

Award Accounts

The Chemical Society of Japan Award for Young Chemists for 2004

Transition Metal-Catalyzed C–C Bond Formation Reactions Using Alkyl Halides

Jun Terao* and Nobuaki Kambe*

Department of Applied Chemistry and Center for Atomic and Molecular Technologies,
Graduate School of Engineering, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565-0871

Received September 28, 2005; E-mail: terao@chem.eng.osaka-u.ac.jp

This account reviews transition metal-catalyzed C–C bond formation reactions using alkyl halides, which have rarely been used as carbon sources in conventional transition metal-catalyzed systems. In the reactions, ate complexes formed by the reaction of transition metals with a Grignard reagent play important roles as the active catalytic species. The reactions mentioned here are mechanistically new and provide a promising methodology for the construction of carbon frameworks employing alkyl halides.

1. Introduction and Outline of This Study

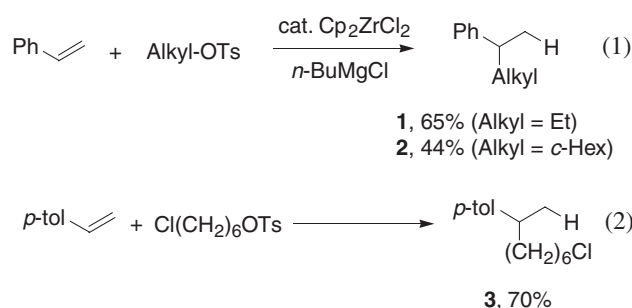
The transition metal-catalyzed C–C bond formation reaction using organic halides or pseudo halides has been extensively studied and employed in wide areas of organic synthesis.¹ Most of these reactions are initiated generally by the oxidative addition of organic halides to M^0 complexes, so that the scope of organic halides has been limited to aryl, alkenyl, allyl, and benzyl halides. This is probably due to the slow oxidative addition of alkyl halides to low valent transition metals and to the rapid β -hydrogen elimination from the σ -alkylmetal intermediates. In order to overcome these problems, we have developed new catalytic systems that do not involve the oxidative addition of alkyl halides toward M^0 complexes. This article describes our recent results focusing on the transition metal-catalyzed C–C bond formation reactions using alkyl halides.

2. Regioselective Alkylation of Alkenes and Conjugated Dienes Using Alkyl Halides

2.1 Nucleophilic Activation of Alkene, Diene, and Allyl Ligands by Forming of Ate Complexes. **2.1.1 Zr-Catalyzed Hydroalkylation of Styrenes Using Alkyl Tosylates:** In 1998, we reported that alkenes underwent silylation by reaction with chlorosilanes employing the Cp_2ZrCl_2/n -BuMgCl system to give alkenyl and/or allylsilanes.² This reaction proceeds via zirconocene–alkene ate complexes and the olefinic carbon acts as a nucleophilic center toward chlorosilanes. When primary and secondary alkyl tosylates are used as electrophiles instead of chlorosilanes, regioselective hydroalkylation of styrenes took place.³

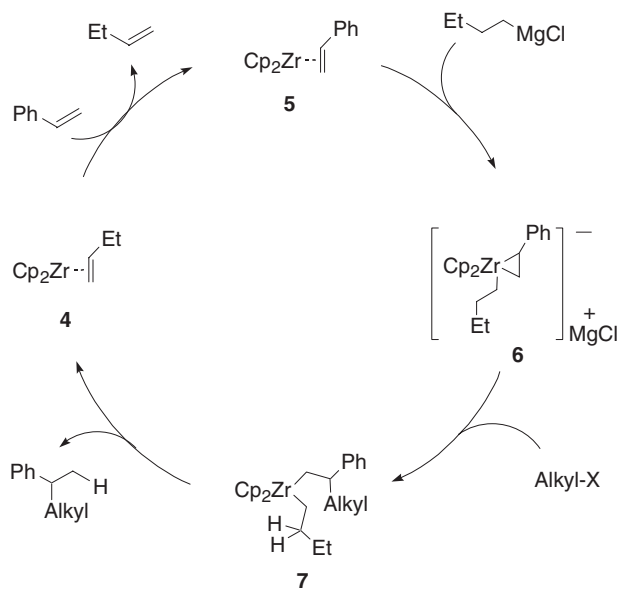
For example, styrene (3.0 mmol) reacted with ethyl tosylate (2 molar amounts) at 50 °C in the presence of a catalytic

amount of zirconocene dichloride (0.05 molar amount) in THF to give *s*-butylbenzene (**1**) in 65% yield (Eq. 1). When *c*-hexyl tosylate was employed, the corresponding hydroalkylation product **2** was formed in 44% yield; although a longer reaction time was required, indicating that secondary alkyl groups can be introduced by this reaction. Chloro substituents were not affected in this reaction system (Eq. 2).



A plausible catalytic cycle is shown in Scheme 1. Zirconocene dichloride reacts with 2 molar amounts of *n*-BuMgCl to generate dibutylzirconocene, which readily decomposes to the Cp_2Zr (butene) complex **4**.⁴ The subsequent alkene exchange reaction between 1-butene and styrene gives the zirconocene–styrene complex **5**. The zirconate complex **6**, formed by the reaction of **5** with *n*-BuMgCl,⁵ reacts with alkyl electrophiles at the benzylic carbon leading to the dialkyl zirconocene complex **7**. The successive β -hydrogen abstraction proceeds at the less hindered butyl group to give the corresponding products along with the regeneration of **4**.⁶

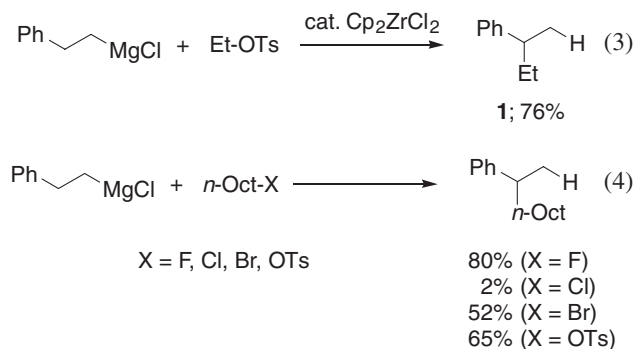
2.1.2 Zr-Catalyzed Coupling Reaction of Alkyl Halides, Tosylates, and Sulfates with β -Phenethyl Grignard Reagents: According to Scheme 1, when the β -phenethyl Grignard reagent is used instead of *n*-BuMgCl, styrene should



Scheme 1.

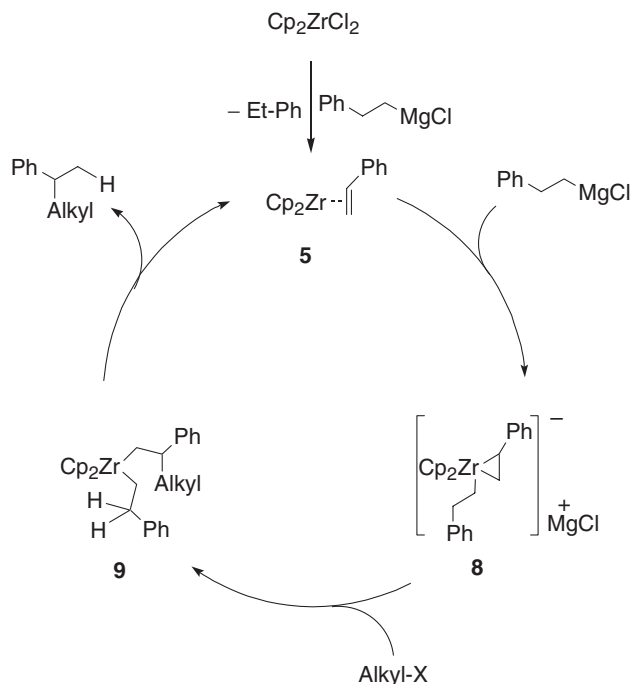
be formed in situ. As expected, the same products were obtained from β -phenethyl Grignard reagents and alkyl tosylates by the aid of the zirconocene catalyst.⁷

The reaction was performed by adding ethyl tosylate (2 mmol) to a THF solution of the β -phenethyl Grignard reagent (1.5 molar amounts) in the presence of a catalytic amount of zirconocene dichloride (0.05 molar amount). After stirring the solution at 50 °C for 6 h, *s*-butylbenzene (**1**) was obtained in 76% yield (Eq. 3). It should be noted that the present reaction proceeds more efficiently with alkyl fluorides as alkylating reagents than with the corresponding chlorides, bromides, or tosylates (Eq. 4).



