Titanocene-Catalyzed Reaction of Alkenes and Dienes with Alkyl Halides and Chlorosilanes

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Abstract: New catalytic reactions for regioselective introduction of alkyl and/or silyl functionalities to alkenes and dienes are described. These reactions proceed efficiently under mild conditions by the use of Cp_2TiCl_2 as a catalyst in the presence of Grignard reagents. The present study would provide a prototype for the practical use of alkyl halides and chlorosilanes in transition metal-catalyzed reactions. In these reactions, ate complexes of titanocene play important roles as the active species. The scope and limitations, as well as reaction pathways, are discussed.

1. Introduction

Introduction of carbon¹ and/or silicon² functional groups across carbon-carbon unsaturated bonds constitutes important processes in organic syntheses. There have been developed a number of catalytic reactions applicable to such transformations, wherein late transition metals have been employed as the catalysts in many cases. Recently, we have accomplished unprecedented alkylation³ and silylation⁴ reactions of alkenes using Cp_2ZrCl_2 as a catalyst in the presence of $^n\text{BuMgCl}$. These successful results prompted us to examine the chemical behavior of Cp_2TiCl_2 leading to development of several unique reactions. In this article, we describe a new type of titanocene-catalyzed reaction⁶ of alkenes and dienes with alkyl halides and/or chlorosilanes, where regioselective C-C and/or C-Si bond forming steps are involved.

2. Regioselective Double-Alkylation of Alkenes⁷

Recently, we have developed a unique double-alkylation reaction of aryl alkenes with alkyl bromides using a titanocene catalyst as shown in eq 1.

For example, to a mixture of styrene, 1-bromopentane (1.1 equiv), *tert*-butyl bromide (1.1 equiv) and Cp_2TiCl_2 (0.05 equiv) was added a THF solution of $^n\text{BuMgCl}$ (2.2 equiv) at 0 °C, and the solution was stirred for 1 h. The double-alkylation product **1** was obtained in 88% yield in which pentyl and *tert*-butyl groups are incorporated regioselectively at the adjacent carbons (Table 1, run 1). The combined use of secondary and primary alkyl bromides (runs 2, 3) or tertiary and secondary alkyl bromides (run 4) afforded the corresponding double-alkylated products **2–4**. Chloro substituents were not affected in this reaction system and the desired product **5** was obtained in good yield (run 5). The same alkyl groups can be introduced at both vicinal carbons when only one alkyl bromide was used. For example, the corresponding products were obtained in good yields by the use of 2.2 equiv of primary or secondary alkyl halides (runs 6–9). Under similar conditions internal alkenes, such as

β -methyl styrene or stilbene, and 1-alkenes having no aryl group, such as 1-octene or 3-ethyl-1-butene were sluggish. This chemoselectivity allows the successful synthesis of diene **10** in 80% yield, using 5-bromo-1-pentene (run 10). Interestingly, when excess amount of 1, 3-dibromopropane or 1, 4-dibromobutane was used, products **11a, b** containing 5- or 6-membered ring were obtained in moderate yields (eq 2).

Table 1. Ti-Catalyzed double alkylation of aryl alkenes

run	aryl alkene	R'-Br, R''-Br	product	yield (%) ^a
1	Ph-CH=CH ₂	^t Bu-Br ⁿ C ₅ H ₁₁ -Br	Ph-CH(^t Bu)-CH(ⁿ C ₅ H ₁₁) ₂ 1	88
2	Ph-CH=CH ₂	2-Norbornyl-Br ⁿ C ₅ H ₁₁ -Br	Ph-CH(2-Norbornyl)-CH(ⁿ C ₅ H ₁₁) ₂ 2	79
3	Ph-CH=CH ₂	ⁱ Pr-Br ⁿ C ₅ H ₁₁ -Br	Ph-CH(ⁱ Pr)-CH(ⁿ C ₅ H ₁₁) ₂ 3	54
4	<i>p</i> -tol-CH=CH ₂	^t Amyl-Br ⁱ Pr-Br	<i>p</i> -tol-CH(^t Amyl)-CH(ⁱ Pr) ₂ 4	52
5	<i>p</i> -ClC ₆ H ₄ -CH=CH ₂	^t Bu-Br Cl(CH ₂) ₅ -Br	<i>p</i> -ClC ₆ H ₄ -CH(^t Bu)-CH(ClCH ₂) ₅ 5	71
6	Ph-CH=CH ₂	ⁿ C ₅ H ₁₁ -Br	Ph-CH(ⁿ C ₅ H ₁₁) ₂ 6	72
7	Ph-CH=CH-Me	ⁿ Oct-Br	Ph-CH(ⁿ Oct)-CH(ⁿ Oct)-Me 7	62
8	Ph-CH=CH-Ph	ⁿ Oct-Br	Ph-CH(ⁿ Oct)-CH(ⁿ Oct)-Ph 8	75
9	Ph-CH=CH ₂	ⁱ Pr-Br	Ph-CH(ⁱ Pr) ₂ 9	73
10	Ph-CH=CH ₂	5-bromo-1-pentene	Ph-CH=CH-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH=CH ₂ 10	80

^a Isolated yield.

