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The Effects of a Remote Stereogenic Center in the Lewis Base Catalyzed Aldol Additions of Chiral Trichlorosilyl Enolates

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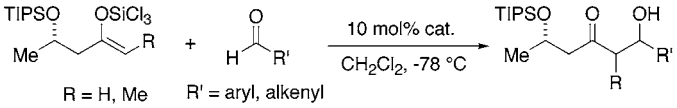
ABSTRACT



Chiral trichlorosilyl enolates bearing a remote stereogenic center were employed in the phosphoramide-catalyzed aldol reaction. The additions of the methyl ketone enolates proceeded with only moderate diastereoselectivities. The addition of the *Z*-enolate to various aldehydes selectively produced the syn relative diastereomers. In both cases, the effect of the *β*-silyloxy stereogenic center was modest, and the internal diastereoselection was mainly controlled by the catalyst.

The asymmetric aldol addition is well-established as a practical approach to assemble polypropionate subunits in a stereoselective manner.[1] Our laboratories have disclosed a conceptually new catalytic, stereoselective aldol reaction that employs trichlorosilyl enolates and a catalytic amount of chiral phosphoramide.[2]

A variety of trichlorosilyl enolates derived from esters, ketones, and aldehydes have been prepared and employed in Lewis base catalyzed aldol additions.[3] More recently, the scope of the enolate structure has been expanded to include chiral enolates containing an α-stereogenic center.[4] When lactate-derived enolates are used in the chiral-phosphoramide-catalyzed aldol additions, the influence of the α-silyloxy stereogenic center dominates the stereochemical outcome of the aldol reaction.[4a,b] On the other hand, the aldol reaction of enolates bearing an α-methyl stereocenter showed only modest intrinsic selectivity, and the configuration of the aldol product is primarily controlled by the catalyst configuration.

Recently, both Paterson and Evans have described examples of 1,5-stereoinduction originating from a remote stereocenter in boron enolate aldol additions.[5] In these reactions of methyl ketones containing *β*-alkoxy functionality, high 1,5-anti selectivities were observed. Interestingly, the use of a chiral isopinocamphoryl ligand on boron exhibited a double stereodifferentiation effect where a significant increase in the 1,5-anti selectivity could be obtained.[5a]

As part of the exploration of the Lewis base catalyzed aldol reaction, we have carried out an investigation on the effect of a remote stereogenic center on the stereochemical course of aldol addition (Scheme 1). Herein we report the

(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. (c) Braun, M. In *Stereoselective Synthesis, Methods of Organic Chemistry* (*Houben-Weyl*), Workbench Edition E 21; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. 3, pp 1603−1748.

(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) Denmark, S. E.; Stavenger, R. A.; Winter, S. B. D.; Wong, K.-T.; Barsanti, P. A. *J. Org. Chem.* **1998**, *63*, 9517.

(4) (a) Denmark, S. E.; Stavenger, R. A. *J. Org. Chem.* **1998**, *63*, 9524. (b) Denmark, S. E.; Pham, S. M. *Org. Lett.* **2001**, *3*, 2201. (c) Denmark, S. E.; Fujimori, S. *Synlett* **2001**, 1024. (d) Denmark, S. E.; Fujimori, S. *Org. Lett.* **2002**, *4*, 3473.

(5) (a) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585. (b) Paterson, I.; Collett, L. A. *Tetrahedron Lett.* **2001**, *42*, 1187. (c) Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett.* **1996**, *37*, 8581. (d) Evans, D. A.; Coleman, P. J.; Cote, B. *J. Org. Chem.* **1997**, *62*, 788.

