JOC*Note*

Titanocene-Catalyzed Regioselective Carbomagnesation of Alkenes and Dienes

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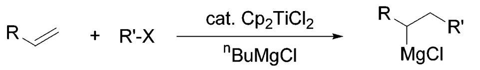
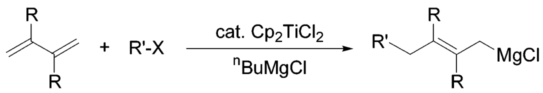
Abstract: A new method for regioselective carbomagnesation of alkenes and dienes has been developed by the use of a titanocene catalyst. This reaction proceeds efficiently at 0 °C in THF in the presence of Cp_2TiCl_2 by the combined use of organic halides (R−X; R = alkyl, aryl and vinyl) and *n*-BuMgCl to afford benzyl, α-silylalkyl, or allyl Grignard reagents, which were trapped with various electrophiles. The present reaction involves (i) addition of carbon radicals toward alkenes or dienes in the carbon−carbon bond-forming step and (ii) transmetalation on Ti of benzyl-, α-silylalkyl-, or allyltitanocene with *n*-BuMgCl in the carbon−magnesium bond-forming step. The scope and limitations of this reaction have also been examined.

Addition of organometallic reagents of nontransition metals (M = Li, Mg, Al, Zn, etc.) across carbon−carbon unsaturated bonds (carbometalation) is a principal and important reaction in organic syntheses for the generation of organometallic compounds having desired carbon skeletons.[1] The most straightforward method for carbomagnesation, which has been studied for more than five decades, is noncatalyzed intermolecular addition of Grignard reagents toward carbon−carbon multiple bonds. However, this reaction usually requires severe conditions, and successful examples of its practical application are quite limited.[2] As an attractive alternative methodology of this transformation, there have been developed several catalytic reactions using transition metal complexes of Ni,[3a−c] Cu,[3d] Ti,[3e] Zr,[3f−j] Mn,[3k,l] or Fe,[3m] however, these reactions also lack generality in the scope of the usable substrates. Here we disclose a carbomagnesation of alkenes and dienes catalyzed by titanocene complex where the carbon moieties of organic halides are introduced via a radical mechanism (eqs 1 and 2).[4, 5]



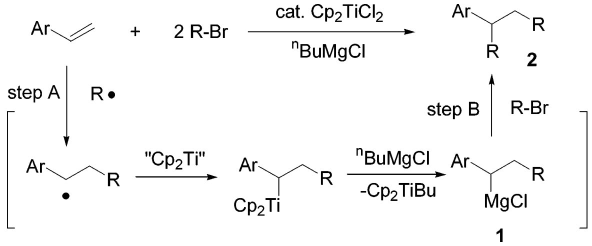
(1)



(2)

Recently, we have developed titanocene-catalyzed double alkylation of arylalkenes using alkyl halides.[6] This reaction involves two different types of carbon−carbon bond-forming processes, i.e., (step A) addition of alkyl radicals at the terminal vinylic carbon and (step B) electrophilic trapping of benzylmagnesium intermediates **1** with alkyl halides (Scheme 1). If step B can be suppressed, this system would make a unique method of carbomagnesation to afford the corresponding Grignard reagents **1** from alkenes and organic halides.

SCHEME 1



At first, we attempted to obtain an intermediate **1a** (Ar = Ph, R = *n*-octyl) by carrying out the reaction of styrene (1 mmol) with a limited amount of *n*-octyl bromide (1 equiv), Cp_2TiCl_2 (5 mol %), and a THF solution of *n*-BuMgCl (2.1 equiv) at 0 °C for 1 h. After quenching with H_2O, however, this reaction provided only the corresponding double alkylated product **2a** (Ar = Ph, R = *n*-octyl) in 42% yield along with 52% of unreacted styrene, indicating that the trapping of **1a** with *n*-Octyl bromide is a rapid process. We then examined the

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(1) For recent reviews, see: (a) Knochel, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 4, pp 865−911. (b) Ley, S. V.; Kouklovsky, C. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon Press: New York, 1995; Vol. 2, pp 549−603. (c) Negishi, E.; Choueiry, D. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon Press: New York, 1995; Vol. 2, pp 951−995.

(2) (a) For a recent review, see: Wakefield, B. J. In *Organomagnesium Methods in Organic Synthesis*; Academic Press, Inc.: San Diego, 1995; pp 73−86. (b) Recently, intermolecular carbomagnesation across vinylsilanes has been developed by exploiting the 2-PyMe$_2$Si group as a removable directing group; see: Itami, K.; Mitsudo, K.; Yoshida, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 2337−2339.

