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Tetrahedron 63 (2007) 8636–8644
Tetrahedron

Unexpected ambidoselectivity in crossed-aldol reactions of α-oxy aldehyde trichlorosilyl enolates

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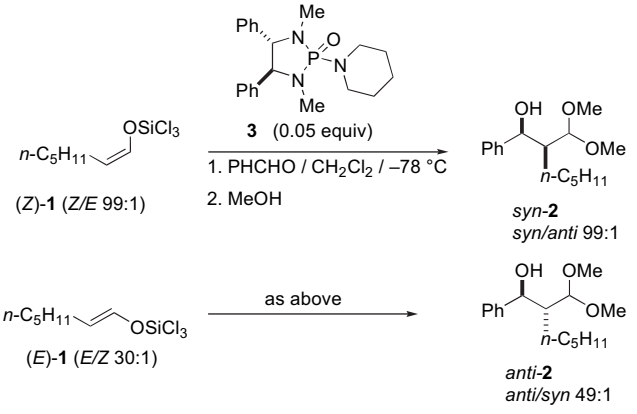
Received 31 January 2007; revised 3 April 2007; accepted 4 April 2007
Available online 12 April 2007

Abstract—The ambido-, stereo- and enantioselectivity of the phosphoramide-promoted aldol reactions of α-oxy aldehyde trichlorosilyl enolates with benzaldehyde has been investigated. Analysis of the products from α-*tert*-butyldimethylsilyloxy α-deuterioacetaldehyde trichlorosilyl enolate confirmed that this 1,2-bis-silyloxyethene derivative reacted as a *tert*-butyldimethylsilyl enolate rather than trichlorosilyl enolate in the aldol reaction with very high ambidoselectivity. The phosphoramide-coordinated trichlorosilyl group acted as an organizing center for the aldol reaction. From the aldol process, excellent *anti*-diastereoselectivity could be achieved. The enantioselectivity remained moderate to low for both *anti*- and *syn*-diastereomer with a wide range of phosphoramide catalysts. α-Triisopropylsilyloxy, phenoxy and benzyloxy acetaldehyde trichlorosilyl enolates also reacted in a similar fashion with benzaldehyde to give aldol products with varying degrees of selectivities.

1. Introduction

Lewis-base-catalyzed, enantioselective, aldol reactions are now well-established as viable methods for the stereocontrolled construction of carbon–carbon bonds from a variety of carbonyl compounds and enolate derivatives.[1] Trichlorosilyl (TCS) enolates derived from both ketones[2] and esters[3] react smoothly with aldehydes to provide aldol products in high yield with good to excellent diastereo- and enantioselectivity. The diastereoselectivity of all these aldolization processes is a near perfect reflection of the geometrical composition of the TCS enolates.[4] Thus both the *syn*- and *anti*-aldol products can be accessed by the use of *Z*- and *E*-TCS enolates, respectively.[5]

Although the crossed-aldol reactions between aldehydes are known for their inherent problems of polycondensation and other side reactions,[6] we have recently reported the Lewis-base-catalyzed aldol reaction of aldehyde TCS enolates with aldehydes.[7] Despite the relatively small size of the aldehyde TCS enolate, this directed, crossed-aldol reaction also affords products in excellent yields and diastereoselectivity albeit with variable enantioselectivity. As is the case with ketone TCS enolates, the diastereoselectivity in the crossed-aldol reaction of aldehyde TCS enolates is also dependent on the enolate geometry. Thus the *Z*-enolate (*Z*)-**1** affords aldol product *syn*-**2**, whereas *E*-enolate (*E*)-**1** affords predominantly *anti*-**2** (Scheme 1). Because of the instability of the crossed aldehyde aldol products (3-hydroxy aldehydes) toward dehydration and oligomer formation, the products are isolated as dimethyl acetals.



Scheme 1. Diastereoselective cross-aldol reaction of enoxytrichlorosilanes.

Application of the aldol reaction to the synthesis of carbohydrates and polyhydroxylated carbon frameworks is well-documented but requires the help of protecting group manipulations and oxidation-state adjustments.[8] A more direct polyhydroxyl carbon skeleton synthesis can be envisioned with the use of an iterative aldol sequence using

Keywords: Aldol; Enolate; Deuterium labeling; Enantioselective; Diastereoselective.
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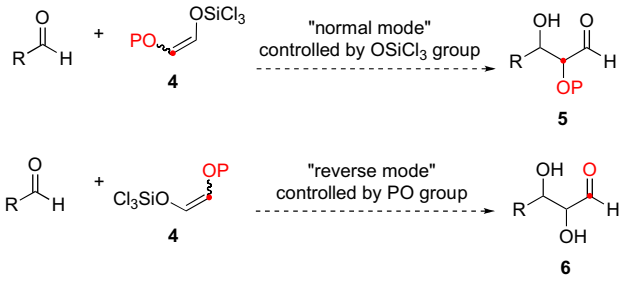
doi:10.1016/j.tet.2007.04.009