Scheme 2 shows a plausible pathway for the present reaction. The reaction of Cp_2ZrCl_2 with 3 molar amounts of the phenethyl Grignard reagent affords the zirconate complex **8** via the zirconocene–styrene complex **5**. Alkylating reagents react at the benzylic position of this complex giving rise to the dialkylzirconocene complex **9**. The successive β -hydrogen abstraction affords the coupling product along with the regeneration of **5**. The present reaction demonstrates superiority of alkyl fluorides as alkylating reagents over the corresponding halides, where the latter compounds may undergo oxidative addition toward **5** leading to the formation of reduction product.

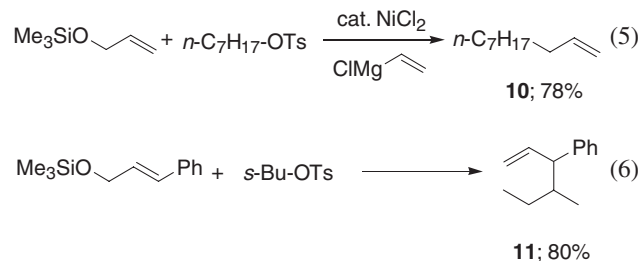
2.1.3 Nickel-Catalyzed Coupling Reaction of Allyl Ethers



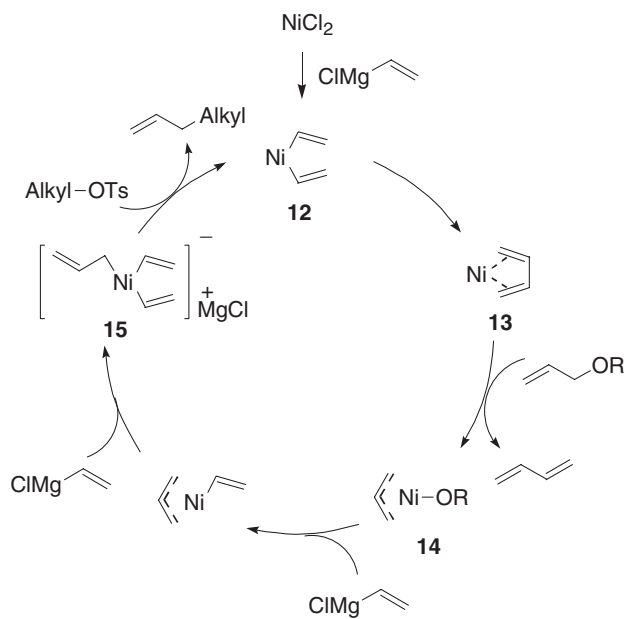
Scheme 2.

with Alkyl Tosylates Leading to Alkene: We then applied this methodology to the nucleophilic activation of allyl ligands by the formation of the ate complex, and the new carbon–carbon bond forming reaction between allyl ethers and alkyl tosylates, giving rise to alkenes, has been developed by the use of Ni catalyst.⁸

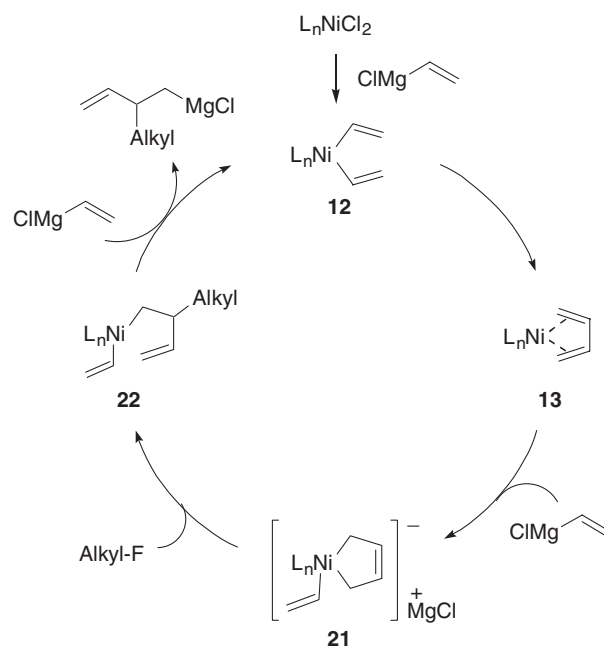
For example, a reaction of allyl trimethylsilyl ether (1 mmol) with heptyl tosylate (1.2 molar amounts) in the presence of $\text{CH}_2=\text{CH-MgCl}$ (2.2 molar amounts) and a catalytic amount of NiCl_2 (0.02 molar amount) in THF at 25 °C for 1 h gave the 1-decene (**10**) in 78% yield (Eq. 5). Under the same conditions, *s*-butyl tosylate reacted with cinnamyl trimethylsilyl ether efficiently to form the coupling product **11** in 80% yield (Eq. 6).



A plausible reaction pathway for this reaction is outlined in Scheme 3. Nickel dichlorides react with 2 molar amounts of vinyl Grignard reagents to generate the divinylnickel complex **12**, which readily forms the nickel–butadiene complex **13** via reductive coupling.⁹ The thus formed **13** undergoes oxidative addition toward allyl ether to afford the π -allylnickel complex **14**.¹⁰ Subsequent reaction of **14** with 2 molar amounts of $\text{CH}_2=\text{CH-MgCl}$ gives the σ -allyl(vinyl)nickelate complex **15**. Then, the allyl ligand of **15** reacts with alkyl tosylates to give coupling the product along with the generation of **12**.



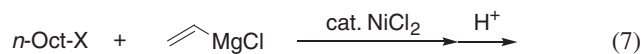
Scheme 3.



Scheme 4.

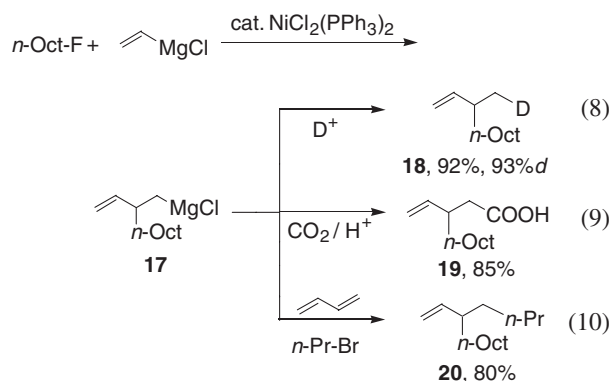
2.1.4 Ni-Catalyzed Alkylation of Vinyl Grignard Reagents Using Alkyl Fluorides: Recently, we have developed the titanocene-catalyzed double silylative dimerization of vinyl Grignard reagents using chlorosilane.¹¹ This reaction proceeds via nucleophilic activation of the 1,3-butadiene ligand by the complexation of a titanocene complex with Grignard reagents. During the course of this study, we found that highly regioselective three-component coupling reactions of 2 molecules of vinyl Grignard reagents with alkyl fluorides can take place by the use of a nickel catalyst.¹² This reaction proceeds efficiently between primary or secondary alkyl fluorides and vinyl Grignard reagents under mild conditions affording a 2-alkyl-3-butenyl Grignard reagent.

