Organozirconocenes in Organic Synthesis: Tandem Epoxide Rearrangement-Carbonyl Addition

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Summary: Addition of catalytic amounts of AgClO₄ to a mixture of organozirconocenes and epoxides results in the rapid formation of chain-extended secondary alcohols.

Epoxides have become highly popular building blocks in organic synthesis in recent years. To a great extent, this development was influenced by the discovery of enantioselective protocols for the formation of functionalized epoxides such as the Sharpless epoxidation and procedures for the diastereoselective ring-opening of epoxides with organometallic reagents.[1] In this paper, we report a highly efficient tandem epoxide rearrangement–carbonyl addition reaction sequence with organozirconocenes. Key features of this new methodology are (1) a rapid opening of the epoxide ring followed by a [1,2] hydride shift in the presence of in situ prepared cationic zirconocene complexes; (2) a C,C-bond formation via transfer of the alkenyl or alkyl ligand from the zirconocene to the aldehyde intermediate; (3) the use of highly functionalized (ester, alkene, silyl ether) Lewis acid-sensitive substrates.

As part of our studies of organozirconocene derivatives in organic synthesis,[2] we decided to investigate their reactions with epoxides in the presence of Lewis acid additives. Alkyl- and alkenylzirconocenes 4 are easily obtained by hydrozirconation of alkenes and alkynes with zirconocene hydrochloride 3.[3]
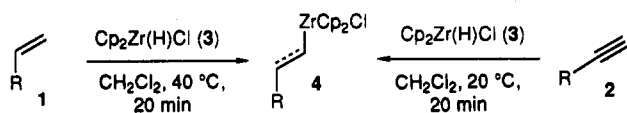
In the presence of 1 equiv of Al(OEt)₃, copper(I)-catalyzed addition of in situ prepared (*E*)-[(*tert*-butyldimethylsilyl)oxy]zirconocene 6 to vinyl epoxide 7 resulted in a 23% yield of an *E:Z* (1:1) mixture of diene 8 after a 12-h reaction time (Scheme I). In contrast, addition of 5 mol % of AgClO₄[4,5] to a mixture of zirconocene 6 and epoxide 7 led to a rapid conversion to the secondary alcohol

Scheme I
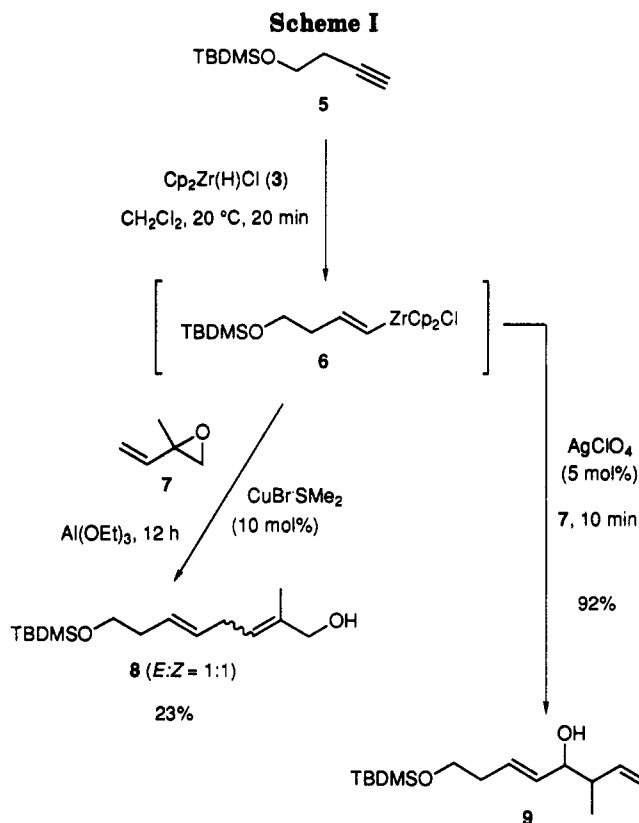
9 in 92% yield. Analogous transformations were observed with a series of epoxides and alkenyl as well as alkylzirconocenes (Table I). In the absence of AgClO₄, no reaction between epoxides and organozirconocenes was detected.

The mechanism of the silver(I)-catalyzed reaction of organozirconocenes with epoxides is likely to involve an initial Cp₂RZr⁺-induced epoxide opening,[7] followed by a

(1) For a review of epoxide chemistry, see: Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* 1983, *39*, 2323.

(2) (a) Wipf, P.; Smitrovich, J. H. *J. Org. Chem.* 1991, *56*, 6494. (b) Wipf, P.; Xu, W. *Synlett* 1992, 718. (c) Wipf, P. *Synthesis,* in press.

(3) (a) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* 1976, *15*, 333. (b) Labinger, J. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8; pp 667–702. Zirconocene hydrochloride was prepared from Cp₂ZrCl₂ according to Buchwald's procedure: Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Tetrahedron Lett.* 1987, *28*, 3895.

(4) (a) Matsumoto, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* 1988, *29*, 6935. (b) Matsumoto, T.; Hosoya, T.; Suzuki, K. *J. Am. Chem. Soc.* 1992, *114*, 3568.

