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# Zirconocene-Catalyzed Alkylation of Aryl Alkenes with Alkyl Tosylates, Sulfates and Bromides

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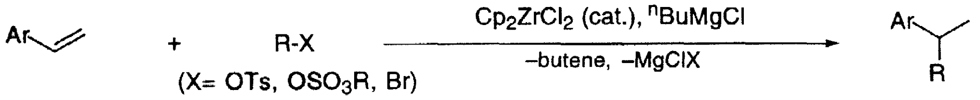
## Abstract

Styrenes were alkylated with alkyl tosylates, sulfates and bromides in the presence of a zirconocene catalyst and $^n$BuMgCl in THF. By the use of this reaction, primary and secondary alkyl groups can be introduced regioselectively at the benzylic carbon of styrenes to give α-substituted ethylbenzenes.

*Keywords*: Alkenes; Alkylation; Grignard reagents; Zirconium and compounds

Zirconocene complexes catalyze the addition of organometallic reagents,[1] such as organoaluminum,[2] -zinc,[3] and -magnesium[4] compounds, to alkenes and alkynes. These reactions are synthetically useful for preparation of organometallic reagents with concomitant formation of carbon-carbon bonds, wherein anionic alkyl, allyl or benzyl groups are introduced into a carbon atom of the unsaturated bonds. We report herein zirconocene-catalyzed alkylation of aryl alkenes with alkyl tosylates, sulfates and bromides. This reaction proceeds under mild conditions using a catalytic amount of a zirconocene complex in the presence of a Grignard reagent to give saturated alkylation products in which an alkyl moiety is introduced in an electrophilic manner at the benzylic carbons regioselectively (eq 1).



(1)

For example, into a mixture of styrene (3.0 mmol), octyl tosylate (2 equiv) and a catalytic amount of zirconocene dichloride (0.05 equiv) was added a THF solution of $^n$BuMgCl (2 equiv, 0.9 M, 6.6 mL) at 20 °C. The solution was stirred at 50 °C for 2 h and the products were extracted with ether. GC analysis of the crude mixture indicated the formation of 2-phenyldecane (**1**) in 62% yield (Table 1, run 1). The product was obtained in pure form in 42% yield by HPLC. In this reaction octane was formed by the reduction of octyl tosylate as a by-product in a trace amount (<3% based on octyl tosylate) along with dodecane (<1%) which was formed probably via the direct reaction of octyl tosylate with $^n$BuMgCl.

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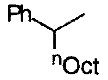
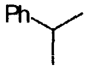
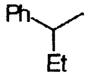
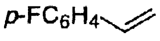
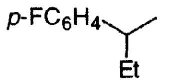
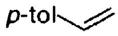
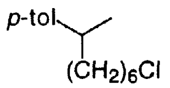
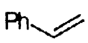
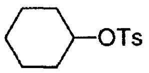
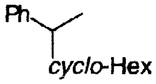
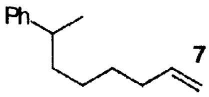
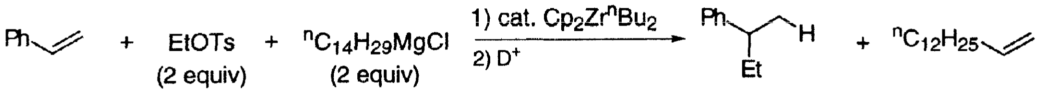
Table 1 Zirconocene-Catalyzed Alkylation of Aryl Alkenes

| run | alkene | R-X | product | yield (%)[a] |
|---|---|---|---|---|
| 1 |  | $^n$Oct-OTs |  **1** | 62 |
| 2 | | Me-OTs |  **2** | 56 |
| 3 | | Et-OTs |  **3** | 65 |
| 4 | | $Et_2SO_4$[b] | **3** | 76 |
| 5 | | $^n$Oct-Br | **1** | 65[c] |
| 6 |  | Et-OTs |  **4** | 59 |
| 7 |  | $Cl(CH_2)_6OTs$ |  **5** | 70 |
| 8 |  |  |  **6** | 44 |
| 9 | |  |  **7** | 70 |

[a] GC yield for runs 1–5 and NMR yield for runs 6–9 based on alkenes unless otherwise stated. All products are known compounds except 5.[5] [b] A stoichiometric amount of ethyl sulfate (3 mmol) was used. [c] Based on 1-bromooctane used. Styrene (1.5 equiv) and $^n$BuMgCl (3 equiv) were used.