When a reaction of octyl fluoride (1 mmol) with vinylmagnesium chloride (3 molar amounts) was conducted in the presence of NiCl₂ (0.03 molar amount) in THF at 25 °C for 7 h, 3-methyl-1-undecene (**16**) was obtained after protonolysis in 94% yield as the sole product (Eq. 7). An interesting feature of this reaction is that alkyl fluorides react as the most suitable alkylating reagent, whereas the corresponding chlorides, bromides, and iodides undergo reduction, elimination, or cross-coupling with the vinyl Grignard reagent concomitantly or predominantly.



| X | Yield of 16 | Yield of <i>n</i> -Oct-CH=CH ₂ | Yield of <i>n</i> -Octane | Yield of Octenes |
|----|--------------------|-------------------------------------------|---------------------------|------------------|
| F | 94% | 0% | 0% | 0% |
| Cl | 63% | 0% | 20% | 0% |
| Br | 2% | 5% | 34% | 1% |
| I | <1% | 9% | 44% | 2% |

The deuterated product **18** and carboxylic acid **19** were obtained in good yields when the reaction mixtures were treated with D₂O and CO₂, respectively (Eqs. 8 and 9). These results imply that the butenyl Grignard reagent **17** is formed in the present reaction medium. So when the in situ formed **17** was subjected to the Ni-catalyzed cross-coupling with another alkyl halide, the second C–C bond formation took place to give the 1-alkene **20** (Eq. 10).¹³



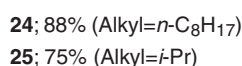
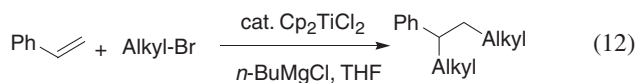
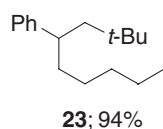
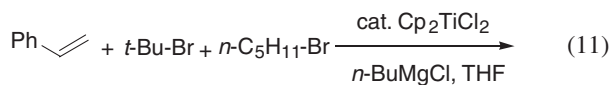
A plausible reaction pathway for the present reaction is outlined in Scheme 4. Nickel dichlorides are reduced by CH₂=CH–MgCl to afford Ni⁰ via the divinylnickel complex **12**.⁹ The thus formed butadiene–nickel complex **13** reacts again with the vinyl Grignard reagent to afford the nickelate complex **21**.¹⁴ Direct reaction of alkyl fluorides with **21** at a γ -vinylic carbon leading to **22** followed by transmetalation with the vinyl Grignard reagent affords **12**. In this system, cationic magnesium would activate C–F bonds by the eminent Mg–F interaction.¹⁵ The present study provides the first example of a catalytic reaction that demonstrates the superiority of alkyl fluorides as alkylating reagents over the corresponding bromides and iodides as well as chlorides.

2.2 Generation of Alkyl Radicals by Electron Transfer

from Transition-Metal Ate Complex to Alkyl Halides.

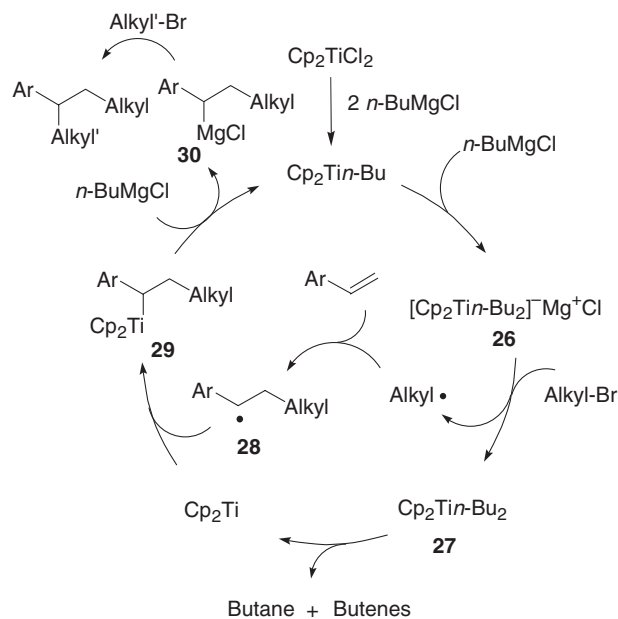
2.2.1 Regioselective Double Alkylation of Styrenes with Alkyl Halides Using a Titanocene Catalyst: We have developed a unique *vic*-double alkylation of styrenes with alkyl bromides using a catalytic amount of Cp_2TiCl_2 in the presence of *n*-BuMgCl.¹⁶ When this reaction was performed by the combined use of primary and secondary, primary and tertiary, or secondary and tertiary alkyl bromides, the double alkylation took place regioselectively in a manner that the more substituted alkyl groups were introduced at the terminal carbon of styrenes and the less substituted ones at the benzylic position.

For example, to a mixture of styrene (1 mmol), 1-bromopentane (1.1 molar amounts), *t*-butyl bromide (1.1 molar amounts), and Cp_2TiCl_2 (0.05 molar amount) was added a THF solution of *n*-BuMgCl (2.2 molar amounts) in THF at 0 °C for 1 h. The double alkylation product **23** was obtained in 94% yield in which pentyl and *t*-butyl groups are incorporated regioselectively at the adjacent carbons (Eq. 11). The same alkyl groups can be introduced at both vicinal carbons when only one alkyl bromide is used (Eq. 12).



This reaction involves radical intermediates as shown in Scheme 5. Titanocene dichloride reacts with 2 molar amounts of *n*-BuMgCl to generate the dibutyltitanate(III) complex **26** via Cp_2TiCl ¹⁷ and $\text{Cp}_2\text{Ti}n\text{-Bu}$.¹⁸ One electron transfer from **26** to alkyl bromides leads to cleavage of the C–Br bond to give an alkyl radical along with dibutyltitanocene (**27**), which readily forms Cp_2Ti via β -hydrogen elimination.¹⁹ The addition of the thus formed alkyl radical to styrene at the terminal carbon affords the benzyl radical species **28**, which recombines with Cp_2Ti to give the corresponding benzyltitanium complex **29**. Subsequent transmetalation²⁰ of **29** with *n*-BuMgCl gives the corresponding benzyl Grignard reagent **30** along with the regeneration of $\text{Cp}_2\text{Ti}n\text{-Bu}$. The double alkylation products are formed by the reaction of **30** with alkyl bromides.

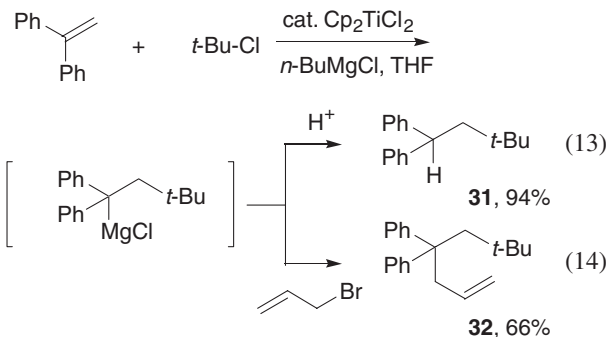
2.2.2 Ti-Catalyzed Regioselective Carbomagnesation of Alkenes and Dienes: Ti-catalyzed *vic*-double alkylation involves two different types of carbon–carbon bond forming steps, i.e., addition of alkyl radicals at the terminal vinylic carbon and electrophilic trapping of the benzylmagnesium intermediates **30** with alkyl halides. If the second alkylation step can be suppressed, this catalytic system would make a unique method of carbomagnesation to afford the corresponding Grignard reagents **30** from olefins and organic halides. We

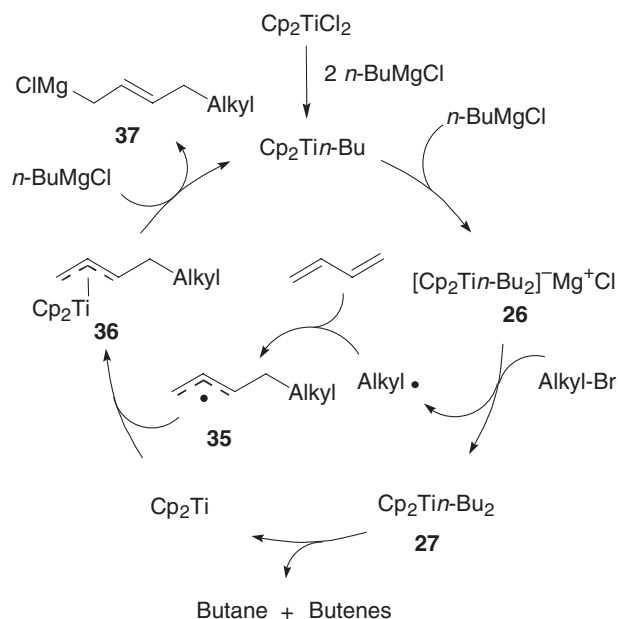


Scheme 5.

