

# New Efficient Organic Activators for Highly Enantioselective Reduction of Aromatic Ketones by Trichlorosilane

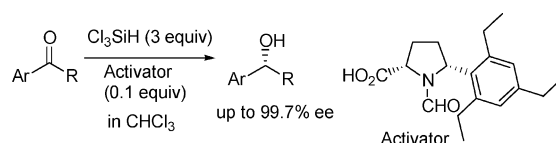
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## ABSTRACT



Aryl ketones were reduced to the corresponding alcohols with excellent enantioselectivity (up to 99.7% ee) by  $\text{Cl}_3\text{SiH}$  in the presence of a catalytic amount of *N*-formyl- $\alpha'$ -(2,4,6-triethylphenyl)-L-proline as an activator. Both carboxyl group at the  $\alpha$ -position of the activator and 2,4,6-triethylphenyl group at the  $\alpha'$ -position were critical for the high enantioselectivity.

Enantioselective reduction of ketones has been one of central topics in asymmetric synthesis over the past two decades.<sup>1</sup> Although a variety of reducing reagents have been used for the purpose,<sup>2</sup> there have been few studies on the use of trichlorosilane ( $\text{Cl}_3\text{SiH}$ ),<sup>3</sup> which is an economical and easy to handle reagent.<sup>4,5</sup> Because  $\text{Cl}_3\text{SiH}$  does not have the ability

to reduce ketones by itself, appropriate activators are necessary for the reduction of ketones by  $\text{Cl}_3\text{SiH}$  with high efficiency. Organic chiral activators are in particular of interest in this respect because they provide a route for asymmetric reduction of ketones. We have reported a first enantioselective reduction of ketones by  $\text{Cl}_3\text{SiH}$  using chiral *N*-formylpyrrolidines (**1q,r**) as organic activators (up to 43% ee),<sup>4</sup> and recently isoquinolinylloxazoline (**2**) was reported to work well as a chiral activator (up to 94% ee).<sup>6,7</sup>

We report herein new efficient organic activators **3–6** (Figure 1), which allow the reduction of aromatic ketones **7**

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(1) Some recent reviews, see: (a) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97–102. (b) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012. (c) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40–73. (d) Riant, O.; Mostefai, N.; Courmarcel, J. *Synthesis* **2004**, 2943–2958.

(2) Recent representative literatures. B-H reagents: (a) Yamada, T.; Nagata, T.; Sugi, K. D.; Yorozu, K.; Ikeno, T.; Ohtsuka, Y.; Miyazaki, D.; Mukaiyama, T. *Chem. Eur. J.* **2003**, *9*, 4485–4509. Hydrogen transfer reactions: (b) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521–2522. Hydrogenation: (c) Ohkuma, T.; Sandoval, C. A.; Srinivasan, R.; Lin, Q.; Wei, Y.; Muniz, K.; Noyori, R. *J. Am. Chem. Soc.* **2005**, *127*, 8288–8289. Si-H reagents: (d) Tao, B.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3892–3894. (e) Evans, D. A.; Michael, F. E.; Tedrow, J. S.; Campos, K. R. *J. Am. Chem. Soc.* **2003**, *125*, 3534–3543. (f) Lipshutz, B. H.; Noson, K.; Chrisman, W.; Lower, A. *J. Am. Chem. Soc.* **2003**, *125*, 8779–8789. (g) Gade, L. H.; César, V.; Bellemín-Lapomnaz, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 1014–1017.

(3) For non-enantioselective reduction, see: (a) Kira, M.; Sato, K.; Sakurai, H. *J. Org. Chem.* **1987**, *52*, 948–949. (b) Kobayashi, S.; Yasuda, M.; Hachiya, I. *Chem. Lett.* **1996**, 407–408.

(4) Iwasaki, F.; Onomura, O.; Mishima, K.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **1999**, *40*, 7507–7511.

