Catalytic, Enantioselective Acetone Aldol Additions with 2-Methoxypropene

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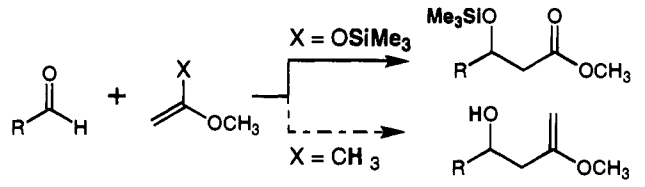
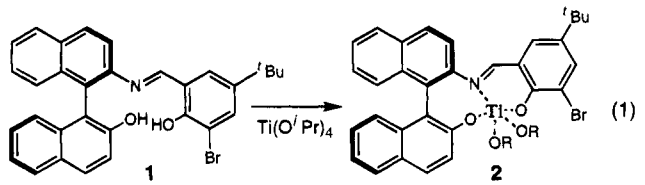
Ketone and ester *O*-silyl enol ether derivatives have been utilized widely in stereoselective aldol addition reactions.[1] Although *O*-silyl enol ether derivatives of simple ketones (cyclohexanone, acetone) are commercially available, in general, the corresponding ester derivatives (silyl ketene acetals) must be prepared in the laboratory prior to use. In some instances the preparative methods require the use of additives such as HMPA and can provide mixtures of *C*- and *O*-silylated products.[2] Thus, the development of stereoselective aldol addition processes employing commercially available enolates or enolate equivalents would be advantageous.[3,4] We report in this communication the enantioselective addition reaction of 2-methoxypropene to aldehydes catalyzed (2–10 mol %) by a chiral Ti(IV) complex. Upon workup the reaction furnishes β-hydroxy ketones in 79–99% yields with 66–98% ee's.

We have previously described an enantioselective acetate aldol addition reaction using an *O*-trimethylsilyl *O*-methyl ketene acetal that is catalyzed (2 mol %) by a chiral Ti(IV) complex and produces adducts in 94–97% ee's.[5,6] The active catalyst is prepared *in situ* from the tridentate ligand **1**, $Ti(O^iPr)_4$, and 3,5-di-*tert*-butylsalicylic acid. We have observed that the 3,5-di-*tert*-butylsalicylic acid is crucial for effective catalyst turnover with silyl ketene acetals. As an alternative to the ester derived *O*-silyl ketene acetals, we have examined the inexpensive, commodity chemical 2-methoxypropene as an acetone enolate equivalent in catalytic, enantioselective aldehyde addition reactions (Scheme 1).[7] We speculated that for such additions, which produce alcohol adducts directly, the use of the simpler parent chiral Ti(IV) complex **2** would suffice (eq 1). Treatment of **1** with $Ti(O^iPr)_4$ in toluene (23 °C) and subsequent evaporation of the solvent *in vacuo* afford an orange crystalline solid **2**.[8,9]

Scheme 1





(1)

When hydrocinnamaldehyde and 2-methoxypropene (1.2 equiv) were dissolved in toluene or ether with 5 mol % of **2**, no addition product was isolated (23 °C). This contrasts the reactivity of silyl ketene acetals toward aldehydes in the presence of **2** (5 mol %), which yields aldol adducts at −10 °C within 4 h. This lack of reactivity is consistent with the attenuated nucleophilicity of 2-methoxypropene relative to silyl ketene acetals.[10] We anticipated that these rate differences could be compensated by using 2-methoxypropene as solvent. In this regard, the fact that 2-methoxypropene is available at a nominal price and may be readily removed *in vacuo* upon completion of the reaction (bp 34–36 °C) seemed particularly attractive.

Under optimal conditions, the aldol addition reaction is conducted by dissolution of **2** (2–10 mol %) in 2-methoxypropene[11] at 0 °C followed by addition of 2,6-di-*tert*-butyl-4-methylpyridine (0.4 equiv) and the aldehyde.[12] After being stirred for 1.5–22 h at 0–23 °C, the reaction mixture was concentrated *in vacuo* and the residue was treated with a biphasic mixture of Et_2O and aqueous 2 N HCl solution to afford the corresponding β-hydroxyketone adduct after workup and chromatography on silica gel.[13] As shown in Table 1, a variety of aldehydes serve as substrates in the addition reaction and yield, upon workup, acetone–aldol adducts in 79–99% yields.[14,15] In addition, for each adduct shown, preparation of the derived (*S*)-MTPA esters allowed the extent of asymmetric induction (66–98% ee's) to be assayed by ^1H NMR spectroscopy. The

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(2) (a) Kita, Y.; Segawa, J.; Haruta, J.; Yasuda, H.; Tamura, Y. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1099. (b) Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157. (c) Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 650.