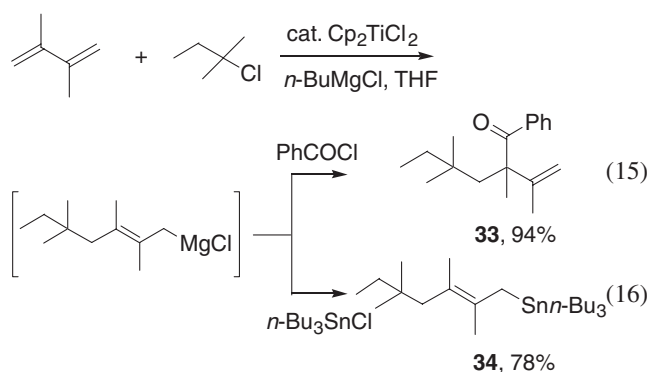
then examined the reaction using less reactive organic halides toward the $\text{S}_{\text{N}}2$ process to suppress the second C–C bond forming step. The use of alkyl chlorides and sterically hindered alkyl bromides under similar conditions as Ti-catalyzed double alkylation led to the development of a unique carbomagnesation of styrenes and 1,3-butadienes.²¹

For example, to a mixture of 1,1-diphenylethylene (1 mmol), *t*-BuCl (2.0 molar amounts), and a catalytic amount of Cp_2TiCl_2 (0.05 molar amount) was added a THF solution of *n*-BuMgCl (3.1 molar amounts, 3.4 mL). After stirring for 2 h at 0 °C, the reaction mixture was quenched with H_2O . The mono-alkylated product **31** possessing a *t*-Bu group at the terminal carbon was formed in 94% yield (Eq. 13). In a similar manner, allylated product **32** was obtained in 66% yield when the reaction mixture was treated with allyl bromide (Eq. 14). A reaction of 2,3-dimethyl-1,3-butadiene with *t*-pentyl chloride under identical conditions afforded an allylic Grignard reagent, which was trapped with PhCOCl to give the sole regioisomer **33** in 94% yield (Eq. 15). When stannyl chloride was used as an electrophile, stannylation took place regioselectively at the terminal carbon of the allylmagnesium intermediate (Eq. 16). This reaction can be synthetically useful since two different functional groups can be included to carbon–carbon double bonds by a one-pot operation.





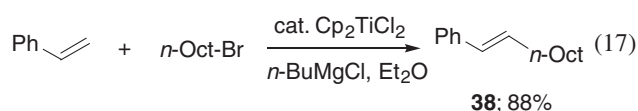
Scheme 6.



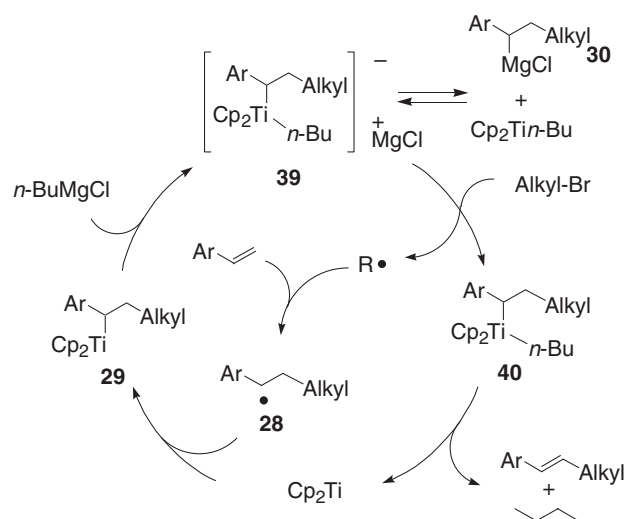
As shown in Scheme 6, this carbomagnesation of 1,3-butadienes reaction would proceed similarly via the allylic radical **35**, allylic titanium **36**, and allylic Grignard **37** species.

2.2.3 Titanocene-Catalyzed Alkylation of Styrenes with Alkyl Halides: Ti also catalyzes Mizoroki–Heck type transformations in ether.²²

For example, 1-bromooctane (1.0 mmol) reacted with styrene (3.0 molar amounts) in the presence of *n*-BuMgCl (1.3 molar amounts) and a catalytic amount of Cp₂TiCl₂ (0.03 molar amount) in ether at 0 °C for 2.5 h to give (*E*)-1-phenyl-1-decene (**38**) in 88% yield based on alkyl bromide with >98% regio- and stereoselectivities (Eq. 17). Primary and secondary alkyl bromides and secondary alkyl chlorides can be used as suitable alkylating reagents to afford only *E*-olefins.²³



Shown in Scheme 7 is the unique effect of solvents in this Cp₂TiCl₂/*n*-BuMgCl catalytic system, i.e., ether affords Mizoroki–Heck type products **38** whereas the *vic*-double alkylation product **24** was obtained in THF (Eq. 12). This fact is explained as follows. In ether solvent, the ate complex **39**, formed by the reaction of benzyltitanocene^{III} with *n*-BuMgCl, transfers

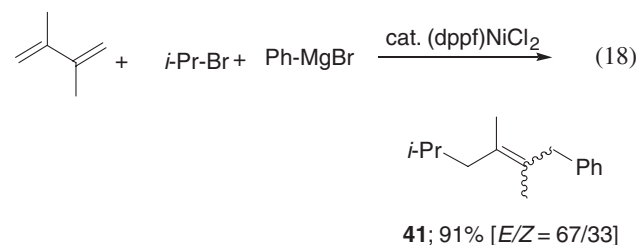


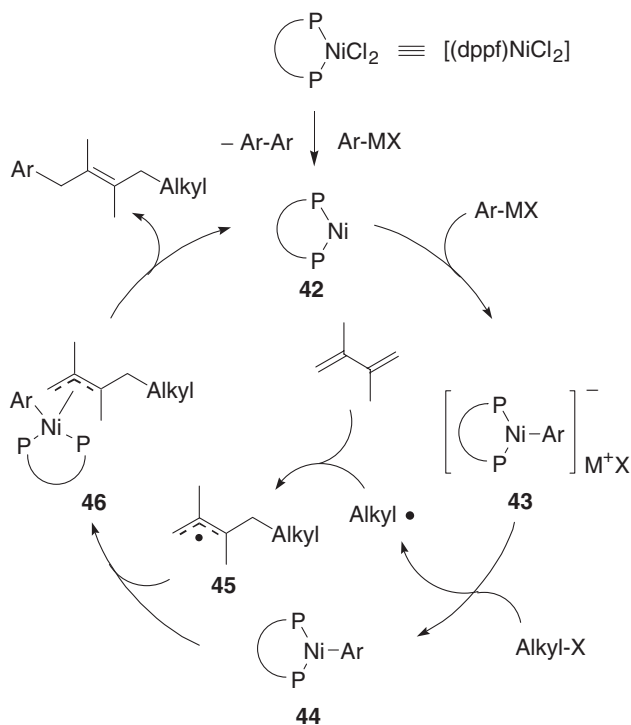
Scheme 7.

one electron to alkyl halides yielding an alkyl radical and benzylbutyltitanocene **40**, which undergoes sitespecific β -hydrogen elimination to afford the corresponding alkenes along with the regeneration of Cp₂Ti. In addition, the reaction of **30** with alkyl bromides is slower in ether than in THF, so **30** recombines with Cp₂Ti(*n*-Bu) to form **39** as an equilibrium process and electron transfer from **39** to alkyl bromides predominates. On the other hand, the reactivity of the benzyl Grignard reagent **30** toward alkyl bromides is enhanced in a strongly coordinating THF and **30** readily reacts with alkyl halides giving rise to *vic*-double alkylation products as shown in Scheme 5.