Table 1 summarizes representative results obtained using various alkenes and the alkylating reagents. Under the same conditions, methyl and ethyl tosylates afforded cumene (**2**) and *sec*–buthylbenzene (**3**) in 56% and 65% yield, respectively (runs 2 and 3). Reactions of styrene with ethyl tosylate using $^i$PrMgBr and EtMgBr in place of $^n$BuMgCl afforded **2** in poor yields (6% and 17%, respectively) but no reaction took place with MeMgCl and PhMgCl under the same conditions. The reaction also failed when ethyl triflate was used as the alkylating reagent due to its rapid reaction with the Grignard reagent, whereas ethyl sulfate afforded **3** in 76% yield (run 4). Although 1–bromooctane gave 2–phenyldecane (**1**) only in 34% yield under the same conditions, **1** was formed in 65% yield based on 1–bromooctane when excess amounts of styrene and $^n$BuMgCl were used (run 5). *p*–Fluorostyrene and *p*–methyl styrene yielded the corresponding products **4** and **5**[5] in 59% and 70% yields, respectively (runs 6,7). The result of run 7 shows that chloro substituents are not affected in this reaction system. When cyclohexyl tosylate was employed as an alkylating reagent the corresponding product **6** was formed in 44% yield (run 8), indicating that secondary alkyl groups can be introduced by this reaction. Since alkenes having no aromatic substituent are reluctant to this alkylation reaction, carbon–chains having a carbon–carbon double bond can also be introduced successfully (run 9). Under the same conditions, $Cp_2TiCl_2$ and $Cp_2HfCl_2$ were ineffective.

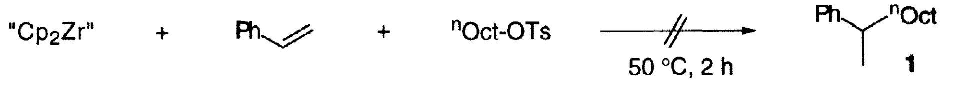
We carried out several control experiments in order to elucidate the reaction pathway. Since it is known that a titanocene complex catalyzes hydromagnesiation of styrene to give benzylmagnesium chloride,[6] we first examined whether a similar hydromagnesiation process is involved in the present reaction. A mixture of styrene, $^nBuMgCl$ (2 equiv), and a catalytic amount of $Cp_2ZrCl_2$ in THF was stirred at 50 °C for 2 h. Subsequent addition of $D_2O$ did not afford monodeuterated ethylbenzene. This result ruled out the hydromagnesiation mechanism. We then carried out a reaction of styrene with ethyl tosylate in the presence of $^nC_{14}H_{29}MgCl$ using a catalytic amount of "$Cp_2Zr$", prepared from $Cp_2ZrCl_2$ and 2 equiv of $^nBuMgCl$ via $Cp_2Zr^nBu_2$.[7] Quenching the reaction with $D_2O$ afforded nearly equal amounts of non-deuterated products **3** and 1–tetradecene (eq. 2). This result suggests that β–hydrogen of the tetradecyl group was removed and transferred into the terminal carbon of styrene leading to **3**.



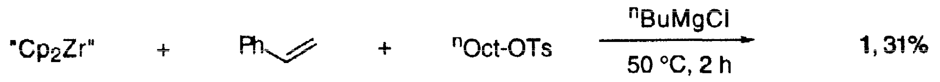
**3**, 62%  59%

(2)

It should also be noted that a stoichiometric reaction of "$Cp_2Zr$" with styrene and octyl tosylate gave neither **1**, octane nor octene (eq. 3).[8] On the other hand, a similar reaction in the presence of $^nBuMgCl$ (1 equiv) afforded **1** in 31% yield (eq. 4). These results indicate that $^nBuMgCl$ promotes the present alkylation reaction.