A plausible reaction pathway is shown in Scheme 1. Titanocene dichloride reacts with ${}^n\text{BuMgCl}$ to generate dibutyltitanate(III) complex **13a** via Cp_2TiCl_2 and butyltitanocene **12**. One electron transfer from **13a** to alkyl bromides leads to cleavage of the C–Br bond to give an alkyl radical¹⁰ along with dibutyltitanocene **14**, which readily forms Cp_2Ti (**15**) via β -hydrogen elimination¹¹. Addition of the thus-formed alkyl radical to styrene at the terminal carbon affords a benzyl radical species, which recombines with **15** to give the corresponding benzyltitanium complex **16**. Subsequent transmetalation¹² of **16** with ${}^n\text{BuMgCl}$ gives the corresponding benzyl Grignard reagent **17** along with regeneration of **12**. The double-alkylated products are formed by the reaction of **17** with alkyl bromides.

Scheme 1

Since it is known that Cp_2TiCl_2 catalyzes hydromagnesiation¹³ of styrene to give benzylmagnesium halide by the use of ${}^i\text{PrMgX}$ in the absence of alkyl halides, we tested whether this hydromagnesiation can take place in the present reaction. When we carried out a reaction of styrene with octyl bromide using ${}^i\text{PrMgCl}$ instead of ${}^n\text{BuMgCl}$, the reduction of octyl bromide¹⁴ predominated and only a trace amount of the double-alkylated product (<2%) was obtained. In this reaction, hydromagnesiation was completely suppressed. The fact that Cp_2TiCl_2 reacts with Grignard reagents (RMgX) to form anionic Ti (III) ate complexes $[\text{Cp}_2\text{TiR}_2]^- \text{MgX}^+$ and that $[\text{Cp}_2\text{Ti}^i\text{Pr}_2]^- \text{MgX}^+$ is unstable at temperatures above -50°C yielding hydride complexes whereas $[\text{Cp}_2\text{TiEt}_2]^- \text{MgX}^+$ is stable at room temperature¹⁵, may support that an ate complex $[\text{Cp}_2\text{Ti}^n\text{Bu}_2]^- \text{MgCl}^+$ has enough life time to play an important role as the active species for the electron transfer to alkyl halides in our reaction. Then, we examined the intermediary of $[\text{Cp}_2\text{Ti}^n\text{Bu}_2]^- \text{MgCl}^+$ as follows. Cp_2TiCl_2 (0.025 M) was treated with a large excess of ${}^n\text{BuMgCl}$ (0.9 M) at 0°C in THF. The ESR spectrum of the resulting dark-brown solution showed a quintet hyperfine splitting at $g=1.989$ with a

coupling constant of 2.4 gauss which might be ascribable to the coupling with the four equivalent α -hydrogens of the two butyl groups of **13a**. This is quite similar to the ESR spectrum of $[\text{Cp}_2\text{TiEt}_2]^- \text{MgCl}^+$ ($g=1.991$, 2.3 gauss) generated by the reaction of Cp_2TiCl_2 with EtMgCl ^{15a}. Addition of cyclohexyl bromide into the THF solution of **13a** quickly changed the color to green and the ESR signal disappeared. This result is in accord with the SET process in Scheme 1 (**13a** to **14**).

In order to confirm the radical mechanism for the carbon-carbon bond forming step in Scheme 1, we carried out the reaction of styrene using (bromomethyl)cyclopropane as the alkylating reagent. As might be expected, cyclopropylmethyl and 3-butenyl units were introduced regioselectively giving rise to **18** as the sole double-alkylation product in 50% yield (eq 3). This result can be explained by the evidence that the rate constant of the ring-opening of the cyclopropylmethyl radical, $k=1.3 \times 10^8 \text{ s}^{-1}$ at 25°C ¹⁶, is much faster than the addition of primary radicals to styrene, $k=5.4 \times 10^4 \text{ M}^{-1}\text{s}^{-1}$ at 25°C ¹⁷.

The intermediary 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 ${}^n\text{BuMgCl}$ in the presence of 5 mol% of Cp_2TiCl_2 . Quenching the reaction mixture with D_2O afforded the mono-alkylated compound **19** which contained a deuterium at the benzylic position (d -content > 95%) in 59% yield (eq 4). This result suggests that a benzylmagnesium chloride **20** was formed in this reaction. While **20** could not be trapped efficiently with 2-norbornylbromide in this reaction, probably due to steric reasons, sterically non-encumbered primary and secondary alkyl bromides react smoothly with α -substituted benzylmagnesium chlorides under the reaction conditions employed. For example, the reaction of **21**¹⁸ (0.36 M) with isopropyl bromide (1.5 equiv) in THF at 0°C afforded **9** in 62% yield after only 10 min¹⁹. Moreover, when we performed a similar reaction using ${}^i\text{PrBr}$ as an alkylating reagent instead of 2-norbornyl bromide, the mono-alkylated product was not detected, resulting in the formation of a double-alkylated compound as the sole product due to the rapid reaction of ${}^i\text{PrBr}$ with the benzylmagnesium intermediate generated *in situ*.

