Cp_2TiCl-Mediated Selective Reduction of α,β-Epoxy Ketones

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Introduction

The selective reduction of α,β-epoxy ketones to β-hydroxy ketones is synthetically important because aldols are key intermediates in the construction of numerous natural products. Several methods have been developed to perform this conversion. Examples include the following: SmI_2,[1] Li/NH_3,[2] Al amalgam,[3] $Bu_3SnH/AIBN$,[4] $H_2/Pd/C$,[5] PET,[6] and chalcogenide-based[7−9] reductions. In this paper, we disclose a novel reaction for the selective reduction of α,β-epoxy ketones. Our approach relies on the utilization of Cp_2TiCl as the active species.[10] Titanocene reagents are operative in pinacol coupling of aldehydes and ketones.[11] The reaction proceeds through the formation of a ketyl radical that dimerizes readily. Cp_2TiCl also induces the deoxygenation of epoxides[12] via a β-alkoxy radical, which derives from the low-valent metal complex through single electron transfer (SET).[13] Thus, the treatment of a substrate in which a ketone function resides adjacent to an epoxide function with 2 equivalents of Cp_2TiCl should result in the selective reduction of the oxirane moiety (Scheme 1).

Scheme 1

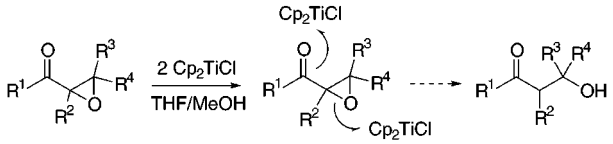
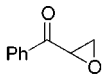
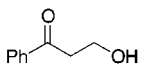
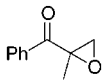
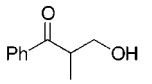
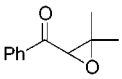
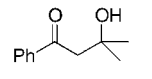
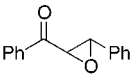
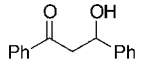
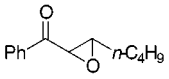
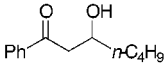
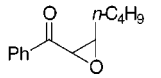
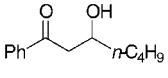
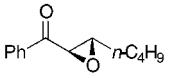
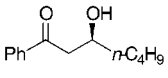
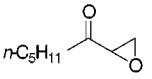
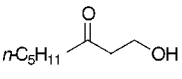
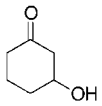
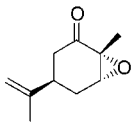
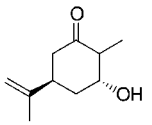


Table 1. Examples of Selective Reduction of α,β-Epoxy Ketones

entry	substrate	product	yield[a]
1			86
2			90
3			74[b]
4			59
5			79
6			83
7			81[c]
8			89[b]
9			80
10			65[b,d]

[a] Isolated yields. [b] Reaction time: 45 min from −78 to 0 °C. [c] Enantiomeric excesses were determined by HPLC using a Chiralcel OD column. [d] Product obtained as a 9/1 mixture of epimers.

Results and Discussion

To investigate this conjecture, various α,β-epoxy ketones were reacted with Cp_2TiCl for 15 min at −78 °C in THF/MeOH (Table 1). The low-valent titanium(III) complex was readily prepared by the in situ reduction of 2.5 equiv of Cp_2TiCl_2 with 5 equiv of powdered zinc for 45 min at room temperature. In most cases, the overall yields were satisfactory. The selective reduction of 2,3-epoxy-1-phenylpropan-1-one afforded the expected aldol product (entry 1). The reaction was also successfully extended to di- and trisubstituted epoxy ketone systems leading to primary (entry 2), benzylic (entry 4), and

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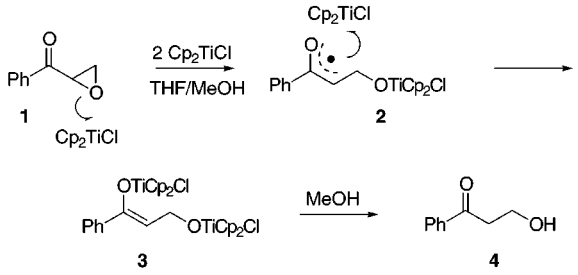
Scheme 2