(3)

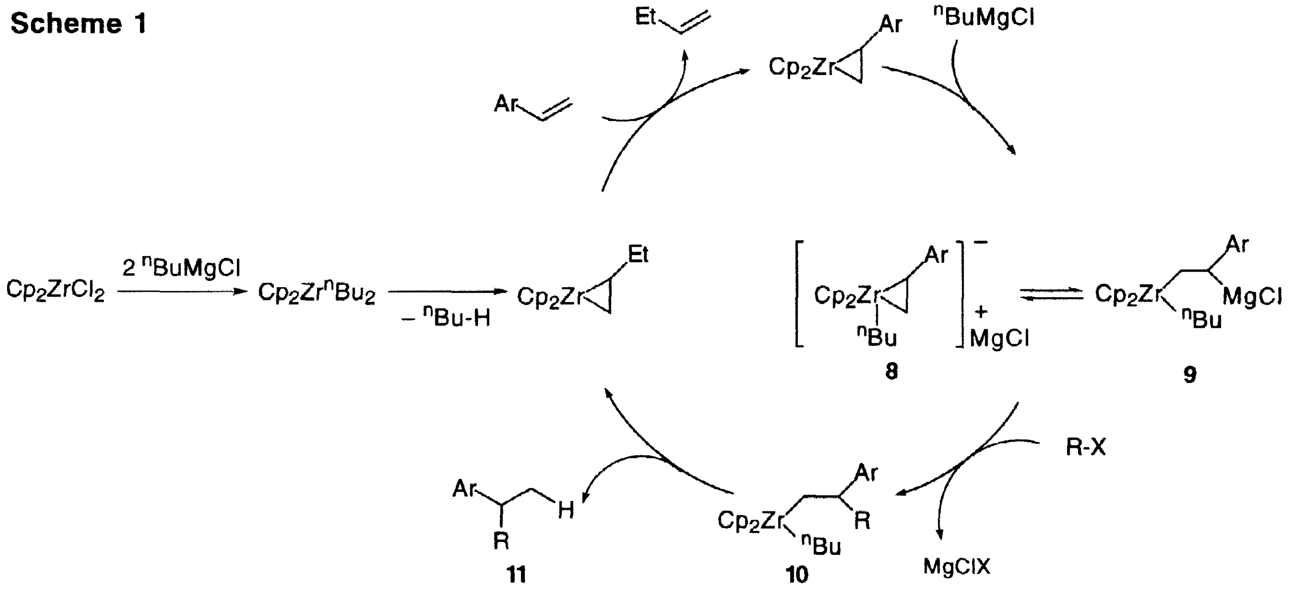


(4)

Although the mechanistic details of this reaction are still under investigation, a plausible reaction pathway is shown in Scheme 1. It is possible that a zirconate complex[9] **8** or a benzylmagnesium compound[10] **9** serves as the key intermediate which reacts with an alkylating reagent at the benzylic carbon leading to the dialkyl zirconocene complex **10**. The successive hydrogen abstraction proceeds exclusively at the less hindered butyl group[11] to afford corresponding alkylated product **11** along with a $Cp_2Zr$(butene) complex which acts as a "$Cp_2Zr$" to complete the catalytic cycle.

The present reaction provides a new and unique transformation of aryl alkenes via regioselective alkylation with alkyl tosylates, sulfates and bromides catalyzed by a zirconocene complex.[12]

**Scheme 1**



## References and Notes

[1] For a review see: Negishi E, Takahashi T. Synthesis. 1988:1-19.

[2] Van Horn DE, Negishi E. J. Am. Chem. Soc. 1978;100:2252-2254.

[3] Negishi E, Van Horn DE, Yoshida T, Rand CL. Organometallics. 1983;2:563-565.

[4] (a) Dzhemilev UM, Vostrikova OS, Sultanov RM. Izv. Akad. Nauk SSSR, Ser. Khim. 1983:218-220. (b) Dzhemilev UM, Vostrikova OS. J. Organomet. Chem. 1985;285:43-51. (c) Hoveyda AH, Xu Z. J. Am. Chem. Soc. 1991;113:5079-5080. (d) Takahashi T, Seki T, Nitto Y, Saburai M, Rouusset CM, Negishi E. J. Am. Chem. Soc. 1991;113:6266-6268. (e) Knight K S, Waymouth RM. J. Am. Chem. Soc. 1991;113:6268-6270. (f) Lewis DP, Muller PM, Whitby RJ. Tetrahedron Lett. 1991;32:6797-6800.

