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Enantioselective Reduction of α,β-Unsaturated Acylsilanes by Chiral Lithium Amides

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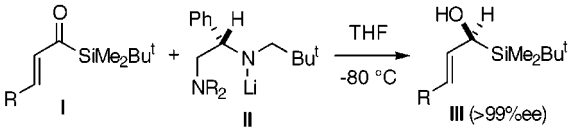
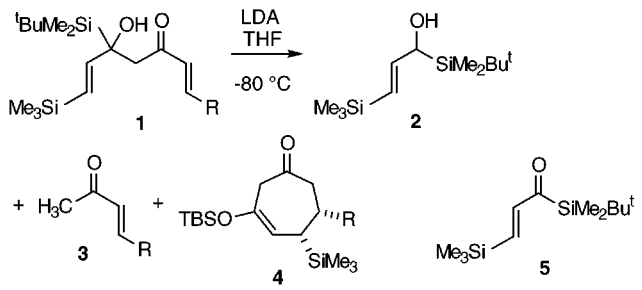
ABSTRACT



Reaction of β-substituted acryloylsilanes I with lithium amides II affords α-silyl allylic alcohols III in high enantiomeric excess (>99%) via formal hydride transfer from the chiral lithium amide.

During our investigation of the mechanism of the Brook rearrangement-mediated [3 + 4] annulation,[1] we observed that treatment of α-silyl-γ-keto alcohol **1** with LDA (1 equiv) afforded α-silyl alcohol **2** in 16% yield in addition to cycloheptenone **4** (37%) and 3-nonen-2-one (**3**) (36%).[2] The formation of **2** suggests that reduction of acryloylsilane **5**, a retro aldol product, by LDA via the hydride transfer of the Meerwein−Ponndorf−Verley type occurred at −80 °C.

Scheme 1



Although there have been reports about the reduction of a carbonyl group by LDA,[3] the ability of LDA as a reducing agent has attracted far less attention, and there has been no report concerning the reduction of α,β-unsaturated acylsilanes by LDA. Therefore, we first examined the reduction of acylsilanes by LDA. When acryloylsilanes **6**[4] were treated with 1 equiv of LDA in THF at −80 °C for 30−60 min, the corresponding α-silyl alcohols **7** were obtained in yields depending on the β-substituent. Thus, the substrates bearing no γ-hydrogen being abstracted afforded better yields of **7** (Table 1, entries 5−9), whereas in the case of the substrate with γ-hydrogen, significant amounts of the starting acryloylsilane were recovered, suggesting the competitive formation of dienolate in the latter cases.[5]

On the basis of the above result, we envisioned that the use of lithium amide of chiral secondary amines instead of LDA would offer the possibility of enantioselective reduction. To the best of our knowledge, there are only two reports

(1) Takeda, K.; Takeda, M.; Nakajima, A.; Yoshii, E. *J. Am. Chem. Soc.* **1995**, *117*, 6400−6401.

(2) Takeda, K.; Nakajima, A.; Takeda, M.; Okamoto, Y.; Sato, T.; Yoshii, E.; Koizumi, T.; Shiro, M. *J. Am. Chem. Soc.* **1998**, *120*, 4947−4959.

(3) For a review of reduction with lithium dialkylamides including LDA, see: Majewski, M.; Gleave, D. M. *J. Organomet. Chem.* **1994**, *470*, 1−16.

(4) Compounds **6a**−**e** and **6f**−**j** were prepared according to the methods of Danheiser and Reich, respectively. (a) Danheiser, R. L.; Nowick, J. S. *J. Org. Chem.* **1989**, *54*, 2798−2802. (b) Reich, H. J.; Kelly, M. J.; Olson, R. E.; Holtan, R. C. *Tetrahedron* **1983**, *39*, 949−960.

(5) The formation of 1,2- and/or 1,4-adducts of the amide to the α,β-unsaturated acylsilanes leading to the recovery of the starting material cannot be ruled out. (a) Kowalski, C.; Creary, X.; Rollin, A. J.; Burke, M. C. *J. Org. Chem.* **1978**, *43*, 2601−2608. (b) Herrmann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2433−2436.

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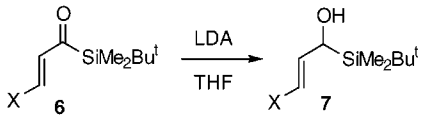
Table 1. Reduction of Acryloylsilanes with LDA



entry	6	X	conditions	yield (%) 7	yield (%) recovery of 6
1	**a**	Me	-80 °C, 30 min	49	50
2	**b**	*i*-Pr	-80 °C, 30 min	64	30
3	**c**	*c*-C_6H_{11}	-80 °C, 30 min	58	37
4	**d**	*c*-C_3H_5	-80 °C, 30 min	36	56
5	**e**	*t*-Bu	-80 °C, 60 min	93	3
6	**f**	$SiMe_3$	-80 °C, 30 min	67	-
7	**g**	$SiMe_2Ph$	-80 °C, 60 min	81	-
8	**h**	$SiMePh_2$	-80 °C, 60 min	82	-
9	**i**	$SiPh_3$	-80 °C, 30 min	88	-
10	**j**	H	-80 °C, 30 min	26	-

