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Kyoto University
Studies on Coupling Reactions of Alkyl Halides with Organomagnesium and Organolithium Reagents by Cobalt and Silver Catalysts

Hidenori Someya
2011
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<tr>
<td>Ac</td>
<td>acetyl</td>
<td>mmol</td>
<td>millimole</td>
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<tr>
<td>acac</td>
<td>acetylacetonate</td>
<td>m/z</td>
<td>mass-to-charge ratio</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
<td>n</td>
<td>normal</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
<td>o</td>
<td>ortho</td>
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<tr>
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<td>broad singlet (spectral)</td>
<td>ppm</td>
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<td>p</td>
<td>para</td>
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<td>quint</td>
<td>quintet (spectral)</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift in parts per million downfield from tetramethylsilane</td>
<td>s</td>
<td>secondary</td>
</tr>
<tr>
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<td>doublet (spectral)</td>
<td>s (sec)</td>
<td>secondary</td>
</tr>
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<td>dioxane</td>
<td>1,4-dioxane</td>
<td>s</td>
<td>singlet (spectral), second(s)</td>
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<td>SI Et HCl</td>
<td>1,3-bis(2,6-diethylphenyl)-4,5-dihydroimidazolium chloride</td>
</tr>
<tr>
<td>DME(dme)</td>
<td>1,2-dimethoxyethane</td>
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<td>1,6-bis(diphenylphosphino)hexane</td>
<td>t (tert)</td>
<td>tertiary</td>
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<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
<td>t</td>
<td>tertiary</td>
</tr>
<tr>
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<td>editor(s)</td>
<td>t</td>
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</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
<td>t</td>
<td>tertiary</td>
</tr>
<tr>
<td>El</td>
<td>electron impact</td>
<td>TFA</td>
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</tr>
<tr>
<td>equiv</td>
<td>equivalent(s)</td>
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<td>N,N,N',N'-tetramethylethylenediamine</td>
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<td>Et</td>
<td>ethyl</td>
<td>TMS</td>
<td>trimethylsilyl</td>
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<td>Torr</td>
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<td>hour(s)</td>
<td>Ts</td>
<td>p-toluenesulfonyl</td>
</tr>
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<td>hexamethylenetetramine</td>
<td>UV</td>
<td>ultraviolet</td>
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<td>Xanthphos</td>
<td>4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene</td>
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<tr>
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<td>hertz (s⁻¹)</td>
<td>µm</td>
<td>micrometer(s)</td>
</tr>
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<td>infrared (spectrum)</td>
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<td></td>
</tr>
<tr>
<td>J</td>
<td>coupling constant (in NMR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>m</td>
<td>multiplet (spectral), meter(s), milli</td>
<td></td>
<td></td>
</tr>
<tr>
<td>molar</td>
<td>molar (1 M = 1 mol dm⁻³)</td>
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</tr>
<tr>
<td>Me</td>
<td>methyl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mg</td>
<td>milligram(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MHz</td>
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1. Introduction

1.1. Transition-Metal-Catalyzed Coupling Reactions of Alkyl Halides with Organomagnesium Reagents

Easy accessibilities of both organomagnesium reagents and alkyl halides have made transition-metal-catalyzed coupling reactions of alkyl halides with organomagnesium reagents straightforward and powerful methods for carbon-carbon bond formations in organic synthesis.\textsuperscript{1,2} Research on coupling reactions has pursued wider substrate scope and milder reaction conditions.\textsuperscript{3} Due to difficulty of using alkyl halides as substrates in transition-metal-catalyzed coupling reactions, the coupling reactions of alkyl halides had not been established at the level of modern organic synthesis until the 1990s while those of aryl and alkenyl halides were developed significantly in the 1970s.\textsuperscript{4} As shown in Scheme 1, the transition-metal-catalyzed coupling reaction of an organic halide with an organomagnesium reagent generally proceeds through oxidative addition of the organic halide to transition metal (A), transmetalation with an organomagnesium reagent (B), and reductive elimination to the desired coupling product (C). When an alkyl halide is used as the organic halide, β-hydride elimination from the alkylmetal intermediate (D) easily occurs after the oxidative addition. In contrast, aryl or alkenyl halides have no hydrogen atom beta to the halogen. So β-hydride elimination is naturally not possible.
In fact, palladium-catalyzed coupling reactions of alkyl halides with organomagnesium reagents are still limited to primary or activated secondary alkyl halides despite the great success of palladium-catalyzed coupling reactions of aryl or alkenyl halides. A recently reported example of palladium-catalyzed coupling reactions of alkyl halides is shown in Scheme 2. Xantphos, which has a large bite angle (111°), was used as a ligand under the optimized reaction conditions. This bulky ligand efficiently prevented β-hydride eliminations from the corresponding benzylic palladium intermediate. However, only benzylic alkyl bromides could be employed in this coupling reaction because palladium-catalyzed coupling reactions of alkyl halides generally proceed through an S₆₂-type oxidative addition. As shown in Scheme 2, the reaction actually afforded the coupling product with inversion of the configuration.
The first transition-metal-catalyzed coupling reaction of alkyl halides with organomagnesium reagents was reported by Tamura and Kochi in 1971 (Scheme 3). However, this reaction afforded the products as mixtures of homo-coupling products, alkanes produced by dehalogenation, alkenes produced by elimination, and the desired coupling products. Consequently, the desired products were obtained only in moderate yields.

**Scheme 3.**

\[
\text{C}_2\text{H}_5\text{Br} + \text{BrMgCl} \xrightarrow{0.3 \text{ mol\% Li}_2\text{CuCl}_4, \text{THF, 0 °C, 3 h}} \text{C}_2\text{H}_5\text{Br} \]

Although improvements occasionally appeared, it took about three decades from the first report until breakthroughs in transition-metal-catalyzed coupling reactions of alkyl halides emerged. In 2000, copper-catalyzed coupling reaction of alkyl halides was reported by Cahiez and co-workers (Scheme 4). Not only primary alkylmagnesium reagents could be applied as organometallic reagents in this reaction, but also secondary and tertiary alkylmagnesium, and alkenylmagnesium reagents. The addition of NMP was essential for affording the coupling products in good yields because NMP prevents elimination from the alkyl halide to the alkene by coordinating to copper and/or organomagnesium reagents. It should be noted that the reaction proceeds so fast that alkyl bromides with functional groups, such as ketones, nitriles, and even alcohols, could be also employed in the coupling reaction. However, secondary and tertiary alkyl halides resisted the reaction.
In 2002, Kambe and co-workers reported nickel-catalyzed coupling reaction of primary alkyl halides (Scheme 5). In this coupling reaction, phenylmagnesium reagent as well as primary and secondary alkylmagnesium reagents could be employed. 1,3-Butadiene was used as the ligand in the reaction. Their proposed mechanism is shown in Scheme 6. First, Ni(0) is generated by the reduction of NiBr₂ by organomagnesium reagents. The subsequent reaction of Ni(0) with two equivalents of 1,3-butadiene affords bis-π-allylnickel(II) complex 1. Complex 1 reacts with one more organomagnesium reagent to afford ate-complex 2. The oxidative addition of the alkyl halide is followed by reductive elimination from complex 3.
A very important key in Scheme 6 is the order of each elementary reaction. The order is transmetalation, then oxidative addition, and finally reductive elimination, which is different from the order in the conventional transition-metal-catalyzed cross-coupling reaction (Scheme 1). In Scheme 6, alkylmetal intermediate 3 is coordinated not only with the ligand but also with the carbanion $R^2$. As a result, a $\beta$-hydride elimination pathway is effectively prevented.

The concept of the order of elementary reactions described in Scheme 6 was also applied to copper-and palladium-catalyzed coupling reactions of alkyl halides. The copper/alkyne system is remarkable because the scope of the reaction is wide (Scheme 7). Alkyl bromides, alkyl chlorides, and even alkyl fluorides could be applied as substrates in the reaction. Primary, secondary, and tertiary alkylmagnesium reagents as well as phenylmagnesium reagent could be employed. The reactions of secondary and tertiary alkyl halides failed to yield the coupling products probably because this reaction would proceed through an $S_n2$-type oxidative addition of alkyl halide. In fact, the copper/alkyne-catalyzed coupling reaction afforded the coupling product with a 10/1 selective inversion of the configuration (Scheme 8).
The previously described work enabled the use of primary alkyl halides as substrates in transition-metal-catalyzed coupling reactions with various organomagnesium reagents. However, the use of secondary alkyl halides in these reactions remained challenging. To achieve the coupling reaction of secondary alkyl halides, cobalt and iron catalysis played very important roles.

In 2002, Oshima and co-workers reported cobalt-catalyzed coupling reaction of alkyl halides with allylmagnesium reagent, in which secondary and tertiary alkyl halides as well as primary alkyl halides could be employed (Scheme 9). The use of 1,3-bis(diphenylphosphino)propane (DPPP) as a ligand was crucial in the coupling reaction. When other bidentate phoshine
ligands, such as 1,4-bis(diphenylphosphino)butane (DPPB), 1,2-bis(diphenylphosphino)ethane (DPPE), and bis(diphenylphosphino)methane (DPPM), were used as ligands instead of DPPP, the coupling product was obtained in lower yield.\textsuperscript{13b} Although the scope of organomagnesium reagents was limited to allylic and benzylic organomagnesium reagents and the yields of the coupling products were relatively moderate, this reaction is remarkable because secondary and even tertiary alkyl halides could be employed.

\textbf{Scheme 9.}

\[
\begin{align*}
R-\text{Br} + \text{BrMg} & \xrightarrow{10 \text{ mol\% CoCl}_2} \xrightarrow{10 \text{ mol\% DPPP}} \xrightarrow{\text{THF}} R-\text{Ph} \\
\text{Ph}_2\text{P} & \xrightarrow{\text{PPh}_2} \text{DPPP}
\end{align*}
\]

<table>
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<th>R-Br</th>
<th>temp.</th>
<th>yield</th>
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<tr>
<td>Ph-\text{Br}</td>
<td>0 °C</td>
<td>30%</td>
</tr>
<tr>
<td>\text{nC}<em>8\text{H}</em>{17}-\text{Br}</td>
<td>0 °C</td>
<td>57%</td>
</tr>
<tr>
<td>\text{nC}<em>8\text{H}</em>{17}-\text{Br}</td>
<td>-20 °C</td>
<td>90%</td>
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Oshima and co-workers proposed that the reaction involves the generation of a carbon-centered radical intermediate. In fact, when a substrate having a carbon-carbon double bond at the proper position was used, sequential cyclization/allylation reaction occurred as shown in Scheme 10. The alkyl radical intermediate 4 was first generated by a single-electron transfer from an electron-rich allylcobalt complex to the alkyl iodide, followed by the loss of the iodide (E). Then, the 5\textit{-exo} radical cyclization proceeded rapidly (F).\textsuperscript{14} Next, capture of the radical by a cobalt complex (G) followed by reductive elimination afforded the product 7 (H). It is notable that the oxidative addition of alkyl halides in this coupling reaction proceeded through a single-electron transfer process, which is in stark contrast from the usual S\textsubscript{N}2-type oxidative addition in palladium catalysis. Generally, the order of the stability of an alkyl radical is tertiary>secondary>primary. Thus, the oxidative addition through a single-electron transfer can
allow for the use of tertiary and secondary alkyl halides as substrates as well as primary alkyl halides. The oxidative addition of alkyl halides via a single-electron transfer has become vital to achieve transition-metal-catalyzed coupling reactions of secondary alkyl halides.

**Scheme 10.**

In 2004, Nakamura, Fürstner, and Hayashi, independently reported iron-catalyzed coupling reactions of secondary and primary alkyl halides with arylmagnesium reagents (Scheme 11). These findings significantly have expanded the utility of secondary alkyl halides in the coupling reactions.
Nakamura and Fürstner reported the use of TMEDA as a ligand. In Hayashi’s report, although the yields of the coupling products were slightly lower than those in the other two reactions, there was no need for the addition of a ligand. These iron-catalyzed coupling reactions proceed through the generation of alkyl radical intermediates as the cobalt-catalyzed coupling reactions do. For example, the reactions of trans- and cis-1-bromo-4-tert-butylcyclohexane afforded the corresponding arylated product in the same diastereomeric ratio (Scheme 12).\textsuperscript{15}
TMEDA is likely to play two roles in the coupling reaction. One is suppression of the elimination of HX (X = a halogen atom) by coordinating to the organomagnesium reagents. Arylmagnesium reagent behaved both as the nucleophile and as the base against the alkyl halide in the reaction. Because coordination of TMEDA to magnesium reduced the Lewis acidity of magnesium center, the interaction between magnesium and the halogen atom in the alkyl halide decreased. As a result, E1 and E2 reactions of alkyl halides with arylmagnesium reagents, which are one of the side reactions in the coupling reaction of alkyl halides, were prevented. The other is contribution to the formation of the catalytically active iron complex 8 (Scheme 13).18 The mechanism of iron-catalyzed coupling is similar to that shown in Scheme 10. The reaction of the iron salt with the arylmagnesium reagent affords diaryliron complex 8. Then the oxidative addition via a single-electron transfer occurs. Finally, reductive elimination results in the coupling product. The catalytically active species 8 is regenerated by the action of the arylmagnesium reagent.
The use of amines as ligands for coupling reactions of secondary alkyl halides was applied to cobalt-catalyzed coupling reactions of secondary alkyl halides with arylmagnesium reagents (Scheme 14).\textsuperscript{19,20} Interestingly, the addition of a catalytic, not stoichiometric, amount of diamine was sufficient to afford the coupling products in good yields in the cobalt-catalyzed coupling reaction.\textsuperscript{19a}

**Scheme 14.**

Compared with the wide scope of alkyl halides, the scope of the organomagnesium reagent in the coupling reactions of secondary alkyl halides were generally narrow (Schemes 9, 11, and 14). However, recent development of well-designed catalysts enabled the use of a wider variety of organomagnesium reagents. In 2006, Oshima and co-workers reported a cobalt-catalyzed...
coupling reaction with 2-trimethylsilylethynylmagnesium reagents (Scheme 15).  

In 2007, Cahiez and co-workers reported an iron-catalyzed coupling reaction with alkenylmagnesium reagents (Scheme 16).  

In 2008, Cahiez also reported a cobalt-catalyzed coupling reaction with alkylmagnesium reagents (Scheme 17).  

Although the mechanisms of these coupling reactions are not clear yet, they seem to be similar to those shown in Scheme 10 and 13.

**Scheme 15.**

\[
\begin{align*}
\text{Br} & \quad + \quad \text{BrMg} & \quad \text{Co(acac)}_2 & \quad 40 \text{ mol}\% & \quad \text{TMEDA, 25 °C} & \quad 15 \text{ min} \\
\text{cyclohexyl} & \quad \rightarrow & \quad \text{SiMe}_3 & \quad 71\%
\end{align*}
\]

**Scheme 16.**

\[
\begin{align*}
\text{Br} & \quad + \quad \text{BrMg} & \quad \text{Fe(acac)}_3 & \quad 5 \text{ mol}\% & \quad \text{THF, 0 °C} & \quad 45 \text{ min} \\
\text{C}_{13}H_{27} & \quad \rightarrow & \quad \text{C}_{13}H_{27} & \quad \text{Z/E} = 97/3 & \quad 69\%
\end{align*}
\]

**Scheme 17.**

\[
\begin{align*}
\text{Br} & \quad + \quad \text{BrMg} & \quad \text{CoCl}_2 \cdot 2 \text{LiI} & \quad 5 \text{ mol}\% & \quad \text{THF, 10 °C} & \quad 1 \text{ h} \\
\text{C}_{17}H_{35} & \quad \rightarrow & \quad \text{C}_{17}H_{35} & \quad 57\%
\end{align*}
\]

The concept of the generation of a carbon-centered radical intermediate through a single-electron transfer (Schemes 10 and 13) led to investigations of new synthetically useful methodologies for organic synthesis as well as the coupling reactions of secondary alkyl halides described above.  

Oshima and co-workers reported a cobalt-catalyzed three-component coupling reaction involving alkyl halides, 1,3-dienes, and trimethylsilylmethylmagnesium reagents (Scheme 18).  

The alkyl radical 11 generated from the alkyl halide (J) reacts with 1-phenyl-1,3-butadiene to afford the allylic radical 12 before capture by the cobalt complex.
Then, capture of 12 by the cobalt complex results in the formation of allylcobalt complex 13 (K). The three-component coupling product is formed by transmetalation with trimethylsilylmethylmagnesium reagent (L), followed by the reductive elimination from the dialkylcobalt complex 14 (M).

**Scheme 18.**

\[
\begin{align*}
\text{Et}_2O, 0 \degree C \\
0.5 \text{h}
\end{align*}
\]

**Proposed mechanism**

Fu and Lou reported a nickel-catalyzed asymmetric coupling reaction of α-bromoketones with arylmagnesium reagents (Scheme 19). Although the scope of alkyl halides is limited to α-bromoketones, it is significant as a pioneering work for highly selective asymmetric transition-metal-catalyzed coupling reactions of secondary alkyl bromides. Because coupling reactions of secondary alkyl halides proceed through generation of the corresponding alkyl...
radical intermediates, the coupling reaction of racemic α-bromoketones could afford one enantiomer of the products.\textsuperscript{25a}

**Scheme 19.**

\[
\begin{align*}
\text{O} & \quad \text{MgBr} & \quad 7 \text{ mol}\% \text{ NiCl}_2(\text{dme}) \\
\text{Ph} & \quad \text{Br} & \quad 9 \text{ mol}\% (R)-L \\
\text{racemic} & \quad & \quad \text{DME, } -60^\circ \text{C} \\
\end{align*}
\]

91%, 95% ee

Wangelin and co-workers reported iron- and cobalt-catalyzed domino magnesiation/coupling reactions between alkyl and aryl halides (Scheme 20\textsuperscript{26} and 21\textsuperscript{27}). There was no need for the preparation of the organomagnesium reagents in advance. In their reports, it was proposed that FeCl\textsubscript{3} catalyzed the formation of arylmagnesium reagents from the corresponding aryl halides first,\textsuperscript{28} and then also catalyzed the coupling reaction of alkyl halides with the generated arylmagnesium reagents. In fact, they showed that the induction period for the formation of 1-naphthylmagnesium bromide in the absence of FeCl\textsubscript{3} was three times longer than in the presence of the catalyst.

