Tetrahedron Letters, Vol. 33, No. 51, pp. 7873-7876, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Preparation and Reactions of Alkoxy Allylic Zirconium Reagents Derived from Acetals of α,β-Unsaturated Aldehydes: Remarkable Substituent Effects on Regioselectivity

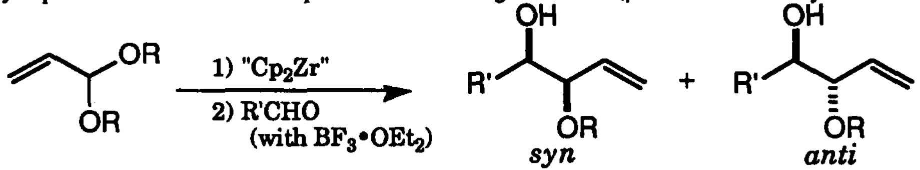
Hisanaka Ito, Takeo Taguchi* and Yuji Hanzawa

Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

Key Words: zirconocene; alkoxy allylic zirconium reagent; allylic 1,2-diols; homoenolate anion

Abstract: Alkoxy allylic zirconium reagents, prepared from acetals of α,β-unsaturated aldehydes and "Cp_2Zr", react with carbonyl compounds to give 1,2-diols or γ-hydroxy aldehyde derivatives.

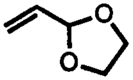
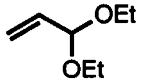
Diastereoselective addition reactions of γ-alkoxy allylic organometallics to carbonyl compounds are an ideal means for the construction of allylic 1,2-diols, important building blocks for natural products synthesis. Reactivity and diastereoselectivity of these reagents have been studied using many kinds of metals.[1] Another useful oxygen functionalized allylic metal is an α-alkoxy allylic metal reagent which may possibly be an important homoenolate anion equivalent of aldehyde. Generation and reactions of this anion have been studied over the past 10 years.[2] We recently developed a new method for generating allylic and allenic/propargylic zirconium reagents by reactions of allylic ethers or propargylic ethers with zirconocene equivalent ("Cp_2Zr")[3] via the elimination of the alkoxyl group at the β-position of zirconacycles.[4] In continuing our work, we found that alkoxy allylic zirconium reagents could be prepared from the acetals of α,β-unsaturated aldehydes. This paper presents the method for this preparation along with diastereoselective reactions of γ-alkoxy allylic zirconium reagents with aldehydes and ketones and spectral evidence for the (Z)-γ-alkoxy allylic zirconium intermediate. Generation of α- or γ-alkoxy allylic zirconium was found to be highly dependent on the substitution pattern of the starting acetals of α,β-unsaturated aldehyde.



R= Et or $-CH_2CH_2-$ **Scheme 1** R=Et or CH_2CH_2OH

Reactions of allylic zirconium reagents derived from acrolein ethylene acetal (Entries 1-10) and diethyl acetal (Entries 11-18) with carbonyl compounds are summarized in Table 1. Reaction of the *in situ* generated allylic zirconium reagent prepared from acrolein ethylene acetal with benzaldehyde proceeded smoothly to give a mixture of diastereomers in 70% yield, favoring the *anti*-allylic 1,2-diol derivative (Entry 1). Reactions with aliphatic aldehyde, however, proceeded slowly (Entries 3, 5, 13 and 15). To improve the yield, reactions were carried out in the presence of $BF_3 \cdot OEt_2$ with significantly positive effect. It is of interest to note that in the $BF_3 \cdot OEt_2$-catalyzed reaction, the *syn*-allylic 1,2-diol derivative became the preferred isomer (Entries 2, 4, 6, 8, 12, 14 and 16).[5] In the case of the α,β-unsaturated aldehyde, selective 1,2-addition occurred (Entries 7 and 8). These reagents also reacted with ketone in the presence of $BF_3 \cdot OEt_2$ to give 1,2-diol derivatives (Entries 10 and 18).

