

Lewis Base Activation of Lewis Acids. Catalytic Enantioselective Addition of Silyl Enol Ethers of Achiral Methyl Ketones to Aldehydes

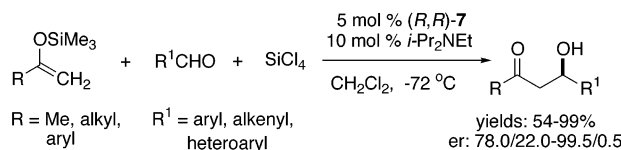
Scott E. Denmark* and John R. Heemstra Jr.

Roger Adams Laboratory, Department of Chemistry, University of Illinois,
600 South Mathews Avenue, Urbana, Illinois 61801

denmark@scs.uiuc.edu

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ABSTRACT

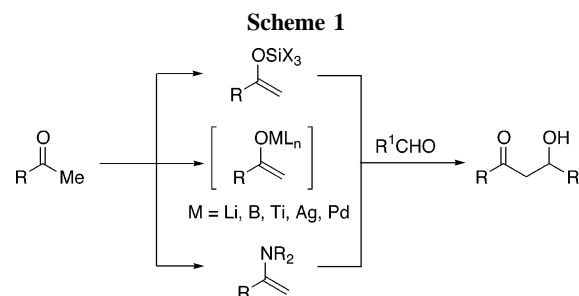


A highly enantioselective addition of silyl enol ethers derived from simple methyl ketones is described. The catalyst system of silicon tetrachloride activated by a chiral bisphosphoramidate (*R,R*)-7 effectively promotes the addition of a variety of unsubstituted silyl enol ethers to aromatic, olefinic, and heteroaromatic aldehydes in excellent yield.

The stereoselective addition of methyl ketone enolates to carbonyl compounds is a synthetically powerful transformation in synthesis. In both auxiliary-mediated¹ as well as catalytic enantioselective methods,² stereochemical control of these additions is generally more difficult than with their ethyl ketone homologues. It has been proposed that the absence of the substituents on the enolate allows for the intervention of competitive transition structures that compromise selectivity. Nevertheless, a number of strategies have been developed for controlling the stereochemical course of the addition (Scheme 1): (1) the use of chiral Lewis acids (also in analogous ene reactions),³ (2) transition metal

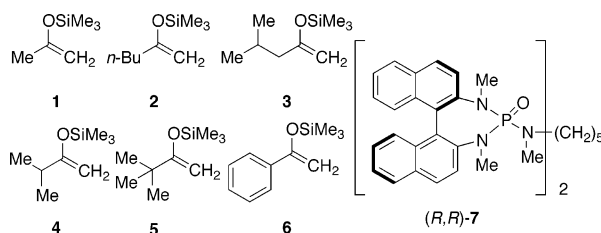
enolates,⁴ (3) direct aldol additions,⁵ and (4) chiral Lewis-base catalysis.⁶ Although each of the above stated methods have shown considerable success, the attention given to chiral Lewis acid catalysis far exceeds that given to the rest. Typically, these catalysts are generated through complexation of chiral ligands to a strongly Lewis acidic, achiral metal atom. However, ligand addition often attenuates the electrophilicity of the metal center due to the donor properties of the ligand.⁷ Therefore, preformation of the catalyst or a high association constant is necessary to suppress the achiral background reaction from the nascent Lewis acid.⁸

- (1) Braun, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 24.
 (2) (a) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357. (b) Carriera, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999; Vol. III, Chapter 29.
 (3) (a) Parmee, E. R.; Tempkin, O.; Masamune, S.; Abiko, A. *J. Am. Chem. Soc.* **1991**, *113*, 9365. (b) Corey, E. J.; Cywin, C. L.; Roper, T. D.; *Tetrahedron Lett.* **1992**, *33*, 6907. (c) Ishihara, K.; Maruyama, T.; Mouri, M.; Gao, Q.; Furuta, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3483. (d) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1993**, *115*, 7039. (e) Ando, A.; Miura, T.; Tatematsu, T.; Shioiri, T. *Tetrahedron Lett.* **1993**, *34*, 1507. (f) Carreria, E. M.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649. (g) Ruck, R. T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 2882.