(3) (a) Duboudin, J.-G.; Jousseaume, B. *J. Organomet. Chem.* **1972**, *44*, C1−C3. (b) Snider, B. B.; Karras, M.; Conn, R. S. E. *J. Am. Chem. Soc.* **1978**, *100*, 4624−4626. (c) Snider, B. B.; Conn, R. S. E.; Karras, M. *Tetrahedron Lett.* **1979**, *19*, 1679−1682. (d) Duboudin, J.-G.; Jousseaume, B.; Bonakdar, A. *J. Organomet. Chem.* **1979**, *168*, 227−232. (e) Akutagawa, S.; Otsuka, S. *J. Am. Chem. Soc.* **1975**, *97*, 6870−6871. (f) Dzhemilev, U. M.; Vostrikova, O. S.; Sultanov, R. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1983**, 218−220. (g) Hoveyda, A. H.; Xu, Z. *J. Am. Chem. Soc.* **1991**, *113*, 5079−5080. (h) Takahashi, T.; Seki, T.; Nitto, Y.; Saburi, M.; Rousset, C. J.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 6266−6268. (i) Lewis, D. P.; Muller, P. M.; Whitby, R. J. *Tetrahedron Lett.* **1991**, *32*, 6797−6800. (j) Fischer, R.; Walther, D.; Gebhardt, P.; Gorls, H. *Organometallics* **2000**, *19*, 2532−2540 and references therein. (k) Okada, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1996**, *118*, 6076−6077. (l) Tang, J.; Okada, K.; Shinokubo, H.; Oshima, K. *Tetrahedron* **1997**, *53*, 5061−5072. (m) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978−979.

(4) (a) EtMgBr-mediated intramolecular carbomagnesation of δ-iodoalkenes involving a radical cyclization process has been reported: Inoue, A.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2000**, *2*, 651−653. (b) Zr-catalyzed carbomagnesation of styrenes has been developed by using alkyl tosylates as the electrophilic carbon source: de Armas, J.; Hoveyda, A. H. *Org. Lett.* **2001**, *3*, 2097−2100.

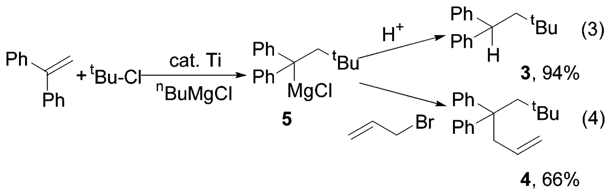
(5) Some examples have been presented in review articles: (a) Terao, J.; Kambe, N. *J. Synth. Org. Chem. Jpn.* **2001**, *59*, 1044−1051. (b) Terao, J.; Kambe, N. In *Latest Frontiers of Organic Synthesis*; Kobayashi, Y., Ed.; Research Signpost, India, 2002; pp 25−48.

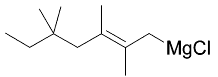
(6) (a) Terao, J.; Saito, K.; Nii, S.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1998**, *120*, 11822−11823. (b) In the presence of chlorosilanes, carbosilylation products are formed: Nii, S.; Terao, J.; Kambe, N. *J. Org. Chem.* **2000**, *65*, 5291−5297.

10.1021/jo0354241 CCC: $27.50

reaction using less reactive organic halides toward S_N2 process to suppress step B.

To a mixture of 1,1-diphenylethylene (1 mmol), *t*-BuCl (2.0 equiv), and 5 mol % of Cp_2TiCl_2 was added a THF solution of *n*-BuMgCl (3.1 equiv, 3.4 mL). After stirring for 2 h at 0 °C, the reaction mixture was quenched with H_2O. The NMR analysis of the crude mixture indicated the formation of the monoalkylated product **3** possessing a *t*-Bu group at the terminal carbon in 94% yield (eq 3). The product was obtained in pure form in 82% yield by a recycling preparative HPLC using $CHCl_3$ as an eluent. In a similar manner allylated product **4** was obtained in 66% NMR yield when the reaction mixture was treated with allyl bromide at 0 °C for 2 h (eq 4). These results indicate the formation of benzyl Grignard reagent **5**. Under similar conditions, styrene and triethylvinylsilane also underwent carbomagnesation to give **6** and **7** by use of secondary alkyl bromides as the alkylating reagents (Table 1, runs 1 and 2).