in the literature about the enantioselective reduction of a carbonyl group via formal hydride transfer from chiral lithium amides. In 1969 Wittig and Thiele reported the enantioselective reduction of phenyl α-naphthyl ketone by lithium (*R*)-(−)-α-phenylethylanilide to give the corresponding alcohol in 25% yield with an ee less than 60%.[6] Cervinka and co-workers used (*S*)-(+)-2-methylpiperidine as a chiral source in the reaction with diaryl ketones with little success.[7] Since α-hydroxysilanes have shown promise as versatile synthons for synthetically useful transformations, the generation of such species in enantiomerically pure form would be desirable.[8,9]

We first examined the enantioselective reduction by known lithium amides **8**−**12**[10] (Figure 1) using **6e** as a substrate

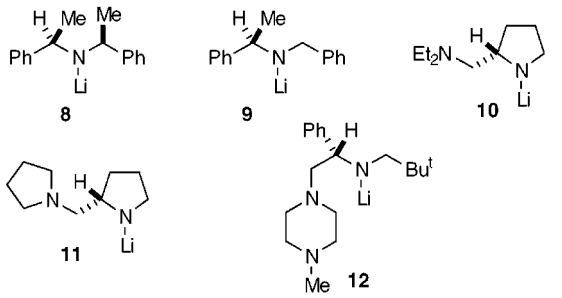
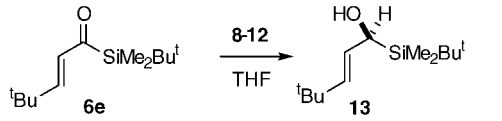


Figure 1.

(Table 2). Among the five lithium amides that were examined, **12** gave the best result in terms of chemical and optical yields; that is, the reaction proceeded smoothly to give alcohol **13** with excellent optical purity. Assignment of absolute configuration of **13** was made by the method of

(6) Wittig, G.; Thiele, U. *Liebigs Ann. Chem.* **1969**, *726*, 1−12.
(7) Cervinka, O.; Dudek, V.; Scholzova, I. *Collect. Czech. Chem. Commun.* **1978**, *43*, 1091−1092.

Table 2. Enantioselective Reduction of **6e**



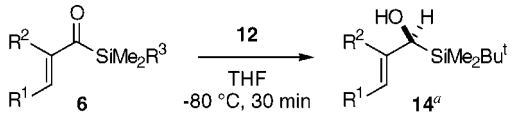
lithium amide	temperature	yield (%)	ee (%)[b]
8	-80 °C to -15 °C	16[a]	66
9	-80 °C to -15 °C	55	57
10	-80 °C	85	9
11	-80 °C	99	14
12	-80 °C	88	>99

[a] Sixty-three percent of **6e** was recovered. [b] The enantiomeric purity was determined by chiral HPLC assay (Daicel Chiralcel-OD).

Trost[11] using *O*-methylmandelate and the modified Mosher method.[12] Changes in the solvent from THF to THF−HMPA (3 equiv) or toluene caused a decrease in chemical yield and/or ee.

Encouraged by these results, we examined the enantioselective reduction of some α,β-unsaturated acylsilanes, including cycloalkenylcarbonylsilanes, by **12**. The results are summarized in Table 3. Although the chemical yield

Table 3. Enantioselective Reduction of α,β-Unsaturated Acylsilanes **6**



	R^1	R^2	R^3	yield (%)	ee (%)	recovery of 6
6a	Me	H	Bu^t	31	>99[b]	53
6b	*i*-Pr	H	Bu^t	55	>99[b]	4
6c	*c*-C_6H_{11}	H	Bu^t	55	>99[b]	32
6d	*c*-C_3H_5	H	Bu^t	68	>99[b]	13
6k	-$(CH_2)_3$-		Ph	63	>99[c]	37
6l	-$(CH_2)_4$-		Ph	55	>99[c]	41
6m	-$(CH_2)_5$-		Ph	61	>99[c]	34

[a] The absolute configuration was assigned by analogy with **13**. [b] The enantiomeric purity was determined by chiral HPLC assay (Daicel Chiralcel-OD and Chiralcel-OJ). [c] The enantiomeric purity was determined by ^1H NMR spectra after conversion into the corresponding Mosher's esters.

