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Titanium(IV) Triflates in the Catalysis of Homoaldol Reactions

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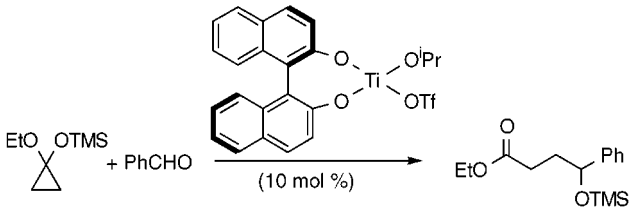
ABSTRACT

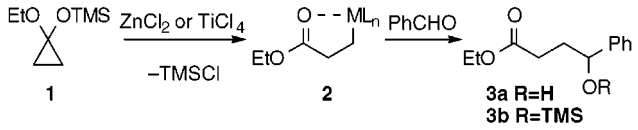


The first example of the use of a titanium catalyst to effect the addition of silyloxycyclopropanes to aldehydes, the homoaldol reaction, is reported. The method features an alkoxytitanium(IV) triflate catalyst, which is conveniently prepared by treatment of Binol−Ti(O^{i}Pr)$_2$ with TMSOTf.

Stereoselective aldol reactions have been the subject of intense study in the past three decades. Recent efforts in this area have focused on the use of chiral Lewis acids to effect enantioselective condensations.[1] Stereoselective *homoaldol* reactions have, in contrast, received significantly less attention.[2,3] This is despite the potential use of this reaction for the stereoselective synthesis of 1,4-oxygenated substrates, including peptidomimetic substructures. In this Letter, we describe a new method for the catalysis of the homoaldol reaction, using alkoxytitanium(IV) triflates as catalysts, which should serve as an effective platform for the development of a highly enantioselective process.

The preparation of discrete homoenolates was pioneered by Nakamura and Kuwajima, who found that 1-alkoxy-1-(trimethylsilyloxy)cyclopropanes (e.g., **1**) could be ring-opened with either titanium(IV) chloride or zinc chloride to afford titanium or zinc homoenolates, respectively, which add to aldehydes in good yields (Scheme 1).[4] The need to form a discrete metal alkyl prior to aldehyde addition makes this reaction fundamentally different from the Mukaiyama aldol process, wherein the Lewis acid generally is involved only in carbonyl activation. This difference makes catalysis of the homoaldol reaction more difficult, reflected by the fact that only $ZnCl_2$ and ZnI_2 are capable of acting as substoichiometric catalysts.[4] Our preliminary investigations indicated that coordinating ligands (e.g., β-amino alcohols, bis-oxazolines)[5] inhibit both zinc halide induced ring opening

Scheme 1



(1) (a) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995. (b) Ojima, I *Catalytic Asymmetric Synthesis*; VCH: Weinheim, 1993.

(2) For reviews on the homoaldol reaction, see: (a) Crimmins, M. T.; Nantermet, P. G. *Org. Prep. Proc.* **1993**, *25*, 43−81. (b) Kuwajima, I.; Nakamura, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergammon: Oxford, 1991; Vol 2, p 441.

(3) For examples of diastereoselective homoaldol reactions, see: (a) Kano, S.; Yokomatsu, T.; Shibuya, S. *Tetrahedron Lett.* **1991**, *32*, 233. (b) DeCamp, A.; Kawaguchi, A.; Volante, R.; Shinkai, I. *Tetrahedron Lett.* **1991**, *32*, 1867. (c) Armstrong, J.; Hartner, F.; DeCamp, A.; Volante, R.; Shinkai, I. *Tetrahedron Lett.* **1992**, *33*, 6599. (d) Houkawa, T.; Ueda, T.; Sakami, S.; Asaoka, M.; Takei, H. *Tetrahedron Lett.* **1996**, *37*, 1045. For examples of stereoselective reactions using homoenolate equivalents, see ref 2 and Ahlbrecht, H.; Beyer, U. *Synthesis* **1999**, 365.

(4) (a) Nakamura, E.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1986**, *108*, 3745−3755. (b) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.*, **1987**, *109*, 8056−8066.