3. Titanocene-Catalyzed Alkylation of Aryl Alkenes Using Alkyl Halides: a Mizoroki-Heck type transformation²⁰

Titanocene-catalyzed addition of two alkyl groups to car-

bon-carbon double bonds was shown in the previous section (eq 1). It is very surprising that changing the solvent from THF to ether led to the formation of different products as shown in eq 5, in which a terminal vinylic hydrogen was replaced with an alkyl group. This reaction provides formally the same transformation as the Mizoroki-Heck reaction which has widely been applied to the preparation of substituted alkenes²¹. This reaction proceeds efficiently in the presence of a palladium catalyst using aryl, 1-alkenyl, benzyl, allyl, and 1-alkynyl halides; however, alkyl halides having β -hydrogens can not be employed in this reaction due to the facile β -hydrogen elimination from the σ -alkylpalladium intermediates²². Our Ti-catalyzed reaction (eq 5) might be a supplementary procedure to this well-known reaction since alkyl groups can be introduced using alkyl halides at the terminal vinylic carbon of alkenes with perfect regioselectivity. The same transformation has been achieved by cobalt^{23a} or nickel^{23b} catalyst.

When an ether solution of 1-bromodecane, styrene (3.0 equiv), $^n\text{BuMgCl}$ (1.3 equiv) and a catalytic amount of Cp_2TiCl_2 (0.03 equiv) was stirred for 2.5 h at 0°C under nitrogen, (*E*)-1-phenyl-1-dodecene **22** was obtained in 63% yield based on alkyl bromide with >98% regio- and stereoselectivities (Table 2, run 1). The use of one equivalent of styrene reduced the yield of **22** to 37% and increased the formation of decane and 1-decene in 25% and 18% yields, respectively. The use of primary bromides (runs 2–6) afforded the corresponding products **23–27**. When cyclohexyl bromide was used as the alkylating reagent, **28** was obtained in moderate yield under the same conditions (46% based on the halide), but the yield of **28** was improved to 71% based on styrene by employing 20 mol% of a titanocene catalyst and 1.5 equivalent of cyclohexyl bromide (run 7). It should be noted that this reaction also proceeded with secondary alkyl chlorides to give **28** and **29**.

A plausible pathway of this alkylation is shown in Scheme 2. In ether solution, the electron transfer from titanate(III) complex **13b** to alkyl halides took place predominantly along with the formation of **30** over the transmetalation leading to benzylmagnesium **17** and **12**. This different behavior of **13b** might be explained by assuming that elimination of benzylmagnesium **17** from **13b** is an equilibrium process and that **17** can react with alkyl halides to give double-alkylation products only in a strongly coordinating solvent such as THF. In ether, **17** recombines with $\text{Cp}_2\text{Ti}^n\text{Bu}$ to regenerate **13b**, which transfers an electron to alkyl halides to give **30**. The successive β -elimination via site selective hydrogen abstraction at the benzylic group of **30** affords the corresponding product and **15**.

4. Carbosilylation of Alkenes and Dienes²⁴

Addition of a carbon and a silicon unit to carbon-carbon unsaturated bonds (carbosilylation) is a synthetically very useful reaction for synthesis of a variety of organosilicon compounds with concomitant construction of the desired carbon skeletons. There have already been developed several

Table 2. Ti-Catalyzed alkylation of aryl alkenes with alkyl halides

run	Aryl Alkenes	alkyl halide	product	yield (%) ^a
1	Ph-CH=CH ₂	ⁿ C ₁₀ H ₂₁ -Br	Ph-CH=CH- ⁿ C ₁₀ H ₂₁ 22	63
2		Br-CH ₂ -CH ₂ -CH ₂ -CH ₃	Ph-CH=CH-CH ₂ -CH ₂ -CH ₂ -CH ₃ 23	70
3	<i>p</i> -ClC ₆ H ₄ -CH=CH ₂	Br-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₃	<i>p</i> -ClC ₆ H ₄ -CH=CH-CH ₂ -CH ₂ -CH ₂ -CH ₃ 24	71
4	Ph-CH=CH ₂	Br-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -Cl	Ph-CH=CH-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -Cl 25	64
5		Br-CH ₂ -CH ₂ -CH ₂ -CH ₃	26	59
6	Ph-CH=CH ₂	Br-(CH ₂) ₆ -Br	Ph-CH=CH-(CH ₂) ₆ -CH=CH-Ph 27	40
7 ^b		Br-C ₆ H ₁₁	Ph-CH=CH-C ₆ H ₁₁ 28	71 ^c
8 ^b		Cl-C ₆ H ₁₁	28	65 ^c
9 ^b	<i>p</i> -MeC ₆ H ₄ -CH=CH ₂	Cl-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₃	<i>p</i> -MeC ₆ H ₄ -CH=CH-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₃ 29	49 ^c

^aIsolated yield is based on alkyl halides unless otherwise stated.

