ORGANIC LETTERS

2001
Vol. 3, No. 13
2097−2100

Zr-Catalyzed Electrophilic Carbomagnesation of Aryl Olefins. Mechanism-Based Control of Zr–Mg Ligand Exchange

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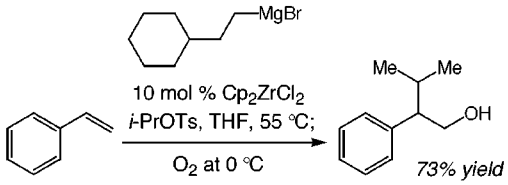
Received May 2, 2001

ABSTRACT



The first examples of efficient electrophilic Zr-catalyzed carbomagnesations are disclosed, where in contrast to previous catalytic carbomagnesations the alkyl moiety of the electrophile is transferred (vs that of the Grignard reagent). The identity of the Grignard reagent is manipulated so that Zr–Mg exchange is facilitated, leading to the formation of alkylmagnesium halide products.

Design and study of efficient and selective catalytic alkylation of unactivated olefins is an important objective in organic synthesis.[1] Past research in these laboratories has led to the development of Zr-catalyzed carbomagnesation of terminal and cyclic disubstituted allylic alcohols and ethers.[2] Despite the demonstrated utility of catalytic carbomagnesation in stereoselective synthesis,[1e] a number of limitations still remain.[3] A notable shortcoming is that alkyl Grignard reagents other than ethylmagnesium halides are less efficient or fail to participate in catalytic carbomagnesation.[4] To address this problem, we recently initiated an investigation regarding Zr-catalyzed olefin alkylations, where various electrophiles (e.g., alkyl tosylates and bromides) are used in the presence of a Grignard reagent and 5−10 mol % of Cp_2ZrCl_2 (see ***i*** → ***ix***, Scheme 1).[5]

There are two significant factors that distinguish the two alkylation pathways: (i) In catalytic ethylmagnesation (***i*** → ***v***, Scheme 1), the Et group of the Grignard reagent is transferred,[6] whereas in the more recent variant (***i*** → ***ix***), the alkyl moiety of the electrophile is incorporated within the product structure. (ii) Whereas the earlier transformations

(1) For representative examples, see: (a) Dzhemilev, U. M.; Vostrikova, O. S. *J. Organomet. Chem.* **1985**, *285*, 43−51. (b) Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 366−368. (c) Tsukada, N.; Sato, T.; Inoue, Y. *Chem. Commun.* **2001**, 237−238. (d) Liepins, V.; Backvall, J. E. *Chem. Commun.* **2001**, 265−266. For reviews on metal-catalyzed enantioselective alkylation of olefins and applications to total synthesis, see: (e) Hoveyda, A. H.; Heron, N. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; pp 431−454. (f) Marek, I. *J. Chem. Soc., Perkin Trans 1* **1999**, 535−544.

(2) Zr-catalyzed diastereoselective alkylations: (a) Hoveyda, A. H.; Xu, Z. *J. Am. Chem. Soc.* **1991**, *113*, 5079−5080. (b) Morken, J. P.; Hoveyda, A. H. *J. Org. Chem.* **1993**, *58*, 4237−4244. (c) Hoveyda, A. H.; Morken, J. P.; Houri, A. F.; Xu, Z. *J. Am. Chem. Soc.* **1992**, *114*, 6692−6697. (d) Houri, A. F.; Didiuk, M. T.; Xu, Z.; Horan, N. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6614−6624.