2.2.4 Ni-Catalyzed Regioselective Three-Component Coupling Reaction of Alkyl Halides, 1,3-Butadienes, and Ar–M (M = MgX and ZnX): As shown in Eqs. 11–17, Ti catalyst plays an important role in generating alkyl radicals from alkyl halide by electron transfer from Ti^{III} ate complexes. These successful results prompted us to examine the chemical behavior of the ate complexes of late transition-metal catalysts, and we developed a regioselective three-component coupling reaction of alkyl halides, 1,3-butadienes, and Ar–M (M = MgX and ZnX) by the aid of Ni catalyst.²⁴

For example, into a mixture of 2,3-dimethyl-1,3-butadiene (1 mmol), isopropyl bromide (1.2 molar amounts), and (dppf)-NiCl₂ (0.08 molar amount) was added a THF solution of Ph-MgBr (1.5 molar amounts) and the solution was stirred at 25 °C for 24 h. The coupling product **41**, bearing isopropyl and phenyl groups at the terminal carbons of the 1,3-butadiene unit, was obtained in 91% yield [*E*/*Z* = 67/33] (Eq. 18). It is noteworthy that secondary and tertiary alkyl chlorides can also be used as suitable alkylating reagents. The reaction also proceeded when arylzinc halide was employed instead of Grignard reagents.





Scheme 8.

A plausible reaction pathway is shown in Scheme 8. Nickel dichloride having a dppf ligand reacts with 2 molar amounts of Ar–MX (M = Mg and Zn) to generate the zerovalent complex **42**, which reacts with Ar–MX to give the nickelate complex **43**.¹⁴ This ate complex acts as an active electron-transfer reagent. An alkyl radical is formed by the electron transfer from **43** to alkyl halides with concomitant generation of the aryl-nickel(I) complex **44**,²⁵ and adds to the terminal carbon of butadienes yielding the allyl radical intermediate **45**. Combination of **44** with **45** gives the allylaryl–Ni^{II} intermediate **46**, which then undergoes reductive elimination to afford the three-component coupling product along with **42** to complete the catalytic cycle. The present reaction involves two different carbon–carbon bond forming steps, i.e., the addition of alkyl radicals toward 1,3-butadienes and reductive elimination of allylaryl–Ni^{II} intermediates.

3. Cross-Coupling Reactions Using Alkyl Halides

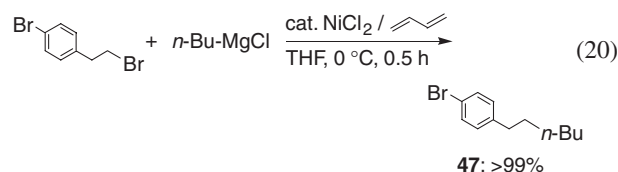
3.1 Ni- or Pd-Catalyzed Cross-Coupling Reaction of Alkyl Halides and Tosylates with Grignard Reagents in the Presence of 1,3-Butadienes. Transition metal-catalyzed cross-coupling reactions between organic halides and organometallic reagents constitute one of the most straightforward methods for the formation of carbon–carbon bonds.²⁶ As for the substrates, a variety of organometallic reagents has been employed containing B, Mg, Li, Sn, Al, and Zn as the metal connecting to alkyl, alkenyl, aryl, alkynyl, allyl, and benzyl groups, whereas the scope of the coupling partner had long been limited to aryl and alkenyl halides. The use of alkyl halides usually gave unsatisfactory results due mainly to the slow oxidative addition to transition-metal catalysts and the fast β -elimination from the σ -alkylmetal intermediates. However, the cross-coupling reaction of alkyl halides with organometallic reagents

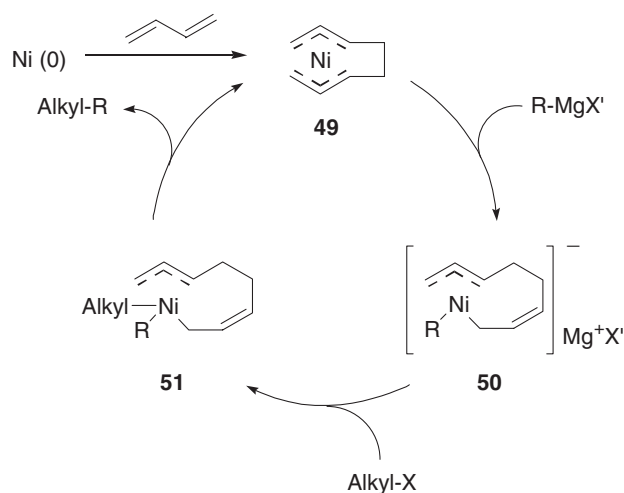
has extensively been studied during the past several years²⁷ and alkyl halides as well as sulfonates have now become promising candidates as reagents in transition metal-catalyzed cross-coupling reactions. We could contribute to the progress of this field by providing a novel catalytic system where Ni^{13,15,28} or Pd²⁹ catalyzes the cross-coupling reaction of alkyl fluorides, chlorides, bromides, and tosylates with Grignard reagents in the presence of 1,3-butadiene as an additive. These results include the first examples of a cross-coupling reaction using inactivated alkyl fluorides^{15,28} and chlorides.¹³

The reaction of decyl bromide (1 mmol) with *n*-BuMgCl (1.3 molar amounts) proceeded efficiently in the presence of isoprene (1.0 molar amounts) and NiCl₂ (0.03 molar amount) in THF at 25 °C to give tetradecane in 92% yield along with trace amounts of decane (<1%) and decenes (2%) (Eq. 19). In the absence of isoprene, tetradecane was obtained in only 2% yield and significant amounts of decane and decenes were formed. In particular, unsubstituted 1,3-butadiene shows the highest activity for this cross-coupling reaction, whereas 2,3-dimethyl-1,3-butadiene, cyclooctadiene, alkynes, and alkenes are far less effective. When nickel complexes bearing phosphine ligands, such as NiCl₂(PPh₃)₂ and NiCl₂(dppp), were used, tetradecane was obtained only in 45 and 22% yields, respectively.

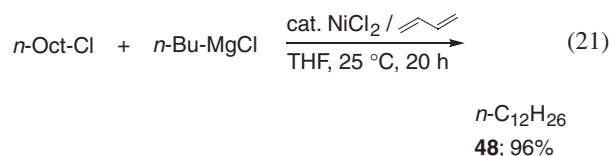
| <i>n</i> -Dec-Br + <i>n</i> -Bu-MgCl | NiCl ₂ (0.03 mol) additive (1 mol) | | |
|--------------------------------------|--------------------------------------------------|------------------|---------|
| | THF, rt, 3 h | | |
| | <i>n</i> -C ₁₄ H ₃₀ | <i>n</i> -Decane | Decenes |
| none | 2% | 39% | 59% |
| | >99% | 0% | 0% |
| | 92% | <1% | 2% |
| | 5% | 9% | 14% |
| Ph–C≡C–Et | 3% | 23% | 7% |
| | 15% | 14% | 25% |

This reaction also shows an interesting chemo-selectivity by which the (sp²)C–Br bond can survive intact in the present system (Eq. 20). Interestingly, alkyl chlorides can also undergo this cross-coupling reaction, giving rise to the desired products in good yields (Eq. 21). This cross-coupling reaction also proceeds efficiently by using alkyl tosylates. Aryl and secondary alkyl Grignard reagents also afforded the corresponding products in moderate to good yields. The present catalytic system has a strong advantage for large scale production since the reaction proceeds efficiently using less expensive alkyl chlorides as the reagent, NiCl₂ as the catalyst, and 1,3-butadiene as the additive instead of phosphines.