(5) The same product, but a reduction in the reaction rate, was observed with other silver(I) salts such as AgOTf:
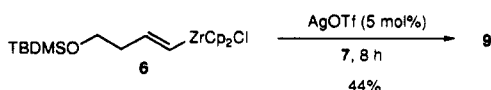
(6) A typical procedure. 1-Phenyl-3-octen-2-ol (14). A mixture of 100 mg (1.22 mmol, 1.2 equiv) of 1-hexyne (12) and 313 mg (1.22 mmol, 1.2 equiv) of Cp₂Zr(H)Cl in 4 mL of CH₂Cl₂ was stirred at 20 °C for 10 min. To the resulting solution was added a solution of 122 mg (1.02 mmol, 1.0 equiv) of styrene oxide (13) in 4 mL of CH₂Cl₂ followed by 11 mg (0.05 mmol, 0.05 equiv) of AgClO₄. After being stirred for 10 min, the reaction mixture was poured into saturated aqueous NaHCO₃ solution and extracted with EtOAc (3×). The combined organic layers were dried (Na₂SO₄), filtered over SiO₂, and concentrated in vacuo. The oily residue was purified by silica gel chromatography (EtOAc/hexanes (1:4) to give 181 mg (87%) of 14 as a colorless oil: IR (CHCl₃) 3370, 3063, 3028, 2957, 2926, 2859, 1603, 1495, 1094, 1076, 1030, 970, 747, 700 cm⁻¹; ¹H NMR δ 7.35–7.23 (m, 5 H), 5.64 (dt, 1 H, *J* = 15.4, 6.5 Hz), 5.55 (dd, 1 H, *J* = 15.4, 6.4 Hz), 4.31 (q, 1 H, *J* = 6.4 Hz), 2.88–2.82 (m, 2 H), 2.06 (q, 2 H, *J* = 6.5 Hz), 1.97 (s, 1 H), 1.42–1.29 (m, 4 H), 0.93 (t, 3 H, *J* = 6.9 Hz); ¹³C NMR δ 138.1, 132.2, 131.9, 129.6, 128.3, 126.3, 73.6, 44.1, 31.8, 31.2, 22.1, 13.9; MS (EI) *m/z* (relative intensity) 204 (M⁺, 1), 186 (2), 143 (3), 129 (4), 113 (60), 95 (50), 92 (90), 57 (100).

(7) For the isomerization of α-pinene oxide to the allylic alcohol over solid ZrO₂, see: Arata, K.; Tanabe, K. *Chem. Lett.* 1979, 1017.

(8) Very recently, Suzuki and co-workers noted indeed an acceleration of the addition of organozirconocenes to aldehydes by addition of Ag-(I)-salts: (a) Maeta, H.; Hashimoto, T.; Hasegawa, T.; Suzuki, K. *Tetrahedron Lett.* 1992, *33*, 5965. These observations are in accord with our postulated mechanism on the AgClO₄-induced reaction of zirconocenes with epoxides.

Table I. Hydrozirconation of Alkynes and Alkenes Followed by AgClO₄-Catalyzed Addition to Epoxides[6]

| entry	alkyne or alkene	epoxide structure	no.	product structure[a]	no.	yield[b] (%)
1	**5**		**10**		**11**	73
2	**12**		**13**		**14**	87
3	**12**		**15**		**16**	56
4	**12**		**17**		**18**	75
5	**19**		**7**		**20**	68
6	**21**		**13**		**22**	75
7	**21**		**7**		**23**	59

[a] All secondary branched alcohols in this series were obtained as 1:1 mixtures of diastereomers. [b] Yields are not optimized and are based on epoxide and isolated alcohol; alkyne/alkene:Cp₂Zr(H)Cl:epoxide:AgClO₄ = 1.20:1.20:1.00:0.05 equiv.

Scheme II
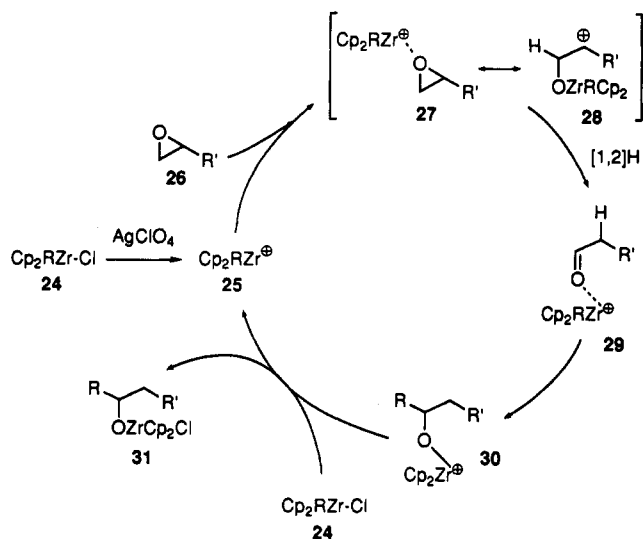
Scheme III
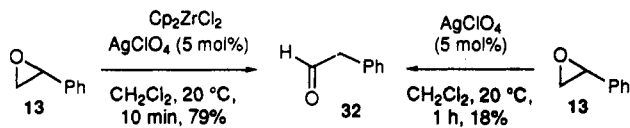
[1,2]H shift and nucleophilic attack[8] on the resulting aldehyde **29** (Scheme II). The Lewis acidic Cp₂RZr⁺ (**25**), initially prepared by Ag(I)-induced chloride abstraction from Cp₂RZrCl (**24**), is regenerated by chloride ion transfer from **24** to alkoxyzirconocene cation **30**.