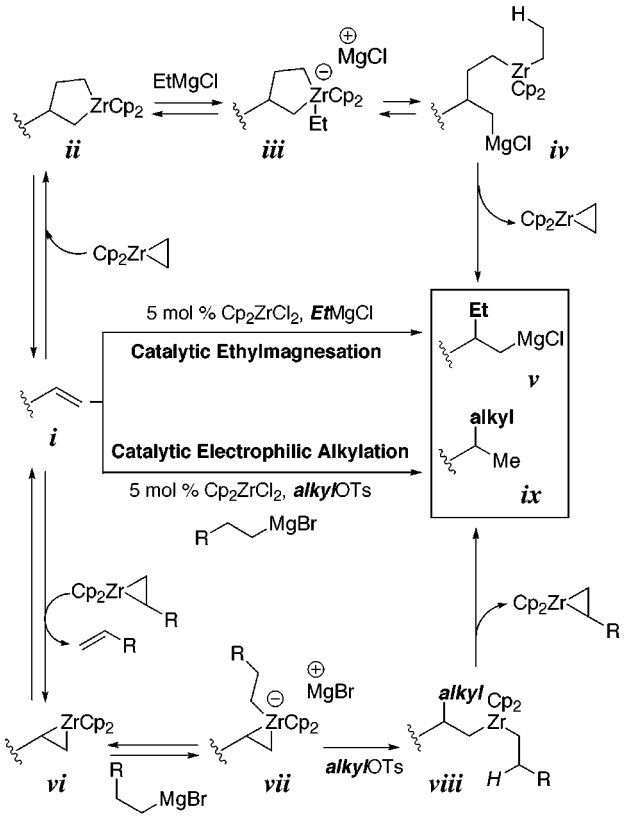
(3) For previous studies from these laboratories that address this issue, see: (a) Didiuk, M. T.; Morken, J. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 7273−7274. (b) Heron, N. M.; Adams, J. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 6205−6206. (c) Gomez-Bengoa, E.; Heron, N. M.; Didiuk, M. T.; Luchaco, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 7649−7650. (d) Adams, J. A.; Heron, N. M.; Koss, A. M.; Hoveyda, A. H. *J. Org. Chem.* **1999**, *64*, 854−860.

(4) Didiuk, M. T.; Johannes, C. W.; Morken, J. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 7097−7104.

(5) (a) de Armas, J.; Kolis, S. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 5977−5983. For related studies, see: (b) Terao, J.; Watanabe, T.; Saito, K.; Kambe, N.; Sonoda, N. *Tetrahedron Lett.* **1998**, *39*, 9201−9204.

10.1021/ol0160607 CCC: $20.00
Published on Web 06/06/2001

Scheme 1. Two Different Methods for Zr-Catalyzed Alkylation of Olefins

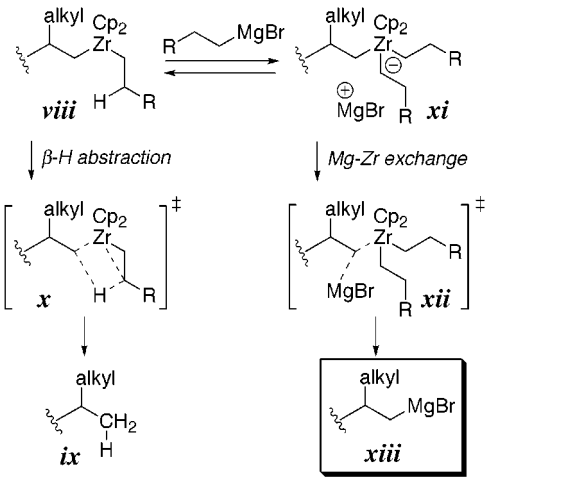


proceed through zirconacyclopentanes (***ii*** and ***iii***, Scheme 1),[6] the more recent processes likely involve regioselective alkylation of the electron-rich zirconate ***vii*** by the electrophile. In catalytic ethylmagnesation, metallacycle intermediate ***iii*** undergoes site-selective Zr−Mg exchange followed by β-H abstraction to afford an *alkylmagnesium halide product* (***v***). Dialkylzirconocene ***viii*** from alkylation of zirconate ***vii*** undergoes a β-H abstraction as well; however, in this case, *hydrocarbon* ***ix*** is generated.

More recently, we set out to develop a new class of Zr-catalyzed *electrophilic* alkylations that deliver *alkylmagnesium* halide products. Such a transformation could carry the advantages of both forms of catalytic alkylation: a wide range of alkyl moieties (not just Et) could be added to alkenes, affording readily functionalizable alkylmagnesium products. Herein, we report the first examples of Zr-catalyzed electrophilic olefin *carbomagnesations*. Various aryl olefins undergo facile carbometalation in the presence of 5−10 mol % of Cp_2ZrCl_2, an alkyl electrophile and a Grignard reagent.