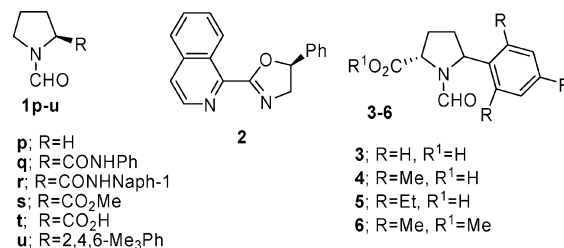
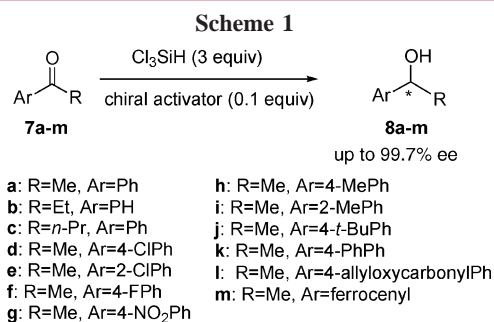


Figure 1. Organic activators for  $\text{Cl}_3\text{SiH}$  to reduce ketones.

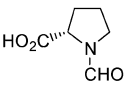
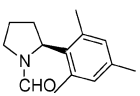
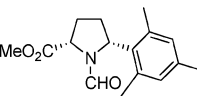
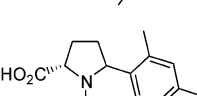
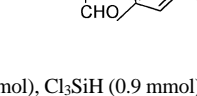
by  $\text{Cl}_3\text{SiH}$  to afford the corresponding alcohols **8** with up to 99.7% ee (Scheme 1).



Chiral activators *cis*-**3**–**5**, *trans*-**3**–**5**, *cis*-**6**, and **1u** used in this study were prepared according to the methods shown in Supporting Information. With those organic activators in hand, we first compared the efficiency of **1u**, *cis*- and *trans*-**4**, and *cis*-**6** as the activator in the reduction of **7a** to **8a** by  $\text{Cl}_3\text{SiH}$ . The results are shown in Table 1, which also shows the results using **1p**, **s**, **t** as comparison.

Noticeable points in Table 1 are as follows: (a) The existence of an  $\alpha$ -methoxycarbonyl group on a pyrrolidine ring (**1s**) decreased the yield of product **8a** (entries 1 and 2). (b) The reduction of **7a** using *N*-formyl-L-proline (**1t**) afforded **8a** in 55% yield (entry 3), which was higher than the yield (39%) in a case using ester **1s** (entry 2). This result suggests an importance of hydrogen bonding between the carboxyl group of **1t** and the carbonyl group of **7a** or some interaction between the carboxyl group with  $\text{Cl}_3\text{SiH}$ . (c) Moderate enantioselectivity (42% ee) was observed in the reduction using **1u**, suggesting an importance of the  $\pi$ – $\pi$  interaction<sup>12</sup> between the activator and aromatic ketones (entry 4). (d)  $\alpha'$ -Arylated proline ester *cis*-**6** showed a high selectivity (70% ee), but the yield was very low (3%) (entry 5). This result suggested an importance of both the  $\pi$ – $\pi$  interaction and some steric factor. (e) *cis*- $\alpha'$ -Arylproline (*cis*-**4**) was found to be highly efficient (entry 6), whereas *trans*-

**Table 1.** Enantioselective Reduction of Ketone **7a** by  $\text{Cl}_3\text{SiH}$  in the Presence of Activators<sup>a</sup>

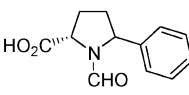
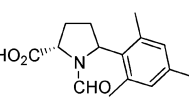
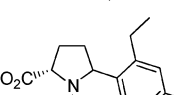
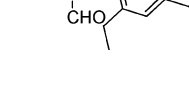
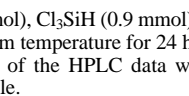
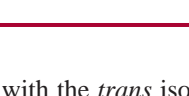
entry	activator	yield (%) of <b>8a</b>	ee (%) <sup>c</sup> (config) <sup>d</sup>
1 <sup>b</sup>	<b>1p</b>	59	– (–)
2 <sup>b</sup>	<b>1s</b>	39	14 ( <i>R</i> )
3	 <b>1t</b>	55	0 (–)
4	 <b>1u</b>	41	42 ( <i>R</i> )
5	 <i>cis</i> - <b>6</b>	3	70 ( <i>R</i> )
6	 <i>cis</i> - <b>4</b>	73	89 ( <i>R</i> )
7	 <i>trans</i> - <b>4</b>	18	25 ( <i>R</i> )