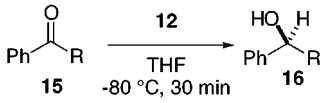
diminished upon the presence of an abstractable γ-hydrogen, as was the case for LDA, α-silyl alcohol **14** was obtained in

(8) For asymmetric reduction of acylsilanes, see the following. Microbial reduction: (a) Linderman, R. J.; Ghannam, A.; Badej, I. *J. Org. Chem.* **1991**, *56*, 5213−5216. (b) Tacke, R. In *Organosilicon and Bioorganosilicon Chemistry*; Sakurai, H., Ed.; Ellis Horwood: New York, 1985; pp 252−262. Use of chiral borans: (c) Buynak, J. D.; Stickland, J. B.; Hurd, T.; Phan, A. *J. Chem. Soc., Chem. Commun.* **1989**, 89−90. (d) Buynak, J. D.; Zhang, H.; Strickland, J. B.; Lamb, G. W.; Khasnis, D.; Modi, S.; Williams, D. *J. Org. Chem.* **1991**, *56*, 7076−7083. (e) Soderquist, J. A.; Anderson, C. L.; Miranda, E. L.; Rivera, I.; Kabalka, G. W. *Tetrahedron Lett.* **1990**, *31*, 4677−4680. Also, see: (f) Cirillo, P. F.; Panek, J. S. *Org. Prep. Proced. Int.* **1992**, *24*, 553−582.

excellent optical yield. Unfortunately, β-silyl derivatives **6f**−**i** produced a complex mixture in sharp contrast to the case of LDA. Elevated reaction temperatures and/or longer reaction times resulted in the Brook rearrangement and in some cases was followed by allylic rearrangement of the generated carbanion.

This method could be applied to benzoylsilanes **15a,b** and nonenolizable phenyl ketones **15c,d**, albeit in lower chemical and optical yields (Table 4).

Table 4. Enantioselective Reduction of Benzoylsilanes and Phenyl Ketones



	R	yield (%)	ee (%) [a]
15a	$SiMe_3$	64	81 [b]
15b	$SiMe_2Bu^t$	37	53 [c]
15c	CF_3	65	23 [b]
15d	β-naphthyl	43	33 [b]

[a] The enantiomeric purity was determined by chiral HPLC assay (Daicel Chiralcel-OD and Chiralcel-OJ). [b] The absolute configuration was assigned by comparison of the sign of optical rotation with the reported value.[14,15] [c] The absolute configuration was assigned by analogy with **16a**. [d] Commercially available.

Although the enantioselectivity can be interpreted as being the result of a process via a six-membered transition state **17** (Figure 2) in which the silyl and the chelated piperazinylmethyl groups occupy an axial position, the precise mechanism is not known and is now under investigation.[13]

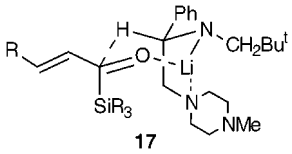


Figure 2.

In conclusion, we have found that the lithium amide of chiral secondary amines can serve as the chiral source in the enantioselective reduction of a carbonyl group, especially α,β-unsaturated acylsilanes. In this method, α-silyl alcohols can be obtained in an optically pure form. Although the chemical yield is not good, the α-silyl alcohol is the only product and it can be easily separated from the recovered acylsilanes. Investigation of the potential application, especially the use of acryloylsilanes as a chiral homoenolate equivalent using a tandem reaction sequence involving enantioselective reduction, and Brook and allylic rearrangements is underway.

Acknowledgment. This research was partially supported by a grant-in-aid for Scientific Research (10671986) from the Japanese Ministry of Education, Sciences, Sports and Culture, Japan, and the Ciba-Geigy Foundation (Japan) for the Promotion of Science.

Supporting Information Available: Full experimental details and characterization data for all new compounds described in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Cirillo, P. F.; Panek, J. S. *J. Org. Chem.* **1994**, *59*, 3055−3063. (b) Sakaguchi, K.; Mano, H.; Ohfune, Y. *Tetrahedron Lett.* **1998**, *39*, 4311−4312.

(10) Compounds **8** and **9** are commercially available. Compounds **10**−**12** were prepared according to literature methods. (a) Sone, T.; Hiroi, K.; Yamada, S. *Chem. Pharm. Bull.* **1973**, *21*, 2331−2335. (b) Shirai, R.; Aoki, K.; Sato, D.; Kim, H.-D.; Murakata, T.; Koga, K. *Chem. Pharm. Bull.* **1994**, *42*, 690−693. For a review on the use of the chiral lithium amides in asymmetric synthesis, see: (c) Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1−26.

(11) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, E. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370−2374.

(12) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

(13) For a mechanistic discussion on the reduction with lithium amides, see ref 3. Although the placement of the large silyl group at the axial position seems unlikely, the preference for the axial conformation of the silyl group relative to the methyl group, which was ascribed to the reduced steric interactions due to the C−Si bond being longer than the C−C bond, was reported: Cho, S.-G.; Rim, O.-K.; Kim, Y.-S. *THEOCHEM* **1996**, *364*, 59−68.

(14) Seebach, D.; Beck, A. K.; Roggo, S.; Wonnacott, A. *Chem. Ber.* **1985**, *118*, 3673−3682.

(15) Wright, A.; West, R. *J. Am. Chem. Soc.* **1974**, *96*, 3227−3232.