ORGANIC LETTERS

2006
Vol. 8, No. 17
3789−3792

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

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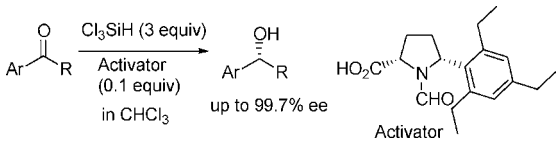
Received June 6, 2006

ABSTRACT



Aryl ketones were reduced to the corresponding alcohols with excellent enantioselectivity (up to 99.7% ee) by Cl_3SiH in the presence of a catalytic amount of *N*-formyl-α′-(2,4,6-triethylphenyl)-L-proline as an activator. Both carboxyl group at the α-position of the activator and 2,4,6-triethylphenyl group at the α′-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.[1] Although a variety of reducing reagents have been used for the purpose,[2] there have been few studies on the use of trichlorosilane (Cl_3SiH),[3] which is an economical and easy to handle reagent.[4,5] Because Cl_3SiH does not have the ability to reduce ketones by itself, appropriate activators are necessary for the reduction of ketones by Cl_3SiH 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 Cl_3SiH using chiral *N*-formylpyrrolidines (**1q,r**) as organic activators (up to 43% ee),[4] and recently isoquinolinyloxazoline (**2**) was reported to work well as a chiral activator (up to 94% ee).[6,7]

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

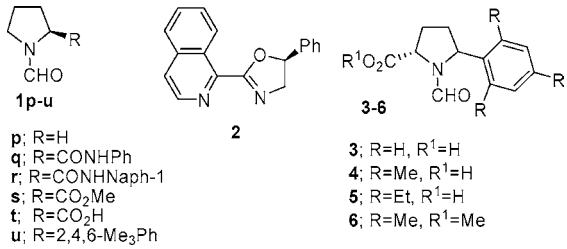


Figure 1. Organic activators for Cl_3SiH to reduce ketones.

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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.; Bellemin-Laponnaz, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 1014−1017.

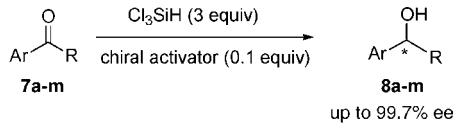
(3) For non-enantioselective reduction, see: (a) Kira, M.; Sato, K.; Sakurai, H. *J. Org. Chem.* **1987**, *52*, 948−949. (b) Kobayashi, S.; Yasuda, M.; Hachiya, I. *Chem. Lett.* **1996**, 407−408.

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

10.1021/ol0613822 CCC: $33.50
Published on Web 07/21/2006

by Cl_3SiH to afford the corresponding alcohols **8** with up to 99.7% ee (Scheme 1).

Scheme 1

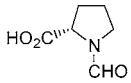
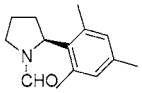
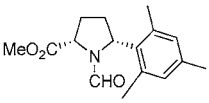
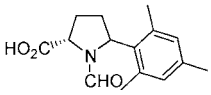


a: R=Me, Ar=Ph
b: R=Et, Ar=PH
c: R=*n*-Pr, Ar=Ph
d: R=Me, Ar=4-ClPh
e: R=Me, Ar=2-ClPh
f: R=Me, Ar=4-FPh
g: R=Me, Ar=4-NO_2Ph
h: R=Me, Ar=4-MePh
i: R=Me, Ar=2-MePh
j: R=Me, Ar=**4**-*t*-BuPh
k: R=Me, Ar=4-PhPh
l: R=Me, Ar=4-allyloxycarbonylPh
m: R=Me, Ar=ferrocenyl

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 Cl_3SiH. 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 α-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 Cl_3SiH. (c) Moderate enantioselectivity (42% ee) was observed in the reduction using **1u**, suggesting an importance of the $\pi-\pi$ interaction[12] between the activator and aromatic ketones (entry 4). (d) α′-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*-α′-Arylproline (*cis*-**4**) was found to be highly efficient (entry 6), whereas *trans*-α′-arylproline (*trans*-**4**) resulted in a low yield of **8a** with low enantioselectivity (entry 7).

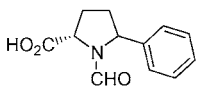
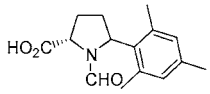
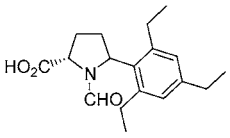
Table 1. Enantioselective Reduction of Ketone **7a** by Cl_3SiH in the Presence of Activators[a]

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

[a] **7a** (0.3 mmol), Cl_3SiH (0.9 mmol), and activator (0.03 mmol) in CH_2Cl_2 (1.5 mL) at room temperature for 24 h. [b] The reported data in ref 4. [c] Determined by HPLC. [d] Identified by comparison of the HPLC data with that of a commercially avilable authentic sample.

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

Table 2. Enantioselective Reduction of Ketone **7a** by Cl_3SiH in the Presence of α′-Arylproline Derivatives[a]

entry	activator		yield (%) of **8a**	ee (%)[c] (config)[d]
1		*cis*-**3**	74	48 (*R*)
2		*trans*-**3**	72	47 (*R*)
3		*cis*-**4**	73	89 (*R*)
4		*trans*-**4**	18	25 (*R*)
5		*cis*-**5**	74	95 (*R*)
6		*trans*-**5**	2	0 (-)

[a] **7a** (0.3 mmol), Cl_3SiH (0.9 mmol), and activator (0.03 mmol) in CH_2Cl_2 (1.5 mL) at room temperature for 24 h. [b] Determined by HPLC. [c] Identified by comparison of the HPLC data with that of a commercially available authentic sample.

