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Diastereoselective Aldol Additions of Chiral β-Hydroxy Ethyl Ketone Enolates Catalyzed by Lewis Bases

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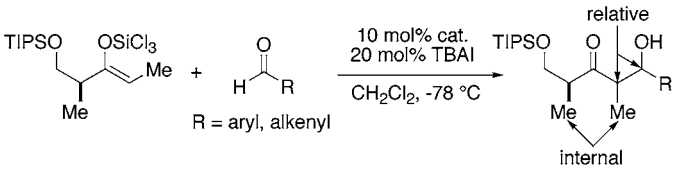
ABSTRACT

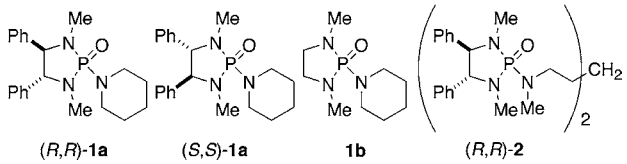


(*R,R*) - cat.; 71 ~ 90 % yield, rel. syn/anti > 9/1; int. syn/anti = 13 - 89/1
(*S,S*) - cat.; 75 ~ 85 % yield, rel. syn/anti > 14/1; int. syn/anti = 1/ 5 - 17

The trichlorosilyl enolates derived from chiral ethyl ketones bearing a β-hydroxyl group and an α-stereogenic center were employed in the phosphoramide-catalyzed aldol reaction. The addition of *Z*-enolates to achiral aldehydes produced aldol products in good yields and high syn relative diastereoselectivities. The internal diastereoselectivity is controlled by the catalyst configuration, allowing for selective formation of either syn diastereomer.

In the synthesis of complex natural products, aldol additions are often employed for stereoselective construction of carbon−carbon bonds.[1] Recently, a catalytic, stereoselective aldol reaction that employs trichlorosilyl enol ethers and a catalytic amount of a chiral phosphoramide has been developed in these laboratories.[2] The key stereochemical control features of this aldol process are believed to arise from a closed-transition structure with all aldolization components assembled around a six-coordinate, cationic silicon center.[3]

Trichlorosilyl enolates derived from esters, ketones, and aldehydes have been prepared and employed in aldol additions, using suitable Lewis bases.[4] In particular, the chiral phosphoramides **1a** are found to be the most effective and selective catalysts for reactions of ketone enolates.



More recently, the additions of trichlorosilyl enolates of chiral methyl and ethyl ketones derived from lactic esters have been investigated to examine the effect of a resident stereogenic center.[5] When these enol ethers are used in the chiral-phosphoramide-catalyzed aldol additions, significant double stereodifferentiation effects are observed as a result

(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 1644−1655.

(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.; Su, X.; Nishigaichi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 12990.

(4) (a) Denmark, S. E.; Stavenger, R. A.; Winter, S. B. D.; Wong, K.-T.; Barsanti, P. A. *J. Org. Chem.* **1998**, *63*, 9517. Addition of ester enolates: (b) Denmark, S. E.; Winter, S. B. D.; Su, X.; Wong, K.-T. *J. Am. Chem. Soc.* **1996**, *118*, 7404. (c) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, *124*, 4233. Addition of aldehyde enolates: (d) Denmark, S. E.; Ghosh, S. K. *Angew. Chem., Int. Ed.* **2001**, *40*, 4059.

(5) (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.

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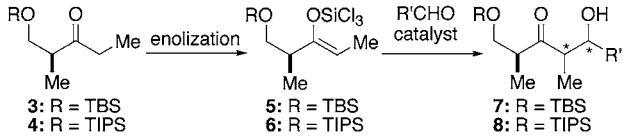
of the strong influence of the α-stereogenic center. When the effects of the resident chiral center and the chiral catalysts are matched, extremely high 1,4-syn diastereoselectivities are observed in the aldol additions of lactate-derived enolates.

In continuation of these studies, an investigation of a different class of chiral enolate structures bearing a *β*-oxygen functionality and an α-stereocenter was undertaken (Scheme 1).[6] These enol ether structures are particularly useful in synthesis because the aldol adducts, **7** and **8**, possess a 1,3,5-oxygenated carbon chain, which is a common motif in polypropionate-type natural products.