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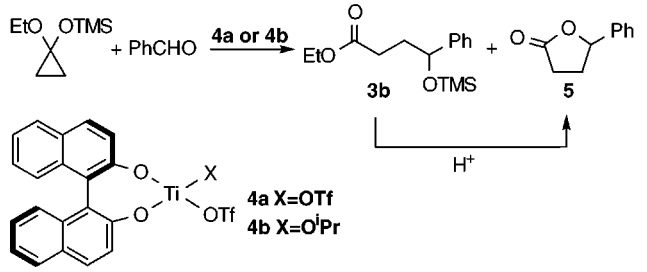
of **1** and the subsequent addition of **2** (M = Zn) to aldehydes, thus making an enantioselective zinc-catalyzed process unlikely. For this reason, we became interested in the possibility of developing titanium(IV) complexes as catalysts for the homoaldol reaction. Although there have been no reports of titanium catalysis of this reaction, the potential advantages of titanium catalysts, the most important of which is the relative ease with which chiral ligands may be incorporated,[6] encouraged us to explore their development.

We envisioned a catalytic enantioselective homoaldol process in which a chiral titanium complex, presumably containing a bidentate alkoxide ligand, would react with cyclopropane **1** to form an alkoxytitanium homoenolate. Subsequent addition of this species to an aldehyde, followed by in situ silylation of the resulting homoaldolate, would complete a catalytic cycle. Modification of the known $TiCl_4$-mediated reaction by incorporation of a bidentate alkoxide ligand presented two main concerns. The first was that the alkoxide ligand would reduce the Lewis acidity of the metal complex, retarding the rate of ring opening of **1**. Second, the large difference in bond strengths between Ti−Cl and Ti−O bonds,[7] when compared to the slight difference in bond strengths for Si−Cl and Si−O bonds,[8] indicates that silylation of titanium homoaldolates with trimethylsilyl chloride is thermodynamically unfavorable. Thus, catalytic turnover with alkoxytitanium chlorides was not expected.[9] To address these concerns, we chose to explore titanium triflates as catalysts. It was anticipated that a triflate counterion would offset the decrease in Lewis acidity, thus allowing the ring opening of **1** to proceed at a reasonable rate. Additionally, although the bond dissociation energy for titanium triflates has not been reported, it seemed reasonable to assume that the difference in bond strength between a titanium triflate and a titanium alkoxide would be much smaller, thus making catalytic turnover more likely.

(*R*)-Binol−$Ti(OTf)_2$ (**4a**) was prepared by treatment of (*R*)-Binol−$TiCl_2$[10] with silver triflate in toluene (Scheme 2).[11]

Scheme 2



Addition of **1** (1 equiv) and benzaldehyde (1 equiv) to a solution of **4a** (0.25 equiv) in $CDCl_3$ at 0 °C and monitoring the subsequent reaction by ^1H NMR revealed the formation of TMS ether **3b** and lactone **5**. Benzaldehyde and most of the cyclopropane were consumed within 40 h. After workup, analysis of the mixture by capillary GC indicated a 63% yield of homoaldol adducts (16% **3b**, 47% **5**), indicating that some catalyst turnover had taken place. To assess the enantioselectivity of the reaction, all homoaldol products were converted to lactone **5** by treatment with HF in acetonitrile. Analysis by capillary GC (Chirasil-dex column) revealed that the reaction had occurred with a modest level of enantioselectivity (17% ee). The reaction catalyzed by monotriflate complex **4b**[12] (0.25 equiv) was slower, requiring 143 h for complete consumption of **1**. However, the yield of products (61%) and enantioselectivity (15% ee) were comparable to those obtained with the ditriflate **4a**.

A significant enhancement in the reaction rate was achieved using an alternative catalyst preparation. Addition of TMSOTf (0.25 equiv) to a solution of (*R*)-Binol−$Ti(O^iPr)_2$[13] (0.25 equiv) in $CDCl_3$ at 0 °C rapidly generates $TMSO^iPr$, as observed by ^1H NMR.[14] Presumably, catalyst **4b** is also formed, for subsequent addition of **1** (1 equiv) and benzaldehyde (1 equiv) proceeds to completion within 20 h to produce **3b** in 74% isolated yield (10% ee).[15] This modified catalyst preparation is operationally more facile than the silver triflate procedure and, more importantly, results in a significantly faster reaction rate.[16] Further optimization of the reaction was achieved by examining a variety of solvents. Although the reaction rate was retarded in strongly coordinating solvents such as Et_2O or THF, it was significantly enhanced in the presence of a weakly coordinating solvent, CD_3CN. The optimum conditions utilize a mixture of CD_3CN and $CDCl_3$ (3:1), which results in a decrease in the reaction time to less than 2 h and an increase in the yield (82%). The mixture of solvents is necessary as the titanium

(5) (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49−69. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.