As illustrated in Scheme 2, to favor the formation of a carbomagnesation (vs hydrocarbon) product (***xiii***), reaction conditions must be chosen so that the formation of dialkylzirconate ***xi*** is preferred (vs dialkylZr ***viii***). This is for two

Scheme 2. β-H Abstraction of Dialkylzirconiums versus Zr−Mg Ligand Exchange through Zirconates



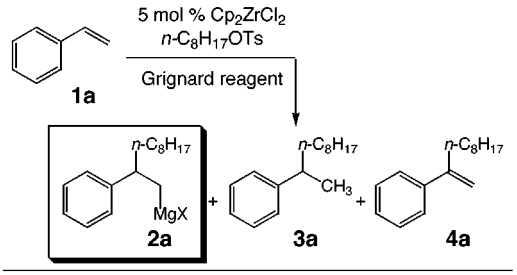
reasons: (1) In contrast to dialkylZr ***viii***, zirconate ***xi*** does not possess a vacant d orbital required for β-H abstraction. (2) Previous studies[2c,d] suggest that the formation of carbomagnesation product ***xiii*** likely involves Zr−Mg ligand exchange through zirconate ***xi***. Accordingly, we surmised that formation of carbomagnesation product ***xiii*** can be facilitated through increasing the amount of available zirconate. This objective may be accomplished in the following ways: (1) A more nucleophilic alkylmagnesium reagent may shift the dialkylZr/zirconate equilibrium toward the latter. (2) Solvents of higher polarity (e.g., THF vs Et_2O) may favor the formation of the more polar zirconate ***xi***. (3) The alkylmagnesium halide reagent may be selected so that β-H abstraction is sterically less favored (discourage pathway involving ***x***, Scheme 2). This proposal is based on mechanistic studies regarding the rates of β-H abstraction of dialkylzirconocenes, where the following relative reactivity of alkyl groups as β-H donors has been established: β-CH_3 $\approx$ β-CH_2Ar > β-CH_2 > β-CH.[7]

The above mechanistic rationales led us to carry out the Zr-catalyzed alkylations shown in Table 1, where styrene (**1a**) and *n*-$C_8H_{17}OTs$ are used as substrate and electrophile, respectively. As illustrated in entry 1, under previously reported conditions[5a] (*n*-BuMgCl, 55 °C, THF), **2a** is formed only as the minor constituent of the product mixture (10%); the major product (90%) is **3a**, derived from the β-H abstraction pathway shown in Scheme 2 (***viii*** → ***ix***). With the less polar Et_2O as solvent, <2% **2a** is observed (entry 2). As predicted above, the amount of the desired product (**2a**) is increased significantly when the more nucleophilic *n*-Bu_2Mg is employed in THF (entry 3; 62% **2a** in the product mixture vs 10% with *n*-BuMgCl). As depicted in entry 4, a less favorable ratio of **2a**:**3a** is obtained at 22 °C. The data in entries 5−6 show that the use of Et_2O as the reaction medium delivers <2% of **2a**.

(6) (a) References 1a−d. (b) Takahashi, T.; Seki, T.; Nitto, Y.; Saburi, M.; Rousset, C. J.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 6266−6268. (c) Knight, K. S.; Waymouth, R. M. *J. Am. Chem. Soc.* **1991**, *113*, 6268−6270. (d) Lewis, D. P.; Muller, P. M.; Whitby, R. J.; Jones, R. V. H. *Tetrahedron Lett.* **1991**, *32*, 6797−6800.

(7) (a) Buchwald, S. L.; Nielsen, R. B. *J. Am. Chem. Soc.* **1988**, *110*, 3171−3175. (b) Negishi, E.; Nguyen, T.; Maye, J. P.; Choueiri, D.; Suzuki, N.; Takahashi, T. *Chem. Lett.* **1992**, 2367−2370.

Table 1. Zr-Catalyzed Electrophilic Carbomagnesation of Styrene[a]



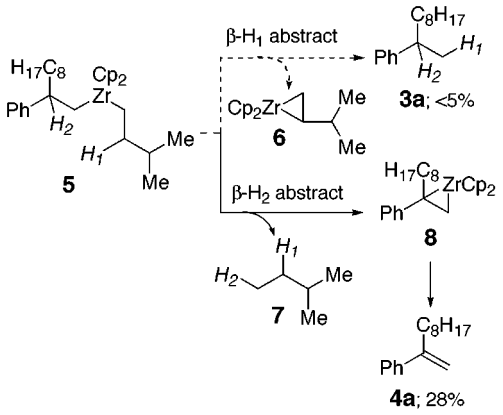
entry	alkylMg reagent	solvent; temp (°C)	**2a** : **3a** : **4a**[b]	yield (%)[c]
1	*n*-BuMgCl	THF; 55	10 : 90 : <2	90
2	*n*-BuMgCl	Et_2O; 35	<2 : >98 : <2	76
3	*n*-Bu_2Mg	THF; 55	62 : 38 : <2	89
4	*n*-Bu_2Mg	THF; 22	52 : 48 : <2	83
5	*n*-Bu_2Mg	Et_2O; 35	<2 : >98 : <2	75
6	*n*-Bu_2Mg	Et_2O; 22	<2 : >98 : <2	90
7	*i*-BuMgBr	THF; 55	NO REACTION	
8	$Me_2CH(CH_2)_2MgBr$	THF; 55	67 : 05 : 28	68
9	$(Me_2CHCH_2CH_2)_2Mg$	THF; 55	72 : 05 : 23	72
10	**$CyCH_2CH_2MgBr$**	**THF; 55**	**81 : 05 : 14**	**76**