**Scheme 20.**

\[
\begin{align*}
& \quad + \\
\text{Br} & \quad \text{Br} & \quad \text{THF, } 0^\circ \text{C, } 3 \text{ h} \\
\end{align*}
\]

71%

**Scheme 21.**

\[
\begin{align*}
& \quad + \\
\text{Br} & \quad \text{Br} & \quad \text{THF, } 0^\circ \text{C, } 6 \text{ h} \\
\end{align*}
\]

73%

(diamine = \textit{N,N,N',N'-tetramethyl-trans-1,2-cyclohexanediamine})
In contrast to the coupling reactions of primary and secondary alkyl halides, that of tertiary alkyl halides still remains challenging because the bulkiness of tertiary alkyl halides makes the oxidative addition much slower and β-hydride eliminations from the tert-alkylmetal intermediates much faster. In fact, only cobalt can catalyze the coupling reaction with allyl and benzylmagnesium reagents (Scheme 9).13a

1.2. Transition-Metal-Catalyzed Coupling Reactions of Alkyl Halides with Organolithium Reagents

While the palladium-catalyzed coupling reaction of vinyl bromides with alkyllithiums was reported by Murahashi and co-workers in 1979,29 transition-metal-catalyzed coupling reactions of alkyl halides with organolithium reagents have not been well investigated yet due to their high basicity and nucleophilicity.30 However, the ready availability as well as the high reactivity of organolithium reagents makes the coupling reactions of alkyl halides with organolithium reagents worth investigating.

In 2004, Fürstner and Martin reported iron-catalyzed coupling reaction of bromocyclohexane with phenyllithium as one isolated example (Scheme 22).31 There was no in-depth discussion about the coupling reaction with organolithium reagents on the whole.

Scheme 22.

In 2009, Cahiez and co-workers reported a copper-catalyzed coupling reaction of primary alkyl halides with organolithium reagents (Scheme 23).32 Not only alkyllithium reagents but also phenyllithium could be employed in the reaction. Notably, primary alkyl chlorides as well as alkyl bromides could be used as substrates. In contrast to similar coupling reactions with organomagnesium reagents, it is not necessary to use any ligands or additives in this coupling
reaction, which is due to the high reactivity of organolithium reagents. Although transition-metal-catalyzed coupling reactions of alkyl halides with organolithium reagents are still rare, these reactions shown in Scheme 22 and 23 presented the feasibility of the reactions in organic synthesis.

**Scheme 23.**

\[ \text{Li-R} \quad \text{yield} \]

<table>
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<tr>
<th>Li-R</th>
<th>88%</th>
</tr>
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<tr>
<td>Li</td>
<td>70%</td>
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2. **Overview of This Thesis**

The author focused on the development of transition-metal-catalyzed coupling reactions of alkyl halides with organometallic reagents. As described in Section 1, coupling reactions of alkyl halides have been improved by the new catalytic systems that utilize new ligands or new transition metals. Different new catalytic systems were established to find some new coupling reactions under cobalt and silver catalysis. In Chapters 1 and 2, cobalt-catalyzed coupling reactions of 6-halo-1-hexene derivatives with organomagnesium reagents are described. In Chapters 3 and 4, silver-catalyzed coupling reactions of alkyl halides with organomagnesium reagents are detailed. In Chapter 5, silver-catalyzed coupling reaction of alkyl halides with organolithium reagents is presented.

2.1. **Cobalt-Catalyzed Coupling Reactions of 6-Halo-1-hexene Derivatives with Organomagnesium Reagents (Chapters 1 and 2)**

Cobalt complexes are known not only to act as effective catalysts but also to show unique features in coupling reactions of alkyl halides with organometallic reagents.\(^\text{33,34}\) Ligands have a large influence on the scope of organometallic reagents in cobalt-catalyzed coupling reactions.
As shown in Schemes 9, 14, 15, and 17, development of ligands for cobalt salts made coupling reactions with various organomagnesium reagents possible. Cobalt-catalyzed coupling reactions involve the generation of alkyl radical intermediates from alkyl halides, which are produced by a single-electron transfer from electron-rich cobalt complexes to alkyl halides. As shown in Schemes 10 and 18, the alkyl radical intermediates can be applied to attractive transformations with unsaturated compounds, such as a sequential cyclization/coupling reaction (Scheme 10) and a three component coupling reaction (Scheme 18). The author has especially focused on the cobalt-catalyzed sequential cyclization/coupling reaction of 6-halo-1-hexene derivatives with organomagnesium reagents. He demonstrates new ligands for the reactions in Chapter 1 and shows their applications in organic synthesis in Chapter 2.

2.1.1. N-Heterocyclic Carbene Ligands in Cobalt-Catalyzed Sequential Cyclization/Coupling Reactions of 6-Halo-1-hexene Derivatives with Organomagnesium Reagents (Chapter 1)

N-Heterocyclic carbenes (NHCs) are used as two-electron σ-donor ligands for various transition-metal-catalyzed reactions. In Chapter 1, the author describes the possibility of NHC ligands in cobalt-catalyzed sequential cyclization/coupling reactions of 6-halo-1-hexene derivatives with organomagnesium reagents.

Treatment of a 6-iodo-1-hexene derivative with allyldimethylsilylmethylmagnesium chloride in the presence of SIEt-HCl and CoCl₂ provided the corresponding cyclization/coupling product in 81% yield (Scheme 24). This reaction only proceeded with the aid of NHC ligands. The use of other ligands such as phosphines and diamines resulted in much lower yields (<10%). The 3-(silylethyl)pyrrolidine derivative underwent Tamao-Fleming oxidation to furnish the corresponding alcohol.
The reaction of the 6-iodo-1-hexene derivative with 1-hexynylmagnesium bromide in the presence of IMes·HCl and CoCl$_2$ afforded the corresponding alkynylated product in 80% yield (Scheme 25). A variety of alkynylmagnesium bromides reacted smoothly. In the previously reported CoCl$_2$/TMEDA-catalyzed alkynylation of alkyl halides, the scope of alkynylmagnesium reagents available for use was limited to 2-trimethylsilylethylnylmagnesium bromide (Scheme 15).$^{21}$
2.1.2. Cobalt-Catalyzed Sequential Cyclization/Coupling Reactions of 6-Halo-4-oxa-3-sila-1-hexene Derivatives with Organomagnesium Reagents and Their Application to the Synthesis of 1,3-Diols (Chapter 2)

The studies in Chapter 1 clarify the synthetic usefulness of the cobalt-catalyzed cyclization/coupling reactions of 6-halo-1-hexene derivatives with organomagnesium reagents. In Chapter 2, the author presents the application of the reactions to the synthesis of 1,3-diols of synthetic use.

Treatment of a silicon-tethered 6-iodo-1-hexene derivative with arylmagnesium reagents in the presence of diamine and CoCl$_2$ afforded the corresponding oxasilacyclopentane derivatives (Scheme 26). The products were converted to 4-aryl-1,3-butanediol upon treatment with hydrogen peroxide in the presence of potassium fluoride and potassium hydrogen carbonate.

**Scheme 26.**

Dimethylphenylsilylmethylmagnesium chloride also promoted the CoCl$_2$/SIEt•HCl-catalyzed reaction of the silicon-tethered 6-iodo-1-hexene derivative to afford the corresponding product (Scheme 27).

---

**Scheme 26.**

```
\[ \text{BrMg} \rightarrow \text{5 mol\% CoCl}_2 \rightarrow \text{24 mol\% diamine} \rightarrow \text{THF, 25 \degree C} \rightarrow \text{15 min} \rightarrow \text{KF, KHCO}_3 \rightarrow \text{30\% H}_2\text{O}_2 \text{aq} \rightarrow \text{MeOH/THF (1/1)} \rightarrow \text{74\% (50/50)} \]
```
2.2. Silver-Catalyzed Coupling Reactions of Alkyl Halides with Organomagnesium Reagents and Organolithium Reagents (Chapters 3, 4, and 5)

Silver-catalyzed coupling reactions of alkyl halides with organomagnesium reagents were investigated by Tamura and Kochi for the first time in 1971 (Scheme 28), which is the same year of the first reported copper-catalyzed coupling reaction of alkyl halides with organomagnesium reagents (Scheme 3). Kochi’s reaction afforded a mixture of the desired coupling product and homo-coupling products of the alkyl bromide and the organomagnesium reagent. Because of this low selectivity, the silver-catalyzed coupling reaction was mainly investigated as a homo-coupling reaction of organomagnesium reagents. A recently reported silver-catalyzed homo-coupling reaction of organomagnesium reagents is shown in Scheme 29. 1,2-Dibromoethane was used as an oxidant for reoxidation of Ag(0) in this reaction.
Even nowadays, silver catalysis is not sufficiently investigated for use in coupling reactions of alkyl halides with organometallic reagents while copper-catalyzed coupling reactions have been established as described in Section 1.1. Thus, the author focused on the possibility of silver catalysis in transition-metal-catalyzed coupling reaction of alkyl halides with organometallic reagents. He describes silver-catalyzed coupling reactions of alkyl halides with various organomagnesium reagents in Chapter 3 and 4 and application of silver catalysis to the reaction with organolithium reagents in Chapter 5.

### 2.2.1. Silver-Catalyzed Coupling Reactions of Tertiary and Secondary Alkyl Halides with Benzyl and Allylmagnesium Reagents (Chapter 3)

In Chapter 3, the author describes silver-catalyzed coupling reactions of alkyl halides with benzyl and allylmagnesium reagents. In these reactions, tertiary alkyl halides as well as secondary alkyl halides can be employed.

Treatment of tertiary alkyl bromides with benzylmagnesium bromide in the presence of a catalytic amount of AgNO₃ affords the corresponding coupling products in high yields (Scheme 30). Secondary alkyl bromides and iodides can also undergo this benzylation reaction.

**Scheme 30.**

\[
R-X + \text{BrMg} \xrightarrow{1-2.5 \text{ mol\% AgNO}_3} \text{Et}_2\text{O, 25 °C, 3 h}} R-\text{aryl}
\]

- \(n\text{C}_8\text{H}_{17}\)Br 87%
- C\(_8\)H\(_8\)Br 77%
- C\(_8\)H\(_8\)I 67%
These conditions were applicable not only to benzylation but also to allylation (Scheme 31). The reaction with allylmagnesium bromide afforded the coupling product in excellent yield. Methallyl-, crotlyl-, and prenylmagnesium halides could be also used, though crotylation and prenylation of alkyl halides resulted in poor regioselectivities.

**Scheme 31.**

\[
\text{C}_8\text{H}_{17} \text{Br} + \text{BrMg} \xrightarrow{1 \text{ mol}\% \text{AgNO}_3} \text{C}_8\text{H}_{17} \text{MgBr} \quad \text{Et}_2\text{O}, 25^\circ\text{C}, 3 \text{h} \quad 83\%
\]

It is noteworthy that the silver-catalyzed reaction represents a rare example of the use of tertiary alkyl halides as a coupling partner.

### 2.2.2. Silver-Catalyzed Coupling Reactions of Alkyl Bromides with Alkyl and Arylmagnesium Reagents (Chapter 4)

The studies in Chapter 3 showed the unique catalytic activity of silver in transition-metal-catalyzed coupling reactions of alkyl halides with organomagnesium reagents. However, the scope of organomagnesium reagents available for the reaction in Chapter 3 was limited to benzylic and allylic organomagnesium reagents. To expand the scope of the organomagnesium reagents, the author investigated the ligand effect on the silver-catalyzed coupling reaction. In Chapter 4, he presents AgBr/KF-catalyzed coupling reaction with alkylmagnesium reagents and AgBr/P(OPh)_3-catalyzed coupling reaction with arylmagnesium reagents.

Treatment of bromocyclohexane with 3-phenylpropylmagnesium bromide in the presence of 10 mol% AgBr/KF in CH_2Cl_2 at −10 °C afforded the coupling product in 66% yield (Scheme 32). Tertiary alkyl bromides could be also employed as substrates in this reaction.
2.2.3. Silver-Catalyzed Coupling Reactions of Alkyl Halides with Indenyllithium (Chapter 5)

As mentioned in Section 1.2, the use of organolithium reagents in transition-metal-catalyzed coupling reactions of alkyl halides has been less investigated despite the high reactivity and the ready availability of organolithium reagents. Thus, the author investigated the application of silver catalysis to the coupling reaction with organolithium reagents. In Chapter 5, he demonstrates silver-catalyzed coupling reaction of alkyl halides with indenyllithium reagents.

Treatment of a 1-bromo-1-methyclohexane derivative with indenyllithium in the presence of 5 mol% AgBr in Et₂O afforded the corresponding alkylated indene in 74% yield (Scheme 34). The reaction was not stereospecific, which is highly suggestive of the existence of an intermediate having an sp²-hybridized carbon center. This reaction afforded 1-alkylindenes selectively, and no isomerization to 3-alkylindene occurred even under the basic conditions. Regiocontrolled synthesis of 1,3-dialkyindene can be achieved by the silver-catalyzed coupling
reaction with the organolithium reagent derived from 1-alkylindene (Scheme 35).

Scheme 34.

\[
\begin{align*}
\text{Bu} & \quad \text{Li} \\
\text{Br} & \quad \text{Et}_2\text{O}, \text{reflux} \\
(\text{cis/trans} = 84/16)
\end{align*}
\]

Scheme 35.

\[
\begin{align*}
\text{sBuLi} & \quad \text{Et}_2\text{O}, 0 \degree \text{C} \\
1.5 \text{~h} & \quad 10 \text{~mol\% AgBr} \\
\text{Ph} & \quad \text{Et}_2\text{O}, 0 \degree \text{C} \\
12 \text{~h} & \quad 41\% \\
(\text{cis/trans} = 35/65)
\end{align*}
\]

2.3. Conclusion

The author has found that cobalt-catalyzed sequential cyclization/coupling reactions of 6-halo-1-hexene derivatives with alkynyl and silylmethylmagnesium reagents could proceed smoothly with the aid of NHC ligands, and has showed their application to synthesis of 1,3-diols. He has also developed silver-catalyzed coupling reactions of alkyl halides with various organomagnesium reagents and indenyllithium reagents, in which tertiary alkyl halides as well as secondary and primary alkyl halides could be employed. These studies reveal new possibilities of cobalt and silver catalysis in transition-metal-catalyzed coupling reactions of alkyl halides towards useful carbon-carbon bond formations.
References and Notes


General Introduction


Chapter 1

N-Heterocyclic Carbene Ligands in Cobalt-Catalyzed Sequential Cyclization/Coupling Reactions of 6-Halo-1-hexene Derivatives with Organomagnesium Reagents

N-Heterocyclic carbene/cobalt systems effectively catalyze sequential cyclization/coupling reactions of 6-halo-1-hexene derivatives with trialkylsilylmethyl- and 1-alkynylmagnesium reagents, which phosphine and amine ligands do not promote.
Chapter 1

Introduction

N-Heterocyclic carbenes (NHCs) have been attracting increasing attention in various fields of organic chemistry. From a viewpoint of transition-metal-catalyzed reactions, they are widely used as two-electron σ-donor ligands for a number of reactions including carbon–carbon bond formations, carbon–heteroatom formations, and C–H activation. Among these reactions, NHC ligands display excellent performance in the palladium-catalyzed cross-coupling reactions. In contrast to the development of the palladium/NHC system, there are few examples of the use of NHC ligands in cobalt-catalyzed cross-coupling reactions. In Chapter 1, the author has been exploring the possibility of NHCs in the cobalt-catalyzed carbon–carbon bond forming process, and presents cobalt-catalyzed coupling reactions of alkyl halides with organomagnesium reagents that involve intramolecular cyclizations, which proceed only with the aid of NHC ligands (Scheme 1).

Scheme 1.

Results and Discussion

In light of the importance of silyl groups as a hydroxy equivalent, a cobalt-catalyzed sequential cyclization/coupling reaction with allyldimethylsilylmethylmagnesium chloride was first investigated. SIÉt·HCl (2a), a 4-aza-6-iodo-1-hexene derivative 1a, and CoCl₂ were mixed in dioxane. Then allyldimethylsilylmethylmagnesium chloride was added over 5 s at 25 °C. An exothermic reaction immediately took place. The mixture was stirred at 25 °C for 30 min to
afford the corresponding cyclization/coupling product 3a in 81% yield (Scheme 2). The 3-(silyethyl)pyrrolidine derivative 3a underwent deallylative fluorination followed by Tamao–Fleming oxidation\(^8\) to furnish the corresponding alcohol 4a. This reaction mechanism consists of the following sequence:\(^6\) (1) generation of the corresponding carbon-centered radical from 1a by a single-electron transfer from an electron-rich cobalt complex, (2) radical cyclization, (3) capture of the 3-pyrrolidinomethyl radical by a cobalt complex, and (4) reductive elimination.

**Scheme 2.**

A variety of imidazolium salts were screened to reveal that SIEt·HCl (2a) was the best ligand (Table 1). The use of 1,3-di(tert-butyl)-substituted imidazolium salt 2c afforded less than 5% yield of 3a (entry 3), and a significant amount of 1-toluenesulfonyl-3-methylenepyrrolidine was formed via β-hydride elimination. On the other hand, 1,3-dimesityl-substituted derivative IMes·HCl (2d) showed modest activity (entry 4), and the use of SIMes·HCl (2b), the dihydro analogue of 2d, further improved the yield of 3a up to 54% (entry 2). Diisopropylphenyl-substituted imidazolium salt (IPr·HCl, 2e) which bears larger aryl groups than IMes·HCl (2d) provided none of the coupling product, leaving behind most of the starting material (entry 5). The use of other ligands such as phosphines (PPh\(_3\) and P\(^{+}\)Bu\(_3\)) and \(N,N,N',N'\)-tetramethyl-trans-1,2-cyclohexanediamine\(^6\) resulted in much lower yields (entries
The carbene ligand may promote facile oxidative addition through a single-electron transfer mechanism and fast reductive elimination from an alkylcobalt intermediate without suffering from β-hydride elimination. The choice of solvent had a significant effect on the yields of the coupling product. Dioxane proved to be the best solvent. Other solvents such as THF and Et₂O gave much lower yields of the coupling product (30–40%).