<sup>a</sup> **7a** (0.3 mmol),  $\text{Cl}_3\text{SiH}$  (0.9 mmol), and activator (0.03 mmol) in  $\text{CH}_2\text{Cl}_2$  (1.5 mL) at room temperature for 24 h. <sup>b</sup> The reported data in ref 4. <sup>c</sup> Determined by HPLC. <sup>d</sup> Identified by comparison of the HPLC data with that of a commercially available authentic sample.

$\alpha'$ -arylproline (*trans*-**4**) resulted in a low yield of **8a** with low enantioselectivity (entry 7).

Next, we checked the substituent's effect on the  $\alpha'$ -aromatic ring using activators *cis*-**3**–**5** and *trans*-**3**–**5** (Table 2). The results showed an advantage of the *cis* isomer in

**Table 2.** Enantioselective Reduction of Ketone **7a** by  $\text{Cl}_3\text{SiH}$  in the Presence of  $\alpha'$ -Arylproline Derivatives<sup>a</sup>

entry	activator	yield (%) of <b>8a</b>	ee (%) <sup>c</sup> (config) <sup>d</sup>
1	 <i>cis</i> - <b>3</b>	74	48 ( <i>R</i> )
2	 <i>trans</i> - <b>3</b>	72	47 ( <i>R</i> )
3	 <i>cis</i> - <b>4</b>	73	89 ( <i>R</i> )
4	 <i>trans</i> - <b>4</b>	18	25 ( <i>R</i> )
5	 <i>cis</i> - <b>5</b>	74	95 ( <i>R</i> )
6	 <i>trans</i> - <b>5</b>	2	0 (–)

<sup>a</sup> **7a** (0.3 mmol),  $\text{Cl}_3\text{SiH}$  (0.9 mmol), and activator (0.03 mmol) in  $\text{CH}_2\text{Cl}_2$  (1.5 mL) at room temperature for 24 h. <sup>b</sup> Determined by HPLC. <sup>c</sup> Identified by comparison of the HPLC data with that of a commercially available authentic sample.

comparison with the *trans* isomer, and as a result, the most promising activator among the ones examined was *cis*-2,4,6-triethylphenyl-L-proline (*cis*-**5**).

(5) (a) Akutagawa, S. *J. Synth. Org. Chem. Jpn.* **1986**, *44*, 513–518. (b) Okamoto, H.; Kato, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2128–2130. (c) Zulehler, W.; Neure, B.; Rau, G. *Ullmann's Encyclopedia of Industrial Chemistry*; VCH: Weinheim, 1993; Vol. A23, pp 721–741.

(6) Malkov, A. V.; Stewart Liddon, A. J. P.; Ramírez-López, P.; Bendová, L.; Haigh, D.; Kočovský, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 1432–1435.

(7) Enantioselective reduction of imines was also achieved by  $\text{Cl}_3\text{SiH}$  using organic activators: **1r** (up to 66% ee),<sup>8</sup> *N*-formyl-*N*-methyl-L-valine arylamide (up to 92% ee),<sup>9</sup> *N*-formyl-L-pipecolic acid derivative (up to 96% ee),<sup>10</sup> and *N*-picolinoyl-(2*S*)-(diphenylhydroxymethyl)pyrrolidine (up to 80% ee).<sup>11</sup>

(8) Iwasaki, F.; Onomura, O.; Mishima, K.; Kanematsu, T.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **2001**, *42*, 2525–2527.

(9) (a) Malkov, A. V.; Mariani, A.; MacDougall, N. K.; Kočovský, P. *Org. Lett.* **2004**, *6*, 2253–2256. (b) Malkov, A. V.; Stončius, S.; MacDougall, N. K.; Mariani, A.; McGeoch, G. D.; Kočovský, P. *Tetrahedron* **2006**, *62*, 264–284.