(6) Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807

(7) Bond strengths for Ti-X are estimated at 103 and 115 kcal/mol for $TiCl_4$ and $Ti(O^iPr)_4$, respectively. See: Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*, Springer-Verlag: **1986**.

(8) Bond strengths for Si−X are estimated at 113 and 116 kcal/mol for TMS−Cl and TMS−OEt, respectively. See: Walsh, R. In *The Chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1989; p 371.

(9) Consistent with these concerns, we observed that while $TiCl_3(O^iPr)$ and $TiCl_2(O^iPr)_2$ were both capable of mediating the homoaldol reaction, the reactions were very slow, afforded low yields of homoaldol adducts, and, as with $TiCl_4$, required stoichiometric amounts of the metal salt.

(10) (*R*)-Binol−$TiCl_2$ was prepared by treatment of (*R*)-2,2′-binaphthol with n-BuLi (2 equiv) in ether followed by addition of $TiCl_4$. See: Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949.

(11) For synthesis of alkoxytitanium(IV) triflates, see: (a) Mikami, K.; Sawa, E.; Terada, M. *Tetrahedron: Asymmetry* **1991**, *2*, 1403. (b) Joergensen, K. A.; Gothelf, K. V. *J. Chem. Soc., Perkin Trans. 2* **1997**, 111.

(12) Catalyst **4b** was prepared by treatment of (*R*)-2,2′-binaphthol with n-BuLi (2 equiv) in ether followed by addition of $Ti(O^iPr)Cl_3$. The resulting Binol−$Ti(O^iPr)Cl$ was then added to a suspension of silver triflate in toluene to generate triflate **4b**.

(13) Prepared by ligand exchange. See: Seebach, D.; Plattner, D. A.; Beck, A. K.; Wang, Y. M.; Hunziker, D.; Petter, W. *Helv. Chim. Acta* **1992**, *75*, 2171.

(14) Chen, H.; White, P. S.; Gagne, M. R. *Organometallics* **1998**, *17*, 5853−5366.

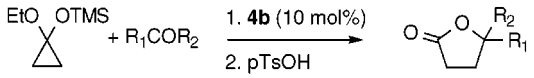
(15) The exact structure of the active catalyst in these reactions has not yet been determined. ^1H NMR spectra of the putative catalysts **4a** and **4b** indicate the presence of a mixture of interconverting species at room temperature.

(16) Ditriflate complex **4a** apparently cannot be prepared by this method, as the addition of 2 equiv of TMSOTf to Binol−$Ti(O^iPr)_2$ followed by addition of **1** and benzaldehyde results in complete decomposition of the starting materials.

complexes are only very slightly soluble in acetonitrile alone.

With these modifications in hand, we developed an optimized protocol for the reaction which utilizes 10 mol % of catalyst[17] and 1.5 equiv of cyclopropane **1** in 3:1 $CD_3CN/CDCl_3$. These conditions were designed to maximize conversion of the carbonyl substrate and afford excellent yields for many aldehydes (Table 1). Highlighting the thermal

