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Unprecedented Reactions of Substituted Styrene Derivatives with Zirconocene-(1-Butene) Complex

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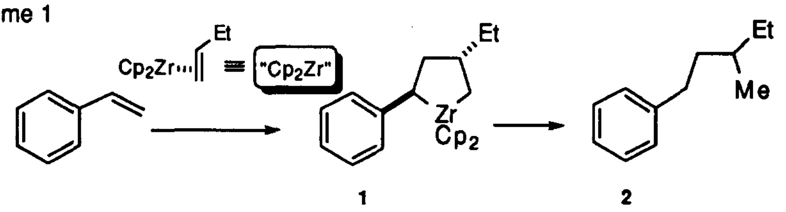
Abstract: *Reactions of alkoxymethyl substituted styrene derivatives with a stoichiometric and/or catalytic amount of zirconocene-(1-butene) complex ("Cp_2Zr") causes an unexpected zirconocene insertion into benzylic position and/or homolytic coupling reaction of the styrene derivatives.*

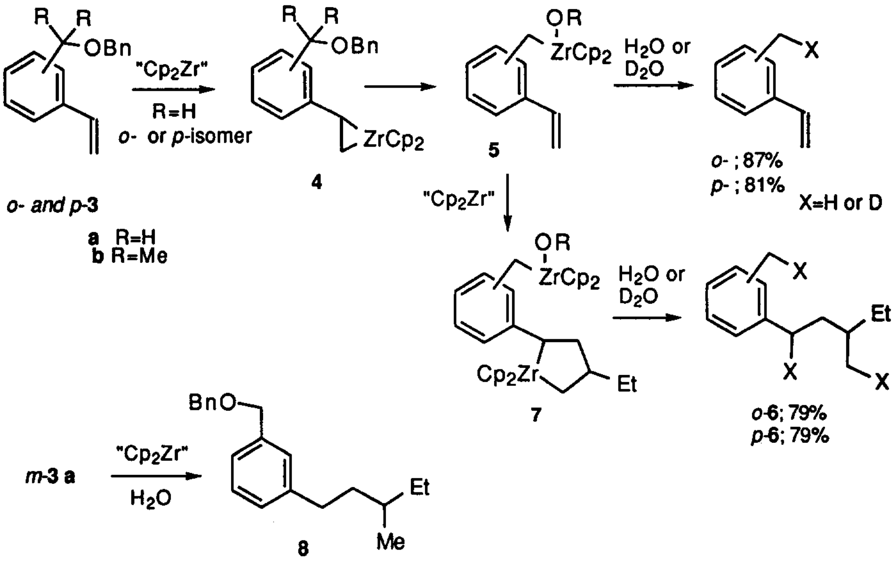
Easy generation of a zirconocene-(1-butene) complex ("Cp_2Zr"), which reacts as a zirconocene equivalent through a ligand exchange with unsaturated compounds to give zirconacyclopropane derivatives, draws a lot of attention from synthetic organic chemists.[1] During the course of our studies on the development of new synthetic methods with "Cp_2Zr", we reported that β-alkoxy elimination of the zirconacyclopropane intermediate is an efficient process to generate reactive organozirconocene derivatives.[2] While our "Cp_2Zr" chemistry is in progress, we found unexpected results from the reaction of alkoxymethyl substituted styrene derivatives with "Cp_2Zr". In this paper, we disclose the unexpected and unprecedented coupling reactions of alkoxymethyl substituted styrene derivatives in a catalytic system. The reaction of styrene with "Cp_2Zr" has been determined to give a styrene-butene coupled product **2** in good yield via organozirconocene intermediate **1**.[3] In this coupling reaction, two outstanding observations were noted; i) phenyl and ethyl groups are located regio- and stereoselectively at the indicated positions in **1** (Scheme 1) and ii) less than 10% of the styrene-styrene and/or butene-butene homocoupled dimers were obtained under the thermodynamically equilibrated conditions.[3]