**Table 1. Ligand effect**

<table>
<thead>
<tr>
<th>entry</th>
<th>Ligand</th>
<th>yield /%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><a href="%E6%94%AF%E6%9F%B1">[Scheme]</a> 2a (SIEt·HCl)</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td><a href="%E6%94%AF%E6%9F%B1">[Scheme]</a> 2b (SIMes·HCl)</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td><a href="%E6%94%AF%E6%9F%B1">[Scheme]</a> 2c</td>
<td>&lt;5</td>
</tr>
<tr>
<td>4</td>
<td><a href="%E6%94%AF%E6%9F%B1">[Scheme]</a> 2d (IMes·HCl)</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td><a href="%E6%94%AF%E6%9F%B1">[Scheme]</a> 2e (IPr·HCl)</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>
Various substrates were examined, and the results are listed in Table 2. Halo acetals bearing a terminal alkene moiety underwent the cyclization/coupling reactions to give the corresponding silylethyl-substituted tetrahydrofuran derivatives in good yields (entries 1–3). Carbocycle 3e was obtained exclusively in the reaction of 6-iodo-1-hexene (1e) in 67% yield (entry 4). The corresponding bromide 1f was less reactive (entry 5). Dimethylphenylsilylmethylmagnesium chloride was also available for this reaction (entry 6). The cobalt/NHC system could be employed for coupling reactions of primary alkyl halides without a cyclization process. For instance, treatment of isobutyl iodide (1g) with allyldimethylsilylmethylmagnesium chloride in dioxane in the presence of SIEt•HCl (2a) and CoCl₂ for 30 min at 25 °C afforded the corresponding coupling product 3g in 79% yield (Scheme 3). Unfortunately, the reactions of secondary alkyl halides resulted in failure and gave mixtures of alkane and alkene, which could be generated by protonation and β-hydride elimination from an alkylcobalt intermediate.

Table 1. (Continued)

<table>
<thead>
<tr>
<th>entry</th>
<th>Ligand</th>
<th>yield /%</th>
</tr>
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<tr>
<td>6</td>
<td>PPh₃</td>
<td>&lt;1</td>
</tr>
<tr>
<td>7</td>
<td>P₃Bu₃</td>
<td>&lt;1</td>
</tr>
<tr>
<td>8</td>
<td>NMe₂</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Table 2. Cobalt/NHC-catalyzed sequential cyclization/coupling reaction with allyldimethylsilylmethylmagnesium reagent

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>yield /%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1b</td>
<td>3b</td>
<td>72 (85/15)</td>
</tr>
</tbody>
</table>
Table 2. (Continued)

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>1</th>
<th>product</th>
<th>3</th>
<th>yield /%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>(n\text{C}_4\text{H}_9\text{O}_2\text{O})\</td>
<td>1c</td>
<td>(n\text{C}_4\text{H}_9\text{O}_2\text{O})\</td>
<td>3c</td>
<td>81 (67/33)</td>
</tr>
<tr>
<td>3</td>
<td>(n\text{C}_4\text{H}_9\text{O}_2\text{O})\</td>
<td>1d</td>
<td>(n\text{C}_4\text{H}_9\text{O}_2\text{O})\</td>
<td>3d</td>
<td>78 (54/46)</td>
</tr>
<tr>
<td>4</td>
<td>(\text{X} = \text{I})</td>
<td>1e</td>
<td>(\text{X} = \text{I})</td>
<td>3e</td>
<td>67 (X = I)</td>
</tr>
<tr>
<td>5</td>
<td>(\text{X} = \text{Br})</td>
<td>1f</td>
<td>(\text{X} = \text{Br})</td>
<td>3f</td>
<td>18 (X = Br)</td>
</tr>
<tr>
<td>6b</td>
<td>(\text{Ts})</td>
<td>1a</td>
<td>(\text{Ts})</td>
<td>3f</td>
<td>78</td>
</tr>
</tbody>
</table>

\(^a\) A 1:1 mixture of diastereomers.
\(^b\) Dimethylphenylsilylmethylmagnesium chloride was employed.

Scheme 3.

Next, the author turned his attention to the sequential cyclization/coupling reactions of 6-halo-1-hexene derivatives with 1-alkynylmagnesium reagents (Schemes 4 and 5). The use of NHC ligand was essential for the successful reaction as in the case of the reaction with trialkylsilylmethylmagnesium reagents. For example, treatment of 1a with 1-hexynylmagnesium bromide (5a) in the presence of IMes·HCl (2d) and CoCl₂ provided alkynylated products 6a in 80% yield. The use of the 1,3-dimesityl-substituted imidazolium salt (2d) was crucial to attain satisfactory results. The reactions with the aid of other NHC ligands
such as SIEt·HCl (2a), SIMes·HCl (2b), and IPr·HCl (2e) yielded none of coupling product, and most of the starting material 1a was recovered. Other ligands such as phosphines and diamines were also ineffective. Various alkynylmagnesium reagents were examined. The magnesium acetylides 5b and 5c, bearing a sterically bulky group and a siloxy group, respectively, reacted smoothly. However, 2-trimethylsilyl-phenylethynyl or phenylethynylmagnesium reagent provided none of the expected product and gave a mixture of the nonalkynylated cyclic product and starting material 1a. Treatment of 1c provided lactone 7 in 73% yield through cyclization/alkynylation followed by Jones oxidation.

**Conclusion**

NHC ligands 2a and 2d have emerged as irreplaceable ligands in cobalt-catalyzed sequential cyclization/coupling reactions. With the aid of the NHC ligands, the author has developed new and useful variants of sequential cyclization/coupling reactions of 6-halo-1-hexene derivatives.
with trialkysilylmethyl- and 1-alkynylmagnesium reagents.
Experimental Section

Instrumentation and Chemicals

$^1$H NMR (300 and 500 MHz) and $^{13}$C NMR (125.7 MHz) spectra were taken on Varian Mercury 300 and UNITY INOVA 500 spectrometers and were recorded in CDCl$_3$. Chemical shifts (δ) are in parts per million relative to CHCl$_3$ at 7.26 ppm for $^1$H and relative to CDCl$_3$ at 77.2 ppm for $^{13}$C unless otherwise noted. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck Silica gel 60F$_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. Mass spectrum was determined on a JEOL Mstation 700 spectrometer. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Anhydrous CoCl$_2$ was purchased from Wako Pure Chemicals and was used after removal of water. Specifically, in each experiment, CoCl$_2$ was dried in a reaction flask carefully under reduced pressure (0.5 torr) by heating with a hair dryer for 2 min immediately before use. SI$\text{Et}$-HCl (2a) and SI$\text{Mes}$-HCl (2b) were prepared according to the literature. Imidazolium salt 2c, IM$\text{Mes}$-HCl (2d) and IPr-HCl (2e) were purchased from Strem Chemicals. Trialkylsilylmethylmagnesium chloride was prepared from magnesium metal and the corresponding (chloromethyl)trialkylsilane in diethyl ether. Diethyl ether was purchased from Kanto Chemical Co., stored under nitrogen, and used as it is. $N,N,N',N'$-tetramethyl-trans-1,2-cyclohexanediamine was prepared according to the literature. Dioxane was dried over slices of sodium. All reactions were carried out under argon atmosphere.

General procedure for a cobalt/NHC-catalyzed sequential cyclization/coupling reaction of 6-halo-1-hexene derivatives with trialkylsilylmethylmagnesium chloride

The reaction of 1a with allyldimethylsilylmethylmagnesium chloride (Scheme 2) is representative. Anhydrous cobalt(II) chloride (3.2 mg, 0.025 mmol) was placed in a 20-mL
Chapter 1

reaction flask and was heated with a hair dryer in vacuo for 2 min. After the color of the cobalt salt became blue, anhydrous dioxane (2 mL), SiEt-HCl (2a, 9.3 mg, 0.025 mmol) and substrate 1a (182 mg, 0.50 mmol) were sequentially added under argon. Allyldimethylsilylmethylmagnesium chloride (1.0 M diethyl ether solution, 1.5 mL, 1.5 mmol) was then added over 5 s to the reaction mixture at 25 °C. While the organomagnesium reagent was being added, the mixture turned brown. After being stirred for 30 min at 25 °C, the reaction mixture was poured into a saturated ammonium chloride solution. The products were extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried over Na₂SO₄ and concentrated. Silica gel column purification (hexane/ethyl acetate = 10/1) of the crude product provided the corresponding cyclization/coupling product 3a (140 mg, 0.40 mmol) in 81% isolated yield.

**Oxidation of cyclization/coupling product 3a**

A solution of 3a (88 mg, 0.25 mmol) in CHCl₃ (5 mL) was placed in a 30-mL flask. Potassium hydrogenfluoride (82 mg, 1.05 mmol) and trifluoroacetic acid (0.09 mL, 1.25 mmol) were sequentially added to the reaction mixture. After being stirred for 18 h at room temperature, the solvent was evaporated under a reduced pressure to give a yellow oil. The crude product was dissolved in methanol-THF (8 mL, 1:1 mixture). Potassium hydrogen carbonate (115 mg, 1.15 mmol) and 30% H₂O₂ aq (0.52 mL) were successively added. After being stirred at room temperature for 18 h, the reaction mixture was poured into a saturated sodium thiosulfate solution. The product was extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried over Na₂SO₄ and concentrated. Purification by silica gel column chromatography (hexane/ethyl acetate = 1/1) provided the alcohol 4a (50 mg, 0.18 mmol) in 74% isolated yield.

**General procedure for a cobalt/NHC-catalyzed sequential cyclization/coupling reaction of 6-halo-1-hexene derivatives with 1-alkynylmagnesium reagent**
The reaction of 1a with 1-hexynylmagnesium bromide (Scheme 4) is representative.

**Preparation of 1-hexynylmagnesium bromide**

Isopropylmagnesium bromide (1.0 M diethyl ether solution, 1.25 mL, 1.25 mmol) was placed in a 30-mL reaction flask under argon. 1-Hexyne (134 mg, 1.63 mmol) was added, and the reaction mixture was stirred for 2 h at room temperature.

**A cobalt/NHC-catalyzed coupling reaction**

Anhydrous cobalt(II) chloride (3.2 mg, 0.025 mmol) was placed in a 20-mL reaction flask and was heated with a hair dryer in vacuo for 2 min. After the color of the cobalt salt became blue, anhydrous dioxane (1 mL) and IMes-HCl (2d, 8.5 mg, 0.025 mmol) were sequentially added under argon. Substrate 1a (91 mg, 0.25 mmol) was added. 1-Hexynylmagnesium bromide (1.0 M diethyl ether solution, 1.25 mL, 1.25 mmol) was then added over 5 s to the reaction mixture at 25 °C. While the organomagnesium reagent was being added, the mixture turned brown. After being stirred for 30 min at 25 °C, the reaction mixture was poured into a saturated ammonium chloride solution. The products were extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried over Na$_2$SO$_4$ and concentrated to provide a yellow oil. Silica gel column purification (hexane/ethyl acetate = 10/1) furnished 6a (64 mg, 0.20 mmol) in 80% isolated yield.

**Characterization Data**

The substrates 1a–1f were prepared according to the literature.$^{6a,6b,bg,10}$

1-(p-Toluenesulfonyl)-3-[2-(allyldimethylsilyl)ethyl]pyrrolidine (3a)

![Image of 3a](image-url)

oil. IR (neat) 663, 1099, 1162, 1248, 1346, 2916, 2952 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ –0.06 (s, 6H),
0.37–0.47 (m, 2H), 1.13–1.25 (m, 2H), 1.39 (m, 1H), 1.42–1.48 (dm, $J = 8.0$ Hz, 2H), 1.89–1.99 (m, 2H), 2.44 (s, 3H), 2.80 (dd, $J = 10.0, 7.5$ Hz, 1H), 3.20 (ddd, $J = 10.0, 8.5, 7.5$ Hz, 1H), 3.32 (ddd, $J = 10.0, 8.5, 4.5$ Hz, 1H), 3.43 (dd, $J = 10.0, 7.5$ Hz, 1H), 3.73 (dddd, $J = 17.5, 13.5, 9.5, 8.0$ Hz, 1H), 7.32–7.34 (dm, $J = 8.5$ Hz, 2H), 7.71–7.73 (dm, $J = 8.5$ Hz, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ –3.72 ($\times$ 2C), 13.36, 21.73, 23.20, 27.47, 31.25, 42.17, 47.79, 53.29, 113.13, 127.77, 129.80, 134.29, 135.02, 143.45; Found: C, 61.21; H, 8.09%. Calcd for C$_{18}$H$_{29}$NO$_2$Si: C, 61.49; H, 8.31%.

2-[1-(p-Toluenesulfonyl)-3-pyrrolidinyl]ethanol (4a)

![2-[1-(p-Toluenesulfonyl)-3-pyrrolidinyl]ethanol (4a)](image)

oil. IR (neat) 1043, 1160, 1340, 2880, 2930, 3566 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 1.41 (m, 1H), 1.52 (q, $J = 6.5$ Hz, 2H), 1.62 (br-s, 1H), 1.96 (m, 1H), 2.16 (septet, $J = 8.0$ Hz, 1H), 2.43 (s, 3H), 2.83 (t, $J = 9.0$ Hz, 1H), 3.17 (m, 1H), 3.36 (m, 1H), 3.46 (dd, $J = 10.0, 8.5$ Hz, 1H), 3.56–3.64 (m, 2H), 7.31–7.33 (dm, $J = 8.5$ Hz, 2H), 7.70–7.72 (dm, $J = 8.5$ Hz, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 21.72, 31.65, 35.88, 35.91, 47.62, 53.38, 61.42, 127.69, 129.84, 133.99, 143.58; Found: C, 58.12; H, 7.30%. Calcd for C$_{13}$H$_{19}$NO$_3$S: C, 57.97; H, 7.11%.

Allyl[2-(2,9-dioxa-4-bicyclo[4.3.0]nonanyl)ethyl]dimethylsilane (3b, Major isomer)

![Allyl[2-(2,9-dioxa-4-bicyclo[4.3.0]nonanyl)ethyl]dimethylsilane (3b, Major isomer)](image)

oil. IR (neat) 898, 1147, 1251, 1629, 1773, 2877, 2921 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ –0.01 (s, 6H), 0.41–0.54 (m, 2H), 1.28 (m, 1H), 1.34–1.40 (m, 2H), 1.51–1.53 (dm, $J = 8.5$ Hz, 2H), 1.50–1.63 (m, 3H), 1.97 (m, 1H), 2.73 (m, 1H), 3.62 (dd, $J = 10.5, 8.0$ Hz, 1H), 3.65 (m, 1H), 3.75 (m, 1H), 3.95 (t, $J = 8.0$ Hz, 1H), 4.81–4.86 (m, 2H), 5.28 (d, $J = 4.0$ Hz, 1H), 5.76 (dddd, $J = 18.5$, 16.5,
10.5, 8.5 Hz, 1H); $^{13}$C NMR (CDCl$_3$) δ –3.65 (× 2C), 13.62, 19.29, 21.29, 23.28, 23.49, 36.51, 44.57, 61.21, 70.20, 102.30, 113.14, 135.11; Found: C, 66.11; H, 10.51%. Calcd for C$_{14}$H$_{26}$O$_2$Si: C, 66.09; H, 10.30%.

**Allyl[2-(4-butoxy-2,2-dimethyl-3-oxacyclopentyl)ethyl]dimethylsilane (3c) (67:33 mixture of diastereomers)**

![Structure of 3c](image)

oil. IR (neat) 893, 1097, 1250, 1558, 2932, 2960 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ –0.01 (s, 6H), 0.40–0.60 (m, 2H), 0.91 (t, $J$ = 7.0 Hz, 3H), 1.01 (s, 0.67×3H), 1.13 (s, 0.33×3H), 1.14–1.21 (m, 1H), 1.23 (s, 0.33×3H), 1.32 (s, 0.67×3H), 1.33–1.41 (m, 4H), 1.49–1.64 (m, 4H), 1.72 (m, 0.33×1H), 2.04–2.11 (m, 0.67×2H), 2.45 (ddd, $J$ = 13.0, 8.0, 6.0 Hz, 0.33×1H), 3.30–3.37 (m, 1H), 3.64–3.72 (m, 1H), 4.81–4.85 (m, 2H), 4.95 (d, $J$ = 4.5 Hz, 0.67×1H), 5.04 (dd, $J$ = 6.0, 4.5 Hz, 0.33×1H), 5.77 (dddd, $J$ = 18.0, 16.5, 10.0, 8.0, Hz, 1H); $^{13}$C NMR (CDCl$_3$) δ –3.63 (× 2C), 14.11 (× 2C), 14.22, 14.30, 19.64, 19.66, 23.31, 23.33 (× 2C), 23.76, 24.22, 24.41, 28.51, 30.32, 32.14, 32.19, 39.33, 39.54, 49.23, 51.98, 66.68, 67.87, 82.92, 83.64, 102.01, 103.20, 113.01 (× 2C), 135.23 (× 2C); Found: C, 68.31; H, 11.45%. Calcd for C$_{17}$H$_{34}$O$_2$Si: C, 68.39; H, 11.48%.