Scheme 1

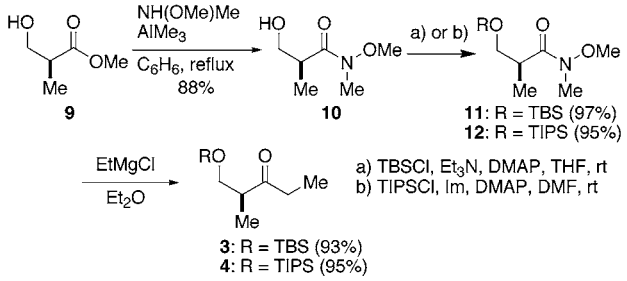


Indeed, these types of enolates have been studied for boron and tin enolate aldol additions and employed in various macrolide syntheses.[7] With a combination of a chiral auxiliary and a chiral enolate, Paterson has shown that the diisopinocamphoryl boron enolates derived from the benzyl analogue of **3** undergo aldol additions with various aldehydes in good diastereoselectivities.[8] The stereochemical course of the reaction was dominated by the configuration of the auxiliary, and the intrinsic selectivity was found to be almost nonexistent.

We then examined the effect of the α-methyl stereocenter in the ethyl ketone enolates on the stereochemical course of the phosphoramide-catalyzed aldol addition. In addition, the behavior of acyclic ketone enolates in this reaction would be studied. We report herein the preparations and aldol additions of chiral enolates **5** and **6** catalyzed by the chiral phosphoramides.

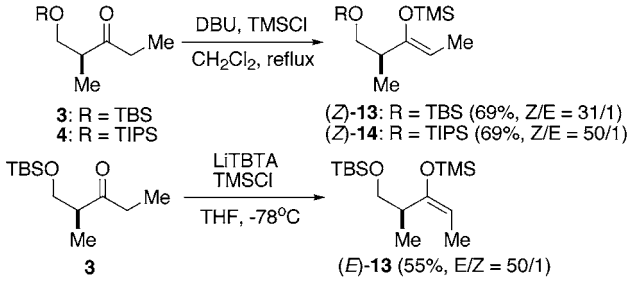
The chiral ethyl ketones **3** and **4** were readily prepared in three steps from the corresponding *β*-hydroxy ester **9** (Scheme 2). The ester **9** was converted to the Weinreb amide **10** in good yield using trimethylaluminum.[9] The hydroxyl group of the amide was protected as either a *tert*-butyldimethylsilyl ether **11** or a triisopropylsilyl ether **12**. After protection of the hydroxyl group, these amides were converted to the corresponding ethyl ketones in excellent yields.

Scheme 2



Constitutionally and geometrically controlled enolizations were achieved with the following reagent combinations (Scheme 3). The use of DBU/ TMSCl in refluxing methylene chloride gave high *Z*/*E* ratios for the preparations of (*Z*)-**13** and (*Z*)-**14**.[10] The enol ether (*E*)-**13** was obtained by enolization of **3** using lithium *tert*-butyl trityl amide (LiTBTA) and TMSCl.[11] In both enolization conditions, the constitutional isomers were formed in small amounts, and they were easily separated by silica gel chromatography.

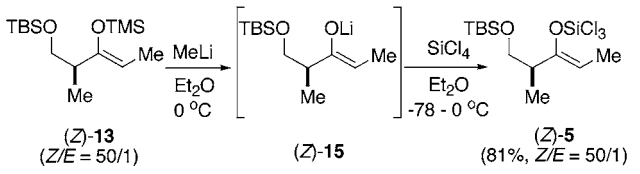
Scheme 3



For the conversion of TMS enol ethers to trichlorosilyl enol ethers, the metal-catalyzed transsilylation using either $Hg(OAc)_2$ or $Pd(OAc)_2$ was initially attempted.[4a] Unfortunately, the obtained *E*/*Z* ratio of the trichlorosilyl enolate **5** was close to 1/1 regardless for the *E*/*Z* ratio of **13**. The ^{1}H NMR analysis of aliquots from the reaction mixture showed that the geometry of the TMS enol ether was scrambled before it was converted to the trichlorosilyl enolate.[12]

The alternative route to trichlorosilyl enolate involves the direct O-to-O transsilylation through formation of the lithium enolate **15** (Scheme 4).[4d] The lithium enolate was formed from the TMS enol ether by using methyllithium and was subsequently combined with a large excess of silicon tetrachloride. With this strategy, trichlorosilyl enolates **13** and **14** were obtained with high *E*/*Z* ratios from the corresponding TMS enol ethers. In all cases, however, variable amounts of bisenoxydichlorosilane species were observed in the isolated trichlorosilyl enolates.