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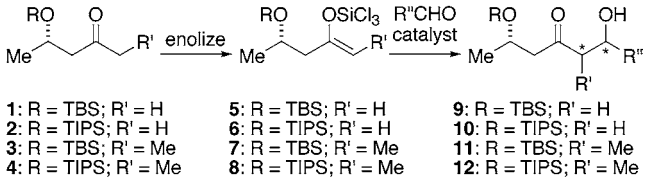
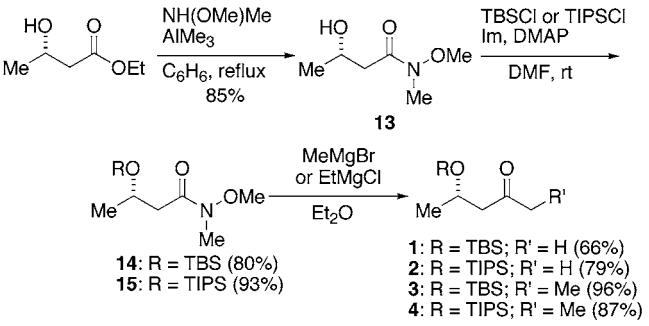
preparations and the Lewis base catalyzed aldol additions of enolates **5**−**8** bearing a *β*-silyloxy stereogenic center.

Scheme 1



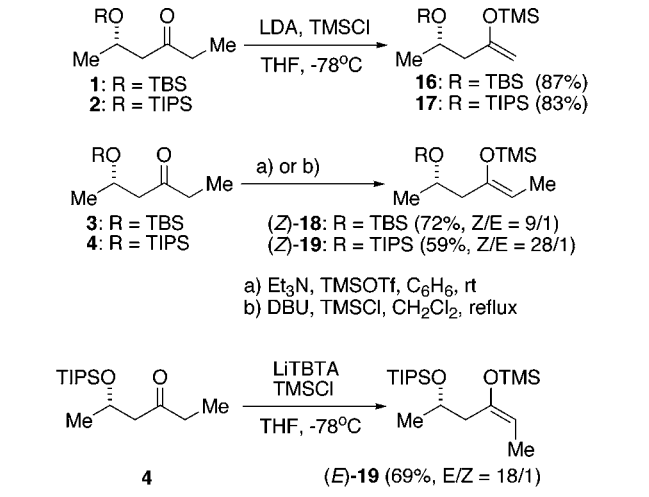
The chiral ethyl ketones **1**−**4** were readily prepared in three steps from ethyl (*S*)-3-hydroxybutyrate (Scheme 2). Conversion to the Weinreb amide **13** proceeded in good yield using trimethylaluminum.[6] This hydroxyamide was protected as either the *tert*-butyldimethylsilyl ether **14** or the triisopropylsilyl ether **15**. After the protection of a hydroxyl group, the amides were converted to the corresponding methyl and ethyl ketones in good yields.

Scheme 2



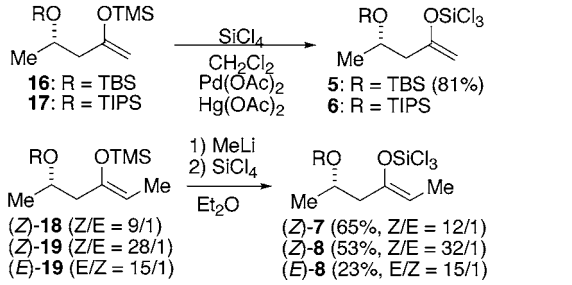
These chiral ketones **1**−**4** were converted into the corresponding TMS enol ethers **16**−**19** (Scheme 3). The selective enolization of the methyl ketones was achieved by simply using LDA and TMSCl. Geometrically defined TMS enol ethers were obtained using the following combinations of reagents for the enolization of ethyl ketones. The *Z*-selective enolization was achieved using either Et_3N/TMSOTf[7] or DBU/TMSCl combination in refluxing methylene chloride to produce (*Z*)-**18** and (*Z*)-**19**.[8] The *E*-selective enolization was effected by lithium *tert*-butyl trityl amide (LiTBTA) and TMSCl.[9]

Scheme 3



For the preparation of the methyl ketone enolates **5** and **6**, transition metal catalyzed metathesis using either 1 mol % $Hg(OAc)_2$ or 5 mol % $Pd(OAc)_2$ was employed.[3] The trichlorosilyl enolates generated by this procedure are isolated by fractional distillation. When $Hg(OAc)_2$ is used as the catalyst, the resulting enolate can be directly used in the subsequent aldol addition (Scheme 4).