**Allyl[2-(4-butoxy-2-pentyl-3-oxacyclopentyl)ethyl]dimethylsilane (3d) (54:46 mixture of diastereomers)**

![Structure of 3d](image)

oil. IR (neat) 893, 1097, 1250, 1458, 1631, 2957 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ –0.01 (s, 6H),
0.43–0.58 (m, 2H), 0.89–0.94 (m, 6H), 1.19 (m, 0.54×1H), 1.26–1.65 (m, 17H), 1.99 (m, 0.46×1H), 2.11 (dd, J = 17.5, 7.5 Hz, 0.54×1H), 2.27 (ddd, J = 13.0, 9.5, 5.5 Hz, 0.46×1H), 3.31–3.39 (m, 1H), 3.56–3.62 (m, 1H), 3.65–3.70 (m, 1H), 4.81–4.86 (m, 2H), 5.02 (d, J = 5.0 Hz, 0.54×1H), 5.07 (dd, J = 5.0, 2.5 Hz, 0.46×1H), 5.73–5.81 (m, 1H); ¹³C NMR (CDCl₃) δ −3.64 (× 2C), −3.62 (× 2C), 13.54, 13.60, 14.08, 14.12, 14.27, 14.30, 19.66, 19.69, 22.89 (× 2C), 22.31, 23.35, 26.26, 26.47, 27.38, 27.75, 32.11, 32.18, 32.19, 32.26, 34.89, 37.25, 39.59, 45.94, 47.04, 66.89, 67.26, 82.85, 85.58, 103.61, 103.71, 112.95, 113.00, 135.23, 135.29; Found: C, 70.54; H, 11.93%. Calcd for C₂₀H₄₀O₂Si: C, 70.52; H, 11.84%.

Allyl(2-cyclopentylethyl)dimethylsilane (3e)

oil. IR (neat) 893, 1150, 1250, 1630, 2910, 2952 cm⁻¹; ¹H NMR (CDCl₃) δ −0.02 (s, 6H), 0.50–0.55 (m, 2H), 1.03–1.10 (m, 2H), 1.25–1.31 (m, 2H), 1.46–1.62 (m, 6H), 1.67–1.78 (m, 3H), 4.80–4.86 (m, 2H), 5.79 (dddd, J = 18.0, 16.5, 10.0, 8.0 Hz, 1H); ¹³C NMR (CDCl₃) δ −3.59, 13.93, 23.44, 25.49, 30.22, 32.57, 43.59, 112.69, 135.59; Found: C, 73.38; H, 12.32%. Calcd for C₁₂H₂₄Si: C, 73.21; H, 12.16%.

1-(p-Toluenesulfonyl)-3-[2-(dimethylphenylsilyl)ethyl]pyrrolidine (3f)

oil. IR (neat) 815, 1113, 1163, 1345, 2919, 2953 cm⁻¹; ¹H NMR (CDCl₃) δ 0.22 (s, 6H), 0.61–0.69 (m, 2H), 1.17–1.27 (m, 2H), 1.35 (m, 1H), 1.89–1.98 (m, 2H), 2.44 (s, 3H), 2.77 (dd, J = 10.0, 7.5 Hz, 1H), 3.18 (ddd, J = 10.0, 8.5, 7.5 Hz, 1H), 3.31 (ddd, J = 10.0, 8.5, 4.0 Hz, 1H), 3.42 (dd, J = 10.0, 7.5 Hz, 1H), 7.31–7.33 (dm, J = 8.5 Hz, 2H), 7.34–7.37 (m, 3H), 7.45–7.47 (m,
2H), 7.70–7.72 (dm, J = 8.5 Hz, 2H); \(^{13}\)C NMR (CDCl\(_3\)) δ −3.14, −3.08, 14.32, 21.70, 27.45, 31.13, 42.05, 47.77, 53.22, 127.68, 127.97, 129.15, 129.77, 133.62, 134.00, 138.96, 143.44; Found: C, 65.08; H, 7.39%. Calcd for C\(_{21}\)H\(_{29}\)SNO\(_2\)Si: C, 65.07; H, 7.39%.

**Allyl(3-methylbutyl)dimethylsilane (3g)**

![Allyl(3-methylbutyl)dimethylsilane](image)

oil. IR (neat) 412, 1507, 1559, 2956, 3650, 3854 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) δ −0.03 (s, 6H), 0.47–0.51 (m, 2H), 0.86 (d, J = 11.5 Hz, 6H), 1.13–1.18 (m, 2H), 1.44 (m, 1H), 1.51 (td, J = 8.0, 1.0 Hz, 2H), 4.80–4.85 (m, 2H), 5.78 (ddt, J = 17.0, 10.0, 8.0 Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\)) δ −3.62 (× 2C), 12.37, 22.37 (× 2C), 23.43, 31.16, 32.98, 112.72, 135.56; HRMS (m/z) obsd 170.1490 (Δ = −0.7 ppm), calcd for C\(_{10}\)H\(_{22}\)Si 170.1491.

**1-(p-Toluenesulfonyl)-3-(2-heptynyl)pyrrolidine (6a)**

![1-(p-Toluenesulfonyl)-3-(2-heptynyl)pyrrolidine](image)

oil. IR (neat) 664, 1039, 1094, 1162, 1346, 2872, 2957 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) δ 0.89 (t, J = 7.5 Hz, 3H), 1.32–1.44 (m, 4H), 1.57 (m, 1H), 1.92 (m, 1H), 2.05–2.12 (m, 4H), 2.22 (septet, J = 7.0 Hz, 1H), 2.43 (s, 3H), 2.98 (dd, J = 10.0, 7.5 Hz, 1H), 3.23 (dt, J = 10.0, 8.5 Hz, 1H), 3.31 (m, 1H), 3.42 (dd, J = 10.0, 7.5 Hz, 1H), 7.31–7.33 (dm, J = 8.5 Hz, 2H), 7.71–7.73 (dm, J = 8.5 Hz, 2H); \(^{13}\)C NMR (CDCl\(_3\)) δ 13.77, 18.44, 21.70, 22.07, 22.17, 30.57, 31.17, 38.19, 47.60, 52.59, 77.11, 81.95, 127.74, 129.77, 133.81, 143.51; Found: C, 67.78; H, 8.06%. Calcd for C\(_{18}\)H\(_{25}\)NO\(_2\)S: C, 67.67; H, 7.89%.
1-(p-Toluenesulfonyl)-3-(4,4-dimethyl-2-pentynyl)pyrrolidine (6b)

white solid. IR (nujol) 665, 1160, 1340, 2854, 2923 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.12 (s, 9H), 1.57 (m, 1H), 1.90 (m, 1H), 2.05 (dd, \(J = 16.5, 7.0\) Hz, 1H), 2.10 (dd, \(J = 16.5, 6.0\) Hz, 1H), 2.22 (septet, \(J = 7.0\) Hz, 1H), 2.43 (s, 3H), 2.94 (dd, \(J = 10.0, 7.5\) Hz, 1H), 3.22–3.30 (m, 2H), 3.42 (dd, \(J = 10.0, 7.5\) Hz, 1H), 7.31–7.33 (dm, \(J = 8.5\) Hz, 2H), 7.71–7.72 (dm, \(J = 8.5\) Hz, 2H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 21.70, 21.96, 27.48, 30.45, 31.39, 38.16, 47.69, 52.51, 75.48, 90.83, 127.80, 129.82, 134.00, 143.52; Found: C, 67.38; H, 7.82%. Calcd for C\(_{18}\)H\(_{25}\)NO\(_2\)S: C, 67.67; H, 7.89%. m.p. 76–80 °C.

1-(p-Toluenesulfonyl)-3-[7-(trimethylsilyloxy)-2-heptynyl]pyrrolidine (6c)

oil. IR (neat) 664, 842, 1094, 1162, 1251, 1346, 2866, 2952 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 0.11 (s, 9H), 1.46–1.60 (m, 5H), 1.91 (m, 1H), 2.05–2.12 (m, 4H), 2.22 (septet, \(J = 7.0\) Hz, 1H), 2.43 (s, 3H), 2.97 (dd, \(J = 10.0, 7.5\) Hz, 1H), 3.22 (dt, \(J = 10.0, 7.5\) Hz, 1H), 3.31 (m, 1H), 3.41 (dd, \(J = 10.0, 7.5\) Hz, 1H), 3.58 (t, \(J = 6.0\) Hz, 2H), 7.31–7.33 (dm, \(J = 8.5\) Hz, 2H), 7.70–7.72 (dm, \(J = 8.5\) Hz, 2H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) –0.26, 18.66, 21.73, 22.32, 25.59, 30.71, 32.05, 38.31, 47.63, 52.68, 62.30, 77.48, 81.73, 127.81, 129.82, 134.13, 143.52; Found: C, 62.15; H, 8.22%. Calcd for C\(_{21}\)H\(_{33}\)NO\(_3\)Si: C, 61.87; H, 8.16%.

4-(2-Heptynyl)-4,5-dihydro-5,5-dimethylfuran-2(3H)one (7)
oil. IR (neat) 960, 1123, 1272, 1388, 1773, 2959 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 0.90 (t, \(J = 7.5\) Hz, 3H), 1.33 (s, 3H), 1.35–1.48 (m, 4H), 1.50 (s, 3H), 2.12–2.17 (m, 2H), 2.29 (dt, \(J = 6.5, 2.5\) Hz, 2H), 2.39–2.46 (m, 2H), 2.71 (q, \(J = 9.5\) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 13.77, 18.50, 19.79, 22.06, 22.15, 28.35, 31.10, 35.18, 44.62, 76.67, 82.79, 86.45, 175.32; Found: C, 74.70; H, 9.60%. Calcd for C\(_{13}\)H\(_{20}\)O\(_2\): C, 74.96; H, 9.68%.
References and Notes


(3) Kuno, A.; Saino, N.; Kamachi, T.; Okamoto, S. Tetrahedron Lett. 2006, 47, 2591–2594. In this report, a CoCl2/NHC system served as effectively as a Co(acac)3 catalyst without any additional ligands. No significant advantage of NHC in cobalt-catalyzed cross-coupling reactions was observed.


Chapter 2

Cobalt-Catalyzed Sequential Cyclization/Coupling Reactions of 6-Halo-4-oxa-3-sila-1-hexene Derivatives with Organomagnesium Reagents and Their Application to the Synthesis of 1,3-Diols

Cobalt/N-heterocyclic carbene or cobalt/diamine combination effectively catalyzes sequential cyclization/coupling reactions of 6-halo-4-oxa-3-sila-1-hexene derivatives with aryl- and trialkylsilylmethylmagnesium reagents. The sequential cyclization/coupling reactions are applied to the synthesis of 1,3-diols.
Introduction

1,3-Diol units are often observed in biologically active compounds, and can be oxidized into 1,3-diketones or naturally occurring polyketides. The synthesis of 1,3-diols is thus well explored.\textsuperscript{1} The significant importance of 1,3-diols prompted the author to apply the sequential cyclization/coupling reactions to the synthesis of 1,3-diols. In Chapter 2, he demonstrates the applications of cobalt-catalyzed sequential cyclization/coupling reactions of 6-halo-4-oxa-3-sila-1-hexene derivatives with aryl- and silylmethylmagnesium reagents to the synthesis of 1,3-diols. His approach to 1,3-diols starting from epoxides is outlined in Scheme 1. Ring-opening of epoxides with hydrogen iodide followed by silylation with chlorodimethylvinylsilane would provide siloxy-tethered\textsuperscript{2} 6-iodo-1-hexene derivatives. Then, cobalt-catalyzed sequential cyclization/coupling protocol would yield oxasilacyclopentanes. Finally, Tamao-Fleming oxidation\textsuperscript{3} would afford 1,3-diols with the substituent R\textsubscript{3} from the organomagnesium reagent employed.

Scheme 1.

\[ \text{R}^1\text{R}^2\text{O} \xrightarrow{\text{HI}} \text{R}^1\text{R}^2\text{I} \xrightarrow{\text{ClSi}} \text{R}^1\text{R}^2\text{SiMe}_2 \xrightarrow{\text{XMg-R}^3} \text{R}^1\text{R}^2\text{SiMe}_2\text{R}^3 \xrightarrow{\text{H}_2\text{O}_2} \text{R}^1\text{R}^2\text{OH} \]

Results and Discussion

The author chose cyclohexene oxide as a starting material. Cyclohexene oxide underwent ring-opening by the action of lithium iodide and acetic acid in THF to give 2-iodo-1-cyclohexanol.\textsuperscript{4} Treatment of the crude \textit{vic}-iodohydrin with chlorodimethylvinylsilane in the presence of triethylamine in dichloromethane provided siloxy-tethered substrate 1a quantitatively.
Table 1. Cobalt/diamine-catalyzed sequential cyclization/coupling reaction of siloxy-tethered 6-iodo-1-hexene with arylmagnesium reagents

<table>
<thead>
<tr>
<th>entry</th>
<th>BrMg–Ar</th>
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<th>5</th>
<th>yield (%)</th>
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<td>5b</td>
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<td>3e</td>
<td>5e</td>
<td>44</td>
</tr>
</tbody>
</table>

\(^a\) rac-N,N,N',N'-Tetramethyl-trans-1,2-cyclohexanediamine.

Silicon-tethered 6-iodo-1-hexene derivative 1a was employed for the reaction with arylmagnesium reagent in the presence of cobalt/diamine catalyst (Table 1).\(^5\) Treatment of 1a with phenylmagnesium bromide (3a) in THF in the presence of rac-N,N,N',N'-tetramethyl-trans-1,2-cyclohexanediamine (2) and CoCl\(_2\) afforded the corresponding benzylated cyclic product 4a in good yield. The oxasilacyclopentane 4a was converted to 4-aryl-1,3-butanediol 5a efficiently upon treatment with hydrogen peroxide in the presence of potassium fluoride and potassium hydrogencarbonate.

A series of arylmagnesium reagents were examined. All of the corresponding products were
subjected to oxidation with alkaline hydrogen peroxide to yield diols in good yields. Not only phenylmagnesium bromide but also o-tolylmagnesium bromide, 4-methoxyphenyl-, and 3-trifluoromethylphenylmagnesium bromides could participate in the reaction efficiently. The cyclization/arylation with 2-naphthylmagnesium reagent also proceeded smoothly. Methyl substitution at the 2-position did not retard the reaction. However, mesitylmagnesium reagent was not applicable. Products 5a–5e were always 1:1 mixtures of diastereomers, which originate from the relationship between the cis-fused bicyclic system and arylmethyl group. This arylation–oxidation sequence could be effectively applied to iodides 1b and 1c, and the corresponding diols 7a and 9a were obtained in good yields. (Schemes 2 and 3).

Next, the cyclization/coupling reaction of the siloxy-tethered substrates with dimethylphenylsilylmethylmagnesium chloride has been examined (Table 2). The cobalt/NHC-catalyzed reaction of 1a with dimethylphenylsilylmethylmagnesium chloride afforded the corresponding cyclization/coupling product 10a, which could be easily transformed into 5-silyl-1,3-pentanediol 11a upon treatment with alkaline hydrogen peroxide. Other siloxy-tethered substrates 1b and 1c were examined. The reaction of iodide 1b having
five-membered ring afforded 11b with slight diastereoselectivity. The primary alkyl iodide 1c served as a substrate to provide diol 11c in 54% overall yield. These products 11a–c could be precursors of 1,3,5-triol and related compounds.

**Table 2.** Cobalt/NHC-catalyzed sequential cyclization/coupling reaction of siloxy-tethered 6-iodo-1-hexene with silylmethylmagnesium reagent

<table>
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<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>yield of 11 %</th>
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<tr>
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<tr>
<td>2</td>
<td>1b</td>
<td>11b</td>
<td>65 (67/33)</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>11c</td>
<td>54 (50/50)</td>
</tr>
</tbody>
</table>
Chapter 2

**Conclusion**

The cobalt-catalyzed sequential cyclization/coupling reaction of 6-halo-4-oxa-3-sila-1-hexane derivatives with trialkylsilylmethyl- and arylmagnesium reagents could be applied effectively to the construction of 1,3-diol units.
Experimental Procedure

Instrumentation and Chemicals

$^1$H NMR (300 and 500 MHz) and $^{13}$C NMR (125.7 MHz) spectra were taken on Varian Mercury 300 and UNITY INOVA 500 spectrometers and were recorded in CDCl$_3$ or C$_6$D$_6$. Chemical shifts (δ) are in parts per million relative to CHCl$_3$ at 7.26 ppm or C$_6$H$_6$ at 7.16 ppm for $^1$H and relative to CDCl$_3$ at 77.2 ppm or C$_6$D$_6$ at 128.4 ppm for $^{13}$C unless otherwise noted. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck Silica gel 60F$_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Anhydrous CoCl$_2$ was purchased from Wako Pure Chemicals and was used after removal of water. Specifically, in each experiment, CoCl$_2$ was dried in a reaction flask carefully under reduced pressure (0.5 torr) by heating with a hair dryer for 2 min just before use. SIEt·HCl was prepared according to the literature. Trialkylsilylmethylmagnesium chloride was prepared from magnesium metal and the corresponding (chloromethyl)trialkylsilane in diethyl ether. Diethyl ether was purchased from Kanto Chemical Co., stored under nitrogen, and used as it is. rac-$N,N,N',N'$-Tetramethyl-trans-1,2-cyclohexanediame was prepared according to the literature. Arylmagnesium bromide was prepared from magnesium metal and the corresponding bromoarene in THF. THF was purchased from Kanto Chemical Co., stored under nitrogen, and used as it is. Dioxane was dried over slices of sodium. All reactions were carried out under argon atmosphere.

