of *N*-formylated cyclic amine derivatives **1** is present in the system. In addition, we developed new chiral catalysts such as L-proline derivatives **1b,c** for the activation of Cl_3SiH to reduce ketones affording enantiomerically enriched *sec*-alcohols under mild conditions. Further study on the mechanistic aspect and the improvement of the ees are currently under investigation.

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9. A typical experimental procedure for the reduction of **2**: To a **2p** (2 mmol) and activators (3 mmol) in CH_2Cl_2 (10 mL) was added Cl_3SiH (3 mmol) in CH_2Cl_2 (2 mL) at 0°C. The mixture was stirred for 12 h at rt, and MeOH/H_2O (15 mL, 1/2 (v/v)) was added. Water was then added and insoluble materials were removed by filtration. The organic layer was separated and concentrated in vacuo. The yields of **3p** were determined by HPLC analysis.
10. Temperature effect: The reduction of **2p** using 0.1 equiv. of (*S*)-**1b** at −20°C for 40 h in CH_2Cl_2 afforded **3p** with 29% ee (yield; 79%). On the other hand, the reduction of **2p** using 0.5 equiv. of (*S*)-**1b** at −78°C for 6 h in CH_2Cl_2 afforded **3p** with 32% ee (yield; 27%).
11. Solvent effect: The reduction of **2p** using 0.1 equiv. of (*S*)-**1b** at 0°C to rt for 24 h in ethyl acetate, toluene, acetonitrile, and tetrahydrofuran afforded **3p** with 23% ee (yield; 42%), 10% ee (yield; 67%), 5% ee (yield; 59%), and 31% ee (yield; 25%), respectively.