(3) Two aldehyde addition processes have been described which employ commercially available enolate precursors: (1) the Au(I)-ferrocenylphosphine-catalyzed (1 mol %) aldol addition of α-isocyanoacetates to aldehydes affording 5-alkyl-2-oxazoline-4-carboxylate products, see: (a) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405. (b) Ito, Y.; Sawamura, M.; Hayashi, T. *Tetrahedron Lett.* **1987**, *28*, 6215. (2) the Ln(III)-BINOL-catalyzed (10 mol %) Henry reaction with nitromethane, see: (a) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418. (b) Sasai, H.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 1571.

(4) For a recent compilation of references to enzyme-catalyzed asymmetric aldol addition reactions using readily available enolate precursors, see: Gijsen, H. J. M.; Wong, C.-H. *J. Am. Chem. Soc.* **1994**, *116*, 8422.

(5) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837.

(6) Since our initial communication we have observed that the aldol addition of methyl acetate *O*-silyl enol ethers and aldehydes can be conducted with as little as 0.5 mol % of catalyst in equally good yields and enantioselectivities.

(7) The $Yb(OTf)_3/H^+$-promoted addition of 2-methoxypropene to aldehydes to give protected vinyl ethers has been recently reported, see: Deaton, M. V.; Ciufolini, M. A. *Tetrahedron Lett.* **1993**, *34*, 2409. The Me_2AlCl-promoted addition of 1-methoxycylohexene to cyclohexanecarboxaldehyde has also been reported, see: Shoda, H.; Nakamura, T.; Tanino, K.; Kuwajima, I. *Tetrahedron Lett.* **1993**, *34*, 6281.

(8) Evaporation of toluene *in vacuo* has been reported to effect the removal of the ^{i}PrOH liberated upon complex formation of $Ti(O^iPr)_4$ with bidentate ligands such as α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanols, see: Seebach, D.; Plattner, D. A.; Beck, A. K.; Wang, Y. M.; Hunziker, D.; Petter, W. *Helv. Chim. Acta* **1992**, *75*, 2171 and references therein.

(9) The structure of the active catalyst has not yet been determined. The illustrated structure of the Ti(IV) complex is only intended as a heuristic model. For the addition reactions reported herein, optimal enantioselectivities are observed with 2:1 ligand:$Ti(O^iPr)_4$. It has not yet been established whether the second equivalent of ligand substitutes for the isopropoxides; further studies on the solution structure of the active catalyst are in progress and will be reported shortly.

(10) A scale of relative nucleophilicities has been recently compiled by Mayr and co-workers. In their work, 2-methoxypropene is shown to be 1 order of magnitude less reactive toward bis(*p*-chlorophenyl)methyl cation than the *O*-trimethylsilyl enolate of methyl isobutyrate, see: Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938.

(11) We have observed that optimal results are obtained when the 2-methoxypropene is purified by filtration through Activity 1 basic alumina followed by distillation.

(12) We have conducted the addition reactions in the absence of added base in good yields and selectivities. However, because of the sensitivity of the solvent 2-methoxypropene and the reaction products to decomposition in the presence of adventitious H^+, we have found it convenient to employ a hindered base as an H^+ scavenger. The addition of Et_3N, $^iPr_2NEt$, or 2,6-lutidine leads to diminution of the reaction rate.

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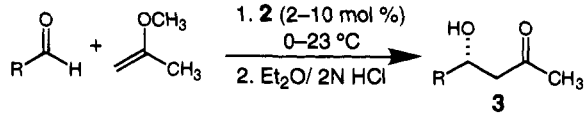
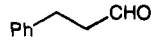
Table 1. Catalytic Asymmetric Aldol Additions of 2-Methoxypropene

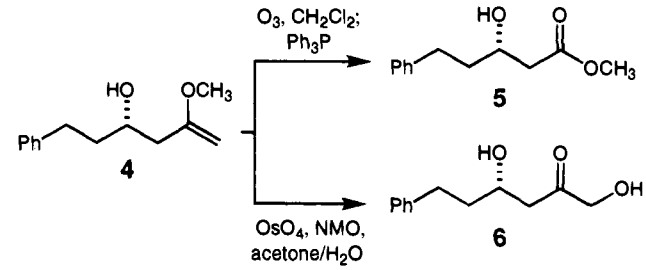


Entry	Aldehyde	Temp.	Yield	ee[a,b]
1	$Ph(CH_2)_3$—≡—CHO	0 °C	99%	98%
2	$TBSOCH_2$—≡—CHO	0 °C	85%[c]	93%
3	Ph—≡—CHO	0 °C	99%	91%
4		0–23 °C	98%	90%
5	PhCHO	0–23 °C	83%	66%
6	c-$C_6H_{11}CHO$	0–23 °C	79%	75%