a. Conditions: 5 mol % Cp_2ZrCl_2, 2 equiv alkylMg, 1.1 equiv *n*-$C_8H_{17}OTs$, 4h. *b.* Ratios determined by analysis of unpurified reaction mixture by ^1H and ^{13}C NMR and GC/MS after quenching with 5% D_2SO_4 in D_2O at 0 °C. *c.* Isolated yield of products after silica gel chromatography.

To improve the efficiency of the electrophilic carbomagnesation, we began to modify the structure of the Grignard reagent so as to discourage the competitive β-H process. We reasoned that if β-H abstraction were to involve a sterically more hindered CH bond (vs the CH_2 group in *n*-BuMg reagents), lower amounts of **3a** would be generated. As shown in entry 7, when *i*-BuMgBr is used, <2% reaction takes place. This is presumably because the sterically hindered alkylmetal inhibits formation of the reactive zirconate intermediate (see ***vii***, Scheme 1). However, *with i-amylMgBr as the alkylating agent (entry 8), **2a** becomes the major component of the product mixture (67%) and only 5% **3a** is generated*. Nonetheless, another minor product in the reaction of entry 8 is alkene **4a** (28%). Use of (*i*-amyl)$_2$Mg improves selectivity in favor of **2a** (72% vs 67%; compare entries 9 and 8). Finally, the most efficient conditions for the formation of carbomagnesation adduct **2a** are shown in entry 10; in the presence of 2 equiv of 2-cyclohexylethylmagnesium bromide the product mixture contains 81% **2a**, 5% **3a**, and 14% **4a**.

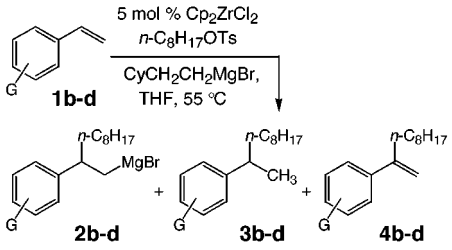
Several additional issues regarding the data in entries 8−10 merit mention. (1) As shown in Scheme 3, with *i*-amylMgBr as the Grignard reagent (entry 8), even though β-H abstraction involves a methylene CH_2 (see H_1 in **5**, Scheme 3), the steric influence of the terminal dimethyl unit significantly diminishes formation of **3a** (5%). (2) Although β-H abstraction involving the benzylic H_2 does not appear to be a competitive pathway when *n*-BuMgCl or *n*-Bu_2Mg is used (entries 1−6), with the sterically demanding Grignard reagents in entries 8−10, 14−28% of **4a** is generated via zirconacyclopropane **8** (see below for further discussion regarding formation of styrenyl alkylation products).

Scheme 3



As illustrated in Table 2, electron-rich styrenes **1b−c** undergo catalytic electrophilic carbomagnesation with levels of selectivity similar to that of styrene (**1a**). The slightly higher selectivity in the reaction of **1c** is likely due to the steric inhibition imposed in the course of benzylic β-H abstraction that would lead to **4c** (<2% formed, see entry 2). The exclusive formation of **4d** in the reaction of electron-deficient **1d** is consistent with the mechanistic work of Buchwald;[7a] accumulation of electron density at the benzylic carbon during β-H abstraction (to afford **4d**) is favored by the para electron-withdrawing group.