(10) Wang, Z.; Ye, X.; Wei, S.; Wu, P.; Zhang, A.; Sun, J. *Org. Lett.* **2006**, *5*, 999–1001.

(11) Onomura, O.; Kouchi, Y.; Iwasaki, F.; Matsumura, Y. *Tetrahedron Lett.* **2006**, *47*, 3751–3754.

(12) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525–5534.

The solvent effects were examined to optimize the reduction of **7a** by Cl<sub>3</sub>SiH using *cis*-**5**, showing that the reduction depended on the solvent as shown in Table 3. The

**Table 3.** Solvent Effect in the Reduction of **7a** by Cl<sub>3</sub>SiH in the Presence of *cis*-**5**<sup>a</sup>

entry	solvent	h	yield (%) of <b>8a</b>	ee (%) (config)
1	CH <sub>2</sub> Cl <sub>2</sub>	24	74	95 ( <i>R</i> )
2	CHCl <sub>3</sub>	6	90	95 ( <i>R</i> )
3	CCl <sub>4</sub>	12	87	76 ( <i>R</i> )
4	AcOEt	24	70	81 ( <i>R</i> )
5	THF	24	0	
6	toluene	24	82	85 ( <i>R</i> )
7	MeCN	24	73	51 ( <i>R</i> )
8	Et <sub>2</sub> O	24	57	46 ( <i>R</i> )

<sup>a</sup> **7a** (0.3 mmol), Cl<sub>3</sub>SiH (0.9 mmol), and *cis*-**5** (0.03 mmol) in solvent (1.5 mL) at room temperature.

condition using CHCl<sub>3</sub> as a solvent (entry 2) gave the best result.

On the basis of those results, various aryl ketones **7b–k** were reduced by Cl<sub>3</sub>SiH using an activator *cis*-**5** in CHCl<sub>3</sub>. The results are summarized in Table 4, which involves the

**Table 4.** Enantioselective Reduction of Ketones **7a–k** by Cl<sub>3</sub>SiH in the Presence of Activator *cis*-**5** in CHCl<sub>3</sub> for 6 h at Room Temperature<sup>a</sup>

entry	ketone	Ar	R	yield (%) of <b>8a–k</b>	ee (%) <sup>b</sup> (config) <sup>c</sup>
1	<b>7a</b>	Ph	Me	90	95 ( <i>R</i> )
2	<b>7b</b>	Ph	Et	90	95 ( <i>R</i> )
3	<b>7c</b>	Ph	<i>n</i> -Pr	90	95 ( <i>R</i> )
4	<b>7d</b>	4-ClPh	Me	93	97 ( <i>R</i> )
5	<b>7e</b>	2-ClPh	Me	61	96 ( <i>R</i> )
6	<b>7f</b>	4-FPh	Me	91	94 ( <i>R</i> )
7	<b>7g</b>	4-NO <sub>2</sub> Ph	Me	93	97 ( <i>R</i> )
8	<b>7h</b>	4-MePh	Me	91	93 ( <i>R</i> )
9	<b>7i</b>	2-MePh	Me	91	96 ( <i>R</i> )
10	<b>7j</b>	4- <i>t</i> -BuPh	Me	94	93 ( <i>R</i> )
11	<b>7k</b>	4-PhPh	Me	93	95 ( <i>R</i> )

<sup>a</sup> **7a–k** (0.3 mmol), Cl<sub>3</sub>SiH (0.9 mmol), and activator (0.03 mmol) in CHCl<sub>3</sub> (1.5 mL) at room temperature for 6 h. <sup>b</sup> Determined by HPLC. <sup>c</sup> Identified by comparison of the optical rotation of the products with the reported data or by comparison of the HPLC data with those of authentic samples.

result of reduction of **7a**.

As shown in Table 4, the stereoselectivity for the reduction of ketones **7a–k** to corresponding alcohols **8a–k** was very high (93–97% ee) and the absolute configuration of enantiomerically enriched alcohols was *R* in every case.