simple α-oxy aldehydes. Enolates of α-alkoxy ketones or enol ethers/esters have been used in aldol reactions for the synthesis of polyhydroxylated carbonyl compounds with varying levels of stereocontrol.[9] A few reports are also available for the crossed-aldol reaction of α-oxy aldehyde with impressive success although the inherent problem of self-aldolization remains and diastereoselectivity cannot be controlled by substrate structure.[10] The practical execution of this strategy would require the implementation of a new crossed-aldol technology: a selective aldol reaction of α-oxy aldehyde substrate with another aldehyde with no self-aldolization or polycondensation. On the basis of our previous studies on crossed-aldol reaction of simple aldehyde trichlorosilyl enolates, we envisaged that a crossed aldehyde aldol reaction of TCS enolates derived from α-oxy aldehydes might offer a solution to this problem. Unlike simple aldehydes, α-oxy aldehyde TCS enolate **4** has two chemically reactive centers and can thus react via two distinct pathways as shown in Scheme 2. If the trichlorosilyloxy group controls the aldol addition (normal mode), product **5** is expected to form, whereas oxy-group-controlled aldol reaction (reverse mode) would produce product **6**. A previous study from these laboratories showed that trialkylsilyl enol ethers of acetaldehyde could engage in aldol additions to aromatic aldehydes under the catalytic action of silicon tetrachloride and a chiral bisphosphoramide.[11] Thus, it was uncertain if the activated trichlorosilyloxy group would dominate over the (silyl)oxy group in controlling the course of the aldol addition. We describe herein the synthesis and the ambidoselective[12] crossed-aldol reactions of α-oxy acetaldehyde TCS enolates.



Scheme 2. Ambidoselectivity modes for aldolization of α-oxy trichlorosilyl enolates.

2. Results

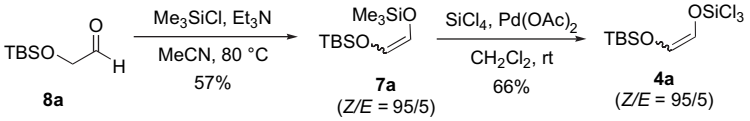
2.1. Synthesis of α-oxy acetaldehyde TCS enolates

To test the feasibility of this concept, the generation of stereodefined TCS enolates of α-oxy acetaldehyde was required. Over the past decade, a number of synthetic methods have been developed in these laboratories for the generation of TCS enolates of ketones, esters and aldehydes. Amongst them, the metal-catalyzed metathesis of a trialkylsilyl enol ether with silicon tetrachloride has been described in detail.[2c,5,7c] In these studies, the geometry of the resultant TCS enolate could be controlled by appropriate selection of the silylation method, but was largely dependent on the structure of the starting ketone. Gratifyingly, the palladium acetate catalyzed trans-silylation of either (*E*)- or (*Z*)-trimethylsilyl enol ethers of heptaldehyde with silicon tetrachloride afforded an 85/15 *E*/*Z* mixture of geometrical isomers, the resulting TCS enolate. This outcome was deemed sufficient to explore the aldol addition chemistry of these species.

The *tert*-butyldimethylsilyl (TBS) group was initially selected as the oxygen substituent because previous studies[2] have shown the compatibility of the TBSO group with TCS enolates and other trichlorosiliconium species.[13] The enol trimethylsilyl ether **7a** of α-*tert*-butyldimethylsilyloxyacetaldehyde **8a** was prepared using trimethylsilyl chloride and triethylamine in hot acetonitrile (Scheme 3).[14] The 1,2-disilyloxyethene **7a** was isolated in 57% yield and with a high geometrical purity (*Z*/*E*=95/5). For the preparation of the TCS enolate **4a**, the metathesis of enol trimethylsilyl ether **7a** with silicon tetrachloride in the presence of many metal salts under various reaction conditions was examined. A few representative examples are shown in Table 1. The exchange reaction was extremely slow with $Hg(OAc)_2$ and no reaction took place with $Tl(OAc)_3$, but both $Pd(OAc)_2$ and $Pd(TFA)_2$ were effective catalysts (entries 3–7). Interestingly, lowering the catalyst loading led to faster reactions and also improved the yield of the distilled product. It was found that if the palladium loading is too high, the TCS enolate decomposes during distillation, producing a significant amount of TBSCl as a by-product. Keeping the reaction concentration low was also crucial to obtain a good yield. The optimal conditions employed 2.0 equiv of silicon tetrachloride and 0.034 equiv of $Pd(OAc)_2$ at 0.5 M concentration in dichloromethane at room temperature (entry 6), which provided the TCS enolate **4a** in 66% yield. The geometrical purity of the enolate **4a** was determined by the integration of the distinguishable peaks for the olefinic protons and was found to be very high (*Z*/*E*=95/5). The diagnostic ^{13}C NMR signals for the *Z*- and *E*-enolate were also discernable. It is also worth mentioning that the geometrical composition of the TCS enolate was independent of the geometrical composition of the starting enol trimethylsilyl ether used. This observation obviously restricts this method to the production of *E*-TCS enolates.

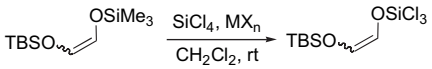
2.2. Crossed-aldol reaction of α-*tert*-butyldimethylsilyloxyacetaldehyde TCS enolate 4a

2.2.1. Background reaction at −65 °C. To assess the efficiency of Lewis bases in promoting the aldol reactions, it was necessary to perform a control reaction without promoters. Thus, TCS enolate **4a** and benzaldehyde were combined in equimolar proportions at −65 °C in chloroform.



Scheme 3. Preparation of α-oxy trichlorosilyl enolates.

