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Highly Diastereoselective Aldol Additions of a Chiral Ethyl Ketone Enolate under Lewis Base Catalysis

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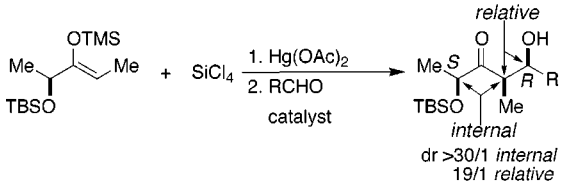
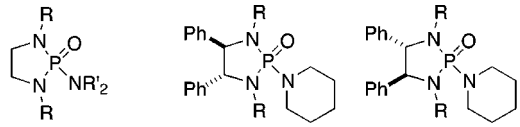
ABSTRACT



The aldol addition of a chiral ethyl ketone enolate bearing an oxygen substituent (OTBS) at the α-position proceeds with high internal and relative diastereoselectivities with various achiral aldehydes in good yields. The profound influence of the resident stereogenic center allows for the use of an achiral catalyst, such as HMPA, with minor attenuation in internal stereoselectivity.

Modern variants of the aldol reaction are among the most important methods for achieving acyclic stereoselection in synthesis.[1] Our most recent contribution to this edifice of chemical technology is the development of trichlorosilyl enolates as asymmetric aldolization partners with various aldehydes in the presence of chiral Lewis bases.[2] This reaction is believed to proceed through a closed, chairlike transition structure centered around a cationic, hexacoordinate silicon center. Kinetic analysis and nonlinear asymmetric induction studies have shown that the reactions are second order with respect to catalyst when **2a** is employed.[3]



1a, R = Me, R' = Me
1b, R = Me, R' = -$(CH_2)_5$-
1c, R = Ph, R' = -$(CH_2)_5$-

(*R*,*R*)-**2a**, R = Me
(*R*,*R*)-**2b**, R = Ph

(*S*,*S*)-**2a**, R = Me
(*S*,*S*)-**2b**, R = Ph

To extend the utility of these agents, we recently reported the use of chiral methyl ketone enolates in aldol reactions with achiral aldehydes.[4] The sensitive trichlorosilyl enolate could be prepared in situ from the corresponding TMS enol ether via a mercury-catalyzed trans-silylation. The resultant trichlorosilyl enolate can then be combined with aldehydes in the presence of catalytic amounts of chiral phosphoramides to afford aldol products in good yields over two steps. When using α-oxygenated ketone enolates, high 1,4-syn diastereoselectivity is achieved with (*R*,*R*)-**2a**. However, it was not possible to reverse the sense of diastereoselection with the use of (*S*,*S*)-**2a**. Interestingly, reactions using a chiral methyl ketone enolate bearing a *β*-oxygen substituent give good 1,4-syn diastereoselectivity when (*R*,*R*)-**2a** is employed but afford 1,4-anti adducts with (*S*,*S*)-**2a**.[5] In continuation of our studies, we have extended the scope of chiral enolate structures to include an α-oxygenated chiral *ethyl* ketone enolate.[6] We describe herein the in situ generation and aldol addition of

(1) Reviews: (a) Paterson, I.; Cowden, C. J.; Wallace, D. J. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 9. (b) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1.

(2) (a) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432. (b) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T.; Su, X. *J. Am. Chem. Soc.* **1999**, *121*, 4982.

(3) (a) Denmark, S.; Su, X.; Nishigaichi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 12990. (b) Denmark, S. E.; Pham, S. M. *Helv. Chim. Acta* **2000**, *83*, 1846.

(4) Denmark, S. E.; Stavenger, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 8837.

(5) Denmark, S. E.; Fujimori, S. *Synlett* **2001**, 1024.

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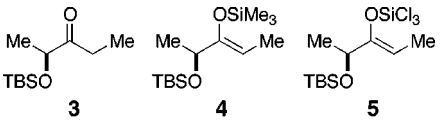
enolate **5** to achiral aldehydes using chiral and achiral phosphoramides to accelerate the reaction and enhance the stereoselectivity.

