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ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · FEBRUARY 1998

Impact Factor: 4.72 · DOI: 10.1021/jo972168h

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Lewis Base-Catalyzed, Asymmetric Aldol Additions of Methyl Ketone Enolates†

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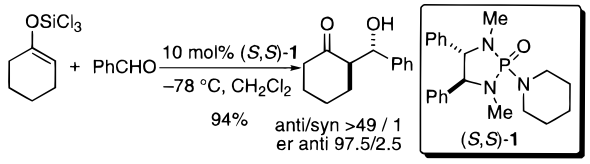
Received December 2, 1997

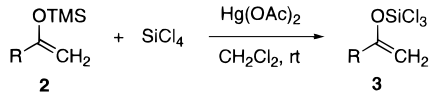
The development of a general and highly effective catalytic asymmetric aldol addition reaction has been the subject of intense research in recent years.[1] Most strategies rely on a chiral Lewis acid to both activate the aldehyde and control the stereochemical course of the reaction. As these reactions most likely proceed through open transition structures where nonbonding interactions dominate,[2] acetate and methyl ketone substrates often perform less well than their substituted homologues.[3] Recently, we reported a conceptually novel approach that employs Lewis base activation of the trichlorosilyl enolate of methyl acetate.[4a,b] Although selectivities were modest, our initial hypothesis of reaction through an organized, closed transition structure was borne out by the highly diastereo- and enantioselective additions of geometrically defined trichlorosilyl enolates of ketones catalyzed by the stilbene diamine-derived phosphoramide (*S*,*S*)-**1**, Scheme 1.[4c] We felt that this strategy should prove to be general for ketone enolates regardless of substitution on the enol double bond and, hence, began investigating the more challenging methyl ketone enolates. We wish to report that trichlorosilyl enolates of methyl ketones undergo aldol addition in the presence of catalytic (5−10 mol %) amounts of (*S*,*S*)-**1** to produce *β*-hydroxy ketones with very good enantioselectivity.[5]

Scheme 1



The trichlorosilyl enolate of acetone (**3a**) has previously been prepared from chloroacetone by treatment with trichlorosilane and tri-*n*-butylamine.[6] Although this reaction worked well in our hands, experimental limitations and the lack of readily available α-chloro ketone substrates prompted us to investigate other methods of preparation. Ideally, we sought a reagent combination to prepare trichlorosilyl enolates directly from readily available trialkylsilyl enol ethers. Combination of **2d** and $SiCl_4$ (neat and in $CDCl_3$ solution) led to no reaction. However, upon addition of a catalytic amount (1 mol %) of $Hg(OAc)_2$, rapid and clean conversion to the trichlorosilyl enolate, **3d**, with concomitant formation of TMSCl, was observed by ^1H NMR spectroscopy.[7] The enolates **3b**−**g** could be prepared in good yield starting from the TMS enol ethers **2b**−**g**, Table 1.[8,9] Silicon tetrachloride is a remarkably mild reagent as the mercury-catalyzed metathesis reaction proceeds in reasonable yield even with other silyl groups present in the enol ether (Table 1, entry 6).

Table 1. Mercury-Catalyzed Metathesis of TMS Enol Ethers to Trichlorosilyl Enolates[a]



2 **3**

entry	enol ether	R	enolate	yield,[b] %
1	**2b**	*n*-Bu	**3b**	83
2	**2c**	*i*-Bu	**3c**	74
3	**2d**	*i*-Pr	**3d**	83
4	**2e**	*t*-Bu	**3e**	81
5	**2f**	Ph	**3f**	69
6	**2g**	$TBDMSiOCH_2$	**3g**	65

[a] 1.0 equiv of **2**, 2.0 equiv of $SiCl_4$, 0.01 equiv of $Hg(OAc)_2$. [b] Yield of analytically pure material.

Trichlorosilyl enolates **3a**−**g** are efficacious aldol addition reagents that react quickly with benzaldehyde at ambient temperature (0.5 M, CH_2Cl_2), Table 2. In addition, enolate **3b** reacted cleanly with a variety of different aldehydes (Chart 1), Table 3.[10] The uncatalyzed reaction of trimethylacetaldehyde (**10**) was very slow (>2 days) and was accompanied by significant amounts of the elimination product. However, in the presence of 10 mol % HMPA this reaction proceeded rapidly at room temperature and produced only a small amount of unsaturated ketone (Table 3, entry 6).