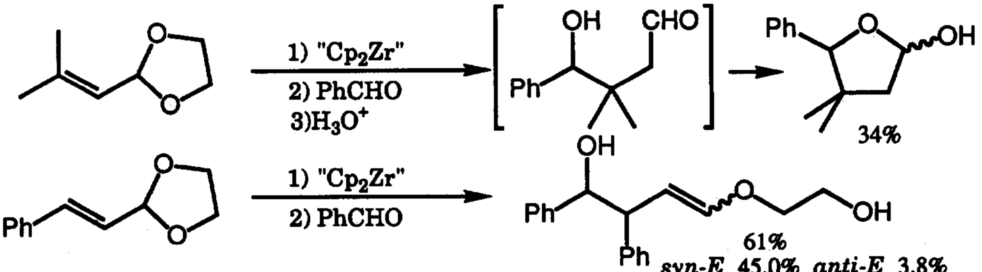
Table 1. Reactions of γ-Alkoxy Allylic zirconium Reagents with Carbonyl Compounds.

Entry	Substrate	Carbonyl Compound	Lewis acid^{a}	Yield (%)^{b}	*syn* vs *anti*^{c,d}
1		PhCHO	A	70	35 : 65
2			B	82	71 : 29
3		cy-HexylCHO	A	40	13 : 87
4			B	61	67 : 33
5		β-Phenylpropionaldehyde	A	---^{e}	--------
6			B	59	67 : 33
7		Cinnamaldehyde	A	52	40 : 60
8			B	71	69 : 31
9		Diethylketone	A	---^{e}	--------
10			B	60	--------
11		PhCHO	A	80	57 : 43
12			B	72	78 : 22
13		cy-HexylCHO	A	59	14 : 86
14			B	85	77 : 23
15		β-Phenylpropionaldehyde	A	---^{e}	--------
16			B	84	68 : 32
17		Diethylketone	A	---^{e}	--------
18			B	43	--------

a) A: No Lewis acid was used. B: 1.3 eq. of $BF_3 \cdot OEt_2$ was used. b) Isolated yield. c) Ratio was determined by 300 MHz ^{1}H-NMR. d) Relative stereochemistries were determined as described in reference 6. e) A complex mixture.

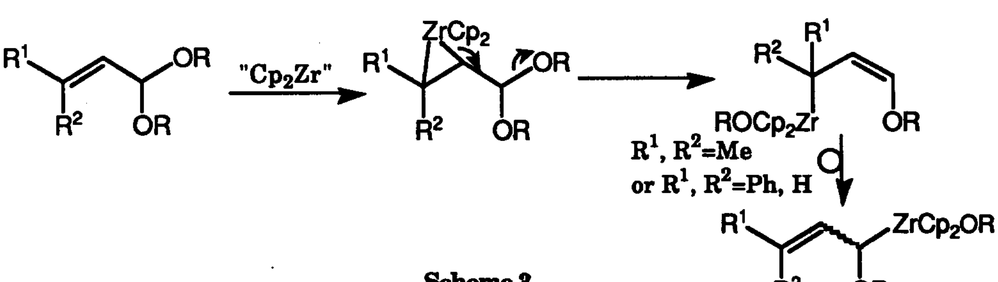
A γ-alkoxy allylic zirconium intermediate would thus appear present, assuming addition of the aldehyde to proceed through the S_E' pathway. The intermediary of γ-alkoxy allylic zirconium reagent was confirmed by an NMR experiment (*vide infra*).

In the case of prenylaldehyde ethylene acetal, following acidic workup, the γ-lactol derivative derived from γ-hydroxy aldehyde derivative was obtained as the sole product (Scheme 2).[7] The allylic zirconium species would thus appear to function as a homoenolate anion of aldehyde. Similar reactivity of the allylic zirconium derived from cinnamaldehyde ethylene acetal was also observed and the intermediate formation of the enol ether derivative was confirmed by isolating the enol ether derivative under neutral workup as shown in Scheme 2.[8] One possible explanation is that steric repulsion between substituents and bulky zirconium metal transfers zirconium to a less hindered site in the allyl unit to give α-alkoxy allylic zirconium, which subsequently reacts with aldehyde through S_E' pathway (Scheme 3).