Table 2. Effect of Aryl Substituents on the Efficiency of Zr-Catalyzed Electrophilic Carbomagnesation[a]

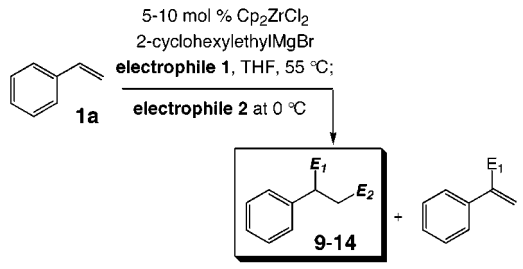


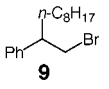
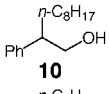
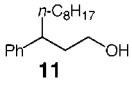
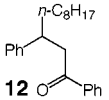
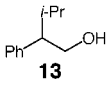
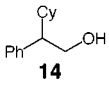
entry	G	**2** : **3** : **4**[b]	yield (%)[c]
1	*p*-OMe **1b**	64 : 11 : 25	92
2	*o*-OMe **1c**	86 : 14 : <2	81
3	*p*-Cl **1d**	<2 : <2 : 98	71[d]

a-c. See Table 1. *d.* 12 h.

In Table 3, Zr-catalyzed electrophilic carbomagnesation may be carried out with a variety of alkyl tosylates (electrophile 1) and the resulting alkylmagnesium

Table 3. Sequential Zr-Catalyzed Reaction of Styrene with Two Different Electrophiles[a]



entry	electrophile 1; electrophile 2	mol % Cp_2ZrCl_2	major product	yield (%);[b] byproduct (%)
1	*n*-C_8H_{17}OTs; NBS	5	 **9**	73; <2[c]
2	*n*-C_8H_{17}OTs; O_2	5	 **10**	81; 20
3	*n*-C_8H_{17}OTs; HCHO	5	 **11**	73; 22
4	*n*-C_8H_{17}OTs; PhCHO	5	 **12**	76; 30[d]
5	*i*-PrOTs; O_2	10	 **13**	73; <2[e]
6	CyOTs; O_2	10	 **14**	70; <2[e]

a. Conditions: 2 equiv 2-cyclohexylethylMgBr, 1.1 equiv electrophile 1, 55 °C, 4 h then 2 equiv electrophile 2, 0 °C. *b.* Isolated yield of reaction products after silica gel chromatography. *c.* Absence of byproduct is likely due to its reaction with NBS. *d.* See Ref 8. *e.* 4 equiv 2-cyclohexylethylMgBr, 12 h; see ref 9.

halide product can be treated with a subsequent electrophile (electrophile 2).[8] In cases where a primary alkyl tosylate is used (entries 1−4), the reaction mixture contains varying amounts of the styrenyl adduct **4**. With secondary alkyl tosylates, however, the carbomagnesation product (**13** or **14**) is formed exclusively (<2% hydrocarbon or styrene byproduct observed by 400 MHz ^{1}H NMR analysis). Such high product selectivity is probably due to the steric repulsion involved in β-H abstraction at the benzylic site caused by the larger alkyl substituent (isopropyl or cyclohexyl vs *n*-alkyl). With the sterically more demanding alkyl tosylates, 10 mol % of catalyst loading is required for appreciable yields; when the reaction in entry 5 is effected with 5 mol % of Cp_2ZrCl_2, **13** is formed in 48% isolated yield (vs 73%).[9]

In summary, we disclose a potentially useful Zr-catalyzed electrophilic olefin alkylation that delivers functionalized alkylmagnesium halide products. Since the resulting carbomagnesation product can be treated with a range of electrophiles, the present protocol provides a new catalytic method for regioselective bisfunctionalization of aryl olefins. The products obtained in this study can be accessed by alternative methods; the mechanistic principles established herein may however be employed in the development of a *catalytic* alternative for C−C bond formation by a fundamentally new disconnection which also has the potential to be enantioselective. Future studies are directed at catalytic carbomagnesation of nonaryl olefins, utilization of other classes of electrophiles, and the development of the corresponding enantioselective variants.

Acknowledgment. This research was supported by the NIH (GM-47480).

Supporting Information Available: Experimental procedures and spectral and analytical data for all reaction products. This material is available free of charge via the Internet at http//:www.acs.pubs.org.

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(8) In situ oxidation of the addition product to afford ketone **12** finds precedence in previous reports regarding the catalytic activity of Zr alkoxides (with secondary alcohols). See: Krohn, K. *Synthesis* **1997**, 1115−1127 and references therein.

(9) The rate of transmetalation is sensitive to the zirconocene/Grignard reagent ratio. When the amount of zirconocene is increased without using an additional amount of the alkylmetal, lower yields of carbomagnesation product are obtained.