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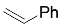
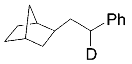
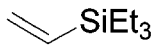
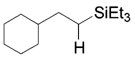
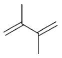
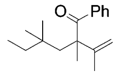
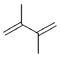
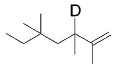
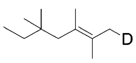
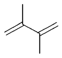
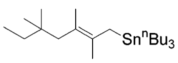
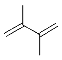
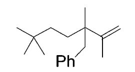
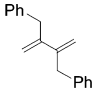
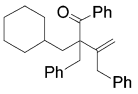
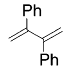
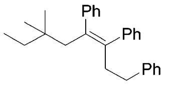
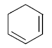
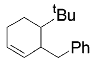
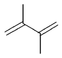
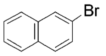
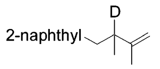
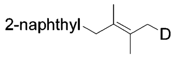
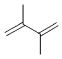
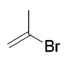
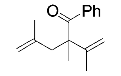
Conjugated dienes also underwent carbomagnesation efficiently. For example, a reaction of 2,3-dimethyl-1,3-butadiene with *tert*-amyl chloride under identical conditions afforded an allylic Grignard reagent **8**, which was trapped with PhCOCl to give a sole regioisomer **9** in 92% isolated yield (run 3). Quenching the reaction mixture with D_2O gave a 35:65 mixture of monoalkylated compounds (**10a**, **b**) in 94% total yield which contain a deuterium at an allylic position (run 4). When stannyl chloride was used as an electrophile, stannylation took place regioselectively at the terminal carbon of the allylmagnesium intermediate due probably to the steric hindrance of the stannyl group (run 5). A reaction of 2,3-dimethyl-1,3-butadiene with *n*-octyl bromide followed by quenching with H_2O gave a mixture of monoalkylated and double alkylated products.[7] So we carried out a similar reaction employing sterically hindered neopentyl bromide. Quenching the resulting mixture with $PhCH_2Br$ afforded the desired product in 70% yield as a single regioisomer (run 6). As for the scope of dienes, phenyl or benzyl substituted 1,3-butadienes and 1,3-cyclohexadiene gave the corresponding products in good to moderate yields (runs 7−9). When internal alkenes, 1-octene, and isoprene were used, reduction of alkyl halides to alkanes and alkenes proceeded predominantly and desired products were not obtained.

TABLE 1. Carbomagnesation of Alkenes and Dienes with Alkyl Halides[a]

run	alkene or diene	R-X	electrophile	product		yield (%)[b]
1		2-Norbornyl-Br	D_2O		**6**	48 (54)
2		*cyclo*-Hex-Br	H_2O		**7**	71 (84)
3		^{t}Amyl-Cl	PhCOCl		**9**	92 (94) 93[c]
4		^{t}Amyl-Cl	D_2O		**10a**	(33)
					**10b**	(61)
5		^{t}Amyl-Cl	^{n}Bu$_3$Sn-Cl	 [*E*/*Z* = 80/20]	**11**	72 (78)
6		^{t}Bu⌄Br	Ph⌄Br		**12**	70
7		*cyclo*-Hex-Br	PhCOCl		**13**	73 (73)
8		^{t}Amyl-Cl	Ph⌄Br	 [*E*/*Z* = 4/96]	**14**	86
9		^{t}Bu-Cl	Ph⌄Br		**15**	40 (73)
10[d]			D_2O		**16a**	61 (66)
					**16b**	13 (15)
11[d]			PhCOCl		**17**	52 (54)

[a] Alkene or diene (1 mmol), R−X (2 mmol), ^{n}BuMgCl (3.1 mmol), Cp_2TiCl_2 (0.05 mmol), THF (3.4 mL), 0 °C, 2 h, then electrophile (1.5 mmol), 0 °C, 2 h. [b] Isolated yield. NMR yield is in parentheses. [c] Reaction was carried out in 10 times scale using 10 mmol of diene. [d] Diene (10 mmol), R−X (1 mmol), ^{n}BuMgCl (2.5 mmol), Cp_2TiCl_2 (0.05 mmol).