Scheme 9.

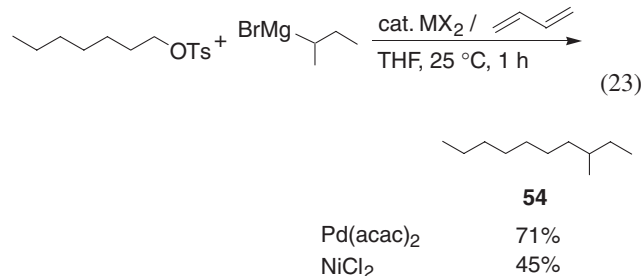


A plausible reaction pathway is depicted in Scheme 9. NiCl₂ is reduced to Ni⁰ by reaction with Grignard reagents. It is known that Ni⁰ reacts with 2 molar amounts of 1,3-butadiene to afford the bis- π -allyl nickel complex **49**,³⁰ which reacts with Grignard reagents to form the η^1, η^3 -octadienediylnickelate complex **50**.^{31,32} Coupling products might be formed by oxidative addition of alkyl halides to **50** yielding the dialkylnickel complex **51**, followed by reductive elimination. 1,3-Butadienes play an important role to convert Ni⁰ to Ni^{II} **49**, which is less reactive toward organic halides but readily reacts with R-MgX' to form **50** as a key intermediate. This complexation might enhance the nucleophilicity of Ni toward alkyl halides. This reaction follows a new catalytic pathway; i.e., the Ni catalyst in our system reacts first with R-MgX' to form an ate complex and then with alkyl halides. This is in large contrast to conventional cross-coupling reactions using phosphine ligands where low valent metal catalysts react first with organic halides (oxidative addition) and then with organometallic reagents (transmetalation) leading to reductive elimination.

Palladium also catalyzes the cross-coupling reaction of alkyl tosylates and bromides with Grignard reagents in the presence of 1,3-butadiene as an additive; however, 1-chlorooctane was sluggish for this coupling reaction.²⁹ This result allows the selective synthesis of the alkyl chloride **52** from 6-chlorohexyl tosylate in 86% yield. On the other hand, when NiCl₂ was used as a catalyst, the double cross-coupling product **53** was obtained in 13% yield (Eq. 22).

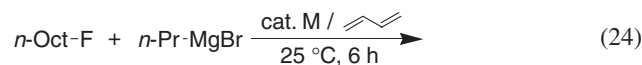


Use of a secondary alkyl Grignard reagent also afforded the coupling product **54** in good yields. NiCl₂ worked less efficiently than in the case of the palladium catalyst when a secondary alkyl Grignard reagent was employed (Eq. 23).



3.2 Ni-Catalyzed Cross-Coupling Reaction of Alkyl Fluorides with Grignard Reagents. Organic fluorides, especially those having an (sp³)C-F bond, have been recognized as the most inert class of organic compounds due to their strong C-F bonds. Hence, to develop reactions that replace fluorine atoms with other atoms or groups is a challenging subject in organic chemistry.³³ During the course of our study on the synthetic application of alkyl halides as shown in the previous section, we have recently developed Ni catalyzed C-C bond forming reactions using non-activated alkyl fluorides.^{15,34}

Reactions of octyl fluoride (2 mmol) with *n*-PrMgBr (2.0 molar amounts) were examined at 25 °C using various Ni catalysts (0.03 molar amount) in the presence of 1,3-butadiene (Eq. 24). Octyl fluoride did not react at all when no additive was employed, even in the presence of Ni catalyst. However, addition of 0.1 molar amount of 1,3-butadiene based on octyl fluoride enabled alkyl-alkyl cross-coupling to proceed giving rise to a 9% yield of undecane accompanied by a small amount of octane. On increasing the amount of 1,3-butadiene up to 2 molar amounts, the yield of undecane improved to 67%.



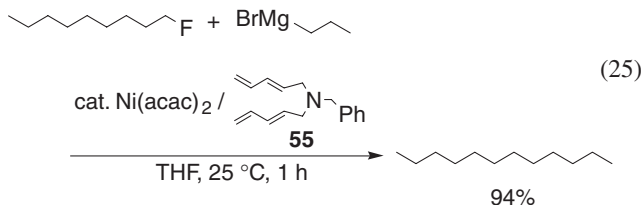
n-Oct-*n*-Pr + Octane + Octenes

| M | 1,3-butadiene (mmol) | <i>n</i> -Oct- <i>n</i> -Pr (%) | Octane (%) | Octenes (%) |
|----------------------------------------------------|----------------------|---------------------------------|------------|-------------|
| (PPh ₃) ₂ NiCl ₂ | 0 | 0% | 0% | 0% |
| (dppf)NiCl ₂ | 0 | 0% | 0% | 0% |
| NiCl ₂ | 0 | 0% | 0% | 0% |
| | 0.1 | 9% | 1% | 0% |
| | 0.5 | 44% | 2% | 1% |
| | 0.7 | 50% | 2% | 2% |
| | 1.0 | 64% | 4% | 2% |
| | 2.0 | 67% | 3% | 1% |

However, further increases of 1,3-butadiene did not lead to significant improvements in the yield. It is probably because under high concentration of 1,3-butadiene, Ni⁰ reacts with more than 2 molar amounts of 1,3-butadiene resulting in the low concentration of the bis- π -allyl nickel complex **49**.³⁵ We could solve this problem by employing 1,3,8,10-tetraenes that construct a bis- π -allyl Ni structure with the Ni⁰ species exclusively.³⁶ These new tetraene ligands have extensively broadened the scope of reagents, both of the alkyl halides and their coupling partners, and dramatically improved the effi-

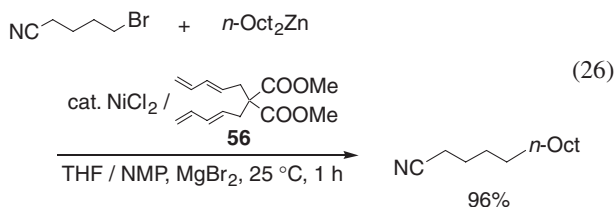
ciency of the Ni-catalyzed cross-coupling reaction.

A remarkable example is the reaction of *n*-nonyl fluoride (1 mmol) with *n*-PrMgBr (1.5 molar amounts), which gave dodecane in 94% yield in the presence of 0.006 molar amount of Ni(acac)₂ and 0.5 molar amount of the tetraene **55** as an additive (Eq. 25). This result provides strong supporting evidence for the intermediary of bis- π -allyl complexes.