Scheme 4



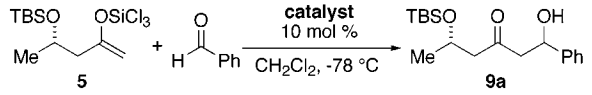
The ethyl ketone enolates were prepared by direct O-to-O transsilylation through formation of the lithium enolate.[10] The lithium enolate was formed from the TMS enol using methyllithium and was subsequently trapped with 10 equiv of $SiCl_4$ (Scheme 4). Thus, the trichlorosilyl enolates **7** and **8** were obtained from the corresponding TMS enol ethers with high *E*/*Z* ratios. With this procedure, however, variable amounts of bisenoxydichlorosilane species were observed in the isolated trichlorosilyl enolates.

With the methods for syntheses of **5** and **6** established, we focused on the aldol addition of these enolates. The aldol addition of the methyl ketone enolate **5** to benzaldehyde was examined using the chiral and achiral phosphoramides **20a** and **20b**. The use of 10 mol % of the catalyst effectively promoted the addition at 0.5 M concentration. The results are summarized in Table 1. Unfortunately, the observed selectivities were not satisfactory considering that the phosphoramide **20a** showed high selectivities in the aldol additions of other methyl ketone enolates.[11] The inherent syn/

(6) Luke, G. P.; Morris, J. *J. Org. Chem.* **1995**, *60*, 3013.
(7) (a) Trost, B. M.; Urabe, H. *J. Org. Chem.* **1990**, *55*, 3982. (b) Vorbruggen, 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.
(8) Taniguchi, Y.; Inanaga, J.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3229.
(9) Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **2000**, *41*, 2515.
(10) Denmark, S. E.; Ghosh, S. K. *Angew. Chem., Int. Ed.* **2001**, *40*, 4059.
(11) Denmark, S. E.; Stavenger, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 8837.

anti selectivity was determined using the achiral catalyst **20b**, and only slight selectivity toward the 1,5-anti isomer was observed (Table 1, entry 3).[12]

Table 1. Aldol Additions of **5** to Benzaldehyde



entry[a]	catalyst	yield (%)[b]	syn/anti[c]
1	(*R*,*R*)-**20a**	72	1/2.5
2	(*S*,*S*)-**20a**	75	1.3/1
3	20b	55	1/1.4

[a] Reaction time was 4 h. [b] Yield of chromatographically homogeneous material. [c] Determined by CSP-SFC.

The addition of the methyl ketone enolates can be performed using the in situ generated enolate for operational simplicity. The results of aldol additions to benzaldehyde using in situ generated **5** and **6** are collected in Table 2. This method not only avoids handling of sensitive trichlorosilyl enolates but also provides improved selectivities for the additions of **5** as compared to the addition of isolated **5** (Table 2, entries 1 and 2 vs Table 1, entries 1 and 2). The stereochemical course of the reaction seems to be controlled only by the catalyst since similar selectivities for both directions were obtained using either enantiomer of **20a**. Although the yield of the reaction was significantly higher, the addition of **6** was less selective than the aldol additions of **5** (Table 2, entries 3 and 4). Thus, the effect of the resident stereocenter is almost nonexistent in the addition of the

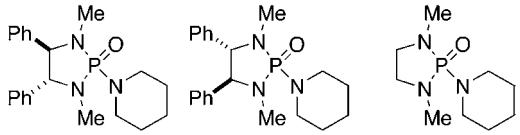
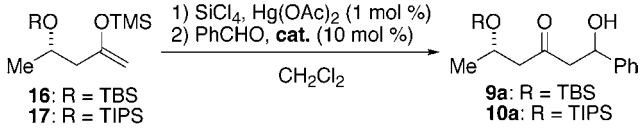