Table 1. Survey of catalysts, loadings and reaction concentration for the *trans*-silylation of **7a** to **4a**

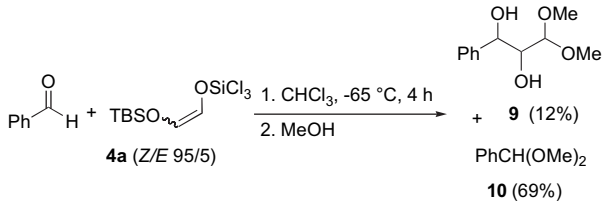


7a (*Z*/*E* 95/5) **4a**

Entry	MX_n (equiv)	Time (h)	Concentration[a] (M)	Conversion[b] (%)	Yield[c] (%)
1	$Hg(OAc)_2$ (0.02)	72	1	5	ND[d]
2	$Tl(OAc)_3$ (0.05)	48	1	No reaction	ND
3	$Pd(OAc)_2$ (0.2)	3	1	>95	16
4	$Pd(OAc)_2$ (0.15)	16	1	>95	24
5	$Pd(OAc)_2$ (0.05)	12	0.3	>95	19
6	$Pd(OAc)_2$ (0.034)	12	0.5	100	66
7	$Pd(OAc)_2$ (0.002)	38	1	>95	38

[a] Refers to concentration with respect to **7a**.
[b] Monitored by ^{1}H NMR.
[c] Refers to isolated yield of distilled product.
[d] ND=not determined.

Quenching the reaction with methanol after 4 h afforded the aldol products in 12% yield along with 69% of benzaldehyde dimethyl acetal **10** (Scheme 4). Thus, the uncatalyzed aldol addition is a very slow process and it was appropriate to evaluate the ability of chiral Lewis bases to catalyze the addition.



4a (*Z*/*E* 95/5)

Scheme 4. Uncatalyzed, background aldol reaction of enolate **4a**.

2.2.2. Crossed-aldol reaction of 4a in the presence of phosphoramide promoters. As is the case with nearly all other enoxytrichlorosilanes, the Lewis-base-promoted aldol addition of enolate **4a** was very fast. Using 20 mol % of chiral phosphoramide **3** (Chart 1), the reaction between **4a** and benzaldehyde in $CDCl_3$ was complete in less than an hour at −70 °C as judged by the disappearance of the enolate by NMR analysis. For preparative purpose, the reaction between **4a** and benzaldehyde was carried out using 20 mol % of chiral phosphoramide **3** in dichloromethane at dry ice/acetone temperature. The reaction was quenched with methanol at low temperature, allowing the mixture to come to room temperature and then pouring mixture into cold saturated, aqueous sodium bicarbonate solution. The dihydroxy dimethyl acetal products *anti*-**9** and *syn*-**9** (*anti*/*syn*=3/1) were isolated as an inseparable mixture in good yield (Scheme 5). The relative configuration of the hydroxyl-bearing centers as well as the absolute configuration of *anti*-**9** and *syn*-**9** diastereomers was unambiguously established by converting the acetals to known di-4-tolylthioacetals.[15] To accomplish this, the mixture of dimethyl acetals **9** was treated with *p*-thiocresol in the presence of $BF_3\cdot OEt_2$, which provided an easily separable mixture of dithioacetals *anti*-**17** (∼60/40 er) and *syn*-**17** (∼55/45 er). The absolute configuration of the major enantiomer *anti*-**17** was found to be (2*S*,3*S*) while that for *syn*-**17** was (2*S*,3*R*).[15]

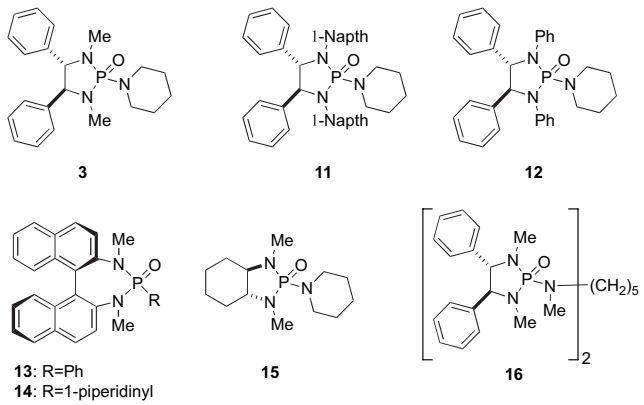
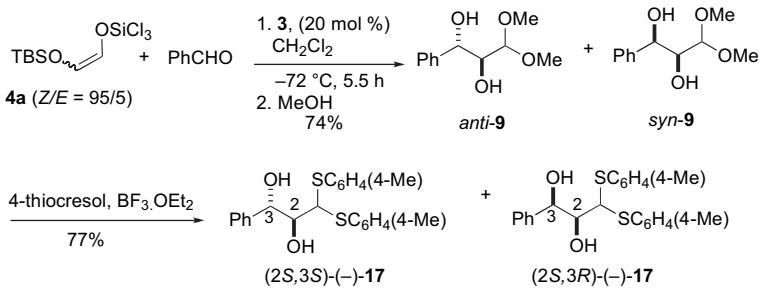


Chart 1. Chiral phosphoramide promoters used for asymmetric aldol reactions.

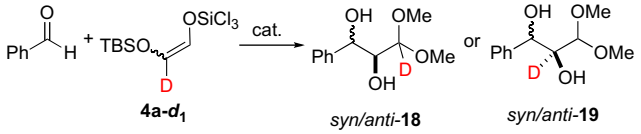
2.2.3. Ambidoselectivity of the aldol addition of 4a. The formation of aldol products *anti*-**9** and *syn*-**9** (from quenching with methanol) obfuscates the pathway by which **4a** reacted, i.e., as a TBS enol ether or as a trichlorosilyl enolate. To resolve this selectivity issue, the deuterium labeled enolate **4a**-d_1 was prepared. If **4a**-d_1 reacts as TBS enol ether in the aldolization with benzaldehyde, then the deuterium will reside at the acetal carbon of the dihydroxy dimethyl acetal **18**. On the other hand, if **4a**-d_1 reacts as the trichlorosilyl enolate, then the deuterium will be positioned at the hydroxyl bearing carbon α-to dimethyl acetal group in **19** (Scheme 6).