General procedure for a cobalt/diamine-catalyzed sequential cyclization/coupling reaction of 6-iodo-4-oxa-3-sila-1-hexene derivative with arylmagnesium reagents

The reaction of 1a with phenylmagnesium bromide (Table 1, entry 1) is representative. Anhydrous cobalt(II) chloride (3.2 mg, 0.025 mmol) was placed in a 20-mL reaction flask and
was heated with a hair dryer in vacuo for 2 min. After the color of the cobalt salt became blue, anhydrous THF (3 mL) and \textit{rac-}N,N,N',N'-tetramethyl-\textit{trans}-1,2-cyclohexanediamine (20 mg, 0.12 mmol) were sequentially added under argon. The mixture was stirred for 3 min. 6-Halo-4-oxa-3-sila-1-hexene derivative \textit{1a} (155 mg, 0.5 mmol) was added. Phenylmagnesium bromide (1.0 M THF solution, 0.75 mL, 0.75 mmol) was then added over 5 s to the reaction mixture at 25 °C. While the organomagnesium reagent was being added, the mixture turned brown. After being stirred for 15 min at 25 °C, the reaction mixture was poured into a saturated ammonium chloride solution. The products were extracted with hexane (20 mL × 2). The combined organic layer was dried over Na₂SO₄ and concentrated to provide a yellow oil. The \textit{1}H NMR analysis with dibromomethane as an internal standard indicated formation of the desired oxasilacyclopentane \textit{4a} in 93% yield. Potassium fluoride (58 mg, 1.0 mmol) and potassium hydrogen carbonate (100 mg, 1.0 mmol) were dissolved in methanol-THF (5 mL, 1:1 mixture). The crude product and 30% H₂O₂ aq (0.52 mL) were successively added. After being stirred at room temperature for 12 h, the reaction mixture was poured into a saturated sodium thiosulfate solution. The product was extracted with ethyl acetate (20 mL × 2). The combined organic layer was dried over Na₂SO₄ and concentrated. Purification by silica gel column chromatography (hexane/ethyl acetate = 2/1) provided 4-phenyl-1,3-butanediol \textit{5a} (81 mg, 0.37 mmol) in 74% isolated yield.

**General procedure for a cobalt/NHC-catalyzed cyclization/coupling reaction of 6-iodo-4-oxa-3-sila-1-hexene derivative with dimethylphenylsilylmethylmagnesium chloride**

The reaction of \textit{1a} with dimethylphenylsilylmethylmagnesium chloride (Table 2, entry 1) is representative. Anhydrous cobalt(II) chloride (3.2 mg, 0.025 mmol) was placed in a 20-mL reaction flask and was heated with a hair dryer in vacuo for 2 min. After the color of the cobalt salt became blue, anhydrous dioxane (2 mL), SIE₅-HCl (9.3 mg, 0.025 mmol) and substrate \textit{1a} (155 mg, 0.50 mmol) were sequentially added under argon. Dimethylphenylsilylmethylmagnesium chloride (1.0 M diethyl ether solution, 1.5 mL, 1.5 mmol)
was then added over 5 s to the reaction mixture at 25 °C. While the organomagnesium reagent was being added, the mixture turned brown. After being stirred for 30 min at 25 °C, the reaction mixture was poured into a saturated ammonium chloride solution. The products were extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried over Na₂SO₄ and concentrated to provide a crude oil. The ¹H NMR analysis of this oil indicated formation of the desired oxasilacyclopentane derivative 10a. Potassium fluoride (58 mg, 1.0 mmol) and potassium hydrogen carbonate (100 mg, 1.0 mmol) were dissolved in methanol-THF (5 mL, 1:1 mixture). The crude product and 30% H₂O₂ aq (0.52 mL) were successively added. After being stirred at room temperature for 12 h, the reaction mixture was poured into a saturated sodium thiosulfate solution. The product was extracted with ethyl acetate (20 mL × 2). The combined organic layer was dried over Na₂SO₄ and concentrated. Silica gel column purification (hexane/ethyl acetate = 2/1) of the crude product provided diol 11a (74 mg, 0.25 mmol) in 51% isolated yield.

**Characterization Data**

The elemental analyses of 5c–e are not described here. The elemental analyses of 5c–e were carried out after converting them to the corresponding diacetates. To obtain the diacetates, the diols were subjected to the standard acetylation conditions (Ac₂O, pyridine, DMAP).

**2-Iodocyclohexyloxy)dimethylvinylsilane (1a)**

![2-Iodocyclohexyloxy)dimethylvinylsilane (1a)](image)

oil. IR (neat) 785, 837, 877, 973, 1109, 1250, 2936 cm⁻¹; ¹H NMR (300 MHz, C₆D₆) δ 0.26 (s, 3H), 0.28 (s, 3H), 0.76–1.20 (m, 4H), 1.48 (m, 1H), 1.74 (m, 1H), 1.87 (dm, 1H), 2.14 (dm, 1H), 3.86 (td, J = 8.7, 3.9 Hz, 1H), 3.87 (m, 1H), 5.78 (dd, J = 20.1, 3.9 Hz, 1H), 5.95 (dd, J = 15.0, 3.9 Hz, 1H), 6.26 (dd, J = 20.1, 15.0 Hz, 1H); ¹³C NMR (C₆D₆) δ −1.14, −0.94, 24.05, 27.43, 35.30, 38.10, 39.72, 76.46, 133.39, 138.11; Found: C, 38.83; H, 6.10%. Calcd for C₁₀H₁₅OSi:
C, 38.71; H, 6.17%.

2-(1-Hydroxy-2-phenylethyl)cyclohexanol (5a) (50:50 mixture of diastereomers)

\[
\text{OH} \\
\text{CH}_2\text{OH}
\]

white solid. IR (nujol) 743, 973, 2924, 3345 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.21–1.32 (m, 1H), 1.32–1.52 (m, 0.5 \times 7H), 1.56–1.87 (m, 0.5 \times 9H), 2.23–2.29 (br-s, 2H), 2.71–2.94 (m, 2H), 3.86 (m, 0.5 \times 1H), 4.04–4.08 (m, 1H), 4.40 (m, 0.5 \times 1H), 7.20–7.35 (m, 5H); \(^1\)C NMR (CDCl\(_3\)) \(\delta\) 18.63, 19.97, 20.35, 25.00, 25.83, 25.88, 33.23, 33.87, 41.38, 41.97, 44.23, 44.77, 67.40, 72.43, 76.59, 77.62, 126.66, 126.75, 128.82, 128.88, 129.44, 129.50, 138.82, 138.83; Found: C, 76.13; H, 9.24%. Calcd for C\(_{14}\)H\(_{20}\)O\(_2\): C, 76.33; H, 9.15%. m.p. 69–72 °C.

2-[1-Hydroxy-2-(2-naphthyl)ethyl]cyclohexanol (5b) (50:50 mixture of diastereomers)

\[
\text{OH} \\
\text{CH}_2\text{OH}
\]

white solid. IR (nujol) 823, 972, 1520, 1600, 3340 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 1.20–1.32 (m, 1H), 1.37–1.52 (m, 0.5 \times 7H), 1.61–1.89 (m, 0.5 \times 9H), 2.58 (br-s, 0.5 \times 1H), 2.85 (br-s, 0.5 \times 1H), 2.94 (s, 0.5 \times 1H), 3.00 (br-s, 0.5 \times 1H), 2.88–3.08 (m, 2H), 3.94 (m, 0.5 \times 1H), 4.06 (m, 0.5 \times 1H), 4.13 (m, 0.5 \times 1H), 4.42 (m, 0.5 \times 1H), 7.34–7.37 (m, 1H), 7.42–7.49 (m, 2H), 7.66 (s, 0.5 \times 1H), 7.68 (s, 0.5 \times 1H), 7.79–7.82 (m, 3H); \(^1\)C NMR (CDCl\(_3\)) \(\delta\) 18.71, 19.98, 20.38, 25.04, 25.82, 25.91, 33.24, 33.86, 41.51, 42.16, 44.26, 44.83, 67.45, 72.40, 77.36, 77.46, 125.67, 125.71, 126.28, 126.32, 127.70 (\(\times\) 2C), 127.80, 127.82 (\(\times\) 3C), 127.91, 128.00, 128.45, 128.50, 132.43, 132.46, 133.76 (\(\times\) 2C), 136.40, 136.45; Found: C, 79.72; H, 8.26%. Calcd for C\(_{18}\)H\(_{22}\)O\(_2\): C,
79.96; H, 8.20%. m.p. 84.6–87.8 °C.

2-[1-Hydroxy-2-(2-methylphenyl)ethyl]cyclohexanol (5c) (50:50 mixture of diastereomers)

Diacetate of 5c (50:50 mixture of diastereomers)
for $C_{19}H_{26}O_5$: C, 71.67%; H, 8.23%.

2-[1-Hydroxy-2-(4-methoxyphenyl)ethyl]cyclohexanol (5d) (50:50 mixture of diastereomers)

2-[1-Hydroxy-2-(4-methoxyphenyl)ethyl]cyclohexanol (5d) (50:50 mixture of diastereomers)

Diacetate of 5d (50:50 mixture of diastereomers)
7.84%.

2-(1-Hydroxy-2-[3-(trifluoromethyl)phenyl]ethyl)cyclohexanol (5e) (50:50 mixture of diastereomers)

![Chemical Structure](image)

oil. IR (neat) 702, 800, 1075, 2862, 2931, 3229 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.24–1.90 (m, 9H), 2.28 (br-s, 2H), 2.77–2.97 (m, 2H), 3.87 (m, 0.5×1H), 4.08 (m, 0.5×1H), 4.12 (m, 0.5×1H), 4.41 (m, 0.5×1H), 7.44–7.45 (m, 2H), 7.50–7.55 (m, 2H); ¹³C NMR (CDCl₃) δ 18.70, 19.91, 20.29, 24.90, 25.70, 25.80, 33.36, 34.07, 41.11, 41.77, 44.73, 44.94, 67.59 (× 2C), 72.48, 76.24, 123.29, 123.45 (q, J = 3.9 Hz), 123.51 (q, J = 3.9 Hz), 124.37 (q, J = 272.1 Hz, × 2C), 126.10 (q, J = 3.9 Hz), 126.18 (q, J = 3.9 Hz), 129.09 (× 2C), 130.97 (q, J = 31.7 Hz, × 2C), 132.88, 132.99, 140.19, 140.31.

Diacetate of 5e (50:50 mixture of diastereomers)

![Chemical Structure](image)

oil. IR (neat) 658, 705, 1023, 1074, 1124, 1163, 1201, 1245, 1329, 1363, 1448, 1734, 2938 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.22–1.96 (m, 9H), 1.86 (s, 0.5×3H), 1.91 (s, 0.5×3H), 2.00 (s, 0.5×3H), 2.11 (s, 0.5×3H), 2.73 (dd, J = 14.0, 8.5 Hz, 1H), 3.08 (dd, J = 14.0, 3.5 Hz, 1H), 4.96–5.04 (m, 1H), 5.12 (dm, J = 2.0 Hz, 0.5×1H), 5.26 (dm, J = 2.0 Hz, 0.5×1H), 7.32–7.41 (m, 3H), 7.45–7.48 (m, 1H); ¹³C NMR (CDCl₃) δ 20.17, 20.39, 20.82, 20.92, 21.41, 21.47, 23.60, 24.07, 25.30 (× 2C), 30.07, 30.50, 38.21, 38.36, 43.67, 44.09, 68.05, 69.83, 73.51, 75.18, 123.55
(q, J = 3.9 Hz), 123.59 (q, J = 3.9 Hz), 125.34 (q, J = 272.1 Hz, × 2C), 126.49 (q, J = 3.9 Hz), 126.66 (q, J = 3.9 Hz), 128.91, 128.98, 130.67 (q, J = 3.9 Hz), 132.94, 133.08, 170.18, 170.30, 170.84, 170.90;  Found: C, 61.53; H, 6.30%.  Calcd for C_{19}H_{23}F_{3}O_{4}: C, 61.28; H, 6.23%.

(2-Iodocyclopentyloxy)dimethylvinylsilane (1b)

oil. IR (neat) 698, 787, 836, 884, 959, 1017, 1074, 1252, 1407, 2958 cm\(^{-1}\); \(^1\)H NMR (300 MHz, C\(_6\)D\(_6\)) \(\delta\) 0.14 (s, 3H), 0.15 (s, 3H), 1.38–1.57 (m, 3H), 1.78–1.95 (m, 2H), 2.08 (m, 1H), 3.96 (m, 1H), 4.43 (m, 1H), 5.71 (dd, J = 20.1, 3.9 Hz, 1H), 5.91 (dd, J = 14.7, 3.9 Hz, 1H), 6.12 (dd, J = 20.1, 3.9 Hz, 1H); \(^{13}\)C NMR (C\(_6\)D\(_6\)) \(\delta\) –1.16, –1.15, 22.80, 32.78, 34.85, 36.39, 83.23, 133.76, 138.08;  Found: C, 36.27; H, 5.48%.  Calcd for C\(_9\)H\(_{17}\)OSiI: C, 36.49; H, 5.78%.

2-(1-Hydroxy-2-phenylethyl)cyclopentanol (7a) (67:33 mixture of diastereomers)

white solid. IR (nujol) 3334 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.60–2.05 (m, 7H), 2.72–3.01 (m, 4H), 3.98 (td, J = 8.1, 3.9 Hz, 0.33×1H), 4.32 (m, 0.67×1H), 4.28–4.38 (m, 0.67×1H), 4.50 (m, 0.33×1H), 7.23–7.38 (m, 5H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 21.50, 22.08, 22.73, 26.72, 35.15, 36.17, 43.02, 43.31, 47.53, 50.18, 73.08, 73.90, 74.38, 77.17, 126.59, 126.74, 128.74, 128.82, 129.44, 129.59, 138.64, 138.80;  Found: C, 75.40; H, 8.76%.  Calcd for C\(_{13}\)H\(_{18}\)O\(_2\): C, 75.69; H, 8.79%.

[1-(Iodomethyl)heptyloxy]dimethylvinylsilane (1c)

Chapter 2
oil. IR (neat) 786, 813, 837, 959, 1010, 1045, 1251, 2929 cm\(^{-1}\); \(^1\)H NMR (500 MHz, \(\text{C}_6\text{D}_6\)) \(\delta\) 0.18 (s, 3H), 0.19 (s, 3H), 0.89 (t, \(J = 7.0\) Hz, 3H), 1.16–1.27 (m, 8H), 1.47–1.49 (m, 2H), 2.96 (d, \(J = 5.5\) Hz, 2H), 3.45 (m, 1H), 5.73 (dd, \(J = 20.5, 4.0\) Hz, 1H), 5.91 (dd, \(J = 15.0, 4.0\) Hz, 1H), 6.16 (dd, \(J = 20.0, 4.5\) Hz, 1H); \(^{13}\)C NMR (\(\text{C}_6\text{D}_6\)) \(\delta\) –0.88 (\(\times 2\)C), 14.33, 14.68, 23.35, 25.85, 29.89, 32.48, 37.62, 72.66, 133.68, 138.37; Found: C, 42.17; H, 7.38%. Calcd for \(\text{C}_{12}\text{H}_{25}\text{OSiI}\): C, 42.35; H, 7.40%.

1-Phenyldecane-2,4-diol (9a) (50:50 mixture of diastereomers)

white solid. IR (nujol) 3391 cm\(^{-1}\); \(^1\)H NMR (300 MHz, \(\text{CDCl}_3\)) \(\delta\) 0.88–0.92 (m, 3H), 1.29–1.60 (m, 10H), 1.66–1.72 (m, 2H), 2.42 (br-s, 2H), 2.76–2.82 (m, 2H), 3.84 (m, 0.5\(\times\)1H), 3.98 (m, 0.5\(\times\)1H), 4.11 (m, 0.5\(\times\)1H), 4.19 (m, 0.5\(\times\)1H), 7.21–7.35 (m, 5H); \(^{13}\)C NMR (\(\text{CDCl}_3\)) \(\delta\) 14.27 (\(\times 2\)C), 22.78 (\(\times 2\)C), 25.48, 25.90, 29.46 (\(\times 2\)C), 31.98 (\(\times 2\)C), 37.63, 38.25, 42.04, 42.53, 44.22, 44.82, 69.51, 70.42, 73.09, 74.18, 126.75, 126.77, 128.80, 128.81, 129.55, 129.62, 138.12, 138.46; Found: C, 76.49; H, 10.23%. Calcd for \(\text{C}_{16}\text{H}_{26}\text{O}_2\): C, 76.75; H, 10.47%.

2-(3-(Dimethylphenylsilyl)-1-hydroxypropyl)cyclohexanol (11a) (50:50 mixture of diastereomers)

oil. IR (neat) 700, 837, 1114, 1248, 1427, 2859, 2931, 3337 cm\(^{-1}\); \(^1\)H NMR (500 MHz, \(\text{CDCl}_3\))
δ 0.27 (s, 3H), 0.28 (s, 3H), 0.61–0.69 (m, 1H), 0.83 (td, J = 13.0, 4.5 Hz, 0.5×1H), 0.91 (m, 0.5×1H), 1.16–1.89 (m, 1H), 2.50 (br-s, 0.5×1H), 2.67 (br-s, 0.5×1H), 2.74 (br-s, 0.5×1H), 2.81 (br-s, 0.5×1H), 3.50 (br-s, 0.5×1H), 3.70 (m, 0.5×1H), 4.05 (br-s, 0.5×1H), 4.22 (br-s, 0.5×1H), 7.35–7.36 (m, 3H), 7.49–7.52 (m, 2H); ¹³C NMR (CDCl₃) δ −3.02, −2.97, −2.91, −2.87, 11.85, 12.04, 18.23, 20.02, 20.44, 25.05, 25.93, 25.97, 29.03, 29.40, 33.40, 34.05, 43.98, 44.16, 67.46, 72.65, 78.04, 79.14, 128.01, 128.02, 129.16 (× 2C), 133.74 (× 2C), 139.24 (× 2C); Found: C, 69.81; H, 9.84%. Calcd for C₁₇H₂₈O₂Si: C, 69.81; H, 9.65%.

2-(3-(Dimethylphenylsilyl)-1-hydroxypropyl)cyclopentanol (11b)

(Major isomer)
¹H NMR (500 MHz, CDCl₃) δ 0.28 (s, 6H), 0.67 (ddd, J = 14.0, 13.0, 4.5 Hz, 1H), 0.88 (ddd, J = 14.0, 13.0, 4.5 Hz, 1H), 1.40–1.88 (m, 9H), 2.44 (br-s, 1H), 2.83 (br-s, 1H), 3.97 (m, 1H), 4.30 (m, 1H), 7.34–7.36 (m, 3H), 7.50–7.52 (m, 2H); ¹³C NMR (C₆D₆) δ −3.00, −2.88, 11.98, 21.22, 22.06, 30.82, 36.22, 47.95, 74.42, 77.37, 128.00, 129.13, 133.76, 139.32. Found: C, 69.13; H, 9.28%. Calcd for C₁₆H₂₆O₂Si: C, 69.01; H, 9.41%.