Table 2. Aldol Additions of In-Situ Generated **5** and **6** to Benzaldehyde



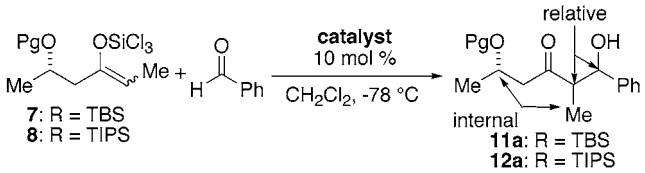
entry[a]	catalyst	yield (%)[b]	syn/anti[c]
1	(*R*,*R*)-**20a**	61	5.5/1
2	(*S*,*S*)-**20a**	58	1/4.4
3	(*R*,*R*)-**20a**	89	1.8/1
4	(*S*,*S*)-**20a**	86	1/2.3

[a] Reaction time was 4 h. [b] Yield of chromatographically homogeneous material. [c] Determined by CSP-SFC.

methyl ketone enolates. The poor selectivities for the additions of these methyl ketone enolates may be related to the protecting group on the β-oxygen. In the boron enolate aldol reactions, it was found that changing the protecting group from a benzyl-type ether to a silyl ether lead to a significant attenuation of 1,5-stereoinduction.[5a] Although clear explanation for this effect was not presented, the nature of the protecting group seems to affect the intrinsic stereoinduction in these substrates.

After the examination of the methyl ketone enolates, we turned our focus to the addition of ethyl ketone enolates. The reaction conditions were optimized using benzaldehyde for enol ethers **7** and **8**; the results are summarized in Table 3. The addition of *Z*-enolates **7** and **8** showed good syn relative diastereoselectivity that mirrored the *Z*/*E* ratio of the enolate (Table 3, entries 1−4). This observation suggests that the aldol addition of *Z*-enolate proceeds through the Zimmerman−Traxler-type transition state.[13] It was surprising to find that the addition of the (*E*)-**8** was relatively syn selective (Table 3, entry 5). It is likely that the competitive boat transition structure is operative for the addition of *E*-enolate and may be slightly more favorable than the chair transition structure.

Table 3. Phosphoramide-Catalyzed Aldol Additions of **7** and **8** to Benzaldehyde



entry[a]	enolate	Z/E	catalyst	yield (%)[c]	relative dr (syn/ anti)[d]	internal dr (syn/ anti)[e]
1	(*Z*)-**7**	12/1	(*R*,*R*)-**20a**	59	6/1	14/1
2	(*Z*)-**7**	12/1	(*S*,*S*)-**20a**	60	12/1	1/14
3	(*Z*)-**8**	16/1	(*R*,*R*)-**20a**	84	30/1	16/1
4	(*Z*)-**8**	16/1	(*S*,*S*)-**20a**	86	26/1	1/10
5	(*E*)-**8**	1/15	(*S*,*S*)-**20a**	80	3/1	1/1
6[b]	(*Z*)-**8**	30/1	**20b**	83	29/1	1.4/1

[a] Reaction time was 8 h. [b] Reaction time was 12 h. [c] Yield of chromatographically homogeneous material. [d] Determined by ^{1}H NMR. [e] Determined by CSP-SFC.

The intrinsic selectivity of the chiral enolate (*Z*)-**8** was again determined using the achiral phosphoramide **20b** (Table 3, entry 6). Similar to the case for methyl ketone, the effect of the resident stereocenter was almost absent, giving almost 1/1 internal diastereoselection. This allowed diastereocontrolled aldol addition to produce either syn relative

(12) The configuration of the aldol product is assigned on the basis of the assumption that the newly formed stereogenic center is (*R*)-configured when (*R*,*R*)-**20a** is used.

(13) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

diastereomer by changing the configuration of **20a**. The use of (*R*,*R*)-**20a** produced the (syn,anti) diastereomer, while the (syn,syn) diastereomer was obtained using the (*S*,*S*)-**20a**.[14] In contrast to the boron enolate aldol reactions where the 1,5-anti stereoinduction dominates the stereochemical outcome, the external effect from the catalyst determined the diastereoselection in these aldol additions. This catalyst-controlled aldol addition enhances the synthetic utility of these trichlorosilyl enolates.

