Regioselective Double Alkylation of Styrenes with Alkyl Halides Using a Titanocene Catalyst

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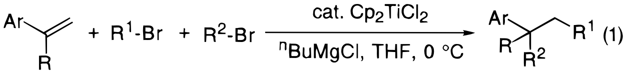
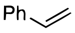
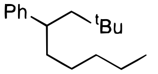
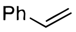
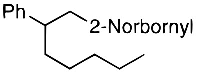
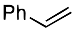
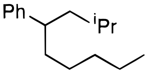
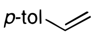
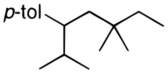
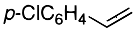
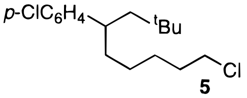
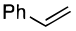
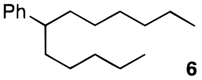
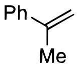
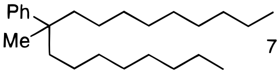
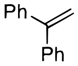
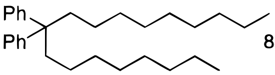
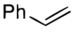
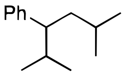
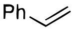
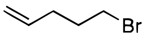
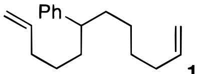
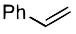
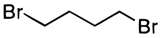
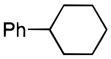
Transition metal catalysts provide powerful tools for 1,2-addition reactions to carbon−carbon double bonds, which enable versatile and useful transformations of alkenes by means of introducing a variety of functionalities at the olefinic carbons. We wish to describe an unprecedented metal-catalyzed double alkylation of alkenes with alkyl halides (eq 1). This reaction proceeds via the use of Cp_2TiCl_2 in the presence of ^{n}BuMgCl and gives rise to *vic*-dialkylated products regioselectively in high yields under mild conditions.[1]



(1)

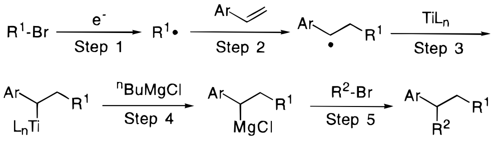
A typical example is as follows. To a mixture of styrene (1.03 mmol), 1-bromopentane (1.1 equiv), *tert*-butyl bromide (1.1 equiv), and titanocene dichloride (0.05 equiv) was added a THF solution of ^{n}BuMgCl (2.2 equiv, 2.5 mL) at 0 °C, and the solution was stirred for 1 h. The NMR analysis of the crude mixture indicated the formation of the double alkylation product **1** in 94% yield in which pentyl and *tert*-butyl groups are regioselectively incorporated at the adjacent carbons (Table 1, run 1). The product was obtained in pure form in 88% yield by a recycling preparative HPLC using $CHCl_3$ as the eluent. No evidence for the presence of the regioisomer of **1** nor dialkylated products which contained the same alkyl moiety was detected. The combined use of secondary and primary bromides (runs 2, 3) or tertiary and secondary bromides (run 4) afforded the corresponding dialkylated products **2**−**4** in good yields with high regioselectivities. In run 2, only the *exo*-isomers were obtained in a diastereomer ratio of ca. 1:1. Chloro substituents were not affected in this reaction system and the desired product **5** was obtained in good yield (run 5). The same primary alkyl groups can be introduced at both vicinal carbons by the use of 2.2 equiv of the corresponding alkyl bromide (runs 6−8). Under the same conditions 1-iodooctane gave 9-phenyloctadecane in 54% yield, whereas no dialkylated product was obtained when 1-chlorooctane was used. Double alkylation also occurred when *sec*-alkyl bromides were used as shown in run 9, but *tert*-butyl bromide failed to give the corresponding dialkylated product under the same conditions. α-Substituted styrenes also efficiently underwent double alkylation (runs 7, 8). The reaction was sluggish with respect to internal alkenes, such as *β*-methyl styrene or stilbene, and to 1-alkenes which contain no aryl group, such as 1-octene or 3-methyl-1-pentene. This chemoselectivity allows the successful synthesis of diene **10** in 82% yield, using 5-bromo-1-pentene (run 10). Interestingly, when 1,4-dibromobutane was used as the alkylating reagent, cyclohexylbenzene was obtained in moderate yield (run 11). Vinyl ethers, sulfides, sulfoxides, and sulfones were not alkylated under the same conditions.