^bSecondary alkyl halides (1.5 equiv) and titanocene catalyst (20 mol %) were used. ^cBased on styrene used.

Scheme 2

methods for the carbosilylation of alkynes²⁵, dienes²⁶ and allenes²⁷. By the use of Cp_2TiCl_2 , we have developed a new catalytic system for carbosilylation of alkenes by the combined use of alkyl halides and chlorosilanes (eq 6). This reaction can also be applied to dienes successfully (eq 7) and the results are summarized in Table 3.

When the reaction of styrene with 1.1 equiv of chlorotriethylsilane and *tert*-butyl bromide was carried out at 0 °C in THF, high yield of carbosilylation product **31** was obtained as a single regioisomer, possessing a *tert*-butyl group at the terminal carbon and a triethylsilyl group at the benzylic carbon (run 1). In this reaction, a trace amount (<1%) of Et₃SiⁿBu was formed by the direct reaction of Et₃SiCl with ⁿBuMgCl. As shown in runs 2, 5, 6, 10 and 11, this reaction proceeds when secondary bromides are used. Primary alkyl bromides can also be employed as the alkylating reagents, but the reaction is somewhat less efficient due to the formation of a double-alkylated compound as a byproduct (run 3). When chloro substituted substrates were used, the reaction took place site selectively at the bromo functional group leaving the chloro substituents intact, giving rise to **34** in 40% yield (run 4). In addition to aryl substituted alkenes, a vinylsilane underwent carbosilylation to give the corresponding *gem*-disilyl product **36** in a moderate yield (run 6).

When 2, 3-dimethyl-1, 3-butadiene was treated with *tert*-butyl bromide and Et_3SiCl under identical conditions, alkyl and silyl units are introduced at the 1- and 4-positions forming **37** in high yield with an *E/Z* ratio of 96/4 (run 7). It should be noted that secondary and tertiary alkyl chlorides can be employed as suitable alkylating reagents in this reaction giving **37** and **38** in good yields (runs 8, 9). Phenyl and benzyl substituted 1, 3-butadienes also gave the corresponding products in good yields (runs 10-12).

The present carbosilylation would proceed via a similar pathway as double-alkylation, i.e., the addition of alkyl radicals toward alkenes or dienes in the carbon-carbon bond forming step and an electrophilic trapping of benzyl- or allyl-magnesium halides with chlorosilanes in the carbon-silicon bond forming step. A plausible pathway of this reaction is outlined in Scheme 3 for the case of dienes.

When the reaction of 6-bromo-1-phenyl-1-hexene with Me_3SiCl was performed under identical conditions, only the cyclized product **42** was obtained probably via 5-exo radical cyclization (eq 8). This result strongly supports a radical mechanism for the carbon-carbon forming process.

In order to prove the active species of the silylation step, allyltitanocene complex **43** was prepared by the reported procedure²⁸, and its reactivity toward chlorosilanes was examined. When a THF solution of **43** and Et₃SiCl (1 equiv) was stirred at 0 °C for 1 h, no reaction took place. On the other hand, **44** was formed in 73% yield when a similar reaction was performed in the presence of a stoichiometric amount of ⁿBuMgCl (eq 9). These results suggest that chlorosilane reacts with the ate complex **45** or with allylmagnesium chloride **46** which is formed by transmetalation from **43** via **45**. Although a possibility that titanate complexes such as **45** react directly with chlorosilanes cannot be ruled out, the results of the next section support that the transmetalation does proceed under the conditions employed.

Table 3. Ti-Catalyzed carbosilylation of alkenes or dienes

run	alkene or diene	R-X R' ₃ Si-Cl	product	yield (%) ^a
1		^t Bu-Br Et ₃ Si-Cl	31	94
2		ⁱ Pr-Br Et ₃ Si-Cl	32	84
3		ⁿ Pr-Br Et ₃ Si-Cl	33	47
4		ClC ₆ H ₁₀ -Br Et ₃ Si-Cl	34 Cl	40
5		2-Norbornyl-Br ⁿ Pr ₃ Si-Cl	35	74
6		2-Norbornyl-Br ⁿ Pr ₃ Si-Cl	36	36
7		^t Bu-Br Et ₃ Si-Cl	37	78 E/Z = 96/4
8		^t Bu-Cl Et ₃ Si-Cl	37	62 E/Z = 98/2
9		cyclo-Hex-Cl Et ₃ Si-Cl	38	53 E/Z = 97/3
10		cyclo-Hex-Br Et ₃ Si-Cl	39	80 E/Z = 10/90
11		cyclo-Hex-Br Et ₃ Si-Cl	40	92 E/Z = 80/20
12		^t Bu-Br Et ₃ Si-Cl	41	81 ^b E/Z = 100/0

^aIsolated yield. ^bNMR yield.