Control reactions of epoxide **13** with 1 equiv of zirconocene dichloride and AgClO₄ (5 mol %) revealed a rapid formation of aldehyde **32** (Scheme III).[9] In the absence of Cp₂ZrCl₂, **32** was still formed by Ag(I)-catalysis,[10] but

Scheme IV
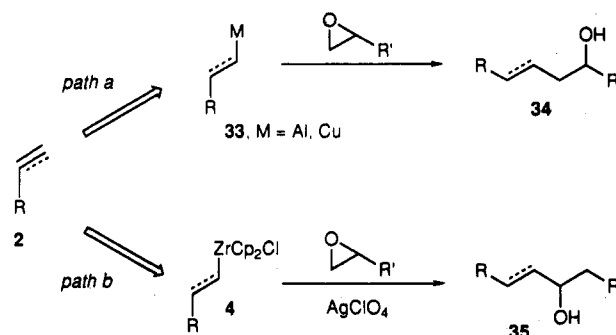
the reaction was sluggish, and several side products were observed by TLC analysis of the crude reaction mixture.

The well-known skeletal rearrangements observed by treatment of epoxides with Grignard reagents[11] generally lead to mixtures of secondary and tertiary alcohols and halohydrins and require high temperatures and apolar solvents (e.g., benzene, reflux).[12,13] The organoaluminum-induced conversion of epoxides is highly selective and tolerates additional functionality, but this method requires the use of exceptionally bulky methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide (MABR) and stops at the aldehyde stage.[14] In contrast, the novel epoxide rearrangements with zirconocenes reported herein allow the use of highly functionalized substrates and proceed rapidly at ambient temperatures. Additionally, a new C,C-bond is formed by transfer of alkenyl or alkyl substituents from zirconium to the aldehyde carbonyl group. If desired, the aldehyde can be obtained by the use of commercially readily available catalytic zirconocene dichloride in place of organozirconocenes.

Some aspects of the synthetic utility of this transformation are summarized in Scheme IV. Whereas there are many protocols for direct nucleophilic addition of organometallics to epoxides to give alcohols **34** (path a),[15] the use of the organozirconocene/AgClO₄ system represents the first example for the one-pot conversion of alkenes or alkynes to the isomeric alcohols **35** (path b).

Supplementary Material Available: Experimental data (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(9) Only catalytic amounts of Cp₂ZrCl₂ are necessary for this transformation. The conversion of **13** to **32** was complete in 72% yield in 10 min in the presence of 10 mol % Cp₂ZrCl₂ and 2 mol % AgClO₄.

(10) For a related rearrangement of halohydrins with silver salts, see: Nace, H. R.; Crosby, G. A. *J. Org. Chem.* **1968**, *33*, 834.

(11) (a) House, H. O. *J. Am. Chem. Soc.* **1955**, *77*, 3070. (b) Naqvi, S. M.; Horwitz, J. P.; Filler, R. *J. Am. Chem. Soc.* **1957**, *79*, 6283.

(12) For a recent review, see: Rickborn, B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Pergamon: Oxford, 1991; Vol. 3; pp 733–775.

(13) For a lithium salt catalyzed epoxide–carbonyl rearrangement followed by a Wittig-olefination, see: (a) Rickborn, B.; Gerkin, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 1693. For the reaction of an alkynyl alane with epoxycyclopentene, see: (b) Crosby, G. A.; Stephenson, R. A. *J. Chem. Soc., Chem. Commun.* **1975**, 287. For TiCl₄-induced epoxy alcohol–aldol rearrangements, see: (c) Maruoka, K.; Hasegawa, M.; Yamamoto, H.; Suzuki, K.; Shimazaki, M.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1986**, *108*, 3827. (d) Shimazaki, M.; Hara, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 5891. (e) Shimazaki, M.; Morimoto, M.; Suzuki, K. *Tetrahedron Lett.* **1990**, *31*, 3335.

(14) (a) Maruoka, K.; Sato, J.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 5449. (b) Maruoka, K.; Ooi, T.; Yamamoto, H. *Tetrahedron* **1992**, *48*, 3303. (c) Maruoka, K.; Ooi, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 6431.

(15) See, for example: (a) Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693. (b) Lipshutz, B. H.; Kato, H. *Tetrahedron Lett.* **1991**, *32*, 5647. (c) Alexakis, A.; Mangeney, P.; Ghribi, A.; Jachiet, D.; Normant, J. F. *Phil. Trans. R. Soc. Lond.* **1988**, *A 326*, 557 and references cited therein.