Pergamon

Tetrahedron 54 (1998) 7025–7032

TETRAHEDRON

Catalytic, Enantioselective Acetate Aldol Additions to α,β–Ynals: Preparation of Optically Active Propargylic Alcohols

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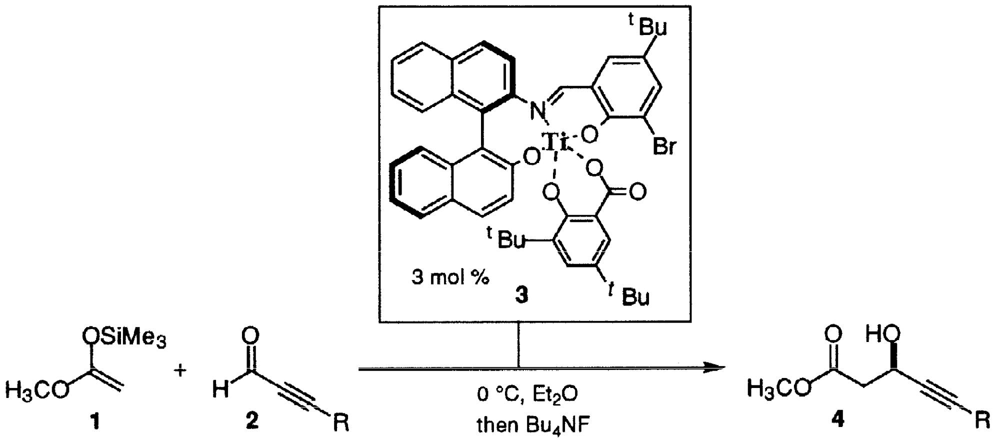
Received 9 January 1998; revised 2 March 1998; accepted 11 March 1998

Abstract. A catalytic, enantioselective acetate–aldol addition reaction of silyl ketene acetals with α,β–ynals and 3 mol % of a chiral Ti(IV) complex is described. This process provides access to optically active β–hydroxy–γ–alkynyl esters in 84–96% yields and 94–97% ee's. © 1998 Elsevier Science Ltd. All rights reserved.

Propargylic alcohols are useful, versatile starting materials in organic synthesis.[1] The extensive chemistry of the carbon–carbon triple bond permits its conversion to numerous other functional groups. Alkynyl carbinols may be reduced to both cis– and trans– allylic alcohols which, in turn, can be subjected to diastereoselective epoxidation, cyclopropanation, dihydroxylation, or hydroboration reactions.[2] The propargylic alcohols derived from terminal alkynes can be employed in carbon–carbon bond–forming processes as well as hydrometalation reactions.[3,4] Additionally, a recently reported one-pot process stereospecifically converts optically active propargylic alcohols to the corresponding disubstituted allenes, a class of molecules that have been shown to participate in asymmetric photocycloadditions.[5,6] Thus, synthetic methods for the preparation of optically active propargylic alcohols would be of considerable value for the synthesis of functionalized, enantiopure materials. In this communication, we report the catalytic, enantioselective aldol addition reaction of methyl acetate derived silyl ketene acetal **1** with α,β–ynals **2** (Scheme 1) to give optically active propargylic

Scheme 1



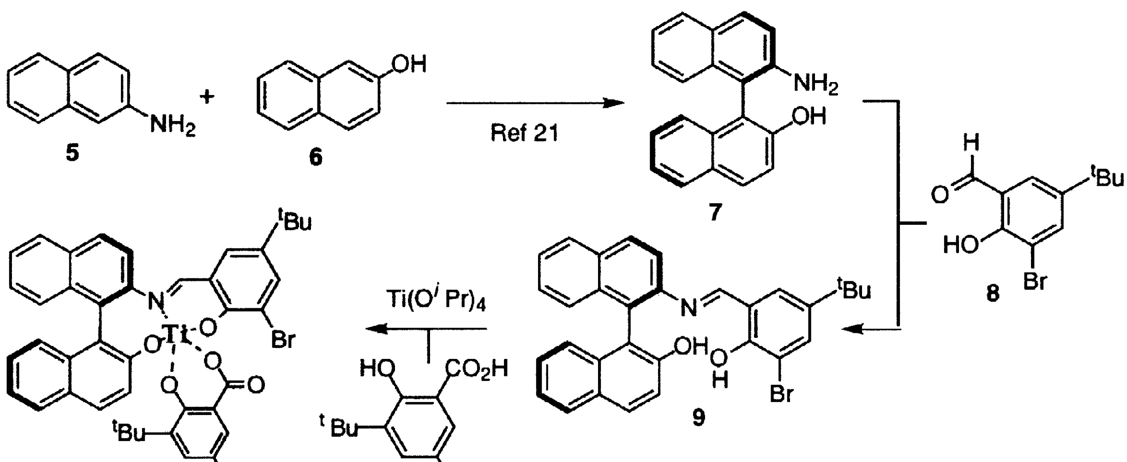
Dedicated to our colleague and friend Professor Madeleine M. Joullie in celebration of forty years of distinguished teaching and research at the University of Pennsylvania