Scheme 4

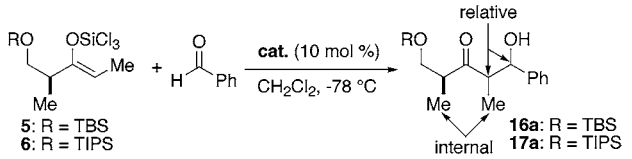


(6) Denmark, S. E.; Fujimori, S. *Synlett* **2001**, 1024.
(7) (a) Feutrill, J. T.; Lilly, M. J.; Rizzacasa, M. A. *Org. Lett.* **2002**, *4*, 525. (b) Paterson, I.; Chen, D. Y−K.; Acena, J. L.; Franklin, A. S. *Org. Lett.* **2000**, *2*, 1513. (c) Paterson, I.; Cowden, C. J.; Woodrow, M. D. *Tetrahedron Lett.* **1998**, *39*, 6037. (d) Paterson, I.; Tillyer, R. D. *Tetrahedron Lett.* **1992**, *33*, 4233.
(8) Paterson, I.; Lister, M. A. *Tetrahedron Lett.* **1988**, *29*, 585.
(9) Luke, G. P.; Morris, J. *J. Org. Chem.* **1995**, *60*, 3013.
(10) Taniguchi, Y.; Inanaga, J.; Yamaguchi M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3229.

With the geometrically defined enolates in hand, we then directed our attention to the aldol additions of these enolates. Initially, the reaction conditions were optimized using (*Z*)-**5** and benzaldehyde. The use of 10 mol % of phosphoramide **1** was able to achieve the complete consumption of benzaldehyde within 4 h at 1.0 M concentration at −78 °C.

The results of aldol additions **5** and **6** to benzaldehyde are summarized in Table 1. The reactions of (*Z*)-**5** and (*Z*)-**6** produced predominantly syn relative diastereomers, suggesting that the aldol addition proceeds through a chairlike transition structure (Table 1, entries 1−3 and 7−9). However, the relative syn/anti ratio for the addition of (*Z*)-**5** did not strictly mirror the *Z*/*E* ratio of the starting enolate (Table 1, entries 1−3). This observation indicates that there is a competitive pathway leading to the anti relative diastereomer. To improve the relative diastereoselection, other Lewis bases were surveyed. Among them, the use of dimeric phosphoramide **2** only slightly increased the relative diastereoselectivity (Table 1, entry 3). This result was surprising since the dimeric phosphoramides significantly improved the selectivity in the aldol additions of aldehyde enolates and related allylation reactions.[4d,13] Fortunately, the use of TIPS-protected (*Z*)-**6** showed significantly higher syn relative diastereoselectivities, although the rate of the reaction was slower (Table 1, entries 7−9).

Table 1. Chiral Phosphoramide Catalyzed Aldol Additions of **5** and **6** to Benzaldehyde



entry	enolate	*Z*/*E*	catalyst	yield (%)[d]	relative dr (syn/ anti)[e]	internal dr (syn/ anti)[f]
1	(*Z*)-**5**	50/1	(*R*,*R*)-**1a**	72	9/1	10/1
2	(*Z*)-**5**	50/1	(*S*,*S*)-**1a**	82	12/1	1/7
3	(*Z*)-**5**	40/1	(*R*,*R*)-**2**[c]	88	12/1	12/1
4	(*E*)-**5**	1/50	(*R*,*R*)-**1a**	72	1/4	6/1
5	(*E*)-**5**	1/50	(*S*,*S*)-**1a**	72	1/2	2/1
6	(*E*)-**5**	1/40	(*R*,*R*)-**2**[c]	80	1/2	9/1
7[a]	(*Z*)-**6**	50/1	(*R*,*R*)-**1a**	84	53/1	24/1
8[a]	(*Z*)-**6**	50/1	(*S*,*S*)-**1a**	82	32/1	1/8
9[b]	(*Z*)-**6**	50/1	**1b**	81	27/1	5/1

[a] Reaction time was 8 h. [b] Reaction time was 12 h. [c] 5 mol % of catalyst was used. [d] Yield of chromatographically homogeneous material. [e] Determined by ^{1}H NMR. [f] Determined by CSP-SFC.