Table 1. Titanocene-Catalyzed Double Alkylation of Olefins with Alkyl Bromides

run	olefin	R^1-Br, R^2-Br	product	yield (%)[a]
1		^{t}Bu-Br ^{n}C$_5$H$_{11}$-Br	 **1**	94 (88)
2		2-Norbornyl-Br ^{n}C$_5$H$_{11}$-Br	 **2**	91 (79)[b]
3		^{i}Pr-Br ^{n}C$_5$H$_{11}$-Br	 **3**	63 (54)[c]
4		^{t}Amyl-Br ^{i}Pr-Br	 **4**	65 (52)[d]
5		^{t}Bu-Br Cl(CH$_2$)$_5$-Br	 **5**	76 (71)
6		^{n}C$_5$H$_{11}$-Br	 **6**	76 (72)
7		^{n}Oct-Br	 **7**	74 (62)
8		^{n}Oct-Br	 **8**	84 (75)
9		^{i}Pr-Br	 **9**	75 (73)
10			 **10**	82 (80)
11			 **11**	46[e]

[a] NMR yield. Isolated yield is in parentheses. [b] *exo*-2-Norbornyl bromide was used in 1.5 equiv. As a by-product, **6** was formed in 7% yield. [c] Besides, **6** and **9** were formed in 22% and 5% yields, respectively. [d] A trace amount of the by-product having two ^{i}Pr groups was formed in <1% which was identified by GC−MS. [e] GC yield. 1,4-Dibromobutane (5 equiv), ^{n}BuMgCl (5 equiv), and Cp_2TiCl_2 (10 mol %) were used.

Scheme 1



A plausible reaction pathway is shown in Scheme 1.[2] Alkyl radicals, formed by the electron transfer to alkyl bromides from

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(1) For recent reviews on synthetic application of titanium complexes, see: (a) Bochmann, M. In *Comprehensive Organiometallic Chemistry II*; Abel, E. W., Ed.; Pergamon Press: Oxford, U.K., 1995; Vol. 4, Chapters 4 and 5. (b) Houri, A. F.; Hoveyda, A. H. In *Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: Chichester, 1995; Vol. 3, pp 1663−1667.

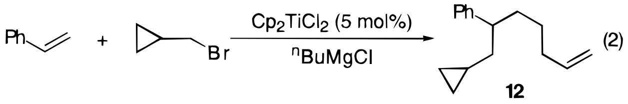
(2) A similar pathway has been proposed for three-component coupling reactions of alkyl iodides, electron-deficient olefins, and carbonyl compounds using excess amounts of manganese or chromium salts. (a) Takai, K.; Ueda, T.; Ikeda, N.; Moriwake, T. *J. Org. Chem.* **1996**, *61*, 7990−7991. (b) Takai, K.; Matsukawa, N.; Takahashi, A.; Fujii, T. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 152−155.

10.1021/ja982732l CCC: $15.00

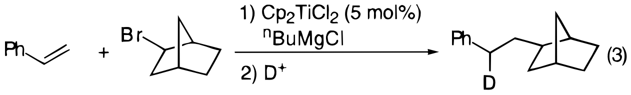
some reduced titanocene complex[3] (step 1), add to the terminal carbon of styrene yielding benzyl radical intermediates (step 2). Recombination of the benzyl radicals with a titanocene complex gives rise to benzyl−Ti intermediates (step 3) which then undergo transmetalation with ^{n}BuMgCl to afford benzylmagnesium chlorides (step 4). The dialkylated products are formed by the reaction of benzylmagnesium chlorides with the alkyl halides (step 5).

This pathway clearly explains the observed regioselectivity by taking into account the features of the following reactions. The rates of alkyl radical formation increase in the order of primary < secondary < tertiary reflecting the stabilities of alkyl radicals. The radical addition to carbon−carbon unsaturated bonds takes place at the terminal carbons exclusively. The alkylation at the benzylic carbon, probably via an S_N2 mechanism, would be favorable for less hindered alkyl halides in the order of primary > secondary > tertiary.

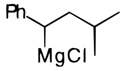
To confirm the validity of the proposed pathway, we employed (bromomethyl)cyclopropane as the alkylating reagent. As might be expected, cyclopropylmethyl and 3-butenyl units were introduced regioselectively giving rise to **12** as the sole dialkylation product in 50% yield (eq 2). This result along with the evidence that ring opening of cyclopropylmethyl radical to 3-butenyl radical is a rapid process which is much faster than the addition of primary radicals to styrene[4] strongly supports the proposal that the first alkylation step is a radical process but that the second step is not.



The intermediacy of benzylmagnesium chlorides in the second alkylation step is supported by the following results. The reaction of styrene with 1.5 equiv of 2-norbornyl bromide was conducted at 0 °C for 1 h using 2.2 equiv of ^{n}BuMgCl in the presence of 5 mol % of Cp_2TiCl_2. Quenching the reaction with D_2O afforded the monoalkylated compound **13** which contained a deuterium at the benzylic position (d-content > 95%) in 59% yield (eq 3).



