Available online at www.sciencedirect.com
ScienceDirect
ELSEVIER
Tetrahedron 63 (2007) 8636–8644
Tetrahedron

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

Scott E. Denmark* and Sunil K. Ghosh

Roger Adams Laboratory, Department of Chemistry, University of Illinois, 600 South Mathews Avenue, Urbana, IL 61801, USA

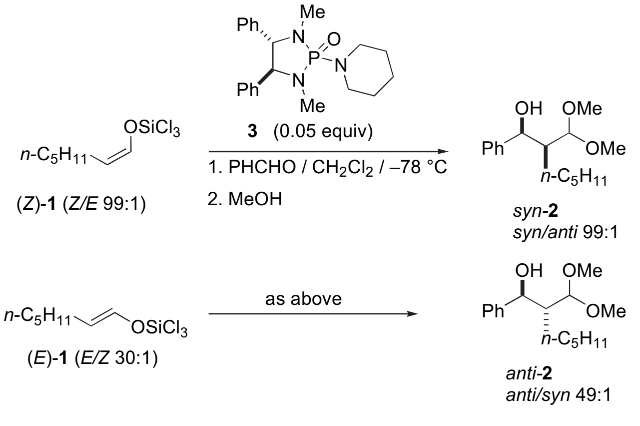
Received 31 January 2007; revised 3 April 2007; accepted 4 April 2007
Available online 12 April 2007

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

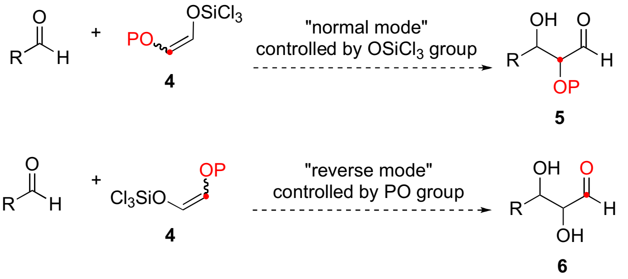
---

Keywords: Aldol; Enolate; Deuterium labeling; Enantioselective; Diastereoselective.

* Corresponding author at present address: 245 Roger Adams Laboratory, Box 18-5, Department of Chemistry, University of Illinois, 600 South Mathews Avenue, Urbana, IL 61801, USA. Tel.: +1 (217) 333 0066; fax: +1 (217) 333 3984; e-mail: denmark@scs.uiuc.edu

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
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

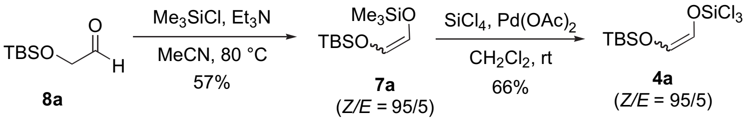
2.1. Synthesis of α-oxy acetaldehyde TCS enolates

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.