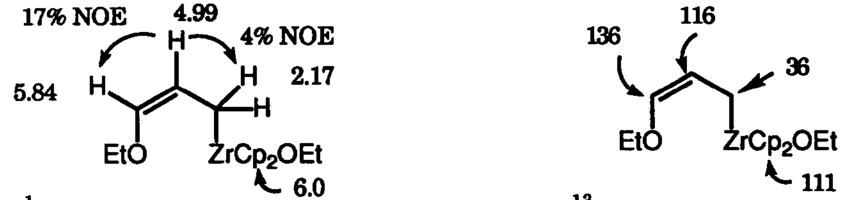
syn-E 45.0% *anti-E* 3.8%
syn-Z 8.8% *anti-Z* 42.4%

Scheme 2



Scheme 3

NMR studies (^{1}H, ^{13}C, and NOE experiment) on the *in situ* generated organozirconium intermediate prepared from acrolein diethyl acetal and "Cp_2Zr" clearly indicated the (Z)-γ-ethoxy allylic zirconium intermediate to exist. Each chemical shift of ^{1}H-(400 MHz) and ^{13}C-(100.6 MHz) NMR and NOE spectra in benzene-d_6 are shown in Scheme 4.[9]



^{1}H-NMR chemical shift (ppm) **Scheme 4** ^{13}C-NMR chemical shift (ppm)

Two olefinic hydrogens at 4.99 ppm (dt, J=6.1, 9.1 Hz, β-H) and 5.84 ppm (dt, J=6.1, 1.2 Hz, γ-H) in the ^{1}H-NMR spectrum of *in situ* generated intermediate demonstrated the presence of the Z-enol ether system. The stereochemistry of the intermediate was further confirmed by significant NOE correlation (17%) between two olefinic hydrogens. The presence of two ethoxy signals in ^{1}H-(CH_2 = 3.94 and 3.71 ppm, CH_3 = 1.29 and 1.10 ppm) and ^{13}C-(CH_2 = 69 and 67 ppm, CH_3 = 20 and 16 ppm) NMR spectra also support the structure in Scheme 4. The *in situ* generated active species is thus clearly shown to be (Z)-γ-ethoxy allylic zirconium. It should be pointed out that the organozirconium intermediate exists mainly as the Z-stereoisomer as indicated by NMR analysis.[10] Although direct evidence could not be obtained by NMR study, the ether oxygen is most likely coordinated to the zirconium from our earlier studies.[11]

The reactions of zirconium intermediate with aldehydes may proceed through different transition states in the absence/presence of $BF_3{\bullet}OEt_2$ (S_Ei' boat like transition state[12] or S_E2' open chain transition state).

Typical experimental procedure.

Under an argon atmosphere, a solution of acetal (0.65 mmol) in toluene (2 ml) was added to a solution of *in situ* generated $Cp_2Zr(nBu)_2$[13] (0.78 mmol) in toluene at -78 °C and the reaction temperature was raised to room temperature and stirred for 3 h. To the reaction mixture was added a solution of carbonyl compounds (and $BF_3{\bullet}OEt_2$) in toluene (2 ml) at -78 °C followed by stirring at the same temperature for 3 h. 1N HCl was then added and the mixture was extracted with dichloromethane. After the usual workup, the residue obtained was purified by silica gel column chromatography to give a diastereomeric mixture of products.

References and notes

1 a) Takai, K.; Nitta, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 5263-5266. and references cited therein. b) Marshall, J. A.; Gung, W. T. *Tetrahedron Lett.* **1989**, *30*, 2183-2186. c) Marshall, J. A.; Luke, G. P. *J. Org. Chem.* **1981**, *56*, 483-485. γ-Alkoxy allylic zirconium reagents prepared by transmetalation of allyllithium derivatives with zirconocene dichloride were also reported.
d) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Organomet. Chem.* **1985**, *285*, 31-42.
e) Yamamoto, Y.; Saito, Y.; Maruyama, K. *J. Organomet. Chem.* **1985**, *292*, 311-318.