Scheme 3

5. Carbomagnesation of Alkenes and Dienes²⁹

We then attempted carbomagnesation by using Cp_2TiCl_2 as the catalyst. A typical example is as follows. To a mixture of 2, 3-dimethyl-1, 3-butadiene, *tert*-amyl chloride (2.0 equiv), and 5 mol% of Cp_2TiCl_2 was added to a THF solution of $n\text{BuMgCl}$ (3.1 equiv) at 0 °C, and the solution was stirred for 2 h. Quenching the reaction mixture with D_2O afforded mono-alkylated compounds **47a** and **47b** containing a deuterium at one of the two allylic positions in 94% total yield as a mixture of regioisomers (**47a**/**47b**=35/65) (eq 10). When the reaction was quenched with benzoyl chloride instead of D_2O , the acylated product **49** was obtained in 92% yield as a single regioisomer (Table 4, run 1). These results suggest the formation of allyl Grignard reagent **48**.

Table 4 shows some representative results of carbomagnesation using various substrates and electrophiles performed in a similar one-pot sequence. When stannyl chloride was used as an electrophile, stannylation took place regioselectively at the terminal position of the allylmagnesium intermediates due to the steric hindrance of the stannyl group (run 2). Secondary alkyl bromides can also be employed as suitable alkylating reagents (runs 3, 8). On the other hands, *n*-octyl bromide gave the desired product only in poor yield, resulting in the formation of a double-alkylated product probably due to the rapid reaction of primary bromide with allylmagnesium chloride generated *in situ*. This can be supported by the evidence that a sterically hindered primary bromide can be employed as a suitable alkylating reagent (run 4). As for the scope of dienes, phenyl and benzyl substituted 1, 3-butadienes and 1, 3-cyclohexadiene afforded the corresponding products in good yields (runs 3, 5 and 6). 1, 1-Diphenylethylene underwent carbomagnesation in the presence of *tert*-BuCl under similar conditions to afford a mono-alkylated product possessing a *tert*-butyl group at the terminal carbon in 76% yield after quenching with H_2O . The allylated product **55** was obtained in 54% yield when the reaction mixture was treated with allyl bromide instead of H_2O (run 7). A vinylsilane also afforded the corresponding product in good yield (run 8). When internal alkenes, 1-octene, and isoprene were used, no reaction took place under similar conditions.

Carbomagnesation of alkenes has long been studied for

Table 4. Ti-Catalyzed carbomagnesation

run	alkene	R-X electrophile	product	yield (%) ^a
1		<i>t</i> Amyl-Cl PhCOCl		92
2		<i>t</i> Amyl-Cl $n\text{Bu}_3\text{Sn-Cl}$		72
3		<i>cyclo</i> -Hex-Br PhCOCl		73
4		<i>t</i> Bu-Br Ph-Br		70
5		<i>t</i> Amyl-Cl Ph-Br	 [<i>E/Z</i> = 4/96]	86
6		<i>t</i> Bu-Cl Ph-Br		73 ^b
7		<i>t</i> Bu-Cl Allyl Bromide		54
8		<i>cyclo</i> -Hex-Br H_2O		71

^a Isolated yield. ^b NMR yield.

more than five decades. The most straightforward method is non-catalyzed intermolecular addition of Grignard reagents to carbon-carbon double bonds, but the reaction usually requires severe conditions and has been applied to only limited substrates³⁰. As an attractive alternative to this method, there have been developed several reactions using a transition metal catalyst such as Ni^{31a} , Cu^{31b} , Ti^{31c} , and Zr^{31d} complexes; however, these reactions also lack generality in the scope of usable substrates. The present reaction will be synthetically useful since a variety of alkyl groups can be introduced to alkenes and dienes by using the corresponding alkyl halides.

6. Double-Silylation of Alkenes and Dienes³²

The double-silylation of unsaturated hydrocarbons has extensively been studied using late transition metal catalysts, such as palladium and platinum complexes, and disilanes or hydrosilanes as the silylating reagents^{1b,33}. In this section, we describe the first example of a transition metal-catalyzed double-silylation of dienes and alkenes with chlorosilanes, which proceeds under mild conditions by the use of Cp_2TiCl_2 in the presence of $n\text{BuMgCl}$.