To expand the scope of this aldol addition, (*Z*)-**8** was chosen to survey other aldehyde structures including aromatic and olefinic aldehydes. The additions of (*Z*)-**8** to these aldehydes are summarized in Table 4. In all cases, high syn relative diastereoselectivities were maintained. When the diastereoselectivities between **12a** and **12b** were compared, 1-naphthaldehyde showed slightly decreased relative selectivity (Table 4, entries 1 and 2 vs 3 and 4). On the other hand, the internal selectivity was higher for **12b** compared to that of **12a**. This may be related to the bulk around the aldehyde carbonyl, and a similar trend was observed for the addition of the ethyl ketone enolate bearing an α-methyl stereocenter.[4c,d] A switch in the internal diastereoselection was observed in all cases, depending on the catalyst configuration. The internal selectivities were found to be significantly higher for aromatic aldehydes compared to those of other olefinic aldehydes (Table 4, entries 1 and 3). Interestingly, the disparity in the internal selectivity between (*R*,*R*)-**20a** and (*S*,*S*)-**20a** was larger in the aromatic aldehydes than in the olefinic aldehydes. The olefinic aldehydes showed similar internal diastereoselectivities ranging from 6/1 to 10/1 (Table 4, entries 5−10).

Thus, we have described the catalytic diastereoselective aldol addition of chiral enolate containing a *β*-silyloxy stereocenter. In contrast to what has been reported in the literature on the boron enolate additions, the effect of the remote stereocenter was minimal in the reaction of trichlorosilyl enolates. However, the addition of the *Z*-enolates showed good diastereoselectivities, and both relative syn diastereomers are selectively produced solely depending on the catalyst configuration.

(14) In this nomenclature, the first descriptor indicates relative, and the second indicates internal stereochemistry. For discussion of these terms, see: Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 10.

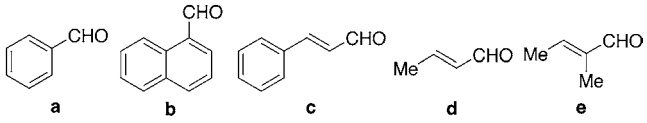
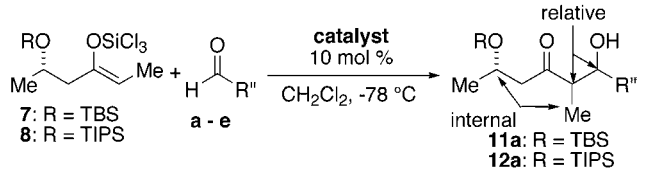


Table 4. Survey of Various Aldehydes in Aldol Additions of (*Z*)-**8** Using **20a** as Catalyst



entry[a]	R″CHO	catalyst	time (h)	yield (%)[c]	relative dr (syn/ anti)[d]	internal dr (syn/ anti)[e]
1[b]	a	(*R*,*R*)-**20a**	6	84	30/1	16/1
2[b]	a	(*S*,*S*)-**20a**	6	86	26/1	1/10
3	b	(*R*,*R*)-**20a**	8	80	17/1	30/1
4	b	(*S*,*S*)-**20a**	8	75	18/1	1/10
5	c	(*R*,*R*)-**20a**	12	83	>50/1	10/1
6	c	(*S*,*S*)-**20a**	12	81	>50/1	1/8
7	d	(*R*,*R*)-**20a**	8	79	28/1	7/1
8	d	(*S*,*S*)-**20a**	8	83	37/1	1/6
9	e	(*R*,*R*)-**20a**	8	83	>50/1	3/1
10	e	(*S*,*S*)-**20a**	8	81	>50/1	1/3

[a] (*Z*)-**8** contained 10% of the bisenoxysilane, and the Z/E ratio was 32/1 by ^{1}H NMR analysis. [b] Z/E ratio was 16/1. [c] Yield of analytically pure material. [d] Determined by ^{1}H NMR analysis. [e] Determined by CSP-SFC.

Extension of these studies including the application of these catalytic methods to polypropionate type natural products is currently in progress.

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

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