It should be noted that aryl and vinyl halides can be employed in the present catalytic system. For example, a reaction of an excess amount of 2,3-dimethyl-1,3-butadiene (10 mmol) with 2-bromonaphthalene (1 mmol) in the presence of Cp_2TiCl_2 (0.05 mmol) and *n*-BuMgCl (2.5 mmol) afforded an 82:18 mixture of monoarylated compounds (**16a**, 66%; **16b**, 15%) containing a deuterium at the allylic positions in 81%.[8] Introduction of a vinyl group could also be attained by the use of 2-bromopropene under similar conditions and **17** was obtained in 52% yield after quenching the corresponding allylmagnesium intermediate with benzoyl chloride (run 11).

As mentioned above, allylmagnesium chlorides can be formed by carbomagnesation of conjugate dienes with alkyl, aryl, and vinyl halides in the presence of Cp_2TiCl_2 and *n*-BuMgCl under mild conditions. Aryl- and silyla-

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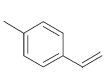
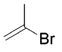
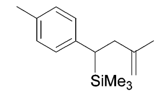
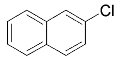
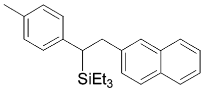
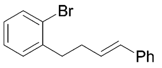
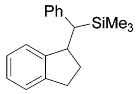
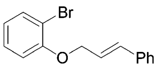
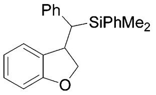
(7) To a mixture of 2,3-dimethyl-1,3-butadiene (87 mg, 1.1 mmol), *n*-octyl bromide (366 mg, 1.9 mmol), *n*-BuMgCl (0.9 M in THF, 3.4 mL, 3.1 mmol) was added Cp_2TiCl_2 (15 mg, 0.06 mmol) at 0 °C under nitrogen. After the mixture was stirred for 2 h, H_2O was added to the solution at 0 °C and the products were extracted with ether. Purification by HPLC with $CHCl_3$ as an eluent afforded monoalkylated products $CH_3(n\text{-}C_9H_{19})C{=}C(CH_3)_2$ and $CH_3(n\text{-}C_9H_{19})CHC(CH_3){=}CH_2$ in 30% and 8% yields, respectively, along with dialkylated products $CH_3(n\text{-}C_9H_{19})C{=}C(n\text{-}C_9H_{19})CH_3$ and $CH_3(n\text{-}C_9H_{19})(n\text{-}C_8H_{17})CC(CH_3){=}CH_2$ in 13% and 9% yields, respectively.

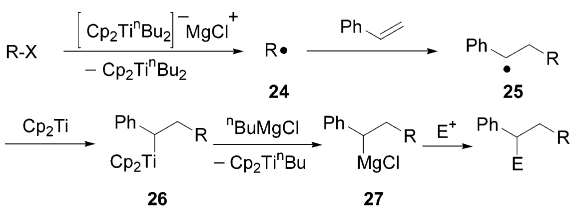
TABLE 2. Arylmagnesation and Vinylmagnesation Using Titanocene Catalyst

run	alkene	halide	electrophile	product	yield[a] (%)
1[b]			Me_3SiCl	 **18**	74
2[b]			Et_3SiCl	 **19**	60
3[c]	 **20**		Me_3SiCl	 **21**	95
4[c]	 **22**		$PhMe_2SiCl$	 **23**	70

[a] Isolated yield based on halide used. [b] Halide (3 mmol), *p*-methylstyrene (10 mmol), ^{n}BuMgCl (3.1 mmol), electrophile (1 mmol), Cp_2TiCl_2 (0.05 mmol), THF (3.4 mL), 0 °C, 2 h. [c] Aryl bromide (1 mmol), electrophile (2 mmol), ^{n}BuMgCl (3.0 mmol), Cp_2TiCl_2 (0.05 mmol), THF (3.3 mL), 0 °C, 2 h.