When *p*-chlorostyrene was treated with 2 equivalents of Et_3SiCl and $n\text{BuMgCl}$ in the presence of a catalytic amount of titanocene dichloride at 0 °C in THF, *vic*-double-silylated product **57** was obtained in 8% yield (eq 11). Use of $\text{Me}_2\text{PhSi-Cl}$ improved the yield of **58** into 29%, but a substantial amount of $\text{Me}_2\text{PhSi}^n\text{Bu}$ was formed. This problem was overcome by using a large amount of catalyst (15 mol %) and by

adopting a dropwise addition of Me_2PhSiCl giving rise to **58** in 76% yield. The present reaction also may proceed via a benzyl radical intermediate which is formed by the addition of a silyl radical species to styrene. Since the dimethylphenyl silyl radical is more stable than the triethylsilyl radical, the former would be generated more readily from the corresponding chlorosilane by one electron transfer from a titanate complex $[\text{Cp}_2\text{Ti}^{\text{III}}\text{Bu}_2]\text{MgCl}^+$ affording better yield of the double-silylation product.

Isoprene underwent double-silylation efficiently, giving rise to 1,4-double-silylated products **59** and **60** in 78% and 91% yields, respectively (eq 12). In contrast to the case of styrene, the reaction of isoprene proceeds efficiently using Et_3SiCl . This may suggest that an alternative mechanism operates in double-silylation of dienes. A possible pathway may involve formation of titanacyclopentenes from Cp_2Ti and dienes as the intermediates, which then undergo transmetalation by the reaction with $^n\text{BuMgCl}$ as shown in the next section.

7. Silylative Coupling of Vinyl Grignard Reagents³⁴

In addition to the regioselective introduction of alkyl and/or silyl functionalities to alkenes and dienes mentioned above, $\text{Cp}_2\text{TiCl}_2/\text{RMgX}$ catalyzed systems have been applied to the reduction of organohalides^{35a} and carbonyl compounds^{35b} or to the hydromagnesation of carbon-carbon unsaturated bonds¹³. In these reactions, however, Grignard reagents have been used as the reducing reagent of titanocene complexes or as the hydrogen source and their carbon moieties have not been incorporated in the products. This section deals with a new type of titanocene-catalyzed coupling reactions in which the organic moieties of Grignard reagents are involved in the products.

When a reaction of Me_2PhSiCl with vinyl Grignard reagent (1 equiv) was conducted in the presence of a catalytic amount of Cp_2TiCl_2 , 1,4-bis(dimethylphenylsilyl)-2-butene (**61**; $\text{R}_3\text{Si} = \text{Me}_2\text{PhSi}$) was obtained in 94% yield with an E/Z ratio of 74/26 (eq 13). Under the conditions employed, the direct reaction of vinylmagnesium bromide with chlorosilane was slow and only a trace amount of $\text{CH}_2=\text{CHSiMe}_2\text{Ph}$ (<1%) was formed as a byproduct. This reaction also proceeds when trialkylsilyl chlorides are used as the silylating reagents, giving rise to **62** and **63** in good yields. When dichlorodiphenylsilane was treated with 2 equivalents of vinyl

Grignard reagent at -20°C for 3 h, cyclization predominated to afford 1,1-diphenyl-1-silacyclo-3-pentene **64** in 73% yield (eq 14).

A plausible reaction pathway of this silylative vinyl coupling is shown in Scheme 4. Titanocene dichloride reacts with 2 equivalents of $\text{CH}_2=\text{CHMgBr}$ to generate divinyltitanocene complex **65**, which readily forms titanocene-butadiene complex **66** or its *s-trans* isomer via reductive coupling^{36,37}. Then, **66** isomerizes to titanacyclopentene **67**³⁸. The successive transmetalation of **67** with vinyl Grignard reagent affords allylmagnesium species **68**, which reacts with a chlorosilane to give allylsilane **69** carrying a titanocene group on the other allylic position. Subsequent transmetalation of **69** with $\text{CH}_2=\text{CHMgBr}$ followed by trapping with a chlorosilane gives the corresponding product along with regeneration of **65**.

Scheme 4

8. Conclusion

A novel catalytic system for regioselective alkylation and/or silylation of alkenes or dienes has been developed by the aid of a titanocene complex. These reactions proceed under mild conditions by the use of alkyl halides and/or chlorosilanes in the presence of Grignard reagents. Although alkyl halides and chlorosilanes are the most easily available and widely used substrates in organic syntheses, their use in transition metal catalyzed reactions has been limited. This is probably due to (i) the slow oxidative addition of alkyl halides to metal complexes and the fast β -hydrogen elimination from σ -alkylmetal intermediates, and (ii) the difficulty of the oxidative addition of the Si-Cl bond to metal complexes.

The reactions mentioned here are attractive from both mechanistic and synthetic viewpoints. This study will open up a new field of transition metal chemistry providing a unique methodology for introduction of alkyl and silyl groups across carbon-carbon unsaturated units.