14



15

This result suggests that a benzylmagnesium chloride **14** was formed in this reaction. While **14** could not be trapped efficiently with 2-norbornyl bromide probably due to steric reasons, sterically nonencumbered primary and secondary alkyl bromides react smoothly with α-substituted benzylmagnesium chlorides under the reaction conditions employed. For example, the reaction of **15**[5] (0.36 M) with isopropyl bromide (1.5 equiv) in THF at 0 °C afforded **9** in 62% yield after only 10 min.[6]

Interestingly, when ^{i}PrMgCl was used instead of ^{n}BuMgCl, the reduction of the alkyl bromides[3,7] predominated, and only a trace amounts of dialkylated products (<2%) were obtained. It should also be noted that the Ti-catalyzed hydromagnesiation of olefins, which can proceed under similar conditions,[8] is completely suppressed in this reaction system. The fact that Cp_2TiCl_2 reacts with Grignard reagents (RMgX) to form anionic Ti(III) ate complexes $Cp_2TiR_2^-$ and that $Cp_2Ti^iPr_2^-$ is unstable at temperatures above −50 °C yielding hydride complexes, whereas $Cp_2TiEt_2^-$ is stable at room temperature,[8b,9] leads us to propose that an ate complex $Cp_2Ti^nBu_2^-$ may play an important role as the active species for the electron transfer to alkyl halides. A detailed study of the mechanism of this titanocene-catalyzed double alkylation is currently under investigation.

In conclusion, we report that a titanocene complex catalyzes the double alkylation of aryl alkenes with various alkyl halides in the presence of ^{n}BuMgCl.[10] Although aryl, vinyl and allyl halides have widely been used for a number of transformations catalyzed by transition metals, the use of alkyl halides in transition metal chemistry is very limited mainly due to the facile β-elimination from the alkylmetal intermediates.[11] The present study outlines a novel methodology for overcoming this drawback by the use of a titanocene catalyst and will provide a useful synthetic method, especially for the construction of carbon skeletons, with the concomitant formation of two carbon−carbon bonds at the adjacent carbons.

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Supporting Information Available: Experimental details and characterization for all new compounds (9 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA982732L

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[3] It is known that alkyl radicals are formed in the titanocene-catalyzed reduction of alkyl bromides with ^{i}PrMgBr. Rilatt, J. A.; Kitching, W. *Organometallics* **1982**, *1*, 1089−1093.

[4] (a) The rate constant $k = 1.3 \times 10^8$ s^{-1} (at 25 °C) for the isomerization of cyclopropylmethyl radical to 3-butenyl radical has been reported: Maillard, B.; Forrest, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 7024−7026. (b) The rate constant $k = 5.4 \times 10^4$ M^{-1} s^{-1} (at 25 °C) for the addition of 5-hexenyl radical to styrene has been reported: Citterio, A.; Minisci, F. *J. Org. Chem.* **1979**, *44*, 2674−2682. (c) Although cyclopropylmethylmagnesium bromide is known to rearrange to $CH_2{=}CHCH_2CH_2MgBr$, it is not likely that these species are the intermediates, since the rearrangement is too slow ($t_{1/2}$ = 30 h in THF at 27 °C): Silver, M. S.; Shafer, P. R.; Nordlander, J. E.; Ruchardt, C.; Roberts, J. D. *J. Am. Chem. Soc.* **1960**, *82*, 2646−2647.

[5] Prepared following a literature description: Harvey, S.; Junk, P. C.; Raston, C. L.; Salem, G. *J. Org. Chem.* **1988**, *53*, 3134−3140.

[6] Reactivities of Grignard reagents toward alkyl bromides largely depend on the structures of the Grignard reagents. For example, $PhCH_2MgCl$ (1.09 M) reacted with ^{i}PrBr (1.5 equiv) more slowly, giving isobutylbenzene in only 8% at 0 °C for 1 h, and ^{n}BuMgCl was not alkylated by ^{i}PrBr under the same conditions.

[7] Colomer, E.; Corriu, R. *J. Organomet. Chem.* **1974**, *82*, 367−373.

[8] (a) Sato, F.; Ishikawa, H.; Sato, M. *Tetrahedron Lett.* **1980**, *21*, 365−368. (b) Ashby, E. C.; Ainsle, R. D. *J. Organomet. Chem.* **1983**, *250*, 1−12. (c) Gao, Y.; Sato, F. *J. Chem. Soc., Chem. Commun.* **1995**, 659−660. (d) For a review of hydromagnesiation, see: Sato, F. *J. Organomet. Chem.* **1985**, *285*, 53−64.

[9] (a) Brintzinger, H. H. *J. Am. Chem. Soc.* **1967**, *89*, 6871−6877. (b) Troyanov, S. I.; Varga, V.; Mach, K. *J. Organomet. Chem.* **1993**, *461*, 85−90.

[10] The dialkylation of alkenes with alkyl halides proceeds by the use of Li metal or by an electrochemical procedure; however, these reactions are inefficient, and regioselective dialkylation has never been reported, see: (a) Davis, A.; Morgan, M. H.; Richards, D. H.; Scilly, N. F. *J. Chem. Soc., Perkin Trans. 1* **1972**, *52*, 286−288. (b) Satoh, S.; Taguchi, T.; Itoh, M.; Tokuda, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 951−952.

[11] See, for example: Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons: Chichester, 1995.