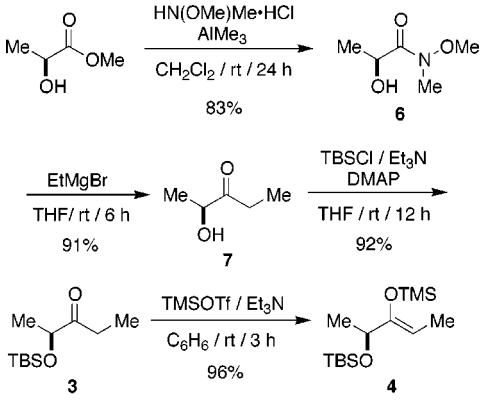


3 **4** **5**

Ethyl ketone **3** was readily prepared in three steps from (*S*)-methyl lactate, Scheme 1. Treatment of the ester with *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of trimethylaluminum afforded the Weinreb amide **6**[7] in 83% yield.[8] Addition of ethylmagnesium chloride to the free hydroxy amide provided hydroxy ketone **7**[9] in 91% yield. Finally, silylation with *tert*-butyldimethylsilyl chloride using a catalytic amount of 4-(dimethylamino)pyridine provided the protected ketone **3** in 92% yield. Initial attempts at enolization of **3** using lithium diisopropylamide (LDA) and trimethylsilyl chloride at −78 °C afforded the desired TMS enol ether **4** and the corresponding regioisomer as a 2/1 mixture. The regioisomers could be separated by silica gel chromatography albeit sacrificially with significant losses from hydrolysis. Using a more sterically demanding base, such as lithium tetramethylpiperidide,[10] afforded little to no improvement. Although this procedure was adequate for providing small quantities of enol ether for our initial studies, a more selective method for the generation of **4** is required if this process is to be synthetically useful. Ultimately we found that the use of a more electrophilic silylating agent improved selectivity for the desired regioisomer. Thus, treatment of **3** with trimethylsilyl trifluoromethanesulfonate[11] and Et_3N in benzene at room temperature afforded TMS enol ether **4** as a single regioisomer with a *Z*/*E* ratio greater than 20/1 (by ^{1}H NMR analysis). Yields as high as 96% were obtained following fractional distillation.

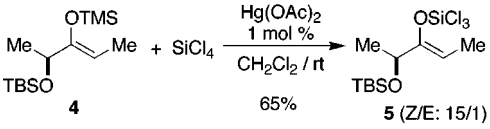
With a reliable method for the selective preparation of **4** in hand, we then focused on the preparation of trichlorosilyl enolate **5**. Achieving high geometric selectivity for the trans-silylation was of great concern, since the relative diastereoinduction[12] in the aldol process through a closed transition

Scheme 1



structure would be highly dependent upon the ratio of *E* and *Z* enolate isomers. Orienting studies revealed that the trichlorosilyl enolate geometry is independent of the starting TMS enol ether geometry. Moreover, the size of the spectator group plays a significant role in determining the ratio of *Z*/*E* isomers; bulkier substituents such as *tert*-butyl and phenyl afford the *Z*-trichlorosilyl enolate almost exclusively.[13] Cognizant of these features, we treated TMS enol ether **4** with $SiCl_4$ and 1 mol % of $Hg(OAc)_2$ to effect trans-silylation, Scheme 2. The metathetical process was easily monitored by ^{1}H NMR and was found to be complete in 18 h. Gratifyingly, **5** could be isolated in 65% yield following distillation to afford a 15/1 mixture of *Z*/*E* trichlorosilyl enolates. Through the course of optimizing the trans-silylation of **4**, we were able to improve the selectivity of the reaction such that **5** could be reproducibly generated as a 19/1, *Z*/*E* mixture of enolates.