Labeled TCS enolate **4a**-d_1 was prepared as shown in Scheme 7. Dimethyl L-tartrate was converted to acetonide **20**[16] that was reduced with lithium aluminum tetradeuteride (isotopic content >99%-*d*) to give the tetradeuterated diol **21**. The acetonide group was removed and the primary hydroxyl groups of the resulting tetrol **22** were selectively protected as the TBS ethers to give **23**. Sodium periodate cleavage gave the α,α-dideuterated α-*tert*-butyldimethylsilyloxyacetaldehyde **8a**-d_2 in very good overall yield. The enol trimethylsilyl ether **7a**-d_1 was prepared as before using trimethylsilyl chloride and triethylamine in hot acetonitrile. The 1,2-disilyloxyethane **7a**-d_1 was isolated in 64% yield with a high geometrical purity (*Z*/*E*=94/6). At this stage, the isotopic composition of the enol TMS ether **7a**-d_1 was found to be 99.2% enriched by mass spectrometric analysis. Metathesis of enol TMS ether **7a**-d_1 with 2.0 equiv of silicon tetrachloride and 0.007 equiv of $Pd(OAc)_2$ at 0.5 M in dichloromethane at room temperature provided enolate **4a**-d_1 in 73% yield. As expected, enolate **4a**-d_1 was highly enriched in the *Z* isomer (*Z*/*E*=92/8) as judged ^{1}H NMR analysis.

Crossed-aldol addition of enolate **4a**-d_1 with benzaldehyde in the presence of phosphoramide **3** took place smoothly and a methanolic work-up provided a mixture of a pair of *anti*- and a pair of *syn*-aldol products (*anti*/*syn*=13/1, Scheme 8). In both the *anti*- and the *syn*-manifold, the ratio of **18**/**19** was found to be 94/6. Therefore, enolate **4a** reacted predominantly as a nucleophilic silyl enol ether rather than as a trichlorosilyl enolate. This outcome was rather unexpected in light of the powerful catalytic effect of the phosphoramide. Clearly, the trichlorosilyl unit is playing an important role to activate the addition, however, unlike the



Scheme 5. Aldolization of TCS enolate **4a** under catalysis with **3**.

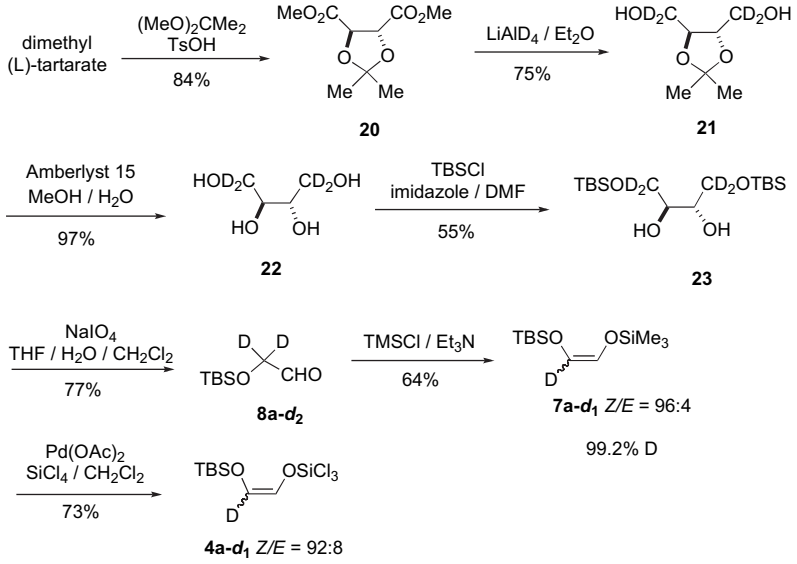


Scheme 6. Aldolization of deuterium labeled TCS enolate **4a**-d_1.

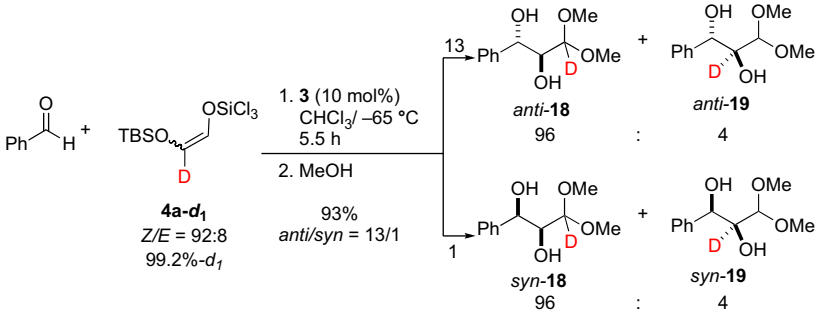
reactions of simple aldehyde, ketone and ester TCS enolates, in this case, it is the carbon bearing the trichlorosilyloxy group that serves as the nucleophile. Thus, this transformation represents an unprecedented pathway for bond construction with TCS enolates and therefore presents new opportunities to probe the experimental and structural factors that control the diastereo- and enantioselectivity.

2.3. Optimization of the crossed-aldol addition of 4a

2.3.1. Influence of reaction conditions. The results of the deuterium-labeling study clearly established that: (1) the aldol addition of **4a** is governed by the nucleophilicity of the TBS enol ether and (2) the trichlorosilyloxy group plays a major role in activating the aldehyde toward addition. However, it was unclear if the TCS group was serving as an organizational center as has been established in all of the previous examples of these additions through the



Scheme 7. Synthesis of D-labeled TCS enolate **4a**-d_1.