(Minor isomer)
¹H NMR (500 MHz, C₆D₆) δ 0.28 (s, 6H), 0.72 (ddd, J = 14.0, 13.0, 4.5 Hz, 1H), 0.97 (ddd, J = 14.0, 13.0, 4.5 Hz, 1H), 1.45–1.86 (m, 9H), 2.19 (br-s, 1H), 2.24 (br-s, 1H), 3.64 (m, 1H), 4.40 (m, 1H), 7.34–7.36 (m, 3H), 7.50–7.52 (m, 2H); ¹³C NMR (C₆D₆) δ −2.92, −2.89, 11.37, 22.66, 26.57, 30.80, 35.36, 50.06, 74.54, 75.09, 128.02, 129.15, 133.76, 139.29.

1-[Dimethylphenylsilyl]undecane-3,5-diol (11c) (50:50 mixture of diastereomers)
oil. IR (neat) 700, 837, 1114, 1248, 1427, 2856, 2928, 3347 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.28 (s, 6H), 0.64–0.72 (m, 1H), 0.81–0.89 (m, 4H), 1.28–1.63 (m, 14H), 2.18 (br-s, 1H), 2.26 (br-s, 1H), 3.75 (m, 0.5×1H), 3.79–3.84 (m, 1H), 3.89 (m, 0.5×1H), 7.33–7.39 (m, 3H), 7.49–7.52 (m, 2H); ¹³C NMR (CDCl₃) δ –3.00 (× 2C), –2.97, –2.93, 11.28, 11.70, 14.29 (× 2C), 22.81 (× 2C), 25.51, 25.96, 29.51 (× 2C), 31.81, 32.02 (× 2C), 32.49, 37.69, 38.47, 41.85, 42.42, 69.67, 71.87, 73.38, 75.62, 128.01 (× 2C), 129.16 (× 2C), 133.75 (× 2C), 139.18 (× 2C); Found: C, 70.93; H, 10.89%. Calcd for C₁₉H₃₄O₂Si: C, 70.75; H, 10.62%.
References and Notes


Silver-Catalyzed Coupling Reactions of Tertiary and Secondary Alkyl Halides with Benzyl and Allylmagnesium Reagents

Treatment of alkyl halides, including tertiary alkyl bromides, with benzylic and allylic organomagnesium reagents in the presence of a catalytic amount of AgNO₃ in Et₂O yielded the corresponding coupling products in high yields. The coupling reactions of tertiary alkyl halides provide an efficient access to quaternary carbon centers.
**Introduction**

Recent researches in transition-metal-catalyzed coupling reactions pursue much wider scope for establishing universal coupling methodology and new catalysts that exhibit extremely high catalytic activity and/or unique reactivity. Among them, replacement of palladium and nickel catalysts by other transition metal catalysts has been attracting increasing attention. The replacement does not only offer economical and environmental advantages but also results in discovery of new reactivity. The success of copper, manganese, cobalt, and iron catalysts in the coupling reactions prompted the author to survey other transition metals further, the catalytic performance of which remains unexplored in the field of the coupling reactions. In Chapter 3, he shows that silver salts can efficiently catalyze coupling reactions of alkyl halides including tertiary alkyl halides with benzyl and allylmagnesium reagent (Scheme 1). Use of tertiary alkyl halides as a coupling partner is still challenging and has to be established.

**Scheme 1.**

![Scheme 1](image)

**Results and Discussion**

Treatment of 2-methyl-2-bromodecane (1a) with benzylmagnesium bromide in the presence of a catalytic amount of AgNO₃ in Et₂O afforded coupling product 2a in high yield (Table 1, entry 1). The silver-catalyzed benzylation features facile creation of quaternary carbon centers (entries 1–6). Tertiary alkyl chloride 1b reacted smoothly in refluxing Et₂O (entry 2). Tertiary alkyl iodide was likely to be too reactive under the reaction conditions (entry 3). The reaction of 1-bromoadamantane (1d) was slow, and the completion of the reaction took 24 h (entry 4). The reaction of 1e was not stereospecific (entry 5), which is highly suggestive of the existence of an intermediate having an sp³-hybridized carbon center. Proper protective groups such as a benzyloxy group were compatible under the highly basic conditions (entry 6). The conversions of the tertiary alkyl halides were quantitative, and the byproducts were the corresponding alkenes and alkanes.
**Table 1.** Silver-catalyzed coupling reaction of alkyl halides with benzylmagnesium reagent

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<tr>
<th>Entry</th>
<th>R–X</th>
<th>1</th>
<th>cat. /mol%</th>
<th>2</th>
<th>Yield /%</th>
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<td>nC₆H₁₇Br</td>
<td>1a</td>
<td>1.0</td>
<td>2a</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>nC₆H₁₇Cl</td>
<td>1b</td>
<td>1.0</td>
<td>2a</td>
<td>66ᵇ</td>
</tr>
<tr>
<td>3</td>
<td>I</td>
<td>1c</td>
<td>1.0</td>
<td>2b</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>nC₆H₁₃Br</td>
<td>1d</td>
<td>1.0</td>
<td>2c</td>
<td>80ᶜ</td>
</tr>
<tr>
<td>5</td>
<td>Br</td>
<td>1eᵈ</td>
<td>1.0</td>
<td>2d</td>
<td>81ᵉ</td>
</tr>
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<td>6</td>
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<td>2e</td>
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<td>77</td>
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<td>nC₇H₁₅I</td>
<td>1k</td>
<td>2.5</td>
<td>2h</td>
<td>32</td>
</tr>
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</table>

ᵃ Conditions: 1 (0.50 mmol), benzylmagnesium bromide (0.65 mmol, 1.0 M in Et₂O), Et₂O (2 mL).ᵇ Performed in refluxing Et₂O for 10 h.ᶜ Performed for 24 h.ᵈ cis/trans = 81/19.ᵉ cis/trans = 34/66.ᶠ Performed in refluxing Et₂O for 4 h.
Secondary alkyl bromides and iodide underwent the benzylation, although a higher catalyst loading was necessary (entries 7–9). The reaction of primary alkyl halides suffered from low yields (entries 10 and 11). Secondary and primary alkyl chlorides resisted the reaction.

A benzylic organomagnesium reagent having a methyl group at the ortho position reacted with tertiary alkyl bromide $1a$ smoothly to yield $2i$ in good yield (Scheme 2). Methoxy and fluoro groups did not retard the reaction significantly. The steric as well as electronic factor of the benzylic organomagnesium reagents is thus moderate. Under similar reaction conditions, attempted phenylation, methylation, and butylation failed to afford the corresponding coupling products.

**Scheme 2.**

$$
\begin{align*}
\text{nC}_8\text{H}_17\text{Br} & \quad \text{BrMg}_{\quad} & \quad 1.3 \text{ equiv} & \quad \text{1 mol}\% \text{ AgNO}_3 \\
& & & \text{Et}_2\text{O, 25 °C} & \quad 3 \text{ h} \\
\text{nC}_8\text{H}_17 & \quad \text{nC}_8\text{H}_17 & \quad \text{nC}_8\text{H}_17 \\
2i & \quad 76\% & \quad 2j & \quad 55\% & \quad 2k & \quad 56\%
\end{align*}
$$

Compared with a previously reported cobalt-catalyzed coupling reaction of alkyl halides with benzylmagnesium bromide,$^7b$ the present silver-catalyzed reaction is much more efficient in terms of catalyst loading, reactivity, yield, and scope of the substrates. For instance, the cobalt-catalyzed coupling reaction was not useful for benzylation of tertiary alkyl halides.

Treatment of a mixture of tertiary alkyl bromide $1a$ (0.50 mmol) and secondary alkyl bromide $1i$ (0.50 mmol) with benzylmagnesium bromide (0.30 mmol) in the presence of AgNO$_3$ afforded 0.25 mmol of $2a$ and 0.03 mmol of $2g$ (Scheme 3). The predominant conversion of $1a$ suggests that the reaction would include generation of an $sp^2$-hybridized carbon center from $1$. Furthermore, the silver-catalyzed benzylation reactions of *exo-* and *endo-*bromonorbornanes (*exo* and *endo*-11) yielded $2l$ with the same *exolendo* selectivity (Scheme 4), which indicates the existence of a planar carbon center with no original stereochemical information.
When (2-iodocyclohexyloxy)vinylsilane 3 was subjected to the silver-catalyzed benzylation reaction, bicyclic compound 4 was obtained (Scheme 5). Since 4 readily underwent hydrolysis and 4 was hence difficult to handle, 4 was converted to diacetate 5 by Tamao-Fleming oxidation followed by acetylation. Although the yield of 5 was low, the formation of 5 suggests that the silver-catalyzed benzylation reaction would proceed via radical intermediates 6 and 7, not via cationic ones.12

The author proposes a draft mechanism shown in Scheme 6. Formation of electron-rich silver(0)-ate complex13 initially takes place through the reaction of AgNO₃ with two equivalents of benzylmagnesium bromide (A). The ate complex effects a single electron transfer to alkyl halide to form the corresponding alkyl radical as cobalt- and manganese-ate complexes do (B).3b,14 The radical is trapped by benzylsilver(I) to yield an oxidative adduct (C). Reductive elimination gives the coupling product (D), and the initial silver-ate complex is regenerated by
the action of the remaining benzylmagnesium bromide (E).

**Scheme 5.**

```
\[\begin{array}{c}
3 \quad \text{I} \\
\text{O-SiMe}_2 \\
\begin{array}{c}
\text{O-SiMe}_2 \\
\text{Ph}
\end{array} \\
\text{Ph}
\begin{array}{c}
\text{O-SiMe}_2 \\
\text{Ph}
\end{array} \\
\text{Ph}
\begin{array}{c}
\text{O-SiMe}_2 \\
\text{Ph}
\end{array} \\
\text{Ph}
\begin{array}{c}
\text{O-SiMe}_2 \\
\text{Ph}
\end{array} \\
\text{Ph}
\begin{array}{c}
\text{O-SiMe}_2 \\
\text{Ph}
\end{array} \\
\text{Ph}
\begin{array}{c}
\text{O-SiMe}_2 \\
\text{Ph}
\end{array} \\
\text{Ph}
\begin{array}{c}
\text{O-SiMe}_2 \\
\text{Ph}
\end{array} \\
\text{Ph}
\begin{array}{c}
\text{O-SiMe}_2 \\
\text{Ph}
\end{array} \\
\text{Ph}
\begin{array}{c}
\text{O-SiMe}_2 \\
\text{Ph}
\end{array} \\
\text{Ph}
\end{array}\] 

**Scheme 6.**

```
\[\begin{array}{c}
\text{MgBr}_2 \\
\text{AgNO}_3 \\
\text{BrMg} \\
\text{Ag} \\
\text{R} \\
\text{B} \\
\text{C} \\
\text{D} \\
\text{E} \\
\text{F} \\
\text{G} \\
\text{H} \\
\text{I} \\
\end{array}\] 

The initial reduction of silver(I) salt to silver(0) is justified as follows. Treatment of AgNO\(_3\) (0.30 mmol) with benzylmagnesium bromide (0.60 mmol) in Et\(_2\)O at 25 °C for 1 h afforded 1,2-diphenylethane (8) (0.14 mmol) (Scheme 7). The formation of 8, the amount of which is
roughly equal to a half of AgNO₃ used, indicates that Ag(I) is reduced to Ag(0).

**Scheme 7.**

\[
\text{AgNO}_3 + \text{BrMg} \rightarrow \text{Et}_2\text{O}, 25^\circ\text{C}, 1\text{ h} \rightarrow \text{NH}_4\text{Cl aq} \rightarrow \text{Ph} - \text{Ph} \quad 8 \quad 0.14 \text{ mmol} (0.47 \text{ equiv based on AgNO}_3)
\]

The following experiments revealed that monobenzylsilver(0)-ate complex is reactive enough to effect the coupling reaction (Table 2). A reaction mixture prepared from equimolar amounts of AgNO₃ and benzylmagnesium bromide failed to promote the reaction of 1a (entry 1). In contrast, a 1:2 mixture of AgNO₃ and benzylmagnesium bromide was reactive to yield 2a in 42% yield (entry 2). Three equivalents of the benzylmagnesium bromide based on AgNO₃ did not improve the efficiency significantly (entry 3). Although the exact feature of the catalytically active species is not clear, these results support our proposed mechanism shown in Scheme 6.

**Table 2. A mechanistic consideration**

<table>
<thead>
<tr>
<th>entry</th>
<th>X /mmol</th>
<th>yield of 2a /%(^a)</th>
<th>recovery of 1a /%(^a)</th>
<th>yield of 8 /mmol(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.30</td>
<td>0</td>
<td>98</td>
<td>0.08</td>
</tr>
<tr>
<td>2</td>
<td>0.60</td>
<td>42</td>
<td>41</td>
<td>0.14</td>
</tr>
<tr>
<td>3</td>
<td>0.90</td>
<td>53</td>
<td>25</td>
<td>0.22</td>
</tr>
</tbody>
</table>

\(^a\) Based on NMR analysis.

The silver-catalyzed conditions were applicable not only to the benzylation but also to the coupling reactions with allylic organomagnesium reagents. Allylation and methallylation reactions of tertiary and secondary alkyl bromides proceeded smoothly (Table 3). Unfortunately,
silver-catalyzed crotylation and prenylation of alkyl halides resulted in poor regioselectivities (Table 4).

**Table 3. Silver-catalyzed coupling reaction of alkyl halides with allyl- and methallylmagnesium reagents**

<table>
<thead>
<tr>
<th>entry</th>
<th>1</th>
<th>cat. /mol%</th>
<th>Grignard reagent</th>
<th>9</th>
<th>yield /%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(n\textsubscript{C}\textsubscript{6}H\textsubscript{17})Br 1a</td>
<td>1.0</td>
<td>(R' = H) (1.3 equiv)</td>
<td>9a</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>1.0</td>
<td>(R' = Me) (1.5 equiv)</td>
<td>9b</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>(n\textsubscript{C}\textsubscript{6}H\textsubscript{13})Br 1i</td>
<td>2.5</td>
<td>(R' = H) (1.3 equiv)</td>
<td>9c</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>1i</td>
<td>2.5</td>
<td>(R' = Me) (1.5 equiv)</td>
<td>9d</td>
<td>79</td>
</tr>
</tbody>
</table>

**Table 4. Silver-catalyzed coupling reaction of alkyl halides with crotyl- and prenylmagnesium reagents**

<table>
<thead>
<tr>
<th>entry</th>
<th>1</th>
<th>cat. /mol%</th>
<th>R(^1)</th>
<th>R(^2)</th>
<th>yield /%</th>
<th>10/11</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(n\textsubscript{C}\textsubscript{6}H\textsubscript{17})Br 1a</td>
<td>1.0</td>
<td>Me</td>
<td>H</td>
<td>77</td>
<td>10a/11 = 65/35</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>1.0</td>
<td>Me</td>
<td>Me</td>
<td>46</td>
<td>10b/11 = 76/24</td>
</tr>
<tr>
<td>3</td>
<td>(n\textsubscript{C}\textsubscript{6}H\textsubscript{13})Br 1i</td>
<td>2.5</td>
<td>Me</td>
<td>H</td>
<td>76</td>
<td>10c/11 = 70/30</td>
</tr>
<tr>
<td>4</td>
<td>1i</td>
<td>2.5</td>
<td>Me</td>
<td>Me</td>
<td>48</td>
<td>10d/11 = 82/18</td>
</tr>
</tbody>
</table>

**Conclusion**

The author has found that silver-catalyzed coupling reaction of alkyl bromides with benzylic and allylic organomagnesium reagents could proceed smoothly. In the reaction, tertiary alkyl halides as well as secondary ones can be used as substrates.
Experimental Section

Instrumentation and Chemicals

$^1$H NMR (500 MHz) and $^{13}$C NMR (125.7 MHz) spectra were taken on a Varian UNITY INOVA 500 spectrometer and were recorded in CDCl$_3$. Chemical shifts ($\delta$) are in parts per million relative to tetramethylsilane at 0.00 ppm for $^1$H and relative to CDCl$_3$ at 77.23 ppm for $^{13}$C unless otherwise noted. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. TLC analyses were performed on commercial glass plates bearing a 0.25-mm layer of Merck Silica gel 60F$_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Silver nitrate was purchased from Aldrich. Allylmagnesium halide and benzylmagnesium halide were prepared from magnesium metal activated by dibromoethane and the corresponding alkyl halide in diethyl ether at 0 °C. Diethyl ether was purchased from Kanto Chemical Co., stored under nitrogen, and used as it is. All reactions were carried out under argon atmosphere. Tertiary alkyl halides except for 1f were prepared by treatment of the corresponding tertiary alcohols with phosphorus tribromide. Compound 3 was prepared according to the literature.$^{11}$

Synthesis of tert-alkyl halide 1f

A suspension of silver oxide (8.7 g, 37.5 mmol) in CH$_2$Cl$_2$ (25 mL) was placed in a 50-mL flask. Benzyl bromide (4.5 mL, 37.5 mmol) and ethyl 6-hydroxyhexanoate (4.1 mL, 25 mmol) were successively added to the reaction mixture at 0 °C. After being stirred for 12 h at room temperature, the reaction mixture was poured into water. The products were extracted with ethyl acetate (10 mL × 2). The combined organic layer was dried over Na$_2$SO$_4$ and concentrated. Silica gel column purification (hexane/ethyl acetate = 5/1) of the crude oil afforded the corresponding benzyloxy ester (3.8 g, 15 mmol) in 60% isolated yield. The ester (3.8 g, 15
mmol) was added to methylmagnesium iodide (1.0 M diethyl ether solution, 25 mL, 25 mmol) in a 50-mL flask at 0 °C. The reaction mixture was stirred for 2 h at room temperature. Then the reaction mixture was poured into a saturated ammonium chloride solution (40 mL). The products were extracted with ethyl acetate (10 mL × 2). The combined organic layer was dried over Na₂SO₄ and concentrated. Silica gel column purification (hexane/ethyl acetate = 3/1) of the crude oil afforded the corresponding alcohol (3.3 g, 14 mmol) in 93% isolated yield. The alcohol (3.3 g, 14 mmol) and diethyl ether (20 mL) were placed in a 50-mL flask, and phosphorus tribromide (0.53 mL, 5.6 mmol) was then added dropwise to the reaction mixture at −10 °C. After being stirred for 3 h at the same temperature, the reaction mixture was poured into a saturated NaHCO₃ aqueous solution carefully. The products were extracted with hexane (10 mL × 2). The combined organic layer was dried over Na₂SO₄ and concentrated. The crude oil was purified by distillation (1 Torr, 120 °C), and If (2.5 g, 8.4 mmol) was obtained in 60% isolated yield.