An activator *cis*-**5** was reusable several times without any loss of its activity as shown in Table 5.

This method was applicable to highly enantioselective reduction of 4'-(allyloxycarbonyl)acetophenone **7l** to **8l** without any reduction of the C–C double bond in 97% ee

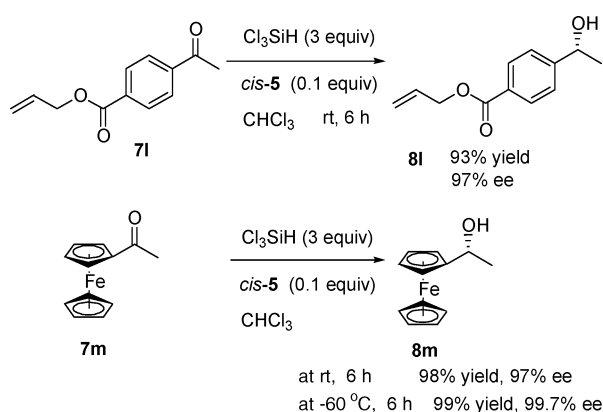
**Table 5.** Reactivity of Recovered *cis*-**5** in the Reduction of Ketone **7a**<sup>a</sup>

iteration	time	yield (%) of <b>8a</b>	ee (%) (config)
1		90	95 ( <i>R</i> )
2		89	95 ( <i>R</i> )
3		91	94 ( <i>R</i> )
4		90	95 ( <i>R</i> )
5		91	95 ( <i>R</i> )

<sup>a</sup> **7a** (0.3 mmol), Cl<sub>3</sub>SiH (0.9 mmol), and *cis*-**5** (0.03 mmol) in CHCl<sub>3</sub> (1.5 mL) at room temperature for 6 h.

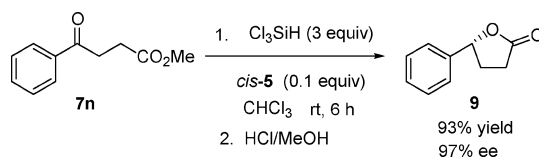
and of acetylferrocene **7m** to **8m** in 99.7% ee at –60 °C (Scheme 2).

**Scheme 2**



Also, by using this method, we succeeded in the preparation of an optically active lactone **9** from keto ester **7n** in 93% yield with 97% ee (Scheme 3). Lactone **9** is an

**Scheme 3**



important intermediate for a preparation of a wide variety of biologically active substance.<sup>13</sup>

In summary, we present a new effective organic activator, *N*-formyl- $\alpha'$ -(2,4,6-triethylphenyl)-L-proline, *cis*-**5**, for Cl<sub>3</sub>-SiH to reduce aryl ketones with excellent enantioselectivity. Both a carboxyl group at the  $\alpha$ -position and a 2,4,6-triethylphenyl group at the  $\alpha'$ -position of *cis*-**5** are critical

(13) (a) Brown, H. C.; Kulkarni, S. V.; Racherla, U. S. *J. Org. Chem.* **1994**, *59*, 365–369. (b) Kamal, A.; Sandbhor, M.; Shaik, A. A. *Tetrahedron: Asymmetry* **2003**, *14*, 1575–1580. (c) Hilborn, J. W.; Lu, Z. H.; Jurgens, A. R.; Fang, Q. K.; Byers, P.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett.* **2001**, *42*, 8919–8921.

for the high enantioselectivity. Further study on the application of this method to nonaromatic ketones and the mechanistic aspect is currently under investigation.

**Acknowledgment.** This study was supported by a Grant-in Aid for Scientific Research on Priority Areas from Mext (no. 444, Advanced Molecular Transformations of Carbon Resources) and the Tokuyama Science Foundation.

**Supporting Information Available:** CIF file of the X-ray structure of *trans*-**5**; characterization data for activators **1u**, *cis*- and *trans*-**3–5**, and their precursors *cis*- and *trans*-**11–15**, alcohols **8a–8m**, and lactone **9**; and experiments involving electrochemical oxidation. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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