Scheme 8. Crossed-aldol reaction of **4a**-d_1 with benzaldehyde.

correlation of enolate geometry with product diastereoselectivity. Obviously, the phosphoramide also plays a vital role because the control reactions are extremely slow. Unfortunately, the enantioselectivity in either the *syn*- or *anti*-pathway is poor (Scheme 5). However, a large number of different phosphoramides have been developed in these laboratories for aldol reactions of TCS enolates of aldehyde, ketone as well as esters with very high diastereo- and enantioselectivity.[1] It should also not be lost upon the reader, that even if these are not TCS-organized transition structures, but rather involve chiral siliconium ion activation of the aldehydes, excellent selectivities have been observed for addition of enoxysilane nucleophiles to aldehydes (with silicon tetrachloride).[13,17] Chart 1 contains various phosphoramides employed in the present study for aldol reaction of enolate **4a** and benzaldehyde. Optimization of the aldol addition of **4a** with benzaldehyde also involved a survey of the reaction solvent and catalyst loading. For an appreciable reaction rate, the reaction concentrations for all the studies were maintained at 0.25 M.

To investigate solvent and catalyst loading, chiral phosphoramide **3** was chosen for study. It has already been shown that **3** was an effective catalyst for the aldol reaction and produced *anti*-**9** as the major diastereomer. A number of solvents were surveyed for the aldol reaction and chloroform was found to be superior for this purpose in terms of rate and yield (entries 1–3 and 7, Table 2). Interestingly, the diastereoselectivity of the aldol addition is highly dependent on the catalyst loading in chloroform. The *anti*-selectivity increased dramatically by reducing catalyst loading from 100 to 5 mol % without effecting the yield, whereas the enantioselectivity in either manifolds was unchanged. Accordingly, the next objective was to survey phosphoramide structures.

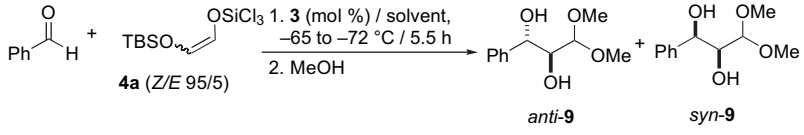
2.3.2. Influence of catalyst structure. To optimize enantioselectivity, a series of monophosphoramides and one bisphosphoramide **16** (Chart 1) were examined at 10–20 mol % loading and 0.25 M in chloroform at −65 °C. Although excellent yields and high *anti*-diastereoselectivities were observed with many different catalyst structures, the enantioselectivities did not improve (Table 3). Interestingly, the bisphosphoramide **16** showed some bias for the *syn*-aldol process although the major product was still *anti*-**9**. With this phosphoramide, the enantioselectivity for the *syn*-aldol product is also better than the monophosphoramides studied so far.

2.4. Effect of substituent at the oxy group on the selectivity of aldol reaction of α-oxy acetaldehyde TCS enolates

Although the rate and diastereoselectivity of the aldol addition of **4a** could be improved by modification of the catalyst and reaction conditions, the enantioselectivity remained unacceptably low. Enantiomeric purity of the products could not be improved and remained low to moderate with a large number of catalysts surveyed. It would be interesting to know the effect of the substituent at the oxy groups of α-oxy aldehyde. Therefore, three substituents, triisopropylsilyl (TIPS), phenyl (Ph) and benzyl (Bn), at the oxy group were chosen. These groups have different steric or electronic properties compared to the TBS group in **8a**. The TCS enolates **4b**–**4d** of these α-oxy acetaldehydes **8b**–**8d** were prepared via their enol trimethylsilyl ethers **7b**–**7d** as shown in Scheme 9. The metathetical exchange of silicon group of these enol ethers with silicon tetrachloride in the presence of palladium catalyst provided the TCS enolates that were not isolated but instead used in situ for aldol reaction. We were gratified that all the TCS enolates reacted with benzaldehyde in the presence of phosphoramide catalysts to give aldol products with good to excellent yields and varying degree of diastereo- and enantioselectivity. The results of aldol reaction of these enolates with benzaldehyde in the presence of phosphoramide catalysts are compiled in Table 4.

The results in Table 4 show that TIPS protection behaved more or less in the same way as TBS group. The phenoxy group also behaved in the same way but the reactivity of this enolate was much lower and the aldol reaction did not proceed to completion under the standard conditions. The benzyloxy group behaved in a different, but less satisfactory way; the diastereo- and enantioselectivity is quite low for this group.

Table 2. Effect of solvent and catalyst loading on aldol reaction between **4a** and benzaldehyde



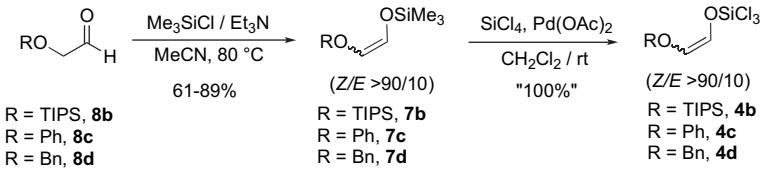
Entry	Solvent	mol % of **3**	Yield[a] (%)	*anti*/*syn*[b]	*anti* er[b] (2*S*,3*S*)/(2*R*,3*R*)	*syn* er[b] (2*S*,3*R*)/(2*R*,3*S*)
1	CH_2Cl_2	20	74	3/1	60/40	57/43
2	Et_2O	20	32[c]	1.2/1	60/40	56/44
3	Toluene	20	43[c]	2.3/1	53/47	61/39
4	$CHCl_3$	100	96	2.3/1	55/45	67/33
5	$CHCl_3$	60	92	4/1	50/50	67/33
6	$CHCl_3$	40	92	5/1	49/51	66/34
7	$CHCl_3$	20	93	9/1	48/52	65/35
8	$CHCl_3$	10	94	10/1	48/52	64/36
9	$CHCl_3$	5	82	14/1	47/53	60/40
10	$CHCl_3$	2.5	64[c]	15/1	49/51	58/42

[a] Yields of chromatographically homogeneous material.
[b] Determined by CSP-SFC(AS; 150 bar, 3 mL/min, 2.5% MeOH).
[c] Incomplete reaction.