2 For reviews, see: a) Kuwajima, I.; Nakamura, E. *Top. Curr. Chem.* **1990**, *155*, 1-39. b) Hoppe, D. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 932-948. c) Syowell, J. C. *Chem. Rev.* **1984**, *84*, 409-435. d) Werstiuk, N. H. *Tetrahedron* **1983**, *39*, 205-268. e) Recent reports, see: f) Cherkauskas, J. P.; Cohen, T. *J. Org. Chem.* **1992**, *57*, 6-8. g) Gung, B. W.; Smith, D. T.; Wolf, M. A. *Tetrahedron Lett.* **1991**, *32*, 13-16. h) Gung, B. W.; Peat, A. J.; Snook, B. W.; Smith, D. T. *Tetrahedron Lett.* **1991**, *32*, 453-456. i) Marshall, J. A.; Yashunsky, D. V. *J. Org. Chem.* **1991**, *56*, 5493-5495.

3 The *in situ* generation of "Cp_2Zr" was reported by Negishi et al.: a) Negishi, E.; Cederbaum, F. K.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829-2832. See also: b) Swanson, D. R.; Negishi, E. *Organometallics* **1991**, *10*, 825-826 and references cited therein.

4 a) Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 1295-1298. b) Ito, H.; Nakamura, T.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 3769-3772.

5 A similar reversal of diastereoselectivity has been reported. See reference 1e.

6 Stereochemistries of the products were determined by comparison of spectral data with authentic samples. Entries 1; Trost, B. M.; Teraglia, A. *Tetrahedron Lett.* **1988**, *29*, 2931-2934. Entries 11; Koreeda, M.; Tanaka, Y. *J. Chem. Soc., Chem. Commun.* **1982**, 845-847. Products of entries 13 and 15 were determined as follows; 1) reduction (Pd/C, H_2) of products. 2) comparison of spectral data of authentic samples prepared by OsO_4 oxidation of the corresponding Z-olefin followed by mono ethyl etherification of diol (EtI, NaH). Products of entries 3 and 5 were determined by derivation to the products of Entries 13 and 15 by reduction of the primary hydroxyl group (TsCl, Py and lithium triethylborohydride). Product of entry 7 was determined by reduction (Pd/C, H_2) of the products following comparison of spectral data of authentic samples prepared by reduction (Pd/C, H_2) of the product of Entry 5.

7 The low yield was possibly due to the difficulty in generating zirconacyclopropane owing to the steric repulsion of tri-substituted olefin and "Cp_2Zr". See reference 4a.

8 Stereochemistries of the reaction products of cinnamaldehyde ethylene acetal were determined as follows; stereochemistries of enol ethers were determined by NOE experiment (*Z*; 15%, *E*; 0%). Relative stereochemistries were determined by comparison of spectral data of 3,4-diphenyl-γ-lactone derived from the enol ether by acid hydrolysis followed by oxidation (Jones reagent). Sekine, M.; Nakajima, M.; Kume, A.; Hashizume, A.; Hata, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 224-238.

9 For the NMR experiment, a sample was prepared in toluene and filtered under an inert atmosphere to remove LiCl. After vacuum line concentration, the resulting residue was diluted with benzene-d_6. Reaction of the remaining NMR sample with benzaldehyde in the presence of $BF_3 \cdot OEt_2$ at -78 °C proceeded smoothly to give 1,2-diol derivatives.

10 A small amount of isomer (less than 10%) was observed but could not be isolated. Yamamoto et al. claimed *E*-geometry for the γ-alkoxy allylic zirconium intermediate, considering the steric bulk of two cyclopentadienyl ligands. However, they presented no spectral evidence for this. See reference 1e.

11 a) Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 4469-4472. b) Hoveyda, A. H.; Xu, Z. *J. Am. Chem. Soc.* **1991**, *113*, 5079-5080. c) Hoveyda, A. H.; Xu, Z.; Morken, J. P.; Houri, A. F. *J. Am. Chem. Soc.* **1991**, *113*, 8950-8952.

12 The *anti*-1,2-diol formation; see reference 1a.

13 See references 3 and 4.

(Received in Japan 15 July 1992)