Orienting studies on the catalytic asymmetric addition of **3a** to benzaldehyde in CH_2Cl_2 at −78 °C with 10 mol % of (*S*,*S*)-**1** provided the adduct **4a** in very good yield and in 92.5/7.5 er.[11] Lowering the temperature to −90 °C had essentially no effect on the selectivity, and performing the reaction in either less or more polar solvents led to poorer

† The Chemistry of Trichlorosilyl Enolates. 4.

(1) For reviews on catalytic, asymmetric aldol additions, see: (a) Bach, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 417. (b) Franklin, A. S.; Paterson, I. *Contemp. Org. Synth.* **1994**, *1*, 317. (c) Braun, M.; Sacha, H. *J. Prakt. Chem.* **1993**, *335*, 653. (d) Sawamura, M.; Ito, Y. In *Catalytic Asymmetric Synthesis*, Ojima, I., Ed.; VCH: New York, 1993; p 367. (e) Yamamoto, H.; Maruoka, K.; Ishihara, K. *J. Synth. Org. Jpn.* **1994**, *52*, 912. (f) Braun, M. In *Stereoselective Synthesis, Methods of Organic Chemistry (Houben-Weyl)*, Edition E21; Helmchen, G., Hoffmann, R., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. 3; p 1730.

(2) (a) Denmark, S. E.; Lee, W. *J. Org. Chem.* **1994**, *59*, 707. (b) Kobayashi, S.; Horibe, M. *Chem. Eur. J.* **1997**, *3*, 1472.

(3) For a specific example, see: Kiyooka, S.-i.; Hena, M. A. *Tetrahedron: Asymmetry* **1996**, *7*, 2181.

(4) (a) Denmark, S. E.; Winter, S. B. D.; Su, X.; Wong, K.-T. *J. Am. Chem. Soc.* **1996**, *118*, 7404. (b) Denmark, S. E.; Winter, S. B. D. *Synlett* **1997**, 1087. (c) Denmark, S. E.; Wong, K.-T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333.

(5) For examples of other catalytic asymmetric aldol additions of methyl ketones, see: (a) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907. (b) Ishihara, K.; Maruyama, T.; Mouri, M.; Gao, Q.; Furuta, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3483. (c) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1993**, *115*, 7039. (d) Carreira, E. M.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649. (e) Sodeoka, M.; Tokunoh, R.; Miyazaki, F.; Hagiwara, E.; Shibasaki, M. *Synlett* **1997**, 463. (f) Ando, A.; Miura, T.; Tatematsu, T.; Shioiri, T. *Tetrahedron Lett.* **1993**, *34*, 1507. (g) Yanagisawa, A.; Matsumoto, Y.; Nakashima, H.; Asakawa, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1997**, *119*, 9319. (h) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871.

(6) Benkeser, R. A.; Smith, W. E. *J. Am. Chem. Soc.* **1968**, *90*, 5307.

(7) We view this formal silicon−silicon metathesis as involving initial formation of an α-mercurio ketone followed by *O*-complexation to $SiCl_4$ and loss of HgX_2 as an electrofugal group. For examples of the synthesis of α-mercurio ketones from silyl enol ethers see: (a) House, H. O.; Auerbach, R. A.; Gall, M.; Peet, N. P. *J. Org. Chem.* **1973**, *38*, 514. (b) Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1982**, *104*, 2323. (c) Bluthe, N.; Malacria, M.; Gore, J. *Tetrahedron* **1984**, *40*, 3277. (d) Drouin, J.; Boaventura, M.-A.; Conia, J.-M. *J. Am. Chem. Soc.* **1985**, *107*, 1726.

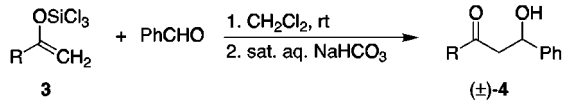
(8) All new compounds were fully characterized by spectroscopic and analytical methods. See the Supporting Information.