Table 1. Titanium-Catalyzed Homoaldol Reactions



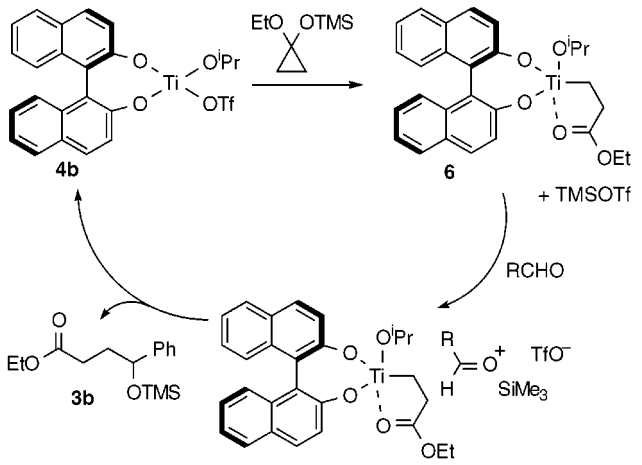
substrate	conditions[a]	yield, %
PhCHO	0 °C, 24 h	99
Ph-C≡CCHO	0 °C, 36 h	76
$Me_3Si-C\equiv CCHO$	0 °C, 36 h	82
p-ClPhCHO	0 °C, 80 h	84
t-C_4H_9CHO	45−50 °C, 54 h[b]	52
$PhCOCH_3$	45−50 °C, 60 h[b]	78

[a] All reactions were performed in $CD_3CN/CDCl_3$ (3:1) using 1.5 equiv of **1**, except where noted. [b] Reaction conducted using 2 equiv of **1**.

stability of the catalyst, we note that even less reactive substrates such as acetophenone and pivaldehyde undergo addition at elevated temperatures. One limitation with the current catalyst system is that it is not optimal for aliphatic aldehydes containing enolizable protons. For example, reaction with cyclohexanecarboxaldehyde results in significant quenching of the homoenolate and gives low yields of the desired product (<40%).

Although the development of this method was based upon an envisaged three-step catalytic cycle involving (1) homoenolate formation, (2) aldehyde addition, and (3) homoaldolate silylation, all current evidence points toward the catalytic process shown in Scheme 3. Thus, it is believed that ring opening of **1** with titanium triflate **4b** results in the formation of an alkoxytitanium homoenolate.[18] The TMSOTf that is liberated in this process reacts with the aldehyde to form an activated complex which undergoes addition with the homoenolate **6** to form **3b** directly.[19] Normally, titanium homoenolates do not require silicon activation in order to add to aldehydes.[4a] However, if direct addition of the homoenolate **6** to the aldehyde occurred, a titanate containing both homoaldolate and isopropoxide ligands would be generated. A control experiment where a mixed titanate, containing Binol, isopropoxide, and homoaldolate ligands, was prepared and treated with TMSOTf resulted in the

Scheme 3



formation of a significant amount of $TMSO^iPr$. In contrast, during the homoaldol reaction, no formation of $TMSO^iPr$ is observed after the initial catalyst preparation, nor at all when the catalysts are prepared using AgOTf. These observations are inconsistent with a direct addition of **6** to an aldehyde, followed by silylation, and suggest addition of **6** to a silyl-activated aldehyde. The absence of coordination of the aldehyde to the titanium complex might also explain the low levels of enantioselection that are observed in this process, as it would result in an open transition state.

A potential means for improving the enantioselectivity of this process is to increase the steric bulk of the ligand. To this end, we have found that the system is not limited to binaphthol as a ligand, as aliphatic 1,2-, 1,3-, and 1,4-diols may be utilized without significantly affecting either the rate or yield of the reaction. The presence of a bidentate ligand is a definite requirement, however, as $(^iPrO)_3TiOTf$ does not promote the reaction to any extent. This implies that the bidentate ligands play an important role in controlling the aggregation state, and thus the reactivity, of the metal catalyst.

In conclusion, we have disclosed the first example of titanium catalysis of the direct homoaldol addition of silyloxycyclopropanes to aldehydes. The methodology features alkoxytitanium(IV) triflates as catalysts and is applicable toward a range of substrates. Of particular advantage for future development is the fact that the catalyst system is tolerant of a variety of ligands and is thermally stable. The ability to incorporate a wide range of alkoxide ligands should allow further development toward a highly enantioselective process, and these efforts will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization for all reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) We have found that the catalyst loading can be reduced to 2% or 5% with little change in yield for the reaction with benzaldehyde. However, longer reaction times were required, which was not practical for less reactive substrates.

(18) In the absence of Binol−$Ti(O^iPr)_2$, TMSOTf does not promote the homoaldol reaction of **1** with aldehydes. For this reason, and by analogy to ref 4, it is presumed that homoenolate **6** is an intermediate in this process. Thus far, it has not been possible to characterize the homoenolate.

(19) Similar activation of aldehydes has been postulated in the zinc-catalyzed process (ref 4).