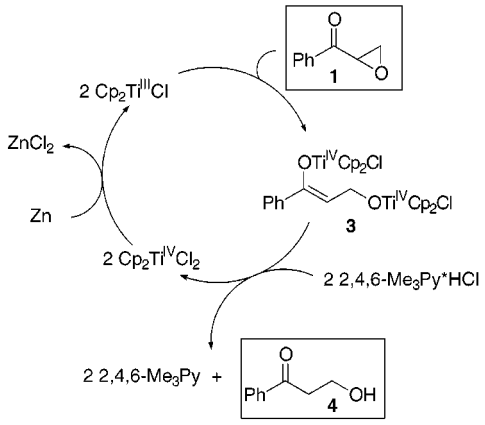
tertiary (entry 3) alcohols, respectively. The effect of the stereochemistry of the starting epoxide was also studied: Both *trans*- (entry 5) and *cis*-2,3-epoxy-1-phenylheptan-1-one (entry 6) reacted similarly toward Cp_2TiCl to give comparable yields of reduced 3-hydroxy-1-phenylheptan-1-one. Since the stereochemical integrity of the β-position should remain intact during the reductive process, the synthesis of optically enriched aldols appeared feasible. Accordingly, treatment of (2*R*,3*S*)-epoxy-1-phenylheptan-1-one[14] (80% ee) under the aforementioned conditions led to (*S*)-3-hydroxy-1-phenylheptan-1-one in 81% yield without any loss of optical purity (entry 7). The procedure worked equally well on aliphatic (entry 8) and cyclic ketone (entry 9) systems. It was gratifying that our method worked on a carvone-derived epoxide (entry 10) for which a previous SmI_2-mediated attempt had failed.[1]

A postulated reaction mechanism is illustrated in Scheme 2 for the reductive ring opening of 2,3-epoxy-1-phenylpropan-1-one **1**. The sequential single electron transfer from Cp_2TiCl to the oxirane and thereafter to the carbonyl generates, in the first step, a radical intermediate **2** which, upon reaction with a second equivalent of Cp_2TiCl, produces enolate β-alcoholate **3**. Subsequent protonation of **3** by methanol affords 3-hydroxy-1-phenylpropan-1-one **4**. The emergence of **3** as intermediate during this transformation was prompted by the observation that, when methanol-*d* was used as cosolvent instead of MeOH, the reduced product **4** was deuterated α to the carbonyl (65% isotopic enrichment).

A similar result (84% yield) was obtained on substrate **1** when a catalytic amount of Cp_2TiCl_2 (20 mol %) in THF was used in the presence of powdered Zn (5 equiv) and collidine hydrochloride (3 equiv). The latter served not only for the double protonation of intermediate **3**, but also for the regeneration[15] of the starting titanocene(IV) dichloride reagent which is in situ reduced by stoichiometric Zn to redox-active Cp_2TiCl. This completes the catalytic cycle (Scheme 3).

In conclusion, we have shown that low-valent Cp_2TiCl selectively reduces selected α,β-epoxy ketones to the corresponding aldol products under mild conditions. The procedure was applied to the synthesis of a chiral, nonracemic β-hydroxy ketone. A catalytic titanocene system was also developed to accomplish the reductive conversion.

Scheme 3



Experimental Section

General Methods. ^1H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz using residual $CHCl_3$ (7.25 ppm) and $CDCl_3$ (77 ppm) as internal standard, respectively. Flash column chromatography was performed on Merck silica gel (60 Å, 230−400 mesh). All reactions were performed under Ar using freshly distilled THF (over Na/benzophenone). Reagents were purchased from Aldrich Chemical Co.

General Procedure for the Selective Reduction of α,β-Epoxy Ketones: 3-Hydroxy-1-phenylpropan-1-one[16] 4 (Entry 1). Stoichiometric Procedure. THF (5 mL) was added to a mixture of Cp_2TiCl_2 (0.42 g, 2.5 equiv) and powdered Zn (0.22 g, 5.0 equiv) in an oven-dried flask purged with argon. The heterogeneous solution was stirred vigorously for 45 min at room temperature. The green slurry of Cp_2TiCl was cooled to −78 °C, and a solution of 2,3-epoxy-1-phenylpropan-1-one (0.1 g, 0.68 mmol, 1 equiv) in THF/MeOH (1.3 mL/0.7 mL) was added dropwise. After 15 min at −78 °C, the reaction was transferred to an Erlenmeyer flask and quenched, at room temperature, with 10 mL of 10% K_2CO_3. The mixture was filtered through a fritted glass funnel, and the aqueous layer was extracted twice with Et_2O and once with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to column chromatography over silica gel (eluent: hexane/AcOEt = 1/1) to yield 3-hydroxy-1-phenylpropan-1-one: oil, 0.087 g, 86%.