[5] Spectral Data of 5: IR (neat) 2956, 2928, 2856, 1514, 1456, 816 cm$^{-1}$; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 144.5, 135.0, 128.8, 126.7, 45.2, 39.6, 38.4, 32.7, 29.1, 27.7, 26.9, 22.6, 21.1; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.11-7.05 (m, 4H), 3.50 (t, $J$ = 6 . 7 Hz, 2H), 2.63 (sextet, $J$ = 7.1 Hz, 1H), 2.32 (s, 3 H), 1.72 (quint-like tt, $J$ = 6.7, 7.4 Hz, 2H), 1.56-1.23 (m, 8H), 1.21 (d, $J$ = 7.1 Hz, 3H); MS (EI) *m/z* (relative intensity, %, $^{35}$Cl) 238 ($M^+$, 14), 120 (10), 119 (100), 117 (16), 91 (14). Anal. Calcd for $C_{15}H_{23}Cl$: C, 75.44; H, 9.71. Found: C, 75.40; H, 9.59.

[6] Sato F, Ishikawa H, Sato M. Tetrahedron Lett. 1980;21:365-368.

[7] (a) Negishi E, Cederbaum FE, Takahashi T. Tetrahedron Lett. 1986;27:2829-2832. (b) Soleil F, Choukroun R. J. Am. Chem. Soc. 1997;119:2938-2939. (c) Dioumaev VK, Harrod JF, Organometallics. 1997;16:1452-1464.

[8] After hydrolysis, ethylbenzene and 1,4-diphenylbutane were formed in 20% and 2% yields, respectively, along with 51% recovery of styrene. It is reported that $Cp_2Zr$(butene) reacts with styrene to form a zirconacyclopentane consisting of butene and styrene units (Swanson DR, Rousset CJ, Negishi E, Takahashi T, Seki T, Saburi M, Uchida Y. J. Org. Chem. 1989;54:3521-3523.), but coupling products of styrene with butene were not detected by GC analysis.

[9] (a) Takagi K, Rousset CJ, Negishi E. J. Am. Chem. Soc.1991;113:1440-1442. (b) Takahashi T, Suzuki N, Kageyama M, Nitto Y, Saburi M, Negishi E. Chem. Lett. 1991:1579-1582. (b) Takahashi T, Seki T, Nitto Y, Saburu M, Rousset CJ, Negishi E. J. Am. Chem. Soc. 1991;113:6266-6268. (c) Hoveyda AH, Morken JP, Houri AF, Xu Z. J. Am. Chem. Soc. 1992;114:6692-6697. (d) Gordon GJ, Whitby RJ. Chem. Commun. 1997:1321-1322. (e) Miqul Y, Igau A, Donnadieu B, Majoral JP, Pirio N, Meunier P. J. Am. Chem. Soc. 1998;120:3504-3505.

[10] When a THF solution of EtBr (1.09 M) with PhCHMeMgCl (**12**, 0.35 M) was warmed from 0 °C to 50 °C in about 5 min and the reaction was quenched with aqueous HCl (1N) , 2-phenylbutane was formed in 79% yield based on **12** indicating that α-substituted benzylmagnesium chlorides readily react with alkyl bromides.

[11] The reactivities of the alkyl ligands on Zr as β-hydrogen donors decrease in the order: β-methyl > β-methylene > β-methine, see: Negishi E, Nguyen T, Maye JP, Choueiri D, Suzuki N, Takahashi T. Chem. Lett. 1992:2367-2370.

[12] We have reported that a zirconocene complex catalyzes silylation of alkenes with chlorosilanes under similar conditions which affords vinyl- and/or allylsilanes having silyl groups at the terminal carbons: Angew. Chem., Int. Ed. Engl. in press. We have also found that a titanocene complex catalyzes double alkylation of aryl alkenes with alkyl halides to give 1,2-dialkylated products: J. Am. Chem. Soc., in press.