Table 3. Effect of catalyst structure on aldol reaction between **4a** and benzaldehyde

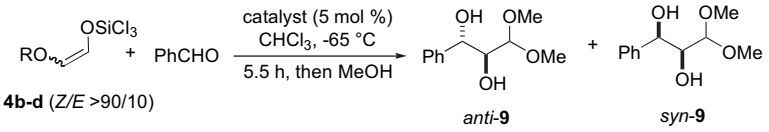
Entry	Catalyst (mol %)	Yield[a] (%)	*anti*/*syn*[b]	*anti* er[b] (2*S*,3*S*)/(2*R*,3*R*)	*syn* er[b] (2*S*,3*R*)/(2*R*,3*S*)
1	**3** (20)	93	9/1	48/52	65/35
2	**11** (10)	82[c]	13/1	47/53	60/40
3	**12** (20)	74[c]	16/1	60/40	51/49
4	**13** (10)	89	22/1	48/52	65/35
5	**14** (20)	90	24/1	47/53	54/46
6	**15** (20)	93	23/1	59/41	31/69
7	**16** (10)	83	5/1	48/52	78/22

[a] Yields of chromatographically homogeneous material.
[b] Determined by CSP-SFC(AS; 150 bar, 3 mL/min, 2.5% MeOH).
[c] Incomplete reaction.



Scheme 9. Preparation of α-oxy TCS enolates with various protecting groups.

Table 4. Crossed-aldol reaction of TCS enolates **4b**–**4d** with benzaldehyde



Entry	TCS enolate	Catalyst	Yield[a] (%)	*anti*/*syn*[b]	*anti* er[b] (2*S*,3*S*)/(2*R*,3*R*)	*syn* er[b,10] (2*S*,3*R*)/(2*R*,3*S*)
1	**4b**	**3**	66	6.1/1	47/53	45/55
2	**4b**	**14**	62	15/1	43/57	38/62
3	**4c**	**3**	30	21/1	48/52	42/58
4	**4c**	**14**	38	20/1	46/54	54/46
5	**4d**	**3**	83	1/1.4	57/43	35/65
6	**4d**	**12**	83	2/1	61/39	60/40
7	**4d**	**13**	83	3/1	30/70	51/49
8	**4d**	**14**	83	1.9/1	31/69	50/50
9	**4d**	**15**	74	1/1.1	46/54	52/48

[a] Yields of chromatographically homogeneous material.
[b] Determined by CSP-SFC (Chiralcel AS; 150 bar, 3 mL/min, 2.5% MeOH).

3. Discussion

The aldol addition of TCS enolate **4a** proceeded rather unexpectedly through a pathway in which the TBS enol ether moiety served as the nucleophilic component. The trichlorosilyl unit must still be playing an activating and perhaps organizational role, because the reaction rate is enhanced and the diastereoselectivity is strongly influenced by phosphoramides. Without the benefit of detailed kinetic studies with this nucleophile we cannot distinguish the two limiting mechanistic scenarios: (1) the aldolization proceeds via a closed transition structure consisting of one molecule each of aldehyde and TCS enolate as was established for all other TCS enolates,[4,7] or (2) the aldolization proceeds via an open transition structure involving two TCS enolates, one to activate the aldehyde and a second to serve a nucleophile as is seen in the $SiCl_4$·phosphoramide catalyst sytems.[13] Even if we assume that the reaction proceeds through a closed transition structure in which phosphoramides are present to activate the addition, it is still very difficult to predict the stereochemical outcome because the bond forming process involves a five-membered, not the usual six-membered chair-like transition structure.[4,7] This disparity is clearly illustrated in the divergent behavior between **4** and **1**. In aldolizations of the latter TCS enolate, the *normal* correlation of enolate geometry with product configuration obtains ((*Z*)-**1**→*syn*-**2** and (*E*)-**1**→*anti*-**2**). However, in the present study, **4** of predominantly *Z*-geometry gave the *anti*-diastereomer as the major product with all catalysts. Moreover, the *anti*-selectivity increased with decreasing catalyst loading. Unfortunately, the enantioselectivities are low and variable for all cases. This outcome suggests that there are competitive pathways operating to give *syn*- and *anti*-aldol products.[18]

The increase in *anti*-diastereoselectivity with decreasing catalyst loading suggests that the *anti*-product is generated from a one-phosphoramide, cationic trigonal bipyramidal transition structure (**A**, Fig. 1) and the *syn*-product is from a two-phosphoramide octahedral, cationic transition structure (**B**, Fig. 1).[1b,4] The benzyloxy-substituted TCS enolate behaved differently and might be enabling another type of

