Stereospecific Double Aldol Reaction of Phenylacetaldehyde Catalyzed by Group 4 Metallocene

Sock-Sung Yun,* IL-Hwan Suh, Sung-San Choi, and Samkeun Lee*†
Department of Chemistry and Department of Physics, Chungnam National University, Taejon 305-764, Korea
†Department of Chemistry, Taejon University, Taejon 300-716, Korea

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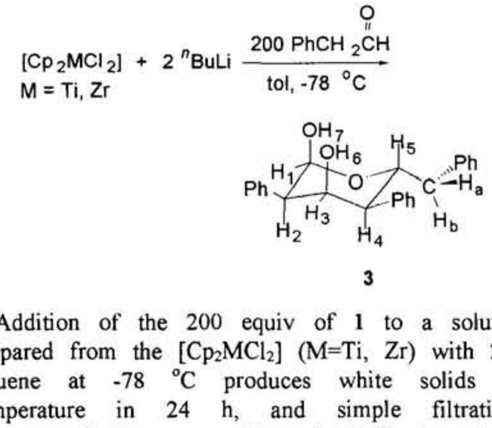
Reaction of phenylacetaldehyde with catalytic amount of "Cp_2M" (M = Ti, Zr) produces spectroscopically pure 5-benzyl-1,3-dihydroxy-2,4-diphenyl pyran as single isomer in good yield, which could be assumed formal trimerization of phenylacetaldehyde.

The catalytic carbon-carbon formation of aldol reactions through an introduction of Ti(IV)[1] complex, $[Cp_2Ti(OTf)_2]$[2] or its chiral derivatives have utilized *O*-silyl enol ether of ketones, esters, thioesters, and *O*-silyl dienolates as nucleophiles.[3] Recent development of double aldol condensation of the acetaldehyde catalyzed by enzyme has emerged as a useful method in controlling the stereospecific and asymmetric carbon center.[4] We now report the double aldol reaction of phenylacetaldehyde (**1**) catalyzed by group 4 metallocene $[Cp_2M(II)]$[5,6] (M = Ti, Zr) (**2**). (eq 1)


$$[Cp_2MCl_2] + 2\,{}^{n}BuLi \xrightarrow[\text{tol, -78 °C}]{200\ PhCH_2\overset{O}{\overset{\|}{C}}H} \qquad (1)$$

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Addition of the 200 equiv of **1** to a solution of **2** prepared from the $[Cp_2MCl_2]$ (M=Ti, Zr) with 2*n*BuLi in toluene at -78 °C produces white solids at room temperature in 24 h, and simple filtration gives spectroscopically pure 5-benzyl-1,3-dihydroxy-2,4-diphenyl pyran (**3**) as single isomer of formal trimerization product of **1** (60%) and evidence for the formation of **3** is based on elemental analysis and mass spectroscopy, IR and NMR spectroscopy and single crystal diffraction studies.[7] Phenylacetaldehyde does react with a catalytic amounts of *n*BuLi, Lewis acid or molecular sieves, however, ^1H NMR spectra of the reaction residues give different from that of **3**. X-ray structure determination of **3** was carried out, and the resulting ORTEP plot and selected bond distances and angles of **3** are shown in Figure 1. It confirms the expected oxygen containing six-membered ring geometries, and three bulky phenyl groups are located in equatorial position. Two hydroxy groups are located in axial positions, and distance of HO1···O2 and HO2···O1 is 1.95 (6) Å and 2.03 (5) Å respectively, indicative of intramolecular hydrogen bondings.

Results of the reaction of **2** (M = Ti, Zr) with other aldehydes and diketone are summarized in Table 1. It is interesting to note that the reaction of **1** with **2** (M = Ti) in THF gives 10% of 2,4-diphenyl-2-butenal (**4**), very small amount of **3**, and a large amount of intractable materials. Benzaldehyde does not react with **2**, and acetaldehyde does catalytically react with **2** to yield oligomeric products. Reaction of 2,4-pentanedione with **2** (M = Ti) in THF undergoes stoichiometric reaction to give $[Ti(acac)_3]$, which has been previously prepared from the reaction of ammonium salt of acetylacetone and $TiCl_3$.[8]

Catalytic double aldol reaction of **1** by **2** is most

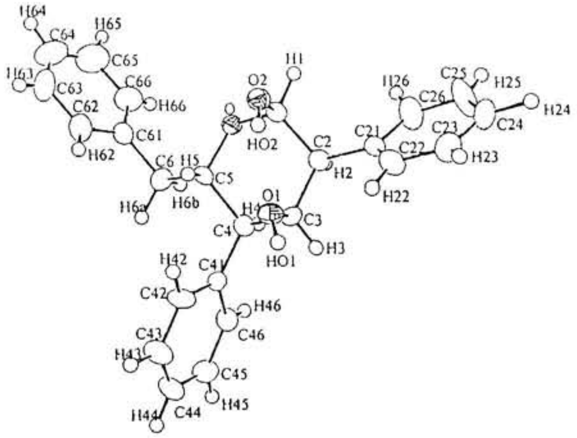


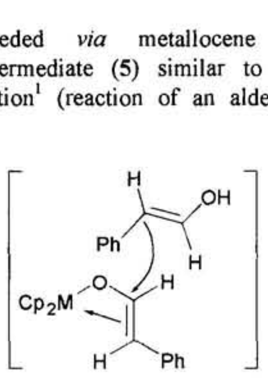
Figure1. ORTEP drawing of **3**. Hydrogen atoms have been included in order to indicate the stereochemistry. Selected bond distances (Å) and angles (deg): O-C1 1.409(6), O-C5 1.431(7), O1-C3 1.428(7), O2-C1 1.400(8), C1-C2 1.533(8), C2-C3 1.517(9), C2-C21 1.507(8), C3-C4 1.532(8), C4-C5 1.535(8), C4-C41 1.489(8), C5-C6 1.510(8), C6-C61 1.496(9), C1-O-C5 116.1(4), O-C1-O2 112.1(5), O-C1-C2 110.5(5), O2-C1-C2 111.6(5), C1-C2-C3 109.4(5), C1-C2-C21 113.5(5), C3-C2-C21 117.9(5), O1-C3-C2 107.9(5), O1-C3-C4 110.2(5), C2-C3-C4 109.6(5), C3-C4-C5 108.8(5), C3-C4-C41 114.0(5), C5-C4-C41 114.3(5), O-C5-C4 111.0(4), O-C5-C6 107.4(5), C4-C5-C6 111.8(5), C5-C6-C61 115.6(5).