PII: S0040-4020(98)00344-5

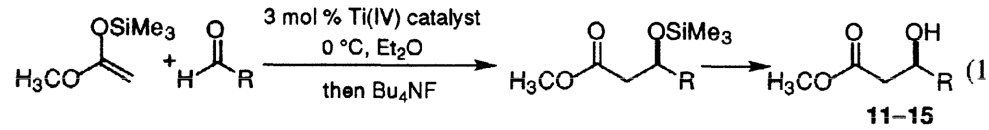
alcohols **4** in 84–96% yields and 94–97% enantioselectivities (Scheme 1). Two general approaches have been described for the enantioselective synthesis of secondary propargylic alcohols: (1) ynone reductions, and (2) aldehyde additions. The stereoselective reduction of α,β–alkynyl ketones has been carried out with several stoichiometric reagents including Alpine–Borane,[7] Chirald–$LiAlH_4$,[8,9] NB–Enantrane,[10] BINAL–H,[11] and DIP–Cl.[12] Additionally, efficient enantioselective, catalytic methods have also been recently documented by Corey and Noyori.[13,14] As an alternative method for the preparation of propargylic alcohols, enantioselective additions of alkylmetal and alkynylmetal reagents to alkynyl and aliphatic aldehydes, respectively, have been developed.[15,16] The catalytic, enantioselective acetate–aldol addition reaction of ynals has only been reported in a single study: using 20–30 mol % of a catalyst prepared from $Sn(OTf)_2$ and a chiral diamine, addition of the *O*–trimethylsilyl enol ether derivative of *S*–ethyl thioacetate with α,β–heptynal, phenyl propynal, and trimethylsilyl propynal proceeded in 77–88% ee's and 71-78% yields.[17,18]

We have described an enantioselective acetate–aldol addition reaction using *O*–trimethylsilyl *O*–methyl ketene acetal that is catalyzed by a chiral Ti(IV) complex **3** and produces adducts in 94–97% ee's for aliphatic and aromatic aldehydes as well as α,β–enals.[19,20] The Ti(IV) catalyst is prepared as an orange solid from $Ti(O^iPr)_4$, tridentate ligand **9**, and 3,5–di–*tert*–butylsalicylic acid (Scheme 2).[21] A salient feature of this catalytic system is that the aldol addition reaction can be effected with only 1 mol % catalyst.[22] Moreover, in contrast to other reported catalyst systems, slow addition of the substrates to the catalyst solution at low temperature (-78 °C) is not necessary.[17]

Scheme 2

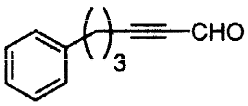
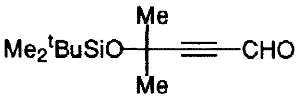


When a solution of 3 mol % of **3** in Et_2O at 0 °C is treated with an alkynyl aldehyde[23] and *O*–trimethylsilyl *O*–methyl ketene acetal[24] (**1**) silylated aldol adducts are isolated in excellent yields (Eq 1 and Table 1). Analysis of the products was facilitated by treatment of the silylated aldolates with Bu_4NF to furnish β–hydroxy esters **11–15** in 84–96% overall yield (two steps). For each adduct, preparation of the derived (*S*)–MTPA esters allows the extent of asymmetric induction to be assayed by ^1H NMR spectroscopy.[25] In each case, the absolute stereochemistry of the products has been established by conversion to known compounds and correlation to reported optical rotations.[6,26]



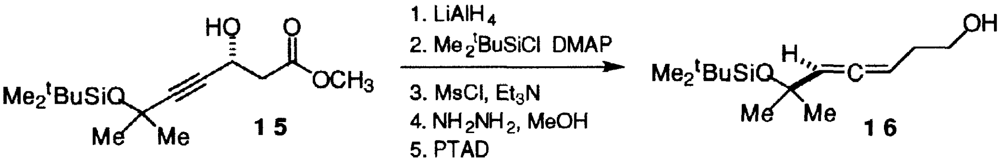
(1)

Table 1. Catalytic, enantioselective aldol additions to ynals.