We have recently described a conceptually novel approach to carbonyl addition reactions that combines the use of chiral Lewis bases to generate catalytically active chiral Lewis acids.⁹ In the presence of catalytic amounts of a chiral phosphoramidate, the weak Lewis acid SiCl₄ can be activated to form a strongly Lewis acidic chiral species through coordination and subsequent ionization of a chloride ligand.¹⁰ Only after coordination of phosphoramidate is SiCl₄ sufficiently Lewis acidic to promote addition under reaction conditions. Thus, the catalyst can be generated in situ without concern for an achiral background reaction. The dramatic sensitivity of this catalyst to substituents on the enolate structure suggested that the asymmetric environment could be suitable for the smaller, less selective methyl ketone enolates. Following the nucleophilicity scales developed by Mayr and co-workers,¹¹ silyl enol ethers of methyl ketones should be viable nucleophiles in this process by virtue of their placement between silyl ketene acetals^{9b} and allylstannanes,^{9a} both of which have been used successfully. Herein, we report the catalytic enantioselective addition of methyl ketone-derived silyl enol ethers to a variety of aldehydes.

The initial survey of the ketone spectator group structure included the simple silyl enol ethers **1–6**. Enolates **1** and **5** were prepared by treatment of the corresponding ketone with a combination of Et₃N and TMSOTf at room temperature.¹² Enolates **2–4** and **6** were prepared by kinetically controlled enolization of the methyl ketones using LDA at –78 °C, and the resulting enolates were then treated with TMSCl to yield the TMS enol ethers shown.¹³



Orienting experiments employed the reaction conditions established for the aldol addition of silyl ketene acetals to benzaldehyde.^{9b} Thus, 1.2 equiv of the silyl enol ether were added to a solution containing 5 mol % bisphosphoramidate

catalyst (*R,R*)-**7**,⁹ 1.1 equiv of SiCl₄, and 1.0 equiv of benzaldehyde in CH₂Cl₂ at –78 °C. After 4 h, the reaction was quenched at 0 °C (Table 1). The reactivity of these enolates was found to be highly dependent on the size of the spectator group. Whereas up to 81% yield was obtained with enolate **2**, the α- and β-branched enolates **3**, **4**, and **6** gave lower yields. Enolate **5**, flanked by a *tert*-butyl group, did not undergo addition under the same reaction conditions. On the other hand, the enantioselectivity observed was uniformly high (up to 99.5/0.5 er) and independent of the spectator group. Encouraged by the excellent enantioselectivities obtained, further studies were undertaken to improve the reaction yields. ¹H NMR analysis of the crude reaction mixture after quenching revealed the presence of only aldol product and unreacted starting materials. Because there were no obvious competing side reactions, the incomplete reaction might arise from inefficient catalyst turnover or slow reaction rate.

Table 1. Initial Aldol Additions of TMS Enol Ethers to Benzaldehyde^a

entry	enolate	R	yield, ^b %	er ^c
1	2	<i>n</i> -Bu	81	99.0/1.0
2	3	<i>i</i> -Bu	70	99.0/1.0
3	4	<i>i</i> -Pr	72	99.5/0.5
4	5	<i>t</i> -Bu	nr	nd
5	6	Ph	76	97.0/3.0

^a All reactions employed 1.1 equiv of SiCl₄, 1.2 equiv of enolate, and 0.05 equiv of (*R,R*)-**7** at 0.2 M in CH₂Cl₂ at –78 °C for 4 h. ^b Chromatographically homogeneous material. ^c Determined by CSP-SFC.

To improve catalyst turnover, a SiCl₄ loading study was performed to investigate the effect of increasing the concentration of SiCl₄ on the product yield (Table 2). Although increasing the SiCl₄ loading to 1.5 equiv gave a slight increase in yield, the higher SiCl₄ loadings did not assist in allowing the reaction to go to completion.