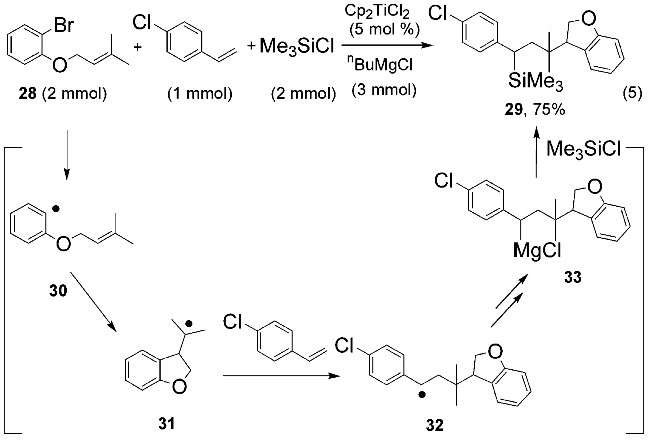
lkenes also afforded the corresponding benzyl- and α-silylalkylmagnesium chlorides by the use of secondary, tertiary and sterically hindered primary alkyl halides. However combination of arylalkenes and aryl or vinyl halides was unsuccessful resulting in the formation of complex mixtures of products due probably to the further reaction of generated benzylmagnesium chloride with arylalkenes. To suppress this undesirable reaction we carried out the reaction of *p*-methylstyrene with 2-bromopropene in the presence of trimethylchlorosilane as an electrophile. As shown in run 1 (Table 2), desired product **18** was formed in 74% yield based on the chlorosilane. 2-Chloronaphthalene also underwent carbomagnesation under identical conditions (run 2). When aryl bromides containing a carbon−carbon double bond at the appropriate position, such as **20** and **22**, were employed, intramolecular carbomagnesation proceeded efficiently probably via radical cyclization (vide infra) giving rise to **21** and **23**, respectively, in good yields (runs 3 and 4).

SCHEME 2



A plausible pathway of this reaction is outlined in Scheme 2 for the case of styrene. Electron transfer from a titanate complex[9] $[Cp_2Ti\text{-}n\text{-}Bu_2]^-MgCl^+$ to an organic halide forms carbon radical species **24** and Cp_2Ti*n*-Bu_2 which decomposes to afford Cp_2Ti along with butane and butanes.[10] Addition of **24** to a double bond at the terminal carbon gives **25** which then reacts with Cp_2Ti to give **26**. Subsequent transmetalation of **26** with *n*-BuMgCl affords a benzylmagnesium chloride **27** and Cp_2Ti*n*-Bu which reacts with *n*-BuMgCl to regenerate $[Cp_2Ti\text{-}n\text{-}Bu_2]^-MgCl^+$. The reaction of dienes would proceed in a similar way via the formation of allylic intermediates instead of benzylic ones.

When the reaction of **28** was carried out in the presence of *p*-chlorostyrene and Me_3SiCl, three-component coupling took place and **29** was obtained as a sole carbosilylation product (eq 5). This result can reasonably be explained by a similar radical mechanism comprising intramolecular cyclization of **30** and intermolecular addition of **31** to *p*-chlorostyrene.



A new method for regioselective carbomagnesation of alkenes and conjugated dienes has been developed by the use of a titanocene catalyst. The titanocene complexes play important roles both in generation of carbon radicals from organic halides via electron transfer from titanate(III) complexes and in transmetalation of titanocene intermediates with Grignard reagent. The present carbomagnesation involves radical mechanisms in the carbon−carbon bond-forming step giving rise to benzyl-, α-silylalkyl-, and allylmagnesium halides with regioselective introduction of alkyl, aryl, and vinyl groups at a terminal carbon of the alkenes and dienes using the corresponding organic halides. Grignard reagents generated by the present method could be trapped with a variety of electrophiles such as benzoyl chlorides, benzyl bromide, a chlorostannane, and chlorosilanes.

Experimental Section

All reagents were used as purchased without further purification. Analytical and purification procedures for NMR, IR, mass,

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(8) If this reaction was conducted using 1 equiv of 2,3-dimethyl-1,3-butadiene (1 mmol) with 2-bromonaphthalene (1 mmol) in the presence of 5 mol % of Cp_2TiCl_2 and 2.5 equiv of *n*-BuMgCl, a 82:18 mixture of monoarylated compounds (**16a**, 17%; **16b**, 6%) containing a deuterium at the allylic positions were obtained in 23% total yield along with 64% of naphthalene. This result suggests that addition of naphthyl radical to butadiene is relatively slow and reduction to naphthalene predominated under these conditions. Debromination of aryl bromides using Grignard reagents in the presence of Cp_2TiCl_2 has been reported: Colomer, E.; Corriu, R. *J. Organomet. Chem.* **1974**, *82*, 367−373.

(9) It is known that Cp_2TiCl_2 reacts with an excess amount of Grignard reagents (RMgX) to form anionic titanate complexes $[Cp_2TiR_2]^-MgX^+$: Brintzinger, H. H. *J. Am. Chem. Soc.* **1967**, *89*, 6871−6877.

(10) McDermott, J. X.; Wilson, M. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1976**, *98*, 6529−6536.