Entry	Aldehyde	Product	Yield	ee[a,b]
1		11	84%	96%
2		12	88%	96%
3		13	96%	94%
4	$^{i}Pr_3Si-C\equiv C-CHO$	14	88%	97%
5		15	88%	96%

(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 by comparison to known compounds (see ref 26).

The optical purity of propargylic alcohols isolated from the aldol addition reactions matches or exceeds the optical purity of related propargylic alcohols prepared using stoichiometric reductants or other catalytic aldol addition methods.[7–12,17] The aldol products may be further elaborated through the alkynyl or ester moiety. For example, we have prepared homoallenic alcohol **16** from **15** in good yields (Eq 2). Optically active homoallenic alcohols such as **16** may be utilized in a variety of synthetic processes such as intramolecular, enantioselective [2+2]–photocycloadditions and directed allene cyclopropanation.[6,27]



(2)

The aldol addition reaction of silyl ketene acetals with acetylenic aldehydes provides access to functionalized β–hydroxy alkynyl ester intermediates for synthesis. With the catalytic system described herein aldol adducts are obtained for a range of substituted ynals in good yields and 94–97% ee's. Moreover, because the Ti(IV) complex can be easily prepared in the laboratory and the ynal addition reactions can be conducted with as little as 3 mol % complex, the catalytic process provides a practical preparation of optically active propargylic alcohols.

EXPERIMENTAL SECTION

General Procedure. All reagents were commercially obtained except where noted. Where appropriate, reagents were purified prior to use. All nonaqueous reactions were performed using oven-dried glassware under an atmosphere of dry nitrogen. Air- and moisture-sensitive liquids and solutions were transferred *via* syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 35 °C at ~25 mmHg (water aspirator). Toluene was distilled from calcium hydride. Spectroscopy grade chloroform (with 1% EtOH) was used for all optical rotation data. Chromatographic purification of products was accomplished using forced flow chromatography on Baker 7024-R silica gel or EM Science Geduran silica gel 60 according to the method of Still.[28] Thin-layer chromatography was performed on EM Reagents 0.25 mm silica gel 60F plates (230-400 mesh). Visualization of the developed chromatogram was performed by either fluorescence quenching, ethanolic *p*-anisaldehyde stain, or aqueous ceric ammonium molybdate (CAM) stain.

NMR spectra were recorded on a Bruker AM-500 operating at 500, 470, and 126 MHz for ^1H, ^{19}F, and ^{13}C, respectively, or a General Electric QE Plus operating at 300 and 75 MHz for ^1H and ^{13}C, respectively. Data for ^1H are reported as follows: chemical shift (δ in ppm), multiplicity (s, singlet; d, doublet; t, triplet; q quartet; m, multiplet), integration, coupling constant (*J* in Hz), and assignment. IR spectra were recorded on a Perkin Elmer 1600 series or a paragon 1000 FTIR spectrometer using NaCl salt plates and are reported in terms of frequency of absorption (ν, cm^{-1}). Optical rotations were determined on a JASCO DIP-181 or DIP-1000 digital polarimeter operating at the sodium D line and are reported as follows: $[\alpha]_{Na}$, concentration (g/100 mL), and solvent.

Aldol addition: General procedure. To a 5.0 mM solution of the chiral Schiff base ligand (0.066 equiv) in toluene was added $Ti(^iPrO)_4$ (0.030 equiv). The orange solution was stirred for 1 h at 23 °C and 3,5-di-*tert*-butylsalicylic acid (0.060 equiv, 0.1 M in toluene) was added. Stirring was continued for an additional hour at 23 °C. The solvent was removed *in vacuo* and the orange solid was dissolved in Et_2O to give a 5.0 mM solution (relative to chiral ligand). After cooling the solution to 0 °C, 2,6-lutidine (0.40 equiv) was added to the solution, followed by the sequential addition of the aldehyde (1 equiv) and silyl ketene acetal (1.2 equiv). After stirring the reaction for 4 h at 0 °C, it was quenched by pouring onto water. The aqueous solution was extracted with Et_2O, and the combined organic extracts were washed with a saturated aqueous NaCl solution. The organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in THF and treated with excess Bu_4NF (2-3 equiv). The solution was partitioned between Et_2O and 1M aqueous HCl. The organic layer was washed with a 5% aqueous $NaHCO_3$ solution and then with a saturated aqueous NaCl solution. The reaction mixture was then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by chromatography on silica gel using 10:1 CH_2Cl_2/hexanes to elute the ligand followed by 10:1 CH_2Cl_2/Et_2O afforded the aldol adduct.