To evaluate the intrinsic selectivity provided by the existing stereocenter, the achiral catalyst **1b** was used (Table 1, entry 9). With this catalyst, a slight selectivity toward the syn internal diastereomer was observed.[14] We were delighted to see the reversal in the internal diastereoselectivities depending on the catalyst configuration of **1a**. Using catalyst (*R*,*R*)-**1a** yielded the syn internal diastereomer with high selectivity, while the anti internal diastereomer was produced using (*S*,*S*)-**1a**, albeit with an attenuated selectivity (Table 1, entries 7 and 8).

On the other hand, the addition of *E*-enolate was not selective in both a relative and an internal sense. Despite the high *E*/*Z* ratio of (*E*)-**5**, the relative configuration was only slightly anti selective (Table 1, entries 4−6). Also, the internal selectivities were poor, and the switch in internal diastereoselection was not observed in these cases. The use of dimeric catalyst **2** did not improve the relative diastereoselectivity. The lack of relative diastereoselection may be due to the competitive chair and boat transition structures for the addition of (*E*)-**5**.

Since the selectivities observed for the addition of (*Z*)-**6** to benzaldehyde were sufficiently high, this enolate was chosen to examine the additions to other aromatic and olefinic aldehydes (Table 2). Surprisingly, the additions to these aldehydes under the previously established conditions were too slow to achieve significant conversion in a suitable time period. From previous studies, it was found that an addition of various ammonium salts can accelerate the aldol addition of trichlorosilyl enolates, presumably by increasing the ionic strength of the reaction medium.[3] Therefore, 20 mol % of tetrabutylammonium iodide (TBAI) was added to the reaction mixture, and the yields of the aldol products were improved without diminishing the diastereoselectivities.

The additions of (*Z*)-**6** to various aldehydes are summarized in Table 2. The relative syn selectivities were maintained in all cases. The degree of relative diastereoselection varied depending on aldehyde structure. By comparing **a** and **b**, as well as **d** and **e**, the bulk around the aldehyde carbonyl group seems to have detrimental effect in the relative diastereoselection (Table 2, entries 1−4 and 7−10). This phenomenon is contrary to the beneficial effect of α-substituents in the addition of methyl ketone enolates.[7] A switch in the internal diastereoselection was also observed in all cases, with (*R*,*R*)-**1a** giving the higher internal diastereomeric ratio. The internal diastereoselectivities were found to be significantly higher for aromatic aldehydes as compared to olefinic aldehydes (Table 2, entries 1 and 3). The olefinic aldehydes showed similar internal diastereoselectivities ranging from 13/1 to 15/1 for the matched cases (Table 2, entries 5, 7, and 9). The additions to aliphatic aldehydes, such as cyclohexanecarboxaldehyde and pivaldehyde, were attempted; however, only trace amounts of aldol products were formed under these conditions. It was found that these aliphatic aldehydes form chlorohydrin

(11) Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **2000**, *41*, 2515.
(12) Similar results were obtained for other acyclic ethyl ketone TMS enol ethers in the metal-catalyzed transsilylation process. Denmark, S. E.; Pham, S. M. Unpublished results.
(13) (a) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001**, *123*, 9488. (b) Denmark, S. E.; Wynn, T. *J. Am. Chem. Soc.* **2001**, *123*, 6199.

(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.

species in the reaction conditions, and these chlorohydrins are unreactive toward aldol reactions with trichlorosilyl enolates.[15]

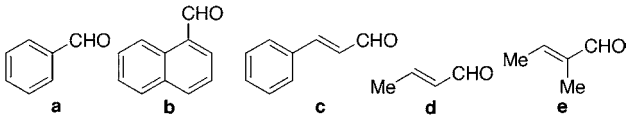
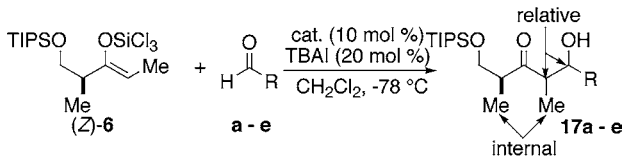