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References

- (a) *Metal-catalyzed Cross-coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; WILEY-VCH: Weinheim, 1997; Chapters 3, 6 and 7. (b) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons, Inc.: Chichester, 1995. (c) *Transition Metals for Organic Synthesis*; Beller, M.; Bolm, C., Eds.; WILEY-VCH, Weinheim, 1998; Vol. 1.
- (a) Ojima, I.; Li, Z.; Zhu, J. In *The Chemistry of Organic Silicon Compounds Volume 2*; Patai, S.; Rappoport, Z., Eds.; John Wiley & Sons: Chichester, 1998; Part 2, pp.1687-1792. (b) Reichel, J. A.; Berry, D. H. In *Advances in Organometallic Chemistry*; Stone, F. G. A.; West, R., Eds.; Academic Press: New York, 1998; pp.197-265.
- Terao, J.; Watanabe, T.; Saito, K.; Kambe, N.; Sonoda, N. *Tetrahedron Lett.* **1998**, 39, 9201.
- Terao, J.; Torii, K.; Saito, K.; Kambe, N.; Baba, A.; Sonoda, N. *Angew. Chem., Int. Ed.* **1998**, 37, 2653.
- Tatsumi, K. In *Kikan Kagaku Sousetu No. 17, Organic Chemistry of the Early Transition Metals*; Gakkai Shuppan Center: Tokyo, 1993, pp.1-20.
- For a recent review on synthetic application of Cp_2TiCl_2 , see: Petasis, N. A.; Hu, Y. -H.; *Current Organic Chemistry* **1997**, 1, 249.
- Terao, J.; Saito, K.; Nii, S.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1998**, 120, 11822.
- For the formation of Cp_2TiCl from Cp_2TiCl_2 in the presence of alkyl Grignard reagents, see: Martin, H. A.; Jellinek, F. J. *Organomet. Chem.* **1968**, 12, 149.
- Reaction of Cp_2TiCl with $^n\text{BuLi}$ affords the thermally unstable **12**, see: Klei, E.; Telgen, J. H.; Teuben, J. H. *J. Organomet. Chem.* **1981**, 209, 297.
- It is known that alkyl radicals are generated in the titanocene-catalyzed reduction of alkyl bromides with $^i\text{PrMgBr}$. Rilatt, J. A.; Kitching, W. *Organometallics* **1982**, 1, 1089.
- It is reported that **14a** decomposes rapidly at -50°C forming **15** along with a 1:1 mixture of *n*-butane and butenes. McDermott, J. X.; Wilson, M. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1976**, 98, 6529.
- Transmetalation of vinyltitanocene complexes with $^i\text{PrMgBr}$ is known. Gao, Y.; Sato, F. *J. Chem. Soc., Chem. Commun.* **1995**, 659.
- Sato, F. *J. Organomet. Chem.* **1985**, 285, 53. Gao, Y.; Sato, F. *J. Chem. Soc., Chem. Commun.* **1995**, 659, and references therein.
- Colomer, E.; Corriu, R. J. *Organomet. Chem.* **1974**, 82, 367.
- (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.
- Maillard, B.; Forrest, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, 98, 7024.
- The rate constant for the addition of 5-hexenyl radical to styrene has been reported: Citterio, A.; Minisci, F. *J. Org. Chem.* **1979**, 44, 2674.
- Prepared following a literature description: Harvey, S.; Junk, P. C.; Raston, C. L.; Salem, G. *J. Org. Chem.* **1988**, 53, 3134.
- 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 $^i\text{PrBr}$ (1.5 equiv) much slower giving *iso*-butylbenzene in only 8% at 0°C for 1 h, and $^n\text{BuMgCl}$ was not alkylated by $^i\text{PrBr}$ under the same conditions.
- Terao, J.; Miyamoto, M.; Kambe, N. Result to be submitted for publication.
- Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, 44, 581. Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, 37, 2320.
- Recently it was reported that the palladium-catalyzed reaction of 1-bromoadamantane with styrenes gave the corresponding Heck-type coupling products in 15-41% yields: Brase, S.; Waegell, B.; Meijere, A. *Synthesis* **1998**, 148.