Scheme 1



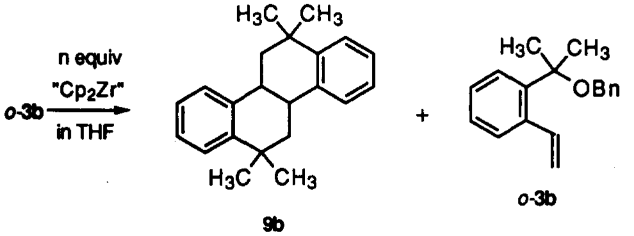
The reaction of *o*-benzyloxymethyl styrene (*o*-**3a**) with a stoichiometric amount of "Cp_2Zr" in THF at room temperature for 3 h gave an oxidatively inserted product *o*-**5**[4] and, to our surprise, no butene-*o*-**3a** coupled product was obtained (Scheme 2). The double bond of *o*-**3a** is indispensable because the reaction of dibenzyl ether with "Cp_2Zr" recovered the starting material under the same reaction conditions. Acidic treatment ($HCl-H_2O$ or $DCl-D_2O$) of *o*-**5** yielded *o*-methylstyrene or monodeuteromethyl congener (87%). By the treatment of *o*-**3a** with 2 equiv of "Cp_2Zr", a butene coupled compound *o*-**6** (X=H) was obtained in 79% yield. The introduction of three deuteriums into *o*-**6** (X=D) by acidic workup ($DCl-D_2O$) suggests the formation of *o*-**7** as an organometallic intermediate. These results indicate the followings: i) The ligand exchange of the first equivalent of "Cp_2Zr" with the double bond of *o*-**3a** gives a zirconacyclopropane derivative *o*-**4**. ii) The transfer of Cp_2Zr moiety of *o*-**4** to a benzylic position affords *o*-**5**.[5] iii) The coupling reaction between butene of the second equivalent of "Cp_2Zr" and the double bond of *o*-**5** gives *o*-**7** in regio- and pair selective manners as has been reported by Negishi et al.[6] Similar results were obtained in the reaction of *para*-substituted isomer *p*-**3a**. In the reaction of *meta*-substituted isomer *m*-**3a**, however, a butene-*m*-**3a** coupled product **8** was obtained as in the case of styrene-"Cp_2Zr" reaction and no zirconocene inserted product into benzylic position was obtained. Dependence of the "Cp_2Zr" reactions on the substitutional patterns of **3a** indicates an importance of an electronic interaction between zirconacyclopropyl and benzyloxymethyl groups through an aromatic π system bringing about the reactions.[7]

Scheme 2



When dimethyl substituted compound *o*-**3b** was treated with an equivalent amount of "Cp_2Zr" in THF at room temperature for 3 h, a homocoupled product **9b** was isolated as a *cis/trans* mixture (1:3) in an 83% yield and no deuterium was introduced into **9b** by the addition of $DCl-D_2O$ to the reaction mixture (Scheme 3).[8] This implies that the dimeric product **9b** was generated not as an organometallic compound in the reaction media. As to the formation of dimeric compound **9b**, a half equiv of "Cp_2Zr" to *o*-**3b** is sufficient to form **9b** (83% yield). Using one third equiv of "Cp_2Zr" gave a mixture of the recovered stating material *o*-**3b** (31%) and **9b** (62%) and the addition of n-BuLi to the mixture of *o*-**3b** and **9b** prior to hydrolytic workup yielded **9b** as a sole product (Scheme 3). These observations indicate that this homo-coupling process by "Cp_2Zr" can be catalytic.

Scheme 3



n	9b	o-3b
1	83%	—
1/2	84%	—
1/3	62%	31%

Thus, the reaction of *o*-**3b** with a catalytic amount of Cp_2ZrCl_2 (10 mol%), and 3 equiv of nBuMgCl or EtMgBr in THF at refluxing temperature for 3 h, expectedly gave the dimeric product **9b** (89%).[9] The catalytic scheme is shown in Figure 1. By virture of the catalytic process, we could obtain a dimeric compound **9a**[10] from *o*-**3a** in 42% yield. Although the precise mechanisms about the formations of *o*-**5** in the stoichiometric[5] and dimeric compounds **9a** and **9b** in catalytic conditions are unclear, it is obvious that *o*-**5** is not an intermediate for the formation of dimeric product **9a** since the treatment of *o*-**5** with an excess of **3a** in the presence of nBuMgCl did not give **9a**.

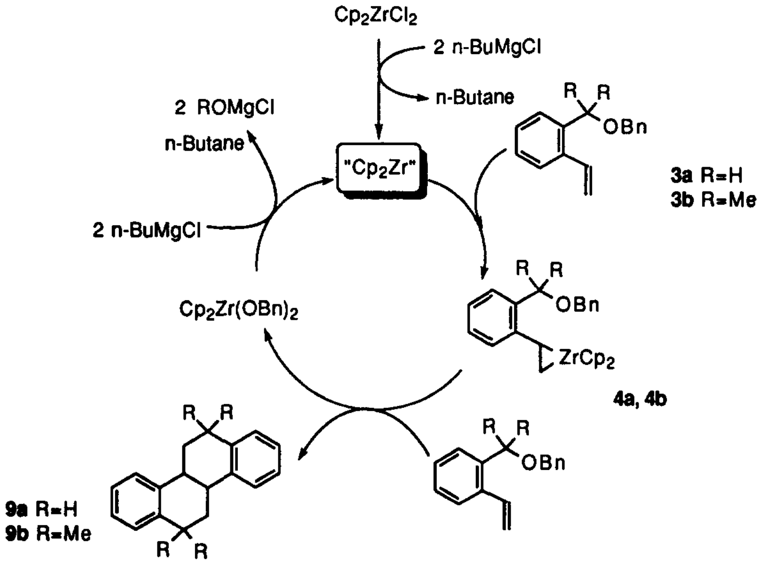
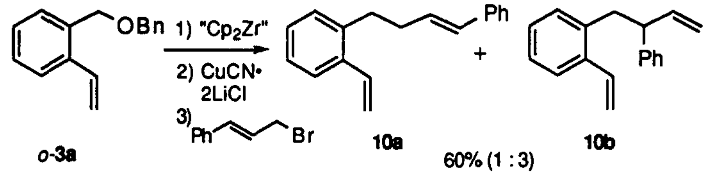