[a] For each entry, the ee was determined by preparation of the derived (*S*)-MTPA ester, analysis by ^1H NMR spectroscopy, and comparison with authentic racemic material. [b] The absolute configuration of the aldol adducts was established in the following manner: entry 3, hydrogenation of the (*S*)-MTPA ester to the corresponding saturated ester and comparison to the known (*S*)-MTPA ester of the adduct of entry 4; entries 4–6, comparison to the known compounds (see ref 16); entries 1 and 2, by analogy to the product of entry 3. [c] The adduct was treated with a solution of TFA/THF instead of Et_2O/2 N HCl.

absolute configuration of the products was established unambiguously by comparison with the known optically active β-hydroxyketones.[16] It is interesting to note that the catalyst system affords the highest enantioselectivities with the smaller, acetylenic aldehydes (Table 1, entries 1–3), while with branched aldehydes (entries 5 and 6), reduced levels of absolute induction are observed. Despite their versatility as synthetic precursors, α,β-ynals have been examined as substrates in enantioselective, catalytic aldol additions in only one other study where they were shown to react with silyl thioketene acetals to give carbinol products in 79–88% ee's.[17] The catalytic process described herein employing acetylenic aldehydes, 2-methoxypropene, and **2** provides a useful method for the preparation of optically active propargylic alcohols.[18,19]

Scheme 2



In the absence of an acidic workup, the vinyl ether products can be isolated, and these can be used in additional synthetic transformations. For example, the adduct **4**, from the reaction of 2-methoxypropene and hydrocinnamaldehyde, was obtained in 84% yield after purification by chromatography on silica gel. Treatment of **4** with a dilute stream of ozone in CH_2Cl_2 yields β-hydroxy ester **5** (Scheme 2); moreover, dihydroxylation of **4** (catalytic OsO_4, NMO) furnishes ketodiol **6**. Thus, in addition to providing access to acetone aldol adducts (Table 1), the methodology described herein can also be used to prepare the corresponding optically active acetate–aldol adducts as well as more highly functionalized α-hydroxyacetone adducts.

A new catalytic, enantioselective aldehyde addition process is described which employs 2-methoxypropene and chiral Ti(IV) complex **2** to afford β-hydroxyketone adducts in good yields and useful levels of enantioselectivity. This methodology provides an alternative to the well-established Mukaiyama aldol additions with silyl enol ether derivatives. The salient features of 2-methoxypropene as an enolate equivalent include the following: (1) 2-methoxypropene is readily available from commercial sources at a nominal price and (2) its use obviates the need for laboratory preparation of the derived silyl enol ethers for aldol addition reactions.

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Supplementary Material Available: Text giving experimental procedures and spectral data for all compounds (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(13) The following detailed experimental procedure is representative: To a 5 mM solution of **1** (0.2 equiv) in toluene was added $Ti(O^iPr)_4$ (0.1 equiv), and the resulting orange solution was stirred for 1 h at 23 °C. The solvent was removed *in vacuo*, and the solid orange residue was taken up in 2-methoxypropene (2 mL, 200 equiv) at 0 °C. 2,6-Di-*tert*-butyl-4-methylpyridine (0.4 equiv) and aldehyde (1 equiv) were added sequentially. After 1.5~22 h, the reaction was concentrated *in vacuo* and the resulting residue was treated with a biphasic mixture of Et_2O and aqueous 2 N HCl for 10–30 min. The reaction mixture was then extracted with Et_2O, and the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by chromatography on silica gel using 4:1 hexanes/EtOAc to elute the ligand **1** followed by 1:1 hexanes/EtOAc afforded the β-hydroxyketone adduct.

(14) Stoichiometric quantities of $Ti(O^iPr)_4$ by itself do not promote addition of 2-methoxypropene with aldehydes. Moreover, the catalytic addition reaction employing **2** can be conducted with excess $Ti(O^iPr)_4$ in the presence of 10 mol % of **2** in equally good yields and enantioselectivities.

(15) Additions to α,β-enals, such as cinnamaldehyde and sorbaldehyde, furnish adducts with good enantioselectivities albeit in low yields. For these substrates, we speculate that the first-formed vinyl ether adducts undergo a Cope rearrangement and subsequent decomposition. Further investigations of these substrates are under study and will be reported at a later time.

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(17) Kobayashi, S.; Furuya, M.; Ohtsubo, A.; Mukaiyama, T. *Tetrahedron: Asymmetry* **1991**, *2*, 635.

(18) Reduction of ynones with optically active boranes provides optically active propargylic alcohols: (a) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867. (b) Brown, H. C.; Ramachandran, P. V. *Acc. Chem. Res.* **1992**, *25*, 16.

(19) The alkynylation of aldehydes promoted by chiral oxazaborolidines also affords optically active propargylic alcohols, see: Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 3151.