Table 1. Titanocene and zirconocene mediated catalytic and stoichiometric activation of aldehydes and diketone

Run	Aldehydes or diketone	Product	Yield/ %[a]	Solvent used
1[b]	**1**	**3**	60	toluene
2[c]	**1**	**4**	10	THF
3[b]	benzaldehyde	no reaction	-	toluene
4[b]	acetaldehyde	intractable oligomers[e]	-	toluene
5[d]	2,4-pentanedione	$[Ti(acac)_3]$	60	THF

[a]Isolated yield after fitration (**3**), silica gel prep. TLC (**4**), and recrystallization $[Ti(acac)_3]$, respectively. [b]Reaction of 200 equiv of aldehyde with **2** (M = Ti, Zr) in toluene. [c]Reaction of 200 equiv of **1** with **2** (M = Ti) in THF. [d]Reaction of 5 equiv of 2,4-pentanedione with **2** (M = Ti) in THF. [e]Based on the ^1H NMR spectrum.

probably proceeded *via* metallocene mediated aldol condensation intermediate (**5**) similar to that reported by Mukaiyama reaction[1] (reaction of an aldehyde with a silyl enol ether).



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Even though isolation of **5** was failed, the characteristic deep blue color of stoichiometric mixture of [Cp_2TiCl_2], 2*n*BuLi and one equiv of **1** in toluene could be observed, which would be speculated for the formation of Ti(III) complex. Protons of enol form of **1** required for aldol reaction could be observed at δ 6.68 (c), 6.49 (c) on ^{1}H NMR spectrum of reaction mixture of [Cp_2TiCl_2], 2*n*BuLi and 200 equiv of **1** in tol-d_8. Inertness of benzaldehyde toward **2** also supports that the formation of enol form is very important in this reaction. Approach of two enol form of **1** to **5** to minimize steric demands among Cp rings and two phenyl groups could give **3**.

Stereospecific double aldol reaction of **1** catalyzed by **2** is an interesting reactions with potential applications in organic synthesis, and extends the known reactivity of group 4 metallocene complexes. Efforts to elucidate the precise mechanism for the catalytic formation of **3** are currently in progress.

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7 Typical experimental procedure: Phenylacetaldehyde (0.58 mL, 5 mmol) was added to a reaction mixture prepared from [Cp_2TiCl_2] (6.2 mg, 0.025 mmol) and *n*-butyllithium (31 μL of 1.6 M, 0.05 mmol) in toluene (5 mL) at -78 °C. The reaction slurry was stirred at room temperature for 24 h. Resulting solid was filtered, washed with cold ether (3 x 3 mL) and dried under reduced pressure. It gives 0.39 g of **3** (60%). Selected data for **3**: Anal. Found: C, 79.6; H, 6.68%. Calcd for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71%. HRMS Calcd for $C_{24}H_{23}O_2$ ([M-OH]$^+$) m/e; 343.1698, found m/e 343.1714; ν_{max}(film)/cm^{-1} 3546 (m), 3452 (m), 3087 (vw), 3061 (w), 3028 (m), 3003 (vw), 2913 (m), 1603 (w), 1496 (s), 1453 (s), 1319 (w), 1266 (m), 1136 (s), 1072 (vs), 1046 (s), 1032 (s), 884 (vw), 751 (s), 736(s), 700 (vs) cm^{-1}. δ_H (acetone-d_6, 300MHz) δ 7.80-7.31 (m, 15H, phenyl protons), 6.39 (d, J = 7.2 Hz, OH_6), 5.60 (br s, H_1), 5.13 (ddd, J = 11.1, 9.8, 2.5 Hz, H_5), 4.91 (d, J = 7.5 Hz, OH_7), 4.45 (br s, H_3), 3.36 (t, J = 2.3 Hz, H_2), 3.14 (dd, J = 11.1, 2.4 Hz, H_4), 2.91 (dd, J = 14.3, 2.3 Hz, H_a of CH_2), 2.76 (dd, J = 14.3, 8.5 Hz, H_b of CH_2); δ_C (acetone-d_6, 75.45 MHz) δ 142.2, 141.1, 140.7 (all s, *ipso* carbons of phenyl), 130.7, 130.7, 130.0, 129.4, 129.2, 129.0, 127.8, 127.5, 127.0 (all s, phenyl carbons), 96.6 (s, C-H_1), 74.9 (s, C-H_3), 68.3 (s, C-H_5), 54.6 (s, C-H_4), 50.4 (s, C-H_2), 40.4 (s, CH_2); Slow diffusion of ether into the concentrated acetone solution of **3** afforded a colorless crystal suitable for diffraction studies. **3** crystallizes in space group *Pnca* with a = 17.487(7) Å, b = 22.777(2) Å, c = 9.676(1) Å, V = 3854.0(16) Å^3, d_{calcd} = 1.242 g cm^{-3}, Z = 8 and T = 25 °C.

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