(9) Although the TMS enol ether derived from acetone is a good substrate for this reaction, removing TMSCl from the volatile enolate **3a** proved difficult, and the modified Benkeser procedure was utilized for the synthesis of this enolate.

(10) We assume that these reactions are proceeding though boatlike closed transition structures as previously demonstrated for Lewis acidic silyl (trichlorosilyl and silacyclobutyl) enolates. See: Denmark, S. E.; Griedel, B. D.; Coe, D. M.; Schnute, M. E. *J. Am. Chem. Soc.* **1994**, *116*, 7026.

S0022-3263(97)02168-3 CCC: $15.00
Published on Web 02/05/1998

Table 2. Uncatalyzed Aldol Additions of 3a−g with Benzaldehyde[a]



3 (±)-4

entry	enolate	time, h	product	yield,[b] %
1	**3a**	4	**4a**	92
2	**3b**	4	**4b**	95
3	**3c**	4	**4c**	94
4	**3d**	5	**4d**	93
5	**3e**	10	**4e**	97
6	**3f**	4	**4f**	91
7	**3g**	6	**4g**	93

[a] All reactions performed at 0.5 M in aldehyde. [b] Yield of analytically pure material.

Chart 1

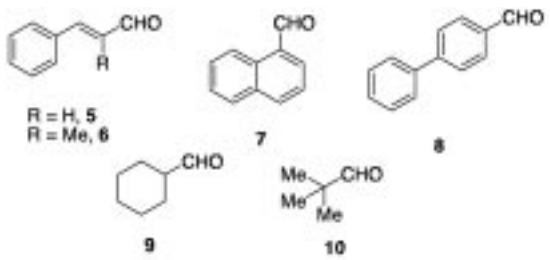
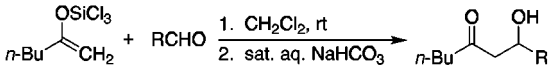


Table 3. Uncatalyzed Aldol Additions of 3b[a]



3b (±)-11-16

entry	RCHO	time, h	product	yield,[c] %
1	**5**	7	**11**	91
2	**6**	14	**12**	92
3	**7**	4	**13**	92
4	**8**	4	**14**	91
5	**9**	9	**15**	93
6[b]	**10**	1	**16**	86

[a] All reactions performed at 0.5 M in aldehyde. [b] 10 mol % HMPA added. [c] Yield of analytically pure material.

results. Higher loadings of catalyst (20 mol %) did not change the er significantly, so we briefly investigated decreasing the catalyst amount and found, gratifyingly, that 5 mol % of (*S*,*S*)-**1** could be used without diminution of either yield or selectivity.

The catalytic additions of enolates **3a**−**g** to benzaldehyde were then investigated with the optimized procedure, utilizing 5 mol % of (*S*,*S*)-**1** in CH_2Cl_2 at −78 °C. The results in Table 4 reveal that the selectivities were all high, with the exception of the pinacolone- (**3e**) and acetophenone-derived (**3f**) enolates. Most satisfying was the observation that even acid-labile functional groups are compatible as demonstrated by the high-yielding and enantioselective reaction of the (*tert*-butyldimethylsilyl)oxy-substituted enolate **3g** (Table 4, entry 7).

Finally, we investigated the dependence of aldehyde structure on the catalytic reaction using **3b**, Table 5. Very

Table 4. Catalyzed Aldol Additions of Enolates 3 with Benzaldehyde[a]

entry	enolate	product	er[b]	yield,[c] %
1	**3a**	(−)-**4a**	93.6/6.4[d]	98
2	**3b**	(−)-**4b**	92.3/7.7	98
3	**3c**	(−)-**4c**	90.7/9.3	95
4	**3d**	(−)-**4d**	91.0/9.0	97
5	**3e**	(−)-**4e**	76.0/24.0	95
6	**3f**	(−)-**4f**	74.5/25.5	93
7	**3g**	(−)-**4g**	93.1/6.9	94