Scheme 2



We could now evaluate the effect of the resident stereogenic center on the stereochemical course of the aldol reactions to benzaldehyde in the presence of various phosphoramides. Following our established procedure, benzaldehyde was added to a 0.1 M solution of **5** and 15 mol % of (*R*,*R*)-**2a** in CH_2Cl_2 at −78 °C. Disappointingly, the reaction was very sluggish compared to that of the corresponding methyl ketone enolates. This is presumably due to the added steric encumbrance encountered by the substituted enolate upon approach to an aldehyde through a closed transition structure which is not present when using simple enolates. Increasing the concentration of the reaction to either 0.5 or 1.0 M allowed the aldol reaction to proceed to completion

(6) (a) For a discussion of aldol additions of boron, titanium, and lithium enolates of chiral ethyl ketones, see: Braun, M. In *Stereoselective Synthesis, Methods of Organic Chemistry (Houben-Weyl)*, Edition E21; Helmchen, G., Hoffman, R., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. 3, pp 1612−1622. For related benzyl and benzoate derivatives, see: (b) Paterson, I.; Wallace, D. J.; Velázquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083. (c) Paterson, I.; Wallace, D. J. *Tetrahedron Lett.* **1994**, *35*, 9087. (d) For a more recent discussion, see: Galobardes, M.; Gascón, M.; Mena, M.; Romea, P.; Urpí, F.; Vilarrasa, J. *Org. Lett.* **2000**, *2*, 2599.

(7) Following a modified procedure: Luke, G. P.; Morris, J. *J. Org. Chem.* **1995**, *60*, 3013.

(8) All compounds have been fully characterized; see the Supporting Information for details.

(9) Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639.

(10) Hall, P. L.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9571.

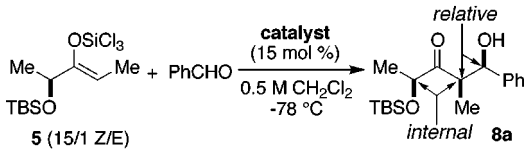
(11) (a) Trost, B. M.; Urabe, H. *J. Org. Chem.* **1990**, *55*, 3982. (b) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234. (c) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

(12) For a discussion regarding internal and relative diastereoselectivity, see: Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 10.

(13) Denmark, S. E.; Pham, S. M. Unpublished results.

within 2 h using (*R*,*R*)-**2a**, Table 1, entry 1. The addition product **8a** was obtained in 87% yield. The *relative* diastereoselectivity for the two new stereogenic centers mirrored the starting trichlorosilyl enolate geometry to give a 16/1 ratio of syn/anti diastereomers. We were delighted to find that the internal diastereoselectivity for the major syn adduct was greater than 50/1 in favor of the (syn,syn) stereoisomer.[14]

Table 1. Survey of Phosphoramides in the Stereoselective Addition of **5** to Benzaldehyde



entry	catalyst	time, h	yield, %[a]	relative dr syn/anti[b]	internal dr syn/anti[b]
1	(*R*,*R*)-**2a**	2	87	16/1	>50/1
2	(*S*,*S*)-**2a**	2	80	15/1	30/1
3	(*R*,*R*)-**2b**	8	65	15/1	3/1
4	**1a**	7	76	15/1	34/1
5	**1b**	7	82	15/1	37/1
6	**1c**	5	67	15/1	3/1
7	HMPA	7	79	15/1	30/1

[a] Yield of chromatographically homogeneous material. [b] Determined by CSP-SFC.