**General procedure for a silver-catalyzed coupling reaction of tert-alkyl halides with benzylmagnesium reagents**

The reaction of 1a with benzylmagnesium bromide (Table1, entry 1) is representative. Silver nitrate (0.8 mg, 0.005 mmol) was placed in a 20-mL reaction flask. Anhydrous diethyl ether (2 mL) and substrate 1a (117.6 mg, 0.50 mmol) were added under argon. Benzylmagnesium bromide (1.0 M diethyl ether solution, 0.65 mL, 0.65 mmol) was then added to the reaction mixture at 25 °C. While the organomagnesium reagent was being added, the mixture turned to a black suspension. After the mixture was stirred for 3 h at 25 °C, black precipitations appeared at the bottom of the reaction flask, and the supernatant solution became colorless. Then the reaction mixture was poured into a saturated ammonium chloride solution (20 mL). The products were extracted with hexane (20 mL × 3). The combined organic layer was dried over Na₂SO₄ and concentrated. Silica gel column purification (hexane) of the crude product provided the corresponding benzylated product 2a (107 mg, 0.44 mmol) in 87% isolated
yield.

**General procedure for a silver-catalyzed coupling reaction of tert-alkyl halides with allylmagnesium reagents**

The reaction of 1a with allylmagnesium bromide is representative (Table 3, entry 1). Silver nitrate (1.7 mg, 0.01 mmol) was placed in a 30-mL reaction flask. Anhydrous diethyl ether (4 mL) and substrate 1a (235.2 mg, 1.0 mmol) were added under argon. Allylmagnesium bromide (0.70 M diethyl ether solution, 1.86 mL, 1.3 mmol) was then added to the reaction mixture at 25 °C. While the organomagnesium reagent was being added, the mixture turned to a black suspension. After the mixture was stirred for 3 h at 25 °C, black precipitations appeared at the bottom of the reaction flask, and the supernatant solution became colorless. Then, the reaction mixture was poured into a saturated ammonium chloride solution (20 mL). The products were extracted with hexane (20 mL × 3). The combined organic layer was dried over Na₂SO₄ and concentrated. Silica gel column purification (hexane) of the crude product provided the corresponding allylated product 9a (163.0 mg, 0.83 mmol) in 83% isolated yield.

**Reaction of 3 to yield 5**

Bicyclic compound 4 was obtained from 3 (155 mg, 0.5 mmol) by the general procedure for silver-catalyzed benzylation. The ¹H NMR analysis of the crude oil indicated the formation of the desired oxasilacyclopentane 4. Potassium fluoride (58 mg, 1.0 mmol) and potassium hydrogencarbonate (100 mg, 1.0 mmol) were dissolved in methanol-THF (3 mL, 1:1 mixture). The crude product 4 dissolved in methanol-THF (3 mL, 1:1 mixture) and 30% H₂O₂ aq (0.52 mL) were successively added. After being stirred at room temperature for 12 h, the reaction mixture was poured into a saturated sodium thiosulfate solution. The product was extracted with ethyl acetate (20 mL × 2). The combined organic layer was dried over Na₂SO₄ and concentrated. The crude product was dissolved in pyridine (0.5 mL), and acetic anhydride (0.28 mL, 3 mmol) was successively added. After being stirred at room temperature for 4 h, the reaction mixture
was poured into brine. The product was extracted with ethyl acetate (20 mL × 2). The combined organic layer was dried over Na₂SO₄ and concentrated. Chromatographic purification (hexane/ethyl acetate = 10/1) of the crude product provided the corresponding diacetylated product 5 (44 mg, 0.14 mmol) in 28% isolated yield.

**Characterization Data**

Compounds 3,¹¹ 1a,⁷b 1b,⁷b 2f,⁷b 2g,⁷b 9a,⁷b 9b,⁷b 10a,⁷b 10b,⁷b 11a,⁷b 11b⁷b, 1e¹⁶ were found in the literature.

**8-Bromo-8-methyl-2-oxa-1-phenylnonane (1f)**

![8-Bromo-8-methyl-2-oxa-1-phenylnonane](attachment:image)

oil. IR (neat) 2936, 2858, 1453, 1369, 1103, 1075, 734, 697 cm⁻¹; ¹H NMR (CDCl₃) δ 1.38–1.44 (m, 2H), 1.50–1.56 (m, 2H), 1.62–1.68 (m, 2H), 1.74 (s, 6H), 1.77–1.81 (m, 2H), 3.48 (t, J = 6.5 Hz, 2H), 4.51 (s, 2H), 7.29 (m, 1H), 7.33–7.35 (m, 4H); ¹³C NMR (CDCl₃) δ 26.35, 26.41, 29.86, 34.46, 47.73, 68.73, 70.48, 73.12, 127.72, 127.85, 128.58, 138.86; Found: C, 60.50; H, 7.48%. Calcd for C₁₅H₂₃BrO: C, 60.21; H, 7.75%.

**2,2-Dimethyl-1-phenyldecane (2a)**

![2,2-Dimethyl-1-phenyldecane](attachment:image)

oil. IR (neat) 3028, 2927, 2854, 1495, 1468, 1454, 1385, 1365 cm⁻¹; ¹H NMR (CDCl₃) δ 0.84 (s, 6H), 0.89 (t, J = 7.5 Hz, 3H), 1.17–1.20 (m, 2H), 1.21–1.35 (m, 12H), 2.49 (s, 2H), 7.09–7.13 (m, 2H), 7.19 (m, 1H), 7.24–7.27 (m, 2H); ¹³C NMR (CDCl₃) δ 14.36, 22.92, 24.41, 27.06, 29.61, 29.96, 30.81, 32.16, 34.38, 42.40, 48.59, 125.85, 127.78, 130.81, 139.82; Found: C, 87.53; H, 12.47%. Calcd for C₁₈H₃₂: C, 87.73; H, 12.27%.

**1-Benzyladamantane (2c)**
colorless crystal. IR (nujol) 2901, 2846, 1600, 1452, 755, 698 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.47 (s, 3H), 1.48 (s, 3H), 1.56 (dm, 3H), 1.66 (dm, 3H), 1.93(br-s, 3H), 2.37 (s, 2H), 7.07-7.09 (m, 2H), 7.19 (m, 1H), 7.23–7.27 (m, 2H); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 28.92, 33.68, 37.20, 42.59, 51.48, 125.85, 127.68, 130.81, 138.49; Found: C, 90.33; H, 9.80%. Calcd for C\(_{17}\)H\(_{22}\): C, 90.20; H, 9.80%. m. p. 35.0–35.5 °C.

1-Benzyl-4-tert-butyl-1-methylcyclohexane (2d) (cis/trans = 34:66 mixture of diastereomers\(^{17}\))

oil. IR (neat) 3028, 2942, 1452, 1365, 706 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 0.76 (s, 0.66×3H), 0.83 (s, 0.34×12H), 0.90 (s, 0.66×9H), 0.94–1.26 (m, 4H), 1.33–1.41 (m, 2H), 1.53–1.64 (m, 3H), 2.47 (s, 0.34×2H), 2.59 (s, 0.66×2H), 7.11–7.13 (m, 2H), 7.19 (m, 1H), 7.24–7.27 (m, 2H); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 21.97, 22.97, 23.12, 27.80, 27.87, 29.89, 32.60, 32.70, 33.76, 34.05, 38.19, 38.28, 41.90, 48.49, 48.55, 52.49, 125.82, 125.87, 127.70, 127.83, 130.81, 130.96, 140.04 (× 2C); Found: C, 88.69; H, 11.81%. Calcd for C\(_{18}\)H\(_{28}\): C, 88.45; H, 11.55%.

2,2-Dimethyl-8-oxa-1,9-diphenylnonane (2e)

oil. IR (neat) 3028, 2933, 2857, 1453, 1365, 1103, 732, 700 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 0.83 (s, 6H), 1.18–1.21 (m, 2H), 1.33–1.36 (m, 4H), 1.63–1.65 (m, 2H), 2.49 (s, 2H), 3.47 (t, \(J = 6.5\) Hz, 2H), 4.51 (s, 2H), 7.09–7.11 (m, 2H), 7.19 (m, 1H), 7.24–7.30 (m, 3H), 7.34 (d, \(J = 4.0\) Hz, 4H);
$^{13}$C NMR (CDCl$_3$) δ 24.26, 27.02, 27.32, 30.07, 34.36, 42.33, 48.63, 70.72, 73.10, 125.89, 127.69, 127.80, 127.84, 128.57, 130.80, 138.94, 139.74; Found: C, 85.40; H, 9.98%. Calcd for C$_{22}$H$_{36}$O: C, 85.11; H, 9.74%.

2,2-Dimethyl-1-(2-methylphenyl)decane (2i)

![](image)

oil. IR (neat) 2927, 2855, 1468, 1364, 738 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 0.85 (s, 6H), 0.89 (t, $J = 7.0$ Hz, 3H), 1.22–1.36 (m, 14H), 2.32 (s, 3H), 2.55 (s, 2H), 7.08–7.15 (m, 4H); $^{13}$C NMR (CDCl$_3$) δ 14.35, 20.84, 22.91, 24.45, 26.93, 29.61, 29.97, 30.87, 32.15, 35.77, 43.43, 44.38, 125.16, 125.96, 130.51, 131.85, 137.38, 138.31; Found: C, 87.90; H, 12.59%. Calcd for C$_{19}$H$_{32}$: C, 87.62; H, 12.38%.

2,2-Dimethyl-1-(3-methoxyphenyl)decane (2j)

![](image)

oil. IR (neat) 2928, 2855, 1602, 1583, 1488, 1466, 1458, 1266, 1155, 1049, 696 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 0.84 (s, 6H), 0.89 (t, $J = 7.0$ Hz, 3H), 1.17–1.20 (m, 2H), 1.22–1.35 (m, 12H), 2.47 (s, 2H), 3.79 (s, 3H), 6.67 (m, 1H), 6.71–6.76 (m, 2H), 7.17 (t, $J = 8.0$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) δ 14.34, 22.91, 24.43, 27.17, 29.60, 29.97, 30.82, 32.15, 34.41, 42.48, 48.63, 55.33, 110.05, 116.73, 123.43, 128.63, 141.47, 159.23; Found: C, 82.30; H, 11.86%. Calcd for C$_{19}$H$_{35}$O: C, 82.55; H, 11.67%.

2,2-Dimethyl-1-(4-fluorophenyl)decane (2k)

![](image)
oil. IR (neat) 2929, 2855, 1607, 1509, 1467, 1365, 1224, 1157, 837, 826 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 0.82 (s, 6H), 0.89 (t, \(J = 7.5\) Hz, 3H), 1.14–1.18 (m, 2H), 1.21–1.32 (m, 12H), 2.46 (s, 2H), 6.92–6.96 (m, 2H), 7.03–7.07 (m, 2H); \(^1\)C NMR (CDCl\(_3\)) \(\delta\) 14.35, 22.91, 24.38, 26.94, 29.59, 29.94, 30.79, 32.15, 34.30, 42.38, 47.72, 114.53 (d, \(J = 21\) Hz), 131.98 (d, \(J = 7.6\) Hz), 135.37 (d, \(J = 3.4\) Hz), 161.58 (d, \(J = 242\) Hz); Found: C, 81.98; H, 11.18%. Calcd for C\(_{18}\)H\(_{29}\)F: C, 81.76; H, 11.05%.

2-Benzylnorbornane (2l) (exo/endo = 94:6 mixture\(^8\))

![2-Benzylnorbornane](image)

oil. IR (neat) 3026, 2949, 2869, 1452, 752, 723, 698 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.09–1.17 (m, 4H), 1.25–1.49 (m, 4H), 1.74 (td, \(J = 13.0, 8.0\) Hz, 1H), 1.99 (s, 0.94×1H), 2.05 (s, 0.06×1H), 2.17 (s, 0.06×1H), 2.22 (s, 0.94×1H), 2.42 (dd, \(J = 14.0, 8.0\) Hz, 0.94×1H), 2.54 (dd, \(J = 14.0, 8.0\) Hz, 0.94×1H), 2.62 (d, \(J = 7.5\) Hz, 0.06×2H), 7.15–7.18 (m, 3H), 7.25–7.28 (m, 2H); \(^1\)C NMR of exo-2l (CDCl\(_3\)) \(\delta\) 29.08, 30.27, 35.31, 37.04, 38.14, 40.64, 43.03, 43.89, 125.77, 128.34, 129.18, 142.07; Found: C, 90.45; H, 9.95%. Calcd for C\(_{14}\)H\(_{18}\): C, 90.26; H, 9.74%.

Diacetylated product of 2-(3-phenyl-1-hydroxypropyl)cyclohexanol (5) (50:50 mixture of diastereomers)

![Diacetylated product](image)

oil. IR (neat) 2936, 2862, 1734, 1448, 1374, 1363, 1244, 1199, 1027, 700 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.21–1.83 (m, 9H), 1.91–1.98 (m, 2H), 1.97 (s, 0.5×3H), 2.01 (s, 0.5×3H), 2.03 (s, 0.5×3H), 2.05 (s, 0.5×3H), 2.49–2.66 (m, 2H), 4.90 (m, 1H), 5.13 (dm, 1H), 7.14–7.19 (m, 3H), 7.25–7.29 (m, 2H); \(^1\)C NMR (CDCl\(_3\)) \(\delta\) 20.21, 20.41, 21.18, 21.28, 21.38, 21.45, 23.80, 23.89,
25.41, 25.43, 30.14, 30.42, 31.38, 31.61, 33.47, 34.11, 43.70, 43.96, 68.22, 69.95, 73.55, 74.80, 126.10 (× 2C), 128.45 (× 2C), 128.60 (× 2C), 141.67, 142.02, 170.75, 171.01 (× 2C), 171.02; Found: C, 71.47; H, 8.23%. Calcd for C_{19}H_{26}O_{4}: C, 71.67; H, 8.44%.

4-Methyl-1-decene (9c)

\[
\text{oil. IR (neat) } 2926, 2856, 1641, 1459, 1442, 1378, 993, 910 \text{ cm}^{-1}; \quad \text{^1H NMR (CDCl}_3\text{) } \delta 0.86 (d, J = 7.0 \text{ Hz, } 3\text{H}), 0.88 (t, J = 7.0 \text{ Hz, } 3\text{H}), 1.10 (m, 1\text{H}), 1.28 (m, 9\text{H}), 1.48 (m, 1\text{H}), 1.87 (m, 1\text{H}), 2.04 (m, 1\text{H}), 4.96–5.01 (m, 2\text{H}), 5.78 (ddt, J = 17.5, 10.5, 7.5 \text{ Hz, } 1\text{H}); \quad \text{^13C NMR (CDCl}_3\text{) } \delta 14.33, 19.67, 22.91, 27.27, 29.82, 32.15, 33.01, 36.81, 41.67, 115.56, 138.07; \quad \text{Found: C, 85.33; H, 14.24%. Calcd for C}_{11}H_{22}: \quad \text{C, 85.63; H, 14.37%}.}

2,4-Dimethyl-1-decene (9d)

\[
\text{oil. IR (neat) } 3074, 2926, 2855, 1648, 1457, 1377, 887 \text{ cm}^{-1}; \quad \text{^1H NMR (CDCl}_3\text{) } \delta 0.83 (d, J = 6.5 \text{ Hz, } 3\text{H}), 0.88 (t, J = 6.5 \text{ Hz, } 3\text{H}), 1.07 (m, 1\text{H}), 1.19–1.34 (m, 9\text{H}), 1.58 (m, 1\text{H}), 1.68 (s, 3\text{H}), 1.79 (ddd, J = 13.5, 8.0, 0.5 \text{ Hz, } 1\text{H}), 2.02 (dd, J = 14.0, 8.0 \text{ Hz, } 1\text{H}), 4.64 (m, 1\text{H}), 4.72 (m, 1\text{H}); \quad \text{^13C NMR (CDCl}_3\text{) } \delta 14.33, 19.66, 22.46, 22.91, 27.28, 29.84, 30.81, 32.16, 37.15, 46.27, 111.37, 145.27; \quad \text{Found: C, 85.63; H, 14.37%. Calcd for C}_{12}H_{24}: \quad \text{C, 85.63; H, 14.37%}.}

Mixture of 5-methyl-2-undecene (10c) and 3,4-Dimethyl-1-decene (11c) (10c/11c = 70/30)

\[
\text{oil. IR (neat) } 2959, 2926, 2856, 1458, 1378 \text{ cm}^{-1}; \quad \text{^1H NMR (CDCl}_3\text{) } \delta 0.73–1.50 (m, 0.7\times17\text{H} + 0.3\times20\text{H}), 1.59–1.66 (m, 0.7\times3\text{H}), 1.86(m, 0.7\times1\text{H}), 2.02 (m, 0.7\times1\text{H}), 2.09 (m,
0.3×1H, 4.92–4.96 (m, 0.3×2H), 5.44 (m, 0.7×1H), 5.49 (m, 0.7×1H), 5.74 (m, 0.3×1H); \(^{13}\)C NMR of 10c (CDCl\(_3\)) δ 13.10, 14.33, 19.79, 22.91, 27.38, 29.87, 32.17, 33.68, 34.37, 36.96, 124.53, 129.75; Found: C, 85.43; H, 14.33%. Calcd for C\(_{12}\)H\(_{24}\): C, 85.63; H, 14.37%.