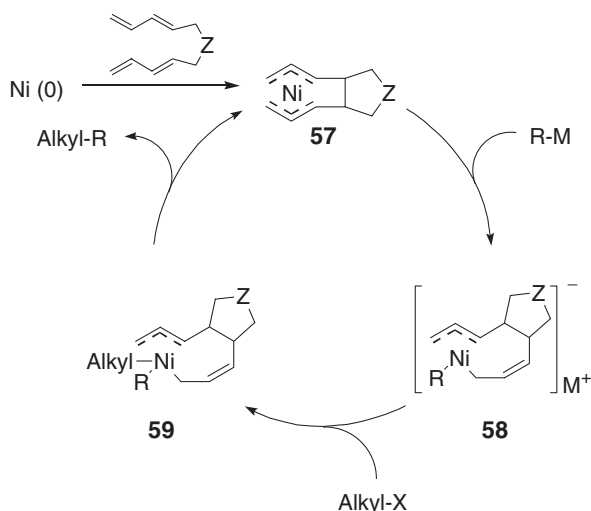


The present cross-coupling system, as stated above, facilitates the cross-coupling of a wide variety of alkyl tosylates and halides such as fluorides, chlorides, and bromides with Grignard reagents; however, a drawback of this methodology is the scope of functional groups being tolerant to this system due to the high reactivity of Grignard reagents. It was also found that the tetraenes **55** and **56** were effective also for the Ni-catalyzed cross-coupling reaction of alkyl halides with organozinc reagents³⁷ in a THF/NMP (*N*-methyl-2-pyrrolidone) mixed solvent containing MgBr₂.²⁸

A dramatic effect of **56** can be demonstrated by a reaction of 5-bromopentanenitrile (1 mmol) with *n*-Oct₂Zn (1.3 molar amounts), where tridecanenitrile was obtained in 96% yield in the presence of MgBr₂ (3 molar amounts), NiCl₂ (0.03 molar amount), and dimethyl 2,2-bis(2,4-pentadieny)malonate (**56**) (0.09 molar amount) at 25 °C for 1 h (Eq. 26).



A plausible reaction pathway is shown in Scheme 10. The bis- π -allylnickel structure **57** is constructed by the oxidative



Scheme 10.

cycloaddition of two butadiene moieties of 1,3,8,10-tetraene to Ni⁰. An organomagnesium or -zinc reagent attacks the bis- π -allyl complex **57** to generate the η^1, η^3 -octadienediyl-nickelate complex **58**, which then reacts with alkyl halides to give a complex **59**. Subsequent reductive elimination affords the coupling product along with **57** to complete the catalytic cycle. Selective and efficient formation of **57** from Ni⁰ and tetraenes in comparison to the case of 1,3-butadiene would account for the facile generation of the ate complex **58** resulting in acceleration of the subsequent oxidative addition process leading to **59**.

4. Conclusion

Novel catalytic systems for C–C bond formation using alkyl halides have been developed by the combined use of transition-metal catalysts and Grignard reagents. The present study provides some practical examples for the use of alkyl halides in transition metal-catalyzed reactions. We hope that this study will lead to the progress of chemical transformations by providing a novel route for the construction of carbon skeletons.

We thank Dr. Noboru Sonoda, Professor Emeritus at Osaka University, for his continuous support of this work. Special thanks are given to Dr. Hitoshi Kuniyasu for stimulating discussions and helpful suggestions. We also thank all the collaborators for their efforts and cooperation, whose names are listed in references cited. This project has been supported in part by a grant from the Ministry of Education, Culture, Sports, Science and Technology of Japan. We are also grateful to the Asahi Glass Foundation, the Sumitomo Foundation, and the Mitsubishi Chemical Corporation Fund for their financial support.

References

- For reviews of transition metal-catalyzed cross-coupling reactions, see: a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., ed. by A. de Meijere, F. Diederich, Wiley-VCH, Weinheim, **2004**. b) *Metal-Catalyzed Cross-Coupling Reactions*, ed. by F. Diederich, P. J. Stang, Wiley-VCH, Weinheim, **1998**. c) *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. by E. Negishi, A. de Meijere, Wiley-Interscience, New York, **2002**, p. 1669.
- J. Terao, K. Torii, K. Saito, N. Kambe, A. Baba, N. Sonoda, *Angew. Chem., Int. Ed.* **1998**, *37*, 2653.
- J. Terao, T. Watanabe, K. Saito, N. Kambe, N. Sonoda, *Tetrahedron Lett.* **1998**, *39*, 9201.
- a) E. Negishi, F. E. Cederbaum, T. Takahashi, *Tetrahedron Lett.* **1986**, *27*, 2829. b) F. Soleil, R. Choukroun, *J. Am. Chem. Soc.* **1997**, *119*, 2938. c) V. K. Dioumaev, J. F. Harrod, *Organometallics* **1997**, *16*, 1452.
- As the similar pathways leading to **6**, it has been proposed that zirconate complex Cp₂ZrEt(CH₂=CH₂)MgBr are formed by the reaction of Cp₂ZrCl₂ with 3 molar amounts of EtMgBr, see: T. Takahashi, N. Suzuki, M. Kageyama, Y. Nitto, M. Saburi, E. Negishi, *Chem. Lett.* **1991**, 1579.
- Reactivities of alkyl groups on Zr as β -hydrogen donors, see: E. Negishi, T. Nguyen, J. P. Maye, D. Choueiri, N. Suzuki, T. Takahashi, *Chem. Lett.* **1992**, 2367.
- J. Terao, S. A. Begum, A. Oda, N. Kambe, *Synlett* **2005**, 1783.