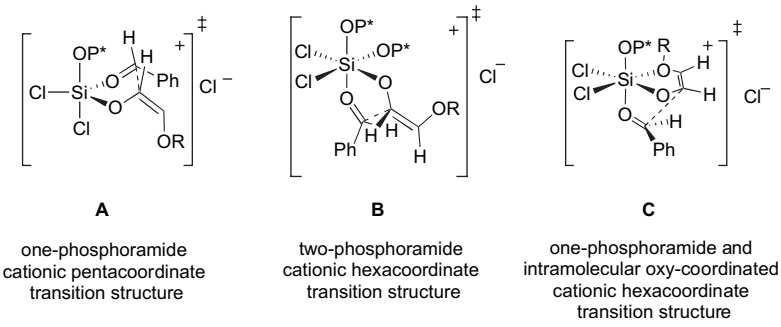


Figure 1. Hypothetically closed transition structures for the crossed aldolization of **4**.

closed transition state structure involving coordination of the alkoxy oxygen to the TCS group in a one-phosphoramide octahedral, transition state structure (**C**, Fig. 1). This transition state can lead to either the *anti*- or the *syn*-product, thus making the situation more complex. Open transition structures are still more difficult to analyze because it is not known where or how many catalyst molecules are bound. Unfortunately, the low er for all catalysts does not permit additional insights.

4. Conclusion

The (*Z*)-TCS enolate of α-*tert*-butyldimethylsilyloxyacetaldehyde ((*Z*)-**4a**) can be prepared from the corresponding trimethylsilyl enol ether by palladium-catalyzed metathesis with silicon tetrachloride. The addition of (*Z*)-**4a** to benzaldehyde is susceptible to catalysis by phosphoramides and the diastereoselectivity of the addition is dependent on the catalyst loading. The ambidoselectivity of the aldol addition was elucidated by deuterium-labeling experiments that confirmed that (*Z*)-**4a** reacted as a TBS enol ether in the aldol process, and that the trichlorosilyl group acted as an organizing center for the reaction. From the aldol addition, excellent *anti*-diastereoselectivity could be achieved. Unfortunately, the enantioselectivity remained moderate to low for both the diastereomers with a wide range of phosphoramide catalysts.

5. Experimental section

5.1. General experimental procedures

See Supplementary data.

5.2. Experimental procedures

5.2.1. General procedure I. Preparation of enol trimethylsilyl ethers of α-*tert*-butyldimethylsilyloxy acetaldehyde: (1*Z*)-1-*tert*-butyldimethylsilyloxy-2-trimethylsilyloxyethene ((*Z*)-7a). A solution of the aldehyde **8a**[19] (4.6 g, 26.4 mmol) in acetonitrile (20 mL) was added to a stirred solution of TMSCl (6.7 mL, 52.8 mmol, 2.0 equiv) in MeCN (30 mL). Triethylamine (14.8 mL, 105.6 mmol, 4.0 equiv) was then added and the reaction mixture was warmed to 80 °C (bath). After 2 h, the reaction mixture was brought to room temperature. Excess TMSCl and volatile components were removed under vacuum. The residual mass was poured into saturated $NaHCO_3$ solution and extracted with pentane. The pentane extract was dried over $MgSO_4$, then filtered and evaporated. The residual oil was purified by chromatography (SiO_2, pentane/ether, 95/5) followed by distillation gave 3.7 g (57%) of the enol ether (*Z*)-**7a** as a clear colorless liquid. The *Z*/*E* ratio was found to be 95/5. Bp: 50 °C (0.2 mmHg); ^{1}H NMR (500 MHz, $CDCl_3$): 6.41 (d, *J*=10, 1H, (*E*)-**7a**), 6.35 (d, *J*=10, 1H, (*E*)-**7a**), 5.55 (d, *J*=3.2, 1H, (*Z*)-**7a**), 5.49 (d, *J*=3.2, (*Z*)-**7a**), 0.93 (s, 9H), 0.18 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): 125.71, 124.45, 25.72, 18.49, −0.37, −5.21; IR (neat): 3042 (w), 2958 (s), 2931 (m), 2897 (w), 2888 (w), 2859 (m), 1663 (m), 1472 (w), 1464 (w), 1389 (m), 1292 (w), 1253 (s), 1147 (s), 1077 (s), 899 (s), 843 (s), 808 (m), 782 (m), 752 (w), 676 (w); MS (EI, 70 eV): 246 (M^+, 3), 189 (M−*t*-Bu$^+$, 31), 147 (20), 73 (Me_3Si, 100). Analysis, $C_{11}H_{26}O_2Si_2$ (246.50) Calculated: C, 53.60; H, 10.63; Si, 22.79%. Found: C, 53.62; H, 10.54; Si, 22.41%.

5.2.2. General procedure II. $Pd(OAc)_2$-mediated *trans*-silylation of 7a: (1*Z*)-2-*tert*-butyldimethylsilyloxy-1-trichlorosilyloxyethene (4a). A solution of the TMS-enolate **7a** (*Z*/*E*=95/5) (6.1 g, 24.8 mmol) in CH_2Cl_2 (25 mL) was drop wise added to a solution of $SiCl_4$ (5.6 mL, 48.3 mmol, 2.0 equiv) and $Pd(OAc)_2$ (118 mg, 0.52 mmol, 0.034 equiv) in CH_2Cl_2 (20 mL) at room temperature. After 12 h, solvent and volatiles were removed under vacuum (up to 10 mmHg). The residual oil was distilled to afford 5.0 g (66%) of the enolate **4a** as a mixture of isomers (*Z*/*E*=95/5). Bp: 50–55 °C (0.1 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$): 6.67 (d, *J*=10, 1H, (*E*)-**4a**), 6.45 (d, *J*=10, 1H, (*E*)-**4a**), 5.85 (d, *J*=3.1, 1H, (*Z*)-**4a**), 5.67 (d, *J*=3.1, (*Z*)-**4a**), 0.94 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): 136.08 ((*E*)-**4a**), 129.30 ((*Z*)-**4a**), 127.57 ((*E*)-**4a**), 121.20 ((*Z*)-**4a**), 25.70 ((*E*)-**4a**), 25.59 ((*Z*)-**4a**), 18.39, −2.95 ((*E*)-**4a**), −5.32 ((*Z*)-**4a**).