A portion of the aldol adduct was converted to the corresponding (*S*)-MTPA-ester as follows. To a solution of the alcohol (0.01 mmol, 1 equiv) and 10 mg DMAP in 1 mL CH_2Cl_2 was added 10 μL triethylamine followed by (*R*)-MTPA-Cl (0.011 mmol, 1.1 equiv). The MTPA-ester was purified by chromatography on silica gel, using 6:1 hexanes/EtOAc as eluent. The diastereomeric excess of the product was determined by integration of the ^1H NMR (300 MHz, $CDCl_3$ or C_6D_6) resonances of the methoxy signals.

Spectral data for aldol adducts

(**11**) $[\alpha]^{19}_{D}$ +19.3° (*c* = 1.01, $CHCl_3$); IR (thin film) ν 3448, 3026, 2948, 2860, 1739, 1602, 1496, 1454, 1438, 1356, 1278, 1167, 1055, 1028, 747, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.17 (m, 5H), 4.77 (q, *J* = 6.1, 1H), 3.73 (s, 3H), 3.08 (d, *J* = 6.1, 1H), 2.75 (d, *J* = 6.1, 2H), 2.70 (t, *J* = 7.4, 2H), 2.22 (t, *J* = 7.0, 2H), 1.82 (dt, *J* = 7.4, 7.0, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 141.4, 128.4, 128.3, 125.8, 85.4, 79.8, 58.9, 51.9, 42.1, 34.6, 29.9, 18.0 ppm. HRMS: (EI) calcd for $C_{15}H_{18}O_3$ $(M)^+$ 246.1256, found 246.1243.

(*S*)-MTPA-ester data: ^1H NMR ($CDCl_3$) methoxy resonances at δ 3.69 and 3.60 ppm; 96% de.

(**12**) $[\alpha]^{19}_{D}$ +17.1° (*c* = 1.13, $CHCl_3$); IR (thin film) ν 3433, 2954, 2930, 2887, 2858, 1741, 1472, 1463, 1439, 1409, 1390, 1362, 1255, 1166, 1131, 1085, 1026, 1006, 837, 815, 779, 722, 666 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.79 (q, *J* = 6.0, 1H), 4.31 (m, 2H), 3.71 (s, 3H), 3.19 (d, *J* = 6.0, 1H), 2.73 (d, *J* = 6.0, 2H), 0.88 (s, 9H), 0.09 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 83.67, 83.72, 58.6, 51.9, 51.6, 41.5, 25.7, 18.2, -5.2 ppm. HRMS: (FAB) calcd for $C_{13}H_{25}O_4Si$ $(M+H)^+$ 273.1522, found 273.1530.

(*S*)-MTPA-ester data: ^1H NMR (C_6D_6) methoxy resonances at δ 3.15 and 3.12 ppm; 96% de.

(**13**) $[\alpha]^{19}_{D}$ +19.2° (*c* = 1.08, $CHCl_3$); IR (thin film) ν 3435, 3057, 3022, 2953, 2849, 2233, 1958, 1889, 1732, 1598, 1572, 1490, 1441, 1403, 1360, 1279, 1215, 1168, 1044, 992, 918, 876, 852, 758, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44-7.27 (m, 5H), 5.01 (q, *J* = 6.0, 1H), 3.74 (s, 3H), 3.37 (d, *J* = 6.0, 1H), 2.85 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 131.7, 128.5, 128.2, 122.1, 87.9, 85.0, 59.1, 52.0, 41.8 ppm. HRMS: (EI) calcd for $C_{12}H_{12}O_3$ $(M)^+$ 204.0786, found 204.0780.

(*S*)-MTPA-ester data: ^1H NMR ($CDCl_3$) methoxy resonances at δ 3.71 and 3.63 ppm; 94% de.

(**14**) $[\alpha]^{19}_{D}$ +20.4° (*c* = 0.94, $CHCl_3$); IR (thin film) ν 3447, 2944, 2866, 1741, 1464, 1438, 1363, 1274, 1168, 1061, 998, 883 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.75 (dd, *J* = 6.7, 6.0, 1H), 3.70 (s, 3H), 3.15 (d, *J* = 6.7, 1H), 2.75 (d, *J* = 6.0, 2H), 1.04 (d, *J* = 1.3, 18H), 1.04 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 106.5, 86.0, 59.2, 51.9, 42.1, 18.4, 11.0 ppm. HRMS: (FAB) calcd for $C_{18}H_{27}O_3Si$ $(M+H)^+$ 319.1729, found 319.1733.