- 8 J. Terao, H. Watabe, H. Watanabe, N. Kambe, *Adv. Synth. Catal.* **2004**, 346, 1674.
- 9 a) G. M. Whitesides, C. P. Casey, J. K. Krieger, *J. Am. Chem. Soc.* **1971**, 93, 1379. b) M. F. Semmelhack, P. Helquist, L. D. Jones, L. Keller, L. Mendelson, L. S. Ryono, J. G. Smith, R. D. Stauffer, *J. Am. Chem. Soc.* **1981**, 103, 6460.
- 10 a) J. J. Eisch, K. R. Im, *J. Organomet. Chem.* **1977**, 139, C45. b) T. Yamamoto, J. Ishizu, A. Yamamoto, *Chem. Lett.* **1979**, 1385. c) T. Yamamoto, J. Ishizu, A. Yamamoto, *J. Am. Chem. Soc.* **1981**, 103, 6863.
- 11 J. Terao, N. Kambe, N. Sonoda, *Tetrahedron Lett.* **1998**, 39, 9697.
- 12 J. Terao, H. Watabe, N. Kambe, *J. Am. Chem. Soc.* **2005**, 127, 3656.
- 13 J. Terao, H. Watanabe, A. Ikumi, H. Kuniyasu, N. Kambe, *J. Am. Chem. Soc.* **2002**, 124, 4222.
- 14 For magnesium nickelate complexes, see: W. Kaschube, K. R. Pörschke, K. Angermund, C. Krüger, G. Wilke, *Chem. Ber.* **1988**, 121, 1921.
- 15 J. Terao, A. Ikumi, H. Kuniyasu, N. Kambe, *J. Am. Chem. Soc.* **2003**, 125, 5646.
- 16 J. Terao, K. Saito, S. Nii, N. Kambe, N. Sonoda, *J. Am. Chem. Soc.* **1998**, 120, 11822.
- 17 H. A. Martin, F. Jellinek, *J. Organomet. Chem.* **1968**, 12, 149.
- 18 Reaction of Cp_2TiCl with $n\text{-BuLi}$ affords the thermally instable $\text{Cp}_2\text{Ti}n\text{-Bu}$, see: a) E. Klei, J. H. Telgen, J. H. Teuben, *J. Organomet. Chem.* **1981**, 209, 297. ($\eta^5\text{-C}_5\text{Me}_5$) $_2\text{Ti}n\text{-Pr}$ was formed by the reaction of ($\eta^5\text{-C}_5\text{Me}_5$) $_2\text{TiCl}$ with $n\text{-PrMgBr}$, see: b) G. A. Luinstra, L. C. Cate, H. J. Heeres, J. W. Pattiasina, A. Meetsma, J. H. Teuben, *Organometallics* **1991**, 10, 3227.
- 19 It is reported that **27** decomposes rapidly at -50°C forming Cp_2Ti along with a 1:1 mixture of $n\text{-butane}$ and butenes: J. X. McDermott, M. E. Wilson, G. M. Whitesides, *J. Am. Chem. Soc.* **1976**, 98, 6529.
- 20 Transmetalation of vinyltitanocene complexes with $i\text{-PrMgBr}$ is known: Y. Gao, F. Sato, *J. Chem. Soc., Chem. Commun.* **1995**, 659.
- 21 S. Nii, J. Terao, N. Kambe, *J. Org. Chem.* **2004**, 69, 573.
- 22 a) J. Terao, N. Kambe, *J. Synth. Org. Chem., Jpn.* **2001**, 59, 1044. b) J. Terao, H. Watabe, M. Miyamoto, N. Kambe, *Bull. Chem. Soc. Jpn.* **2003**, 76, 2209.
- 23 In terms of this type of transformations using alkyl halides regardless of the mechanisms, several catalytic systems have been accomplished by the aid of late transition metals, see: a) S. Bräse, B. Waegell, A. de Meijere, *Synthesis* **1998**, 148. b) S. A. Lebedev, V. S. Lopatina, R. R. Shifrina, E. S. Petrov, I. P. Beletskaya, *Izv. Akad. Nauk SSSR* **1983**, 10, 2414. c) S. A. Lebedev, V. S. Lopatina, T. V. Luk'yanova, S. S. Berestova, R. R. Shifrina, N. N. Shapet'ko, E. S. Petrov, I. P. Beletskaya, *Izv. Akad. Nauk SSSR* **1985**, 22, 652. d) S. A. Lebedev, V. S. Lopatina, E. S. Petrov, I. P. Beletskaya, *J. Organomet. Chem.* **1988**, 344, 253. e) B. P. Branchaud, W. D. Detlefsen, *Tetrahedron Lett.* **1991**, 32, 6273. f) Y. Ikeda, T. Nakamura, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2002**, 124, 6514. g) T. Fujioka, T. Nakamura, H. Yorimitsu, K. Oshima, *Org. Lett.* **2002**, 4, 2257. h) Y. Ikeda, H. Yorimitsu, H. Shinokubo, K. Oshima, *Adv. Synth. Catal.* **2004**, 346, 1631.
- 24 J. Terao, S. Nii, F. A. Chowdhury, A. Nakamura, N. Kambe, *Adv. Synth. Catal.* **2004**, 346, 905.
- 25 It is suggested that oxidative addition of alkyl halides to Ni^0 may proceed via a radical pathway, see: C. W. Weston, A. W. Verstuyft, J. H. Nelson, H. B. Jonassen, *Inorg. Chem.* **1977**, 16, 1313.
- 26 International symposium on 30 years of the cross-coupling reaction: K. Tamao, T. Hiyama, E. Negishi, *J. Organomet. Chem.* **2002**, 653, 1.
- 27 For recent reviews of transition metal-catalyzed cross-coupling reactions using alkyl halides, see: a) D. J. Cárdenas, *Angew. Chem., Int. Ed.* **1999**, 38, 3018. b) T.-Y. Luh, M.-K. Leung, K.-T. Wong, *Chem. Rev.* **2000**, 100, 3187. c) D. J. Cárdenas, *Angew. Chem., Int. Ed.* **2003**, 42, 384. d) M. R. Netherton, G. C. Fu, *Adv. Synth. Catal.* **2004**, 346, 1525. e) J. Terao, N. Kambe, *J. Synth. Org. Chem., Jpn.* **2004**, 62, 1192. f) A. C. Frisch, M. Beller, *Angew. Chem., Int. Ed.* **2005**, 44, 674.
- 28 J. Terao, H. Todo, H. Watanabe, N. Kambe, *Angew. Chem., Int. Ed.* **2004**, 43, 6180.
- 29 J. Terao, Y. Naitoh, H. Kuniyasu, N. Kambe, *Chem. Lett.* **2003**, 32, 890.
- 30 This can be an η^1, η^3 -octadienediylnickel complex or a mixture of these species, see: R. Benn, B. Büssemeier, S. Holle, P. W. Jolly, R. Mynott, I. Tkatchenko, G. Wilke, *J. Organomet. Chem.* **1985**, 279, 63.
- 31 A similar lithium η^1, η^3 -octadienediyl(phenyl)nickelate complex has been reported, see: S. Holle, P. W. Jolly, R. Mynott, R. Z. Salz, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **1982**, 37, 675.
- 32 We recently reported that η^1, η^3 -octadienediylnickelate complexes show unique catalytic activity for carbosilylation of 1,3-butadienes with chlorosilanes and Grignard reagents, see: J. Terao, A. Oda, A. Ikumi, A. Nakamura, H. Kuniyasu, N. Kambe, *Angew. Chem., Int. Ed.* **2003**, 42, 3412.
- 33 Recent reviews for activation and functionalization of C-F bonds, see: a) S. Murai, *Activation of Unreactive Bonds and Organic Synthesis*, Springer, New York, **1999**, p. 243. b) T. Hiyama, *Organofluorine Compounds Chemistry and Applications*, Springer, New York, **2000**.
- 34 The C-C bond formation has been achieved by use of tertiary alkyl and allyl fluorides in the presence of R_3Al or BF_3 as the catalyst: a) T. Ooi, D. Uraguchi, N. Kagoshima, K. Maruoka, *Tetrahedron Lett.* **1997**, 38, 5679. b) K. Hirano, K. Fujita, H. Yorimitsu, H. Shinokubo, K. Oshima, *Tetrahedron Lett.* **2004**, 45, 2555. c) K. Hirano, H. Yorimitsu, K. Oshima, *Org. Lett.* **2004**, 6, 4873. d) M. Namavari, N. Satyamurthy, J. R. Barrio, *J. Fluorine Chem.* **1995**, 72, 89. e) G. A. Olah, S. C. Narang, L. D. Field, *J. Org. Chem.* **1981**, 46, 3727.
- 35 For structures and stabilities of nickel complexes involved in cyclo-oligomerization of 1,3-butadiene, see: S. Tobisch, *Adv. Organomet. Chem.* **2003**, 49, 167, and references therein.
- 36 For Ni-mediated cyclization of 1,3,8,10-tetraenes, see: a) P. A. Wender, M. J. Tebbe, *Synthesis* **1991**, 1089, and references therein. b) M. Takimoto, M. Mori, *J. Am. Chem. Soc.* **2004**, 124, 10008.
- 37 A. E. Jensen, P. Knochel, *J. Org. Chem.* **2002**, 67, 79.

Award recipient



Jun Terao was born in Osaka, Japan, in 1970. He graduated from Osaka University in 1994. He received his Ph.D. degree in 1999 from Osaka University under the direction of Professor Noboru Sonoda. The title of his thesis was "Studies on the alkylation and silylation of alkenes catalyzed by early transition metals." After working as a postdoctoral fellow at Hokkaido University under Professor Tamotsu Takahashi, he joined the Department of Applied Chemistry, Osaka University, as an Assistant Professor. He worked at the University of Oxford with Professor Harry L. Anderson as a postdoctoral fellow from 2002 to 2003. His awards include Banyu Pharmaceutical Award in Synthetic Organic Chemistry in 2001, the Chemical Society of Japan Award for Young Chemists in 2005, and Thieme Journal Award in 2005, and the Japan Petroleum Institute Award for Encouragement of Research and Development in 2006. His research interests include organometallic chemistry and synthetic organic chemistry.



Nobuaki Kambe was born in Hyogo, Japan, in 1953. He studied organic chemistry and received Ph.D. degree from Osaka University in 1981 under the direction of Professor Noboru Sonoda. The title of his thesis was "Studies on the Organic Reactions Based on the Characteristics of Selenium and Tellurium." He joined Department of Applied Chemistry, Faculty of Engineering, Osaka University in 1981 as an Assistant Professor. From 1982 to 1984, he stayed at Colorado State University as a postdoctoral fellow for Professor L. S. Hegedus. He was promoted to Associate Professor of Osaka University in 1989 and to Full Professor in 1999. He received the Chemical Society of Japan Award for Young Chemists in 1988 and the Japan Petroleum Institute Award for Encouragement of Research and Development in 1993. His research interests are in the areas of synthetic organic chemistry, organometallic chemistry, and physical organic chemistry.