Further optimization focused on increasing the reaction rate. Previous studies in the aldol addition of trichlorosilyl enolates had shown that the addition of tetrabutylammonium iodide (TBAI) or tetrabutylammonium triflate (TBAOTf) in the reaction led to increased rates and yields by increasing the ionic strength of the medium.¹⁴ Similarly, our mechanistic hypothesis involves a hexacoordinate SiCl₄-bisphosphor-

(4) (a) Sodeoka, M.; Tokunoh, R.; Miyazaki, F.; Hagiwara, E.; Shibasaki, M. *Synlett* **1997**, 463. (b) Yanagisawa, A.; Matsumoto, Y.; Nakashima, H.; Asakawa, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1997**, *119*, 9319.

(5) (a) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871. (b) Yamada, Y. M. A.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 5561. (c) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168. (d) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (e) Trost, B. M.; Hisanaka, I. *J. Am. Chem. Soc.* **2000**, *122*, 12003. (f) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (g) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573.

(6) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432. (b) Denmark, S. E.; Stavenger, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 8837.

(7) For examples of attenuated electrophilicity of Lewis acids, see: (a) Yamamoto, Y.; Suzuki, I. *J. Org. Chem.* **1993**, *58*, 4783. (b) Santelli, M.; Pos, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press: Boca Raton, FL, 1996.

(8) For an example of the preformation of catalyst, see: Gauthier, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2363.

(9) Denmark, S. E.; Wynn, T. *J. Am. Chem. Soc.* **2001**, *123*, 6199. (b) Denmark, S. E.; Wynn, T.; Beutner, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 13405.

(10) For discussions of the generation of trichlorosilyl cations, see: Bassindale, A. R.; Glynn, S. J.; Taylor, P. G. *The Chemistry of Organosilicon Compounds*; Rappoport, Z., Apeloig, Y., Eds.; Wiley: Chichester, UK, 1998; Vol. 2; p 495.

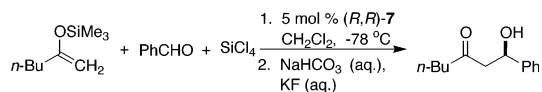
(11) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66.

(12) Myles, D. C.; Bigham, M. H. *Org. Synth.* **1992**, *72*, 331.

(13) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

amide species that also must undergo ionization to form the catalytically active species. Accordingly, the use of TBAI and TBAOTf as additives in the reaction was examined.

Table 2. SiCl₄ Loading Studies on the Addition of **2** to Benzaldehyde^a

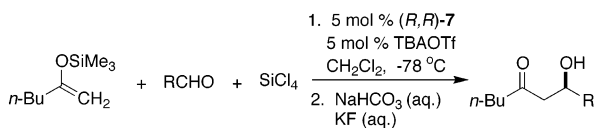


entry	SiCl ₄ , equiv	yield, ^b %	er ^c
1	1.1	81	99.5/0.5
2	1.5	86	99.5/0.5
3	2.0	81	99.5/0.5
4	3.0	81	99.5/0.5
5	4.0	82	99.5/0.5

^a All reactions employed 1.2 equiv of **2** and 5 mol % (*R,R*)-**7** at 0.5 M in CH₂Cl₂ at -78 °C for 2.5 h. ^b Chromatographically homogeneous material. ^c Determined by CSP-SFC.

Both TBAI and TBAOTf were found to improve the reaction yield without affecting the enantioselectivities. However, TBAI also promoted the formation of the unsaturated ketone side product. Therefore, an enolate survey with benzaldehyde was performed with the addition of 5 mol % TBAOTf (Table 3). Although the increase in yield for enolate **2** was encouraging, only a slight improvement in yield was observed in the addition of enolates **3** and **6**, and enolate **4** still provided only a modest yield. Whereas the addition of TBAOTf increased the aldol product yields for all of the enolates surveyed, excluding enolate **5**, the reason for the variation in the yields depending on enolate structure was not immediately obvious. Reactions employing higher catalyst loadings and longer reaction times were also performed without a detectable increase in yield. Therefore, we decided to employ the use of VT NMR to gain insight into what may be occurring during the reaction.