Table 2. Survey of Various Aldehydes in the Aldol Additions of (*Z*)-**6** Using **1a** as Catalyst



entry[a]	RCHO	catalyst	time (h)	yield (%)[c]	relative dr (syn/anti)[d]	internal dr (syn/anti)[e]
1[b]	a	(*R*,*R*)-**1a**	8	84	53/1	24/1
2[b]	a	(*S*,*S*)-**1a**	8	82	32/1	1/8
3	b	(*R*,*R*)-**1a**	8	71	14/1	89/1
4	b	(*S*,*S*)-**1a**	8	79	14/1	1/17
5	c	(*R*,*R*)-**1a**	10	88	9/1	14/1
6	c	(*S*,*S*)-**1a**	10	75	15/1	1/6
7	d	(*R*,*R*)-**1a**	6	90	>50/1	15/1
8	d	(*S*,*S*)-**1a**	6	85	>50/1	1/5
9	e	(*R*,*R*)-**1a**	7	85	13/1	13/1
10	e	(*S*,*S*)-**1a**	7	80	19/1	1/5

[a] (*Z*)-**6** contained 10% of the bisenoxysilane, and the *Z*/*E* ratio was higher than 43/1 by ^{1}H NMR analysis. [b] No TBAI was added. [c] Yield of analytically pure material. [d] Determined by ^{1}H NMR analysis. [e] Determined by CSP-SFC.

The absolute configuration of the aldol adduct **17c** was confirmed by comparing the physical data to the reported synthetic intermediate in the literature.[7c] The configurations of other aldol products were assigned by analogy with the relative elution orders of diastereomers, using the chiral supercritical fluid chromatography.

To rationalize the observed stereochemical outcome, we propose the following transition state models (Figure 1). In the addition of the *Z*-enolates, the rotamer **I** minimizes the steric interaction between the substituents on the spectator side of the enolate and the bulky ligands on the hypervalent silicon. This transition state model leads to the observed (syn,syn)-**17a**.

The poor selectivities observed for the addition of (*E*)-**5** may be explained by the competitive transition state models chair-**II** and boat-**II**. In chair-**II**, the $A_{1,3}$ strain is minimized;[16] however, disposition of the α-methyl group and CH_2OTIPS toward the bulky silicon center may cause a severe steric congestion. This interaction can be significant enough to make the boat-**II** transition model operative. The boat-**II** can be easily achieved by simply placing the silicon to the least crowded quadrant. The anti coordination of silicon to the aldehyde places the phenyl group of benzaldehyde in the pseudoaxial position, leading to the syn relative diastereomer.

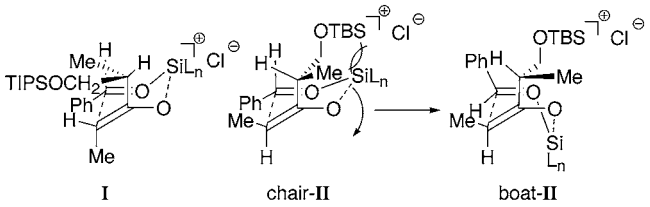


Figure 1. Proposed transition structures for the addition of (*Z*)-**6** and (*E*)-**5** to benzaldehyde.

In summary, we have described the *catalytic* diastereoselective aldol additions of chiral enolates **5** and **6**. The addition of *Z*-enolates produced predominantly the syn relative diastereomer, suggesting the involvement of chairlike closed transition structures. On the other hand, (*E*)-**5** was not selective, presumably as a result of the competitive boat transition structure. The intrinsic selectivity of (*Z*)-**6** was found to modestly favor the (syn,syn) diastereomer. In the matched cases, additions of (*Z*)-**6** to various aldehydes produced (syn,syn)-**17** with high selectivities using (*R*,*R*)-**1a** as catalyst. The aldol products from these reactions are important precursors for various polypropionate natural products.

Extension of these studies to enable addition to aliphatic aldehydes, as well as to obtain relative anti diastereomers selectively, are 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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(15) The chlorohydrin adduct of cyclohexanecarboxaldehyde was isolated under similar conditions and characterized by ^{1}H NMR. Denmark, S. E.; Ghosh, S. K.; Wynn, T. A. Unpublished results.

(16) A similar transition state analysis was proposed by Paterson for (*E*)-boron enolate which takes oxygen lone pair repulsions into account. See ref 1b.