A survey of chiral and achiral phosphoramides showed variation in the influence of the resident stereogenic center on the internal stereoselectivity of the reaction, Table 1. As before, the relative diastereoselectivity of **8a** corresponds well with the initial composition of **5**, suggesting that the aldol reaction proceeds nearly exclusively through a closed, chairlike transition structure. Surprisingly, the configuration of the catalyst employed in the aldol reaction has only a marginal effect on the stereochemical outcome. For example the use of (*S*,*S*)-**2a** led to only a slight decrease in internal diastereoselectivity from 50/1 to 30/1 for (*R*,*R*)-**2a** and (*S*,*S*)-**2a**, respectively. Although from an energetic perspective this change may be significant, from a practical aspect, for synthetic purposes, these numbers are virtually identical. Perhaps the most profound illustration of the influence of the resident stereogenic center was shown when we employed the achiral *N*,*N*′-dimethyl-[1,3,2]-diazaphospholidine catalysts **1a** and **1b**. In both cases, the internal diastereoselectivity was greater than 30/1. Even the use of HMPA afforded **8a** with an internal diastereoselectivity of 30/1, albeit at a reduced rate. Interestingly, only the *N*,*N*′-*diphenyl*-derived phosphoramides (*R*,*R*)-**2b** and **1c** gave significantly attenuated internal diastereoselectivities (vide infra).

To establish the generality of reactions with **5**, we surveyed various aldehydes using both (*R*,*R*)-**2a** and HMPA as catalysts for the aldol reaction. As a further synthetic simplification, we performed the aldol reactions by in situ generation of trichlorosilyl enolate **5**. This obviates the need for handling of a sensitive compound and improves the overall yield of aldol product with respect to the TMS enol ether. Finally, to demonstrate the efficiency of our chiral phosphoramides, the aldol reactions were performed using only 5 mol % of (*R*,*R*)-**2a**, while still using 15 mol % of HMPA, Table 2.

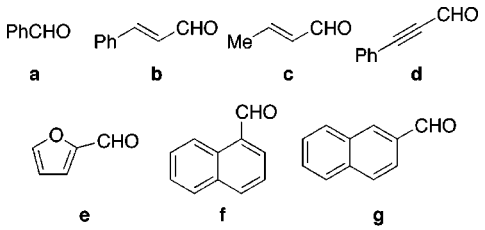
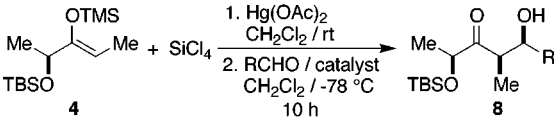


Table 2. Survey of Various Aldehydes in the Stereoselective Aldol Addition



RCHO	catalyst	loading, mol %	yield, %[a]	dr[b] (syn,syn)/minors
a	(*R*,*R*)-**2a**	5	88	95/5
a	HMPA	15	87	94/2/2/2
b	(*R*,*R*)-**2a**	5	81	93/5/2
b	HMPA	15	79	91/6/3
c	(*R*,*R*)-**2a**	5	85	93/4/3
c	HMPA	15	83	84/15/1
d	(*R*,*R*)-**2a**	5	79	95/3/2
d	HMPA	15	82	89/5/4/3
e	(*R*,*R*)-**2a**	5	82	94/6
e	HMPA	15	76	93/5/1
f	(*R*,*R*)-**2a**	5	72	98/1/1
f	HMPA	15	62	83/12/3/1
g	(*R*,*R*)-**2a**	5	71	94/3/3
g	HMPA	15	59	89/6/4/1

[a] Yield of analytically pure material. [b] Ratio determined by CSP-SFC.

The entries in Table 2 illustrate that excellent diastereoselectivities can be achieved even when using catalyst loadings as low as 5 mol %. Moreover, the results reveal a marked improvement for the in situ procedure over one in which the trichlorosilyl enolate is prepared independently. Although the diastereoselectivity and yields using HMPA are slightly poorer, the results remain synthetically viable. Even though (*R*,*R*)-**2a** is easy to prepare,[15] the benefits of using HMPA are clear.

To determine the absolute configuration of the various aldol products, material from reactions using (*R*,*R*)-**2a** were desilylated with 1% HCl in EtOH.[16] The keto diols were

(14) In this nomenclature, the first descriptor is relative, the second is internal. The configuration assignment follows degradation to propanoates and chemical correlation as described below.