Table 3. Aldol Addition Reactions Using TBAOTf as an Additive^a



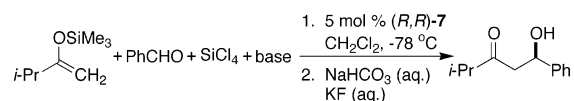
entry	enolate	yield, ^b %	er ^c
1	1	72	98.0/2.0
2	2	95	99.5/0.5
3	3	85	99.0/1.0
4	4	76	99.5/0.5
5	5	nr	nd
6	6	89	99.0/1.0

^a All reactions employed 1.5 equiv of SiCl₄, 1.2 equiv of enolate, 5 mol % TBAOTf, and 5 mol % (*R,R*)-**7** at 0.5 M in CH₂Cl₂ at -78 °C for 2 h. ^b Chromatographically homogeneous material. ^c Determined by CSP-SFC.

VT NMR experiments were carried out systematically omitting various components of the reaction to elucidate the reason for incomplete reactions. When only the enolate and SiCl₄ were combined, the formation of the parent ketone and TMSCl could clearly be seen. This outcome strongly suggests that even though distilled SiCl₄ was used in the reaction, protonolysis by HCl present in the SiCl₄ was destroying the enolate.

In view of this new information, it was decided to include acid-scavenging amine bases in the reaction mixture (Table 4). For comparison, the yield for the aldol addition of enolate **4** without added base was 76%. Using an amine base in the reaction afforded nearly quantitative yields without erosion in enantioselectivities. In addition, excellent yields are seen with loadings as low as 5 mol % of the inexpensive *i*-Pr₂NEt. With acid-scavenging amine bases present, it was no longer necessary to distill the SiCl₄ prior to use. Entry 5 shows that only 10 mol % *i*-Pr₂NEt is sufficient to obtain quantitative yields using SiCl₄ from the supplier¹⁵ without further purification.

Table 4. Aldol Reactions with Amine Bases^a



entry	base	base, equiv	yield, ^b %	er ^c
1	none	0	76	99.5/0.5
2	tri- <i>tert</i> -butylpyridine	1.0	98	99.0/1.0
3	tri- <i>tert</i> -butylpyridine	0.2	98.5	99.0/1.0
4	<i>i</i> -Pr ₂ NEt	0.2	99	99.0/1.0
5 ^d	<i>i</i> -Pr ₂ NEt	0.1	99	99.0/1.0
6	<i>i</i> -Pr ₂ NEt	0.05	96	98.5/1.5

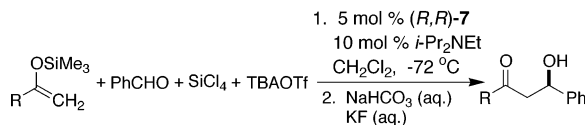
^a All reactions employed 1.5 equiv of SiCl₄, 1.2 equiv of enolate, and 5 mol % (*R,R*)-**7** at 0.5 M in CH₂Cl₂ at -78 °C for 3 h. ^b Chromatographically homogeneous material. ^c Determined by CSP-SFC. ^d Reaction employed undistilled SiCl₄.

With optimized reaction conditions in hand, the enolate survey with benzaldehyde was repeated using undistilled SiCl₄ (Table 5). With the addition of as little as 10 mol % *i*-Pr₂NEt and a catalyst loading of only 5 mol %, ¹⁶ high yields can be obtained in short reaction times (4 h) with all enolates surveyed, with the exception of **5**. Also, the reaction affords excellent enantioselectivities regardless of the spectator group. The generality of the reaction was then evaluated by the addition of the TMS enolate of 2-hexanone (**2**) with a variety of aldehydes (Table 6). In almost all cases, equally

(14) (a) Denmark, S. E.; Su, X.; Nishigaichi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 12990. (b) Short, J. D.; Attenoux, S.; Berrisford, D. J. *Tetrahedron Lett.* **1997**, *38*, 2351.

(15) SiCl₄ was purchased from Gelest and then transferred under N₂ via cannula to a flame-dried bottle with a septum. Between uses, the bottle was stored in a freezer.