(*S*)-MTPA-ester data: ^1H NMR ($CDCl_3$) methoxy resonances at δ 3.69 and 3.60 ppm; 97% de.

(**15**) $[\alpha]^{19}_{D}$ +20.6° (*c* = 1.10, $CHCl_3$); IR (thin film) ν 3459, 2983, 2956, 2931, 2894, 2857, 1744, 1473, 1462, 1438, 1408, 1388, 1377, 1360, 1248, 1164, 1040, 1006, 940, 915, 877, 838, 812, 777, 716, 674, 631 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.78 (q, *J* = 6.0, 1H), 3.73 (s, 3H), 3.03 (d, *J* = 6.0, 1H), 2.73 (d, *J* = 6.0, 2H), 1.43 (s, 6H), 0.85 (s, 9H), 0.14 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 90.5, 81.2, 66.1, 58.7, 51.9, 41.6, 32.8, 25.6, 17.9, -2.9 ppm. HRMS: (FAB) calcd for $C_{15}H_{28}O_4SiNa$ $(M+Na)^+$ 323.1654, found 323.1650.

(*S*)-MTPA-ester data: ^1H NMR ($CDCl_3$) methoxy resonances at δ 3.69 and 3.60 ppm; 96% de.

Acknowledgment. R.A.S. thanks the Fannie and John Hertz Foundation for a Graduate Fellowship award. M.S.S. is grateful to the Office of Naval Research for a graduate fellowship. This research has been generously supported by awards from the Packard Foundation, Camille and Henry Dreyfus Foundation, and Sloan Foundation, as well as funds provided by the NIH, and NSF and gifts from Eli Lilly, Merck, Pfizer, Upjohn, and Zeneca.

Footnotes and References

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20. The structure of the active catalyst has not yet been determined. The illustrated structures of the Ti(IV) complexes are intended to indicate the putative catalyst composition.

21. Since our original report, we have developed a resolution procedure for (±)–2–amino–2'–hydroxy–1,1'–binaphthyl which is prepared according to the procedure of Smrcina, M.; Lorenc, M.; Hanus, V.; Kocovsky, P. *Synlett*, **1991**, 231. We have observed that the (*R*)–(+)–**7**•(*R*)–(–)–camphorsulfonate salt crystallizes from a solution of (10:1) chlorobenzene and absolute ethanol at 60 °C. Following dissolution of the isolated crystals with CH_2Cl_2 and washing with aqueous $NaHCO_3$ solution (*R*)–(+)–**7** (Scheme 2) is isolated in 98% ee and 80% yield. A single recrystallization from benzene then furnishes (*R*)–(+)–**7** in 99% ee; a second recrystallization provides (*R*)–(+)–**7** in >99% ee. Since both (*R*)–(–)– and (*S*)–(+)–camphorsulfonic acids are inexpensive and readily available either (*R*)–(+)– or (*S*)–(–)–**7** can be prepared employing the resolution procedure described.

22. Recently, we have found that the catalytic, enantioselective acetate–aldol additions can be conducted with as little as 0.5 mol% **3**; these results will be reported at a later time.

23. The alkynyl aldehydes used in this study were prepared by treatment of the corresponding lithium acetylides with ethyl formate at -78 °C.

24. Prepared according to the procedure of Kita, Y.; Segawa, J.; Haruta, J.; Yasuda, H.; Tamura, Y. *J. Chem. Soc., Perkin Trans I*, **1982**, 1099.

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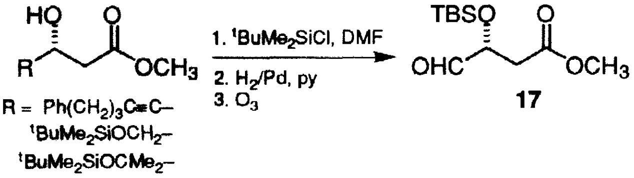
26. Adducts **11**, **12**, and **13** were silylated ($^tBuMe_2SiCl$, imidazole, DMF) and reduced to the corresponding alkene which was subsequently ozonolyzed to give the known aldehyde **17**. Adduct **14** was converted to the (*S*)–MTPA ester and reduced (H_2/Pd) to the corresponding known saturated ester.

Product **15** was reduced to the known ethyl (*S*)–3–hydroxypentanoate, $[\alpha]_D^{19}$ = +18.8 (lit. $[\alpha]_D^{19}$ = +18.6, Tannabe, T.; Izumi, Y. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1550).



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