Fig 1. Catalytic Cycle for the Coupling Reactions of *o*-**3a** and *o*-**3b**

As an appilcation of the present reactions, the allylation of **3a** at benzylic position was carried out to give allylated products **10a** and **10b** (60% yield) in 1:3 ratio (Scheme 4).[11] This procedure shows the creation of a reactive benzylic metal compound from chemically tolerable ether derivatives under mild conditions.

Scheme 4



In conclusion, we found that the reaction between "Cp_2Zr" and alkoxymethyl substituted styrene derivatives is dependendent on the substitutional pattern of the benzene ring and a totally different type of reaction to the reported reaction of styrene. We are now investigating the reaction mechanism of the present reactions.

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References and Notes

1. For recent reviews, see: a) Hanzawa, Y.; Ito, H.; Taguchi, T. *Synlett* **1995**, 299. b) Negishi, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124. c) Mori, M. *Rev. Heteroatom Chem.* **1993**, *8*, 256. c) Negishi, E. *Chem. Scr.* **1989**, *29*, 457. d) Negishi, E.; Takahashi, T. *Synthesis* **1988**, 1.
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4. Typical experimental procedure: A mixture of *o*-**3a** and $Cp_2Zr(n\text{-}Bu)_2$, which is generated by the addition of n-BuLi (2 equiv) to Cp_2ZrCl_2 in THF at -78°C, was gradually heated to room temperature and the mixture was stirred for 3 h. The yield of *o*-**5a** was estimated to be more than 90% from NMR spectrum. The structure of *o*-**5** was determined by NMR analyses (DEPT, H-H COSY, HETCOR). ^1H NMR (400 MHz, benzene-d_6) δ; 2.62 (s, 2H, Ar$\underline{CH_2}$Zr), 4.88 (s, 2H, O$\underline{CH_2}$Ar), 5.25 (dd, 1H, J = 1.7 and 10.9 Hz, vinyl), 5.70 (s, 10H, 2Cp), 5.73 (dd, 1H, J = 1.7 and 17.4 Hz, vinyl), 7.25 (dd, 1H, J = 10.9 and 17.4 Hz, vinyl), 6.96–7.67 (m, 9H, Ar). ^{13}C NMR (100.6 MHz, benzene-d_6) ppm; 43.72, 76.14, 111.33, 112.53, 121.51, 125.93, 126.90, 127.23, 127.61, 128.58, 129.01, 132.08, 137.19, 142.90, 152.50.
5. Although the precise mechanism of the formation of **5** from **4** was unclear, this might be the result of the complexation which is similar to the formation of diene-"Cp_2Zr" complex followed by the elimination of the alkoxyl group and migration of the Cp_2Zr group to the benzylic position.
6. The stereochemistry of **7** was undetermined, however, we assume that the stereochemistry of **7** is *trans* because of the similarity to styrene-"Cp_2Zr" coupling reaction.
7. An attempted NMR measurment of the zirconium complex derived from *p*-**3a** didn't show a clear spectrum.
8. Separation of a mixture (1:3) of *cis*/*trans* isomers **9b** (silica gel MPLC, hexane) and recrystallization of the major isomer from EtOH gave pure *trans* **9b** (mp. 170–172°C). ^1H NMR (400 MHz, $CDCl_3$) δ; 1.44 (s, 12H, 4Me), 1.71 (dd, 2H, J = 12.5 and 11.1Hz, CH-Ha), 2.44 (dd, 2H, J = 12.5 and 1.0Hz, CH-Hb), 2.88 (dd, 2H, J = 11.1 and 1.0Hz, C-H), 7.18-7.46 (m, 8H, ArH). The structure of *trans* **9b** was finally confirmed by an X-ray crystalographic analysis which will be reported in due course.
9. The catalytic process required a THF-refluxing temperature to obtain a reasonable reaction rate.
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