(16) Although a loading as low as 1 mol % gives near quantitative yields and shows no erosion in enantioselectivity, a catalyst loading of 5 mol % was employed to obtain reasonable rates with more sterically demanding substrates.

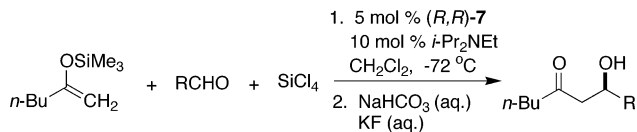
Table 5. Aldol Addition between Benzaldehyde and Various TMS Enol Ethers^a

entry	enolate	product	yields, ^b %	er ^c
1	1	(+)- 8	97	98.0/2.0
2	2	(+)- 9	99	99.5/0.5
3	3	(+)- 10	98	99.0/1.0
4	4	(+)- 11	95	99.5/0.5
5	5	nr	nd	nd
6	6	(+)- 12	98	99.5/0.5

^a All reactions employed 1.5 equiv of SiCl₄, 1.2 equiv of enolate, 10 mol % *i*-Pr₂NEt, and 5 mol % (*R,R*)-**7** at 0.5 M in CH₂Cl₂ at -72 °C for 3 h. ^b Chromatographically homogeneous material. ^c Determined by CSP-SFC.

high selectivity can be seen. Both electron-rich and electron-poor aromatic aldehydes were found to react at rates equal to that of benzaldehyde and show excellent selectivities (entries 5 and 6). Different aromatic structures such as 2-naphthyl and the more hindered 1-naphthyl also gave high yields and selectivities. Heteroaromatic aldehydes are also competent acceptors with only a slight attenuation in yields and selectivities (entries 7 and 8). However, aldehydes with substituents branching in the α position showed both decreased rates and attenuated selectivities as was observed when 2-methylcinnamaldehyde is compared to cinnamaldehyde (entries 1 and 2). Unfortunately, aliphatic aldehydes are found to be completely unreactive with enolate **2** (entry 9).

In conclusion, an efficient, catalytic, highly enantioselective reaction for the addition of TMS enol ethers of methyl ketones to various aldehyde acceptors has been developed. The selectivities seen with aryl and alkenyl aldehydes are some of the best disclosed to date. The ability to use shelf-stable enol silanes represents a preparative advantage over the more labile enoxytrichlorosilanes used in previous work.

Table 6. Aldol Additions of Enolate **2** and Various Aldehydes^a

entry	R	product	time, h	yield, ^b %	er ^c
1	(<i>E</i>)-PhCH=CH	(+)- 13	4	97.5 ^e	99.5/0.5
2	(<i>E</i>)-PhCH=C(CH ₃) ^d	(+)- 14	24	54 ^e	78.0/22.0
3	1-naphthyl	(+)- 15	10	95 ^e	96.0/4.0
4	2-naphthyl	(+)- 16	4	92	99.5/0.5
5	4-CH ₃ OC ₆ H ₄	(+)- 17	4	97.5	99.5/0.5
6	4-CF ₃ C ₆ H ₄	(+)- 18	4	96	99.5/0.5
7	2-furyl	(+)- 19	6	88	95.0/5.0
8	2-thiophenyl	(+)- 20	8	79	99.0/10.0
9	PhCH ₂ CH ₂		24	nr	nd

^a All reactions employed 1.5 equiv of SiCl₄, 1.2 equiv of enolate, 10 mol % *i*-Pr₂NEt, and 5 mol % (*R,R*)-**1** at 0.5 M in CH₂Cl₂ at -72 °C for 3 h. ^b Yield of analytically pure material. ^c Determined by CSP-SFC. ^d Reaction employed 10 mol % (*R,R*)-**1**. ^e Chromatographically homogeneous material.

Also, the ability to use catalytic amounts of hindered amine bases as proton scavengers in the reaction obviates the need to purify the SiCl₄ prior to use. Further studies are currently underway to expand the scope of the reaction to ethyl ketones and overcome the lack of reactivity with aliphatic aldehydes.

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Supporting Information Available: Full experimental procedures and characterization data for all intermediates and aldol products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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