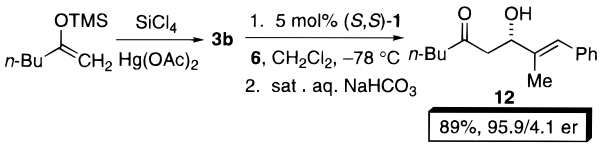
[a] All reactions performed in CH_2Cl_2 at −78 °C with 5 mol % (*S*,*S*)-**1** at 0.5 M in aldehyde for 2h. [b]Determined by CSP HPLC analysis. [c]Yield of analytically pure material. [d] Determined by CSP HPLC analysis of the dinitrophenyl carbamate.

Table 5. Catalyzed Aldol Additions of 3b[a]

entry	RCHO	mol % **1**	time, h	product	er[b]	yield,[c] %
1	**5**	5	2	(−)-**11**	92.0/8.0	94
2	**6**	5	2	(−)-**12**	95.6/4.4	95
3	**7**	5	2	(−)-**13**	92.9/7.1	92
4	**8**	5	2	(−)-**14**	92.7/7.3	95
5	**9**	10	6	(−)-**15**	94.6/5.4[d]	79
6	**10**	10	6	(−)-**16**	96.0/4.0[d]	81

[a] All reactions performed in CH_2Cl_2 at −78 °C, 0.5 M in aldehyde. [b] Determined by CSP HPLC analysis. [c] Yield of analytically pure material. [d] Determined by CSP HPLC analysis of the dinitrophenyl carbamates.

Scheme 2



good selectivity was observed with conjugated aldehydes, and both enolizable (**9**) and hindered (**10**) aldehydes function admirably with this catalyst system, although slightly higher loading (10 mol %) and reaction time (6 h) were necessary to provide acceptable yields of the aldol adducts **15** and **16**.[12,13]

The invention of the mercury-catalyzed metathesis of trimethyl to trichlorosilyl enolates allowed for the in-situ generation of these reactive agents and set the stage for the development of an operationally simple, one-pot reaction protocol, Scheme 2. Thus, treatment of silyl enol ether **2b** (1.25 equiv relative to aldehyde) with 2 equiv of $SiCl_4$ and 1 mol % $Hg(OAc)_2$ in CH_2Cl_2 at room temperature for 1 h, followed by removal of volatiles in vacuo, then dilution with CH_2Cl_2 and addition of 5 mol % (*S*,*S*)-**1**, and **6** at −78 °C led to an 89% yield of adduct **12**, in 96/4 er.

In summary, we have demonstrated that the trichlorosilyl enolates of methyl ketones are reactive toward aldehydes and that these reactions are catalyzed by the phosphoramide (*S*,*S*)-**1** to give aldol adducts in excellent yield and high enantioselectivity. In addition, we have developed a new, mild method for the synthesis of trichlorosilyl enolates and an operationally simple procedure for the in-situ generation and reaction of these species. Our current efforts focus on catalyst design, reaction mechanism, and extension to other enolate types.

Acknowledgment. We are grateful to the National Science Foundation for generous financial support (CHE 9500397). R.A.S. thanks the Eastman Chemical Co. for a graduate fellowship.

Supporting Information Available: Procedures for the preparation and full characterization of **2g**, **3a**−**g**, (±)-**4a**−**g**, (±)-**11**−**16** and enantiomerically enriched **4a**−**g** and **11**−**16** and in situ experimental procedures (40 pages).

JO972168H

(11) Control experiments revealed that the reaction proceeds only marginally under the conditions of the standard catalyzed reaction (0.5 M, −78 °C, 2 h) in the absence of catalyst. With aldehyde **8** and enolate **3b**, only 4% of the aldol adduct **14** and 95% of unchanged **8** were isolated (cf. Table 5, entry 4).

(12) Single-crystal X-ray analysis of the 4-bromobenzoate derived from (−)-**14** established the absolute configuration of the major enantiomer to be *S*. All other configurational assignments were made by analogy.

(13) By analogy to the reactions of the substituted enolates,[4] we believe that these reactions also proceed through closed, chairlike transition states organized around a hexacoordinate silicon atom.