Catalytic Procedure. THF (5 mL) was added to a mixture of Cp_2TiCl_2 (0.034 g, 0.2 equiv, cat.), powdered Zn (0.22 g, 5 equiv), and collidine hydrochloride (0.32 g, 3 equiv) in an oven-dried flask purged with argon. The heterogeneous solution was stirred vigorously for 45 min at room temperature. The green slurry of Cp_2TiCl was cooled to −78 °C, and a solution of 2,3-epoxy-1-phenylpropan-1-one (0.1 g, 0.68 mmol, 1 equiv) in 2 mL of THF was added dropwise. After 15 min at −78 °C, the reaction was slowly warmed to −30 °C over a period of 1 h. The reaction was worked up as before (vide supra) to yield 3-hydroxy-1-phenylpropan-1-one: 0.085 g, 84%; ^1H NMR δ 2.83 (t, J = 5.5 Hz, 1H), 3.21 (t, J = 5.5 Hz, 2H), 4.01 (q like, J = 5.5 Hz, 2H), 7.42−7.48 (m, 2H), 7.53−7.60 (m, 1H), 7.92−7.96 (m, 2H).

3-Hydroxy-2-methyl-1-phenylpropan-1-one[17] (entry 2): oil, 90%; ^1H NMR δ 1.24 (d, J = 7.3 Hz, 3H), 2.26−2.34 (m, 1H), 3.62−3.98 (m, 3H), 7.45−7.61 (m, 3H), 7.94−7.98 (m, 2H).

3-Hydroxy-3-methyl-1-phenylbutan-1-one[18] (entry 3): oil, 74%; ^1H NMR δ 1.34 (s, 6H), 3.44 (s, 2H), 4.16 (s, 1H), 7.44−7.50 (m, 2H), 7.55−7.61 (m, 1H), 7.92−7.96 (m, 2H).

3-Hydroxy-1,3-diphenylpropan-1-one[19] (entry 4): oil, 59%; ^1H NMR δ 3.37 (d, J = 6.1 Hz, 2H), 3.60 (d, J = 3.0 Hz, 1H), 5.35 (dt, J = 3.0, 6.1 Hz, 1H), 7.25−7.61 (m, 8H), 7.93−7.97 (m, 2H).

(14) This compound was prepared by the Sharpless asymmetric epoxidation of (*E*)-1-phenylhept-2-en-1-ol, followed by MnO_2 oxidation of the resulting epoxy alcohol, see: Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. O.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.

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3-Hydroxy-1-phenylheptan-1-one[20] (entries 5−7): oil, 79−83%; ^{1}H NMR δ 0.91 (t, J = 7.3 Hz, 3H), 1.23−1.63 (m, 6H), 3.02 (dd, J = 8.5, 17.7 Hz, 1H), 3.16 (dd, J = 2.4 Hz, 17.7 Hz, 1H), 3.28 (d, J = 3.0 Hz, 1H), 4.15−4.24 (m, 1H), 7.43−7.60 (m, 3H), 7.92−7.96 (m, 2H).

1-Hydroxyoctan-3-one[9] (entry 8): oil, 89%; ^{1}H NMR δ 0.86 (t, J = 7.0 Hz, 3H), 1.18−1.33 (m, 4H), 1.51−1.61 (m, 2H), 2.41 (t, J = 7.3 Hz, 2H), 2.61 (brs, 1H), 2.64 (t, J = 5.2 Hz, 2H), 3.81 (m, 2H).

3-Hydroxycyclohexanone[16] (entry 9): oil, 80%; ^{1}H NMR δ 1.66−2.34 (m, 7H), 2.40 (dd, J = 7.3, 14.0 Hz, 1H), 2.65 (dd, J = 4.3, 14.0 Hz, 1H), 4.14−4.22 (m, 1H).

(3*R*,5*R*)-3-Hydroxy-5-isopropenyl-2-methylcyclohexanone[8] (Entry 10). This compound was obtained as a 9:1 mixture of epimers in a combined yield of 65%. For the major isomer: (2*R*,3*R*,5*R*)-3-Hydroxy-5-isopropenyl-2-methyl-cyclohexanone (oil): ^{1}H NMR δ 1.10 (d, J = 6.8 Hz, 3H), 1.65 (m 1H), 1.74 (s, 3H), 1.84 (m, 1H), 2.14 (m, 1H), 2.26 (t, J = 12.7 Hz, 1H), 2.44−2.57 (m, 2H), 2.84 (m, 1H), 4.30 (m, 1H), 4.75 (s, 1H), 4.77 (s, 1H).

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Supporting Information Available: Reproductions of ^{1}H NMR spectra of the products described in entries **1**−**10**. This material is available free of charge on the Internet at http://pubs.acs.org.

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