GC−MS, elemental analysis, and HPLC were the same as mentioned previously.[6]

3-Benzoyl-2,3,5,5-tetramethyl-1-heptene (9): Typical Experimental Procedure. To a mixture of 2,3-dimethyl-1,3-butadiene (81 mg, 0.99 mmol), *tert*-amyl chloride (217 mg, 2.05 mmol), and *n*-BuMgCl (0.90 M in THF, 3.4 mL, 3.1 mmol) was added Cp_2TiCl_2 (12 mg, 0.05 mmol) at 0 °C under nitrogen. After the mixture was stirred for 2 h, benzoyl chloride (212 mg, 1.5 mmol) was added to the solution at 0 °C, and the mixture was again warmed to 20 °C. A saturated aqueous NH_4Cl solution (50 mL) was added, and the product was extracted with Et_2O (50 mL), dried over $MgSO_4$, and evaporated to give a yellow crude product (94% NMR yield). Purification by HPLC with $CHCl_3$ as an eluent afforded 234 mg (92%) of acylated product **9** as a yellow oil: IR (NaCl) 2963, 2879, 1677, 1446, 1178, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90−7.88 (m, 2H), 7.45−7.41 (m, 1H), 7.36−7.31 (m, 2H), 5.15 (s, 1H), 5.04 (s, 1H), 2.25 (d, J = 14.6 Hz, 1H), 1.88 (d, J = 14.6 Hz, 1H), 1.74 (s, 3H), 1.47 (s, 3H), 1.28−1.21 (m, 2H), 0.87 (s, 3H), 0.76−0.71 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6, 149.5, 138.0, 131.1, 128.5, 127.6, 111.4, 56.4, 46.7, 37.5, 34.2, 28.4, 27.2, 24.1, 20.6, 8.4; MS (EI) m/z (rel intensity) 258 (M^+, 0.2), 243 (0.9), 229 (1.8), 188 (16), 173 (5), 105 (100), 77 (13), 71 (17), 43 (13); HRMS calcd for $C_{18}H_{26}O$ 258.1984, found 258.1985. Anal. Calcd for $C_{18}H_{26}O$: C, 83.67; H, 10.14. Found: C, 83.48; H, 10.16.

This reaction can be applied to large-scale synthesis by identical operations as above employing 2,3-dimethyl-1,3-butadiene (0.83 g, 10.1 mmol), *tert*-amyl chloride (2.08 g, 20 mmol), *n*-BuMgCl (0.83 M in THF, 37.3 mL, 31 mmol), and Cp_2TiCl_2 (125 mg, 0.5 mmol) to afford a yellow crude product (3.55 g) which was purified by column chromatography (silica gel, *n*-hexane/Et_2O 9:1) to give 2.41 g (93%) of **9** as a yellow oil.

3-[Phenyl(trimethylsilyl)methyl]indan (21). To a mixture of 4-(2-bromobenzene)-1-phenyl-1-butene **20** (246 mg, 0.86 mmol), Me_3SiCl (227 mg, 2.1 mmol), and *n*-BuMgCl (0.90 M in THF, 3.3 mL, 3.0 mmol) was added Cp_2TiCl_2 (12 mg, 0.05 mmol) at 0 °C under nitrogen. After the mixture was stirred for 2 h, similar workup gave an orange crude product (98% NMR yield). Purification by HPLC with $CHCl_3$ as an eluent afforded 228 mg (95%) of **21** as a white solid: IR (NaCl) 2954, 2845, 1246, 834, 754, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27−7.23 (m, 2H), 7.17−7.10 (m, 4H), 7.08−7.00 (m, 1H), 6.84 (t, J = 7.57 Hz, 1H), 6.43 (d, J = 7.56 Hz, 1H), 3.77−3.70 (m, 1H), 2.89−2.82 (m, 2H), 2.45−2.37 (m, 1H), 2.32 (d, J = 10.74 Hz, 1H), 1.97−1.89 (m, 1H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 145.1, 144.2, 128.9, 128.8, 126.6, 125.3, 125.0, 124.9, 124.7, 47.7, 43.7, 34.7, 32.4, 0.00; MS (EI) m/z (rel intensity) 280 (M^+, 40), 206 (15), 164 (29), 117 (100), 73 (44); HRMS calcd for $C_{19}H_{24}Si$ 280.1647, found 280.1646. Anal. Calcd for $C_{19}H_{24}Si$: C, 81.36; H, 8.62. Found: C, 81.16; H, 8.58.

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Supporting Information Available: Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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