(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.; Koèovsk×c6, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 1432−1435.

(7) Enantioselective reduction of imines was also achieved by Cl_3SiH using organic activators: **1r** (up to 66% ee),[8] *N*-formyl-*N*-methyl-L-valine arylamide (up to 92% ee),[9] *N*-formyl-L-pipecolinic acid derivative (up to 96% ee),[10] and *N*-picolinoyl-(2*S*)-(diphenylhydroxymethyl)pyrrolidine (up to 80% ee).[11]

(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, K. N.; Mariani, A.; McGeoch, G. D.; Koèovsk×c6, 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_3SiH 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_3SiH in the Presence of *cis*-**5**[a]

entry	solvent	h	yield (%) of **8a**	ee (%) (config)
1	CH_2Cl_2	24	74	95 (*R*)
2	$CHCl_3$	6	90	95 (*R*)
3	CCl_4	12	87	76 (*R*)
4	AcOEt	24	70	81 (*R*)
5	THF	24	0	
6	toluene	24	82	85 (*R*)
7	MeCN	24	73	51 (*R*)
8	Et_2O	24	57	46 (*R*)

[a] **7a** (0.3 mmol), Cl_3SiH (0.9 mmol), and *cis*-**5** (0.03 mmol) in solvent (1.5 mL) at room temperature.

condition using $CHCl_3$ as a solvent (entry 2) gave the best result.

On the basis of those results, various aryl ketones **7b**−**k** were reduced by Cl_3SiH using an activator *cis*-**5** in $CHCl_3$. The results are summarized in Table 4, which involves the

Table 4. Enantioselective Reduction of Ketones **7a**−**k** by Cl_3SiH in the Presence of Activator *cis*-**5** in $CHCl_3$ for 6 h at Room Temperature[a]

entry	ketone	Ar	R	yield (%) of **8a**−**k**	ee (%)[b] (config)[c]
1	**7a**	Ph	Me	90	95 (*R*)
2	**7b**	Ph	Et	90	95 (*R*)
3	**7c**	Ph	*n*-Pr	90	95 (*R*)
4	**7d**	4-ClPh	Me	93	97 (*R*)
5	**7e**	2-ClPh	Me	61	96 (*R*)
6	**7f**	4-FPh	Me	91	94 (*R*)
7	**7g**	4-NO_2Ph	Me	93	97 (*R*)
8	**7h**	4-MePh	Me	91	93 (*R*)
9	**7i**	2-MePh	Me	91	96 (*R*)
10	**7j**	4-*t*-BuPh	Me	94	93 (*R*)
11	**7k**	4-PhPh	Me	93	95 (*R*)

[a] **7a**−**k** (0.3 mmol), Cl_3SiH (0.9 mmol), and activator (0.03 mmol) in $CHCl_3$ (1.5 mL) at room temperature for 6 h. [b] Determined by HPLC. [c] 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

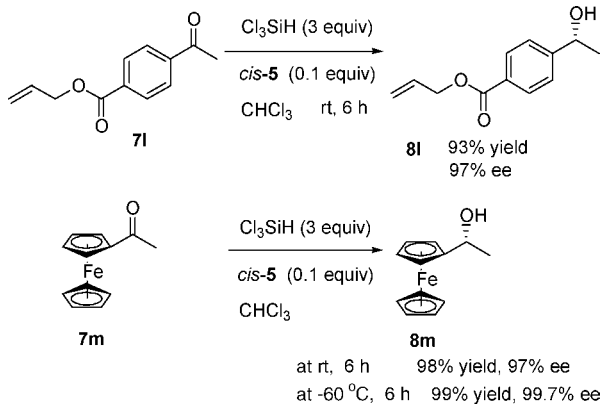
Table 5. Reactivity of Recovered *cis*-**5** in the Reduction of Ketone **7a**[a]

iteration time	yield (%) of **8a**	ee (%) (config)
1	90	95 (*R*)
2	89	95 (*R*)
3	91	94 (*R*)
4	90	95 (*R*)
5	91	95 (*R*)

[a] **7a** (0.3 mmol), Cl_3SiH (0.9 mmol), and *cis*-**5** (0.03 mmol) in $CHCl_3$ (1.5 mL) at room temperature for 6 h.

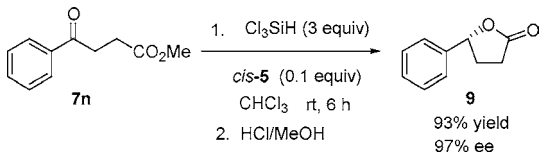
and of acetylferrocene **7m** to **8m** in 99.7% ee at −60 °C (Scheme 2).

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.[13]

In summary, we present a new effective organic activator, *N*-formyl-α′-(2,4,6-triethylphenyl)-L-proline, *cis*-**5**, for Cl_3SiH to reduce aryl ketones with excellent enantioselectivity. Both a carboxyl group at the α-position and a 2,4,6-triethylphenyl group at the α′-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.

OL0613822