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

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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. Most of these reactions are initiated generally by the oxidative addition of organic halides to M 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 α-hydrogen elimination from the α-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 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 Diienes 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 Cp2ZrCl2/n-BuMgCl system to give alkenyl and/or allylsilanes. 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.

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 Cp2Zr(butene) complex 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, 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.
be formed in situ. As expected, the same products were obtained from \(\beta\)-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 \(\beta\)-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, \(\text{s-butylbenzene (1)}\) 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).

\[
\begin{align*}
\text{Ph} & + \text{Et-OTs} \xrightarrow{\text{cat. Cp2ZrCl2}} \text{EtH} \quad \text{(3)} \\
\text{Ph} & + \text{n-Oct-X} \xrightarrow{\text{cat. Cp2ZrCl2}} \text{n-OctH} \quad \text{(4)}
\end{align*}
\]

Scheme 2 shows a plausible pathway for the present reaction. The reaction of Cp\(_2\)ZrCl\(_2\) 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 \(\beta\)-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

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.\(^3\)

For example, a reaction of allyl trimethylsilyl ether (1 mmol) with heptyl tosylate (1.2 molar amounts) in the presence of CH\(_2\)=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, \(\text{s-butyl tosylate reacted with cinnamyl trimethylsilyl ether efficiently to form the coupling product 11 in 80% yield (Eq. 6).}

\[
\begin{align*}
\text{Me3SiO} & + \text{n-C}7\text{H}17\text{-OTs} \xrightarrow{\text{cat. NiCl2}} \text{n-C}7\text{H}17\text{-}10 \quad \text{(5)} \\
\text{Me3SiO} & + \text{s-Bu-OTs} \xrightarrow{\text{ClMg}} \text{11} \quad \text{(6)}
\end{align*}
\]

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 divinynickel complex 12, which readily forms the nickel–butadiene complex 13 via reductive coupling.\(^6\) The thus formed 13 undergoes oxidative addition toward allyl ether to afford the \(\sigma\)-allylnickel complex 14.\(^9\) Subsequent reaction of 14 with 2 molar amounts of CH\(_2\)=CH–MgCl gives the \(\sigma\)-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.
2.1.4 Ni-Catalyzed Alkylative Dimerization 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.

[Scheme 3]

\[
\text{NiCl}_2 + \text{ClMg} \rightarrow \text{Alkyl} + \text{Ni} \quad 12
\]

\[
\text{Ni} \quad 13 \quad \text{MgCl} \rightarrow \text{OR} + \text{ClMg} \quad 14
\]

\[
\text{ClMg} + \text{Ni} \quad 15 \rightarrow \text{MgCl} + \text{Ni} \quad 16
\]

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).

[Scheme 4]

\[
\text{NiCl}_2 + \text{ClMg} \rightarrow \text{Alkyl-F} + \text{Ni} \quad 21
\]

\[
\text{Ni} \quad 12 \quad \text{MgCl} \rightarrow \text{OR} + \text{ClMg} \quad 22
\]

\[
\text{ClMg} + \text{Ni} \quad 15 \rightarrow \text{MgCl} + \text{Ni} \quad 16
\]

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-vinylcarbon leading to 22 followed by transmetallation 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 \( \text{Cp}_2\text{TiCl}_2 \) 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 \( \text{Cp}_2\text{TiCl}_2 \) (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 \( t\)-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).

\[
\begin{align*}
\text{Ph} + t\text{-Bu-Br} + n\text{-C}_5\text{H}_{11}\text{-Br} & \xrightarrow{\text{cat. } \text{Cp}_2\text{TiCl}_2, \text{THF}} \text{PhCat} \quad \text{Eq. (11)} \\
\text{Ph} + \text{Alkyl-Br} & \xrightarrow{\text{cat. } \text{Cp}_2\text{TiCl}_2, \text{THF}} \text{PhCat} \quad \text{Eq. (12)}
\end{align*}
\]

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 \( \text{Cp}_2\text{TiCl}_2 \) and \( \text{Cp}_2\text{Ti-Br}_2 \).\(^{18} \) 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 \( \text{Cp}_2\text{Ti} \) via \( \beta \)-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 \( \text{Cp}_2\text{Ti} \) to give the corresponding benzyltitanium complex \( 29 \). Subsequent transmetallation\(^{20} \) of \( 29 \) with \( n\)-BuMgCl gives the corresponding benzylic Grignard reagent \( 30 \) along with the regeneration of \( \text{Cp}_2\text{Ti-Br}_2 \). 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 then examined the reaction using less reactive organic halides toward the \( \text{S}_2\text{N}_2 \) 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 \( \text{Cp}_2\text{TiCl}_2 \) (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 \( \text{H}_2\text{O} \). The monoalkylated 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 alkyl 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 \( \text{PhCOCl} \) 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.
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 Cp$_2$TiCl$_2$ (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