5.2.3. General procedure III. Aldol reaction of isolated trichlorosilyl enolate: (2*S*,3*S*)-1,1-dimethoxy-3-phenylpropane-2,3-diol (*anti*-9) and (2*S*,3*R*)-1,1-dimethoxy-3-phenylpropane-2,3-diol (*syn*-9). Trichlorosilyl enolate (*Z*)-**4a** (615 mg, 2 mmol) was added to a cold (−67 °C) solution of the phosphoramide **3** (148 mg, 0.4 mmol, 0.2 equiv) in CH_2Cl_2 (7.5 mL) and the mixture was allowed to stir for 10 min. Freshly distilled benzaldehyde (0.204 mL, 2.0 mmol, 1.0 equiv) was then added. After 5.5 h, MeOH (7.5 mL) was added and the mixture was slowly allowed to attain room temperature. The reaction mixture was poured into cold $NaHCO_3$ solution and was stirred for 0.5 h. The reaction mixture was diluted with EtOAc, filtered through

Celite, and washed well with EtOAc. The organic layer was separated and the aqueous layer was once extracted with EtOAc. The combined extracts were dried over $MgSO_4$ and concentrated. Column chromatography (SiO_2, hexane/EtOAc, 40/60) of the residue afforded 313 mg (74%) of a mixture of aldol products *anti*-**9** and *syn*-**9** as a clear colorless thick liquid (*anti*/*syn*, 3/1). ^{1}H NMR (400 MHz, $CDCl_3$): 7.43–7.27 (m, 5H, H-Aryl), 4.91 (dd, J=2.9, 5.1, 1H, *syn*-**9**), 4.79 (dd, J=3.7, 6.1, 1H, *anti*-**9**), 4.36 (d, J=4.9, 1H, *syn*-**9**), 4.27 (d, J=5.4, 1H, *anti*-**9**), 3.85 (ddd, J=3.9, 5.6, 6.3, 1H, *anti*-**9**), 3.74 (dt, J=2.9, 5.1, 1H, *syn*-**9**), 3.49 (s, 3H, *syn*-**9**), 3.48 (s, 3H, *syn*-**9**), 3.46 (s, 3H, *anti*-**9**), 3.42 (s, 3H, *anti*-**9**), 3.24 (d, J=3.9, 1H, OH-*anti*-**9**), 3.03 (d, J=5.1, 1H, OH-*syn*-**9**), 2.51 (d, J=5.4, 1H, OH-*syn*-**9**), 2.14 (d, J=3.9, 1H, OH-*anti*-**9**); SFC: t_R (2*R*,3*S*)-*syn*-**9**, 4.87 min (10.6%); t_R (2*S*,3*R*)-*syn*-**9**, 5.29 min (14.1%); t_R (2*R*,3*R*)-*anti*-**9**, 5.81 min (29.9%); t_R (2*S*,3*S*)-*anti*-**9**, 6.65 min (44.53%) (Column: AS, MeOH 2.5%, pressure 150 psi, flow 3 mL); MS (FI): 212 (M^+, 2), 181 (M−OMe, 11), 180 (M−MeOH, 100), 106 (PhCHO, 16), 75 ($CH(OMe)_2$), 11), 74 (11).

5.2.4. General procedure IV. Aldol addition of in situ generated trichlorosilyl enolate using 8b: (1*S*,4*R*)-5-*tert*-butyldimethylsilyloxy-4-methyl-1-hydroxy-1-phenyl-3-pentanone (*syn*-28a). The TMS-enolate **7b** (*Z*/*E*=94/6) (0.33 mL, 1 mmol) was added drop wise to a solution of $SiCl_4$ (0.24 mL, 2.0 mmol, 2.0 equiv) and $Pd(OAc)_2$ (2.2 mg, 0.001 mmol, 0.01 equiv) in CH_2Cl_2 (1.2 mL). After 13 h at room temperature, solvent and volatile components were removed under vacuum (up to 0.5 MmHg) to afford 350 mg (100%) of the TCS enolate **4b** (*Z*/*E*=90/10). The residue was diluted with chloroform to a total volume of 2 mL. A portion of this chloroform solution (0.5 mL, 0.25 mmol) containing enolate **4b** was added to a solution of the chiral phosphoramide **3** (9.5 mg, 0.10 mmol, 0.10 equiv) in chloroform (0.5 mL) at −63 °C. After 10 min, benzaldehyde (26 μL, 0.25 mmol, 1.0 equiv) was added into the reaction mixture. After 4 h, MeOH (7.5 mL) was added and the mixture was slowly allowed to attain to room temperature. The reaction mixture was poured into cold $NaHCO_3$ solution and was stirred for 0.5 h. The reaction mixture was diluted with EtOAc, filtered through Celite, and washed well with EtOAc. The organic layer was separated and the aqueous layer was once extracted with EtOAc. The combined extracts were dried over $MgSO_4$ and concentrated. Column chromatography (SiO_2, EtOAc/hexanes, 60/40) of the residue gave 35 mg (66%) of a mixture of aldol products *anti*-**9** and *syn*-**9** as a clear colorless thick liquid (*anti*/*syn*, 6/1).

Acknowledgements

We are grateful to the National Science Foundation for generous financial support (NSF CHE0105205 and CHE0414440).

Supplementary data

Complete experimental details for all preparative procedures along with full characterization of all starting materials and products (19 pages) are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.04.009.

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