- (a) Lebedev, S. A.; Lopatina, V. S.; Shifrina, R. R.; Petrov, E. S.; Beletskaya, I. P. *Izv. Akad. Nauk SSSR* **1983**, 10, 2414. Lebedev, S. A.; Lopatina, V. S.; Luk'yanova, T. V.; Berestova, S. S.; Shifrina, R. R.; Shapet'ko, N. N.; Petrov, E. S.; Beletskaya, I. P. *Izv. Akad. Nauk SSSR* **1985**, 22, 652. (b) Branchaud, B. P.; Detlefsen, W. D. *Tetrahedron Lett.* **1991**, 32, 6273.
- Nii, S.; Terao, J.; Kambe, N. *J. Org. Chem.* **2000**, 65, 5291.
- Lewis acid-catalyzed addition of allylsilane: Asao, N.; Yoshikawa, E.; Yamamoto, Y. *J. Org. Chem.* **1996**, 61, 4874. Pd-catalyzed carbosilylation; Chatani, N.; Hanafusa, T. *J. Chem. Soc., Chem. Commun.*, **1985**, 838. Sakurai, H.; Kamiyama, Y.; Nakadaira, Y. *J. Am. Chem. Soc.* **1977**, 99, 3879. Saso, H.; Ando, W. *Chem. Lett.* **1988**, 1567. Sakurai, H.; Imai, T. *Chem. Lett.* **1975**, 891. Chatani, N.; Amishiro, N.; Murai, S. *J. Am. Chem. Soc.* **1991**, 113, 7778. Chatani, N.; Amishiro, N.; Morii, T.; Yamashita, T.; Murai, S. *J. Org. Chem.* **1995**, 60, 1834.
- Obora, Y.; Tsuji, Y.; Kawamura, T. *J. Am. Chem. Soc.* **1995**, 117, 9814.
- Wu, M.; Yang, F.; Cheng, C. *J. Org. Chem.* **1999**, 64, 2471.
- Martin, H. A.; Jellinek, F. *Angew. Chem.* **1964**, 76, 274. Chen, J.; Kai, Y.; Kasai, N.; Yasuda, H.; Yamamoto, H.; Nakamura, J. *Organomet. Chem.* **1991**, 407, 191.
- Nii, S.; Terao, J.; Kambe, N. Result to be submitted for publication.
- Wakefield, B. J. In *Organomagnesium Methods in Organic Synthesis*; Wakefield, B. J. Ed.; Academic Press INC: San Diego, 1995, Chapter 4.
- (a) Duboudin, J. -G.; Jousseume, B. *J. Organomet. Chem.* **1972**, 44, C1-C3. Snider, B. B.; Karras, M.; Conn, R. S. E. *J. Am. Chem. Soc.* **1978**, 100, 4624. Snider, B. B.; Conn, R. S. E.; Karras, M. *Tetrahedron Lett.* **1979**, 19, 1679. (b) Duboudin, J. -G.; Jousseume, B.; Bonakdar, A. *J. Organomet. Chem.* **1979**, 168, 227. (c) Akutagawa, S.; Otsuka, S. *J. Am. Chem. Soc.* **1975**, 97, 6870. (d) Dzhemilev, U. M.; Vostrikova O. S. and Sultanov, R. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1983**, 218. Fischer, R.; Walther, D.; Gebhardt, P.; Gols, H. *Organometallics* **2000**, 19, 2532 and references cited therein.
- Terao, J.; Kambe, N.; Sonoda, N. *Tetrahedron Lett.* **1998**, 39, 9697.
- For reviews, see: Horn, K. A. *Chem. Rev.* **1995**, 95, 1317. See, also: Sakaki, S.; Ogawa, M.; Musashi, Y. *J. Organomet. Chem.* **1997**, 535, 25-28 and references cited therein.
- Watabe, H.; Terao, J.; Kambe, N. *Org. Lett.* **2001**, 3, 1733.
- (a) Colomer, E.; Corriu, R. *J. Organomet. Chem.* **1974**, 82, 367. Rilatt, J. A.; Kitching, W. *Organometallics* **1982**, 1, 1089. Hara, R.; Sato, K.; Sun, W. H.; Takahashi, T. *Chem. Commun.* **1999**, 845. Corriu, R. J. P.; Meunier, B. *J. Organomet. Chem.* **1974**, 65, 187. (b) Sato, F.; Jinbo, T.; Sato, M. *Tetrahedron Lett.* **1980**, 21, 2171. Sato, F.; Jinbo, T.; Sato, M. *Tetrahedron Lett.* **1980**, 21, 2175. Sato, F.; Jinbo, T.; Sato, M. *Synthesis* **1981**, 871.
- (a) Beckhaus, R.; Thiele, K. -H. *J. Organomet. Chem.* **1986**, 317, 23. (b) Beckhaus, R.; Flatau, S.; Trojanov, S.; Hofmann, P. *Chem. Ber.* **1992**, 125, 291. (c) Beckhaus, R. *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 686.
- Similar reaction has also been reported for zirconocene, i.e., Cp_2ZrCl_2 reacts with $\text{CH}_2=\text{CHLi}$ to form $\text{Cp}_2\text{Zr}(\text{CH}=\text{CH}_2)_2$ which undergoes reductive coupling to afford butadiene; Beckhaus, R.; Thiele, K. -H. *J. Organomet. Chem.* **1984**, 268, C7-C8.
- Isomerization of zirconocene-butadiene complex to zirconacyclopentene is known, see: (a) Erker, G.; Wicher, J.; Engel, K.; Rosenfeldt, F.; Dietrich, W.; Krüger, C. *J. Am. Chem. Soc.* **1980**, 102, 6344. (b) Yasuda, H.; Nakamura, A. *Angew. Chem., Int. Ed. Engl.* **1987**, 26, 723.

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