![Scheme 6.](image)

Shown in Scheme 7 is the unique effect of solvents in this Cp$_2$TiCl$_2$/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 one electron to alkyl halides yielding an alkyl radical and benzylbutytitanocene 40, which undergoes site-selective β-hydrogen elimination to afford the corresponding alkenes along with the regeneration of Cp$_2$Ti. In addition, the reaction of 30 with alkyl bromides is slower in ether than in THF, so 30 re-combines with Cp$_2$Ti-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 benzy1 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)-NiCl$_2$ (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 7.](image)
A plausible reaction pathway is shown in Scheme 8. Nickel dichloride having a dpff 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. As for the substrates, a variety of organometallic reagents have been employed containing B, Mg, Li, Sn, Al, and Zn as the metal connecting to alkyl, alkenyl, ary, alkenynyl, 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 years 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 Ni13,15,28 or Pd 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 and chlorides.

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 tetrade can in 92% yield along with trace amounts of decane (<1%) and decenes (2%) (Eq. 19). In the absence of isoprene, tetrade can 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(dpdp), were used, tetrade can was obtained only in 45 and 22% yields, respectively.

\[ \text{n-Dec-Br} + \text{n-Bu-MgCl} \rightarrow \text{NiCl}_2/ \text{THF, rt, 3 h} \]

\[ \text{CH}_3\text{C}_6\text{H}_{14} + \text{n-Decane} + \text{Decenes} \]

\[ \begin{array}{c|c|c|c}
\text{Additive} & \% \text{CH}_3\text{C}_6\text{H}_{14} & \% \text{n-Decane} & \% \text{Decenes} \\
\hline
\text{none} & 2 & 39 & 59 \\
\text{>99%} & 0 & 0 & 0 \\
\text{92%} & <1 & 2 & 2 \\
\text{5%} & 9 & 14 & 2 \\
\text{3%} & 23 & 7 & 2 \\
\text{15%} & 14 & 25 & 2 \\
\end{array} \]

This reaction also shows an interesting chemo-selectivity by which the (sp3)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.

\[ \text{Br} + \text{CH}_3\text{C}_6\text{H}_{14} + \text{n-Bu-MgCl} \rightarrow \text{NiCl}_2/ \text{THF, 0 °C, 0.5 h} \]

\[ \text{Br} + \text{n-Bu} \rightarrow \text{n-Bu} >99% \]
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. 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.

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%.

$$n\text{-Oct-}F + n\text{-Pr-MgBr} \rightarrow \text{M} / 25^\circ C, 6 h \rightarrow n\text{-Oct-n-Pr + Octane + Octenes}$$

<table>
<thead>
<tr>
<th>M</th>
<th>(mmol)</th>
<th>n-Oct-F</th>
<th>n-Pr-MgBr</th>
<th>Octane</th>
<th>Octenes</th>
</tr>
</thead>
<tbody>
<tr>
<td>(PPh₃)₂NiCl₂</td>
<td>0.1</td>
<td>9%</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>(dppt)NiCl₂</td>
<td>0.5</td>
<td>44%</td>
<td>2%</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>NiCl₂</td>
<td>0.7</td>
<td>50%</td>
<td>2%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>NiCl₂</td>
<td>1.0</td>
<td>64%</td>
<td>4%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>NiCl₂</td>
<td>2.0</td>
<td>67%</td>
<td>3%</td>
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</tbody>
</table>

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. 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. 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 dococene 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.

\[
\text{Ni(acac)}_2 / \text{THF, 25 °C, 1 h} \\
\text{cat. Ni(acac)}_2 / \text{THF, 25 °C, 1 h}
\]

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 reagents in a THF/NMP (N-methyl-2-pyrrolidinone) mixed solvent containing MgBr₂.

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).

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 reagents in a THF/NMP (N-methyl-2-pyrrolidinone) mixed solvent containing MgBr₂.

A plausible reaction pathway is shown in Scheme 10. The bis-π-allylnickel structure 57 is constructed by the oxidative cycloaddition of two butadiene moieties of 1,3,8,10-tetraene to Ni⁰. An organonamengesium or -zinc reagent attacks the bis-π-allyl complex 57 to generate the η¹,η³-octadienediylnickelate 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.

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