(15) Denmark, S. E.; Su, X.; Nishigaichi, Y.; Coe, D. M.; Wong, K.-T.; Winter, S. B. D.; Choi, J. Y. *J. Org. Chem.* **1999**, *64*, 1958.

(16) (a) Wetter, H.; Oertle, K. *Tetrahedron Lett.* **1985**, *26*, 5515. (b) Cunico, R. F.; Bedell, L. *J. Org. Chem.* **1980**, *45*, 4797.

then subjected to oxidative cleavage using $NaIO_4$[17] followed by treatment with CH_2N_2 to afford the known methyl propanoate aldol adducts (see the Supporting Information). Chemical correlation via ^1H NMR and optical rotation confirmed the major diastereomer to be (*syn,syn*)-**8**.

To rationalize the stereochemical outcome, we make recourse to the familiar, nonchelation model which places the TBS ether in an antiperiplanar orientation relative to the C−O bond of the enoxytrichlorosilane to reduce dipole−dipole interactions, Figure 1.[1,4] In this manner, approach of benzaldehyde would be toward the face of the enolate (*Si*) which contains the hydrogen to minimize steric interactions. Additionally, the proposed chairlike arrangement would situate the phenyl group of benzaldehyde equatorially, to prevent 1,3-diaxial interactions.[18] As depicted in Figure 1, reaction through **i** containing two phosphoramide molecules would afford (*syn,syn*)-**8a**. Bulky catalysts bearing *N*-phenyl substituents ((*R,R*)-**2b** and **1c**) reduce the coordinating ability of the phosphoramides, such that a "one phosphoramide pathway" for aldolization now becomes competitive.[19] It is conceivable that in such an event the remaining coordination site on the octahedral silicon is occupied by the oxygen in the α-position of the trichlorosilyl enolate. Although the binding propensity of a TBS ether is modest at best,[20] the proximity of this group to a cationic siliconate surely enhances the probability of chelation.[21] Thus, a coordinative

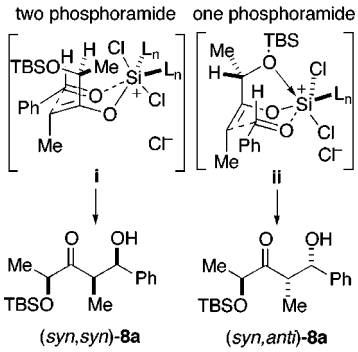


Figure 1. Proposed transition structures for stereoselective aldol reactions with **5**.

pathway would position the TBS ether synperiplanar to the enoxy C−O bond. This forces the aldehyde to approach the opposite enolate face (*Re*) as observed in **i**, but again maintaining the same relative orientation of the phenyl group. Thus, reaction through **ii** containing one phosphoramide molecule would provide (*syn,anti*)-**8a**.

Extension of these studies to other chiral ethyl ketones with more strongly coordinating substituents as well as to chiral ketones with remote stereogenic centers is in progress.

Acknowledgment. We are grateful to the National Science Foundation for generous financial support (NSF CHE-9803124). S.M.P. thanks the University of Illinois and the Eastman Kodak Company for Graduate Fellowships.

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

OL0160497

(17) Following a procedure described by Urpí, ref 6d.

(18) Masamune, S.; Choy, W.; Kerkesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566.

(19) For a detailed discussion regarding the mechanistic aspects of a one phosphoramide pathway vs a two phosphoramide pathway in Lewis base-catalyzed aldol reactions of trichlorosilyl enolates, see ref 3.

(20) For a discussion of the coordinating abilities of various ether substituents, see: (a) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462. (b) Chen, X.; Hortellano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 6130. (c) Mori, S.; Nakamura, M.; Nakamura, E.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1995**, *117*, 5055.

(21) For a discussion of chelation as a stereocontrol element in lactate-derived stannous enolates, see: Paterson, I.. Tillyer, R. *Tetrahedron Lett.* **1992**, *33*, 4233.