**Mixture of 2,5-dimethyl-2-undecene (10d) and 3,3,4-trimethyl-1-decene (11d) (10d/11d = 82/18)**

\[
\begin{align*}
\text{\(n\)C}_6\text{H}_{13} & \quad \text{and} \quad \text{\(n\)C}_6\text{H}_{13} \\
\end{align*}
\]

oil. IR (neat) 2959, 2926, 2856, 1458, 1378 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) δ 0.73–1.43 (m, 0.82×17H + 0.18×23H), 1.59 (s, 0.82×3H), 1.70 (s, 0.82×3H), 1.79 (m, 0.82×1H), 1.97 (m, 0.82×1H), 4.87–4.93 (m, 0.18×2H), 5.13 (m, 0.82×1H), 5.77 (dd, \(J = 17.5, 11.0\) Hz, 0.18×1H); \(^{13}\)C NMR of 10d (CDCl\(_3\)) δ 14.35, 18.04, 19.83, 22.92, 26.07, 27.40, 29.89, 32.18, 33.93, 35.65, 36.98, 123.80, 131.95; Found: C, 85.91; H, 14.32%. Calcd for C\(_{13}\)H\(_{26}\): C, 85.63; H, 14.37%.
References and Notes


(5) Silver is an effective catalyst for the coupling reaction of alkyl halides with alkylmagnesium reagent when the alkyl groups are the same. (a) Kochi, J. K. *J. Organomet. Chem.* 2002, 653, 11–19. (b) Tamura, M.; Kochi, J. K. *Synthesis* 1971, 303–305.


The reactions in hexane, toluene, and THF resulted in lower yields (ca. 70%).

1,2-Diphenylethane (0.12 mmol) was detected.

The reaction was slow when performed in the presence of 0.1 mol% of silver nitrate. After 5 h, 2a was obtained in 79% yields, along with 5% of 1a and 10% of the dehydrobrominated products.


The stereochemistry of the products was tentatively assigned in analogy with the corresponding allylated products. The allylated products were reported in Ref. 7b.

The stereochemistry of the products was tentatively assigned in comparison with the corresponding phenylated products. The phenylated products were reported in the following reference: Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340–1341.
Chapter 4

Silver-Catalyzed Coupling Reactions of Alkyl Bromides
with Alkyl and Arylmagnesium Reagents

Treatment of secondary and tertiary alkyl bromides with alkymagnesium reagents in the
presence of catalytic amounts of AgBr and KF in CH$_2$Cl$_2$ afforded the corresponding coupling
products in reasonable yields. Moreover, silver showed catalytic activity for the coupling
reactions of alkyl bromides with arylmagnesium reagents.
Introduction

Transition-metal-catalyzed coupling reactions of alkyl halides with organomagnesium reagents are very useful methods for carbon-carbon bond formation in organic synthesis. Among them, the use of unactivated secondary and tertiary alkyl halides as substrates is more difficult than that of primary alkyl halides, due to the faster β-hydride elimination from the corresponding alkyl transition-metal intermediates. Recently, the coupling reactions of unactivated secondary alkyl halides with aryl, alkyl, or alkylnlmagnesium reagents have been achieved. However, the coupling reactions of unactivated secondary alkyl halides with alkylmagnesium reagents are still rare, and have to be established.

The author has presented silver-catalyzed coupling reactions of alkyl halides with benzyl and allylmagnesium reagents in Chapter 3. In these reactions, secondary and tertiary alkyl halides can be employed as substrates. In Chapter 4, he demonstrates silver-catalyzed coupling reactions of alkyl bromides with alkyl and arylmagnesium reagents (Scheme 1).

Scheme 1.

Results and Discussion

Treatment of 2-bromo-octane (1a) with 3-phenylpropylmagnesium bromide in the presence of a catalytic amount of AgCl in Et₂O afforded the coupling product 2a in 34% yield (Table 1, entry 1). When PdCl₂, NiCl₂, FeCl₃, or CuCl was used without any ligands instead of AgCl, only trace amounts of 2a were detected. After optimizing reaction conditions, the author found that AgBr was the most effective catalyst (entry 2). Using CH₂Cl₂ as a solvent improved the yield slightly (entry 3). He thought that the low yields were due to the decomposition of alkylsilver intermediates at room temperature, because octane, propylbenzene, and allylbenzene were mainly produced. Indeed, the better yield was achieved at −10 °C (entry 4). However, the reaction...
in entry 4 showed poor reproducibility. When 10 mol% KF was added, he could reproduce the result and obtain the corresponding coupling product 2a in 68% yield (entry 5). AgF was not effective (entry 6). Even though both AgF and LiBr were added, the product 2a was obtained in only 23% yield (entry 7). Although the role of KF is not clear at this stage, KF would dissociate the aggregation of AgBr or stabilize alkylsilver intermediates by coordination to the silver metal.

Table 1. Optimization of conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>Mtl</th>
<th>solvent</th>
<th>temp. /°C</th>
<th>yield /%a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AgCl</td>
<td>Et₂O</td>
<td>25</td>
<td>34b</td>
</tr>
<tr>
<td>2</td>
<td>AgBr</td>
<td>Et₂O</td>
<td>25</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>AgBr</td>
<td>CH₂Cl₂</td>
<td>25</td>
<td>47</td>
</tr>
<tr>
<td>4</td>
<td>AgBr</td>
<td>CH₂Cl₂</td>
<td>−10</td>
<td>44–62</td>
</tr>
<tr>
<td>5</td>
<td>AgBr/KF</td>
<td>CH₂Cl₂</td>
<td>−10</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>AgF</td>
<td>CH₂Cl₂</td>
<td>−10</td>
<td>&lt;5c</td>
</tr>
<tr>
<td>7</td>
<td>AgF/LiBr</td>
<td>CH₂Cl₂</td>
<td>−10</td>
<td>23d</td>
</tr>
</tbody>
</table>

a Based on NMR analysis. b 3% of 1a was recovered. c 26% of 1a was recovered. d 11% of 1a was recovered.

The silver-catalyzed alkylation reactions (10 mol% AgBr/KF) of various substrates are summarized in Table 2. Both cyclic and acyclic secondary alkyl bromides underwent the alkylation reactions (Table 2, entries 1–4). The reaction of tertiary alkyl halide 1e suffered from a moderate yield (entry 5). In this case, 2-methyldecane was mainly obtained. Although the reaction of 1-bromoadamantane (1f) was slow, it resulted in a reasonable yield of 2f (entry 6). It is quite interesting that tertiary alkyl bromides can be used as reaction partners. The substrates having functional groups such as THP ether and sulfonamide could be also employed (entries 7 and 8). The reaction of 1-bromooctane (1i) resulted in low yield (entry 9).
Table 2. Silver-catalyzed coupling reaction of alkyl bromides with alkylnagnesium reagent

<table>
<thead>
<tr>
<th>Entry</th>
<th>R−Br</th>
<th>1</th>
<th>2</th>
<th>Yield /%b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>nC₆H₁₃Br</td>
<td>1a</td>
<td>2a</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>C₅H₁₀Br</td>
<td>1b</td>
<td>2b</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>C₆H₁₃Br</td>
<td>1c</td>
<td>2c</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>C₇H₁₄Br</td>
<td>1d</td>
<td>2d</td>
<td>69</td>
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<tr>
<td>5</td>
<td>nC₈H₁₇Br</td>
<td>1e</td>
<td>2e</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>C₈H₁₆Br</td>
<td>1f</td>
<td>2f</td>
<td>69c</td>
</tr>
<tr>
<td>7</td>
<td>O–O⁻Br</td>
<td>1g</td>
<td>2g</td>
<td>58</td>
</tr>
<tr>
<td>8</td>
<td>Ph–NS⁻Br</td>
<td>1h</td>
<td>2h</td>
<td>44</td>
</tr>
<tr>
<td>9</td>
<td>nC₉H₁₈Br</td>
<td>1i</td>
<td>2i</td>
<td>20</td>
</tr>
</tbody>
</table>

a The organomagnesium reagent was 2.0 M Et₂O solution.
b Isolated yields. c Performed with 3.0 equiv of the organomagnesium reagent at 25 °C for 64 h.

An alkylmagnesium reagent bearing a terminal alkene moiety reacted with secondary alkyl bromide 1d smoothly to afford 2j in 63% yield (Scheme 2). Although KF was added in this alkylation reaction, the reaction conditions were compatible with a tert-butylidimethylsiloxyl
group. Unfortunately, the reactions with secondary and tertiary alkylmagnesium reagents afforded only trace amounts of the corresponding coupling products under these reaction conditions.  

Scheme 2.

Next, the author applied the silver catalysis to the coupling reactions with phenylmagnesium reagent. Under the conditions with KF, he could not obtain the phenylated product and the starting material was recovered. After reoptimization of reaction conditions, he found that treatment of bromocyclohexane (1c) with phenylmagnesium bromide in the presence of 10 mol% AgBr/P(OPh)₃ in refluxing hexane afforded coupling product 3c in 81% yield (Table 3, entry 2). Acyclic alkyl bromides as well as cyclic ones underwent the reactions (entry 1). The reaction of 1-bromoadamantane (1f) took 10 h for completion (entry 3). Primary alkyl bromide 1i underwent the phenylation to give 3i in high yield (entry 4).

-o-Tolylmagnesium reagent can be also employed to afford the corresponding product 4 in 90% yield (Scheme 3). 4-Methoxyphenyl and 3-(trifluoromethyl)phenylmagnesium reagent resulted in low yields.
Chapter 4

Table 3. Silver-catalyzed coupling reaction of alkyl bromides with phenylmagnesium reagent

<table>
<thead>
<tr>
<th>R−Br</th>
<th>10 mol% AgBr</th>
<th>10 mol% P(OPh)$_3$</th>
<th>R</th>
<th>yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>hexane/Et$_2$O reflux, 5 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>entry</td>
<td>R−Br</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>$n$C$<em>6$H$</em>{13}$−Br</td>
<td>1a</td>
<td>3a</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>1c</td>
<td>3c</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>1f</td>
<td>3f</td>
<td>61$^c$</td>
</tr>
<tr>
<td>4</td>
<td>$n$C$<em>8$H$</em>{17}$−Br</td>
<td>1i</td>
<td>3i</td>
<td>88</td>
</tr>
</tbody>
</table>

$^a$ The organomagnesium reagent was 1.0 M Et$_2$O solution.

$^b$ Isolated yields. $^c$ Performed for 10 h.

Scheme 3.

Treatment of 1,10-dibromoundecane (1j) with pentylmagnesium bromide under the AgBr/KF-catalyzed alkylation conditions afforded monoalkylated product 5a in 55% yield (Scheme 4). Dialkylated product 5b was not detected. The reaction of 1j with phenylmagnesium bromide under the AgBr/P(OPh)$_3$-catalyzed arylation conditions yielded monophenylated product 6a and diphenylated product 6b in 43% and 16% yields, respectively. The fact that secondary alkyl bromide reacted faster than primary one suggested that these reactions would involve the generation of the corresponding carbon-centered radical intermediates from alkyl bromides.
Conclusion

The author has developed the silver-catalyzed coupling reaction of alkyl bromides with alkyl and arylmagnesium reagents, where secondary and tertiary alkyl bromides can be used as substrates. The present results unveil the new catalytic potential of silver.
Experimental Section

Instrumentation and Chemicals

$^1$H NMR (500 MHz) and $^{13}$C NMR (125.7 MHz) spectra were taken on a Varian UNITY INOVA 500 spectrometer and were recorded in CDCl$_3$. Chemical shifts (δ) are in parts per million relative to tetramethylsilane at 0.00 ppm for $^1$H and relative to CDCl$_3$ at 77.23 ppm for $^{13}$C unless otherwise noted. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. TLC analyses were performed on commercial glass plates bearing a 0.25-mm layer of Merck Silica gel 60F$_{254}$. Florisil (75–150 μm, 100–200 mesh) was used for filtration. Silica gel (Wakogel 200 mesh) was used for column chromatography. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Silver bromide was purchased from Wako Pure Chemicals. Alkylmagnesium halides and arylmagnesium halides were prepared from magnesium metal and the corresponding organic halides in diethyl ether at room temperature. Diethyl ether was purchased from Kanto Chemical Co., stored under nitrogen, and used as it is. All reactions were carried out under argon atmosphere.

Synthesis of 1g

A suspension of palladium dichloride (88.7 mg, 0.50 mmol) and $p$-benzoquinone (5.3 g, 50 mmol) in DMF (150 mL) was placed in a 300-mL reaction flask. 10-undecenol (10 mL, 50 mmol) and water (10 mL) were successively added to the reaction mixture at 0 °C. After being stirred for 4 h at 90 °C, the reaction mixture was poured into water. The products were extracted with ethyl acetate (30 mL × 2). The combined organic layer was filtered. The filtrate was dried over Na$_2$SO$_4$ and concentrated. Silica gel column purification (hexane/ethyl acetate = 2/1) of the crude oil afforded 11-hydroxy-2-undecanone (8.7 g, 46 mmol) in 93% isolated yield. This alcohol (3.7 g, 20 mmol) and diethyl ether (20 mL) were placed in a 100-mL reaction flask. $p$-Toluenesulfonic acid monohydrate (95 mg, 0.50 mmol) and 3,4-dihydro-$2H$-pyran (2.0 mL, 22
mmol) were successively added to the reaction mixture at room temperature. The reaction mixture was stirred for 3 h. Then the reaction mixture was poured into a saturated NaHCO₃ aqueous solution. The products were extracted with ethyl acetate (10 mL × 2). The combined organic layer was dried over Na₂SO₄ and concentrated. Silica gel column purification (hexane/ethyl acetate = 10/1) of the crude oil afforded the corresponding THP ether (2.5 g, 9.0 mmol) in 45% isolated yield. The THP ether (2.5 g, 9.0 mmol) in ethanol (14 mL) was placed in a 50-mL reaction flask, and sodium borohydride (132 mg, 3.5 mmol) was then added to the reaction mixture at 0 °C. After being stirred for 1 h at room temperature, the reaction mixture was poured into a saturated ammonium chloride solution. The products were extracted with ethyl acetate (10 mL × 2). The combined organic layer was dried over Na₂SO₄ and concentrated. The crude oil and dichloromethane (10 mL) were placed in a 50-mL reaction flask. Then, triethylamine (3.5 mL, 25 mmol) and methanesulfonyl chloride (1.0 mL, 13 mmol) were successively added to the reaction mixture. After being stirred for 4 h at room temperature, the reaction mixture was poured into a saturated ammonium chloride solution. Silica gel column purification (hexane/ethyl acetate = 5/1) of the crude oil afforded the corresponding mesylated product (2.8 g, 8.0 mmol) in 88% isolated yield. This product (2.8 g, 8.0 mmol) in acetone (15 mL) was placed in a 50-mL reaction flask. Lithium bromide (1.4 g, 16 mmol) was then added to the reaction mixture. After being stirred for 5 h in refluxing acetone, the reaction mixture was poured into water. Silica gel column purification (hexane/ethyl acetate = 20/1) of the crude oil afforded 1g (0.80 g, 3.3 mmol) in 41% isolated yield.

**Synthesis of 1h**

Benzylamine (2.2 mL, 20 mmol) in ethanol (20 mL) was placed in a 100-mL reaction flask. Then, triethylamine (4.2 mL, 30 mmol) and p-toluenesulfonyl chloride (4.0 g, 21 mmol) were successively added to the reaction mixture at 0 °C. After being stirred for 7 h at room temperature, the reaction mixture was poured into a saturated ammonium chloride solution. The products were extracted with ethyl acetate (20 mL × 2). The combined organic layer was dried
over Na$_2$SO$_4$ and concentrated. This crude product and THF (100 mL) were placed in a 300-mL reaction flask. Butyllithium (1.6 M hexane solution, 20 mmol, 13 mL) was then added to the mixture at 0 °C. After being stirred for 30 min at the same temperature, 1,10-dibromoundecane (1j) (5.7 g, 18 mmol) was added to the reaction mixture at the same temperature. After being stirred for another 8 h at room temperature, the reaction mixture was poured into a saturated ammonium chloride solution. The products were extracted with ethyl acetate (20 mL × 2). The combined organic layer was dried over Na$_2$SO$_4$ and concentrated. Silica gel column purification (hexane/ethyl acetate = 5/1) of the crude oil afforded 1h (1.2 g, 2.4 mmol) in 47% isolated yield.

**Synthesis of 1j**

11-hydroxy-2-undecanone (7.5 g, 40 mmol), prepared by the method described above, in ethanol (40 mL) was placed in a 100-mL reaction flask. Sodium borohydride (757 mg, 20 mmol) was then added to the reaction mixture at 0 °C. After being stirred for 2 h at room temperature, the reaction mixture was poured into a saturated ammonium chloride solution. The products were extracted with ethyl acetate (10 mL × 2). The combined organic layer was dried over Na$_2$SO$_4$ and concentrated. The crude oil and dichloromethane (40 mL) were placed in a 100-mL reaction flask. Then, triethylamine (31 mL, 224 mmol) and methanesulfonyl chloride (8.7 mL, 112 mmol) were successively added to the reaction mixture. After being stirred for 5 h at room temperature, the reaction mixture was poured into a saturated ammonium chloride solution. The products were extracted with ethyl acetate (10 mL × 2). The combined organic layer was dried over Na$_2$SO$_4$ and concentrated. Then, the crude oil and acetone (40 mL) were placed in a 100-mL flask. Lithium bromide (13.9 g, 160 mmol) was then added to the reaction mixture. After being stirred for 5 h in refluxing acetone, the reaction mixture was poured into water. Silica gel column purification (hexane/ethyl acetate = 50/1) of the crude oil afforded 1j (5.1 g, 16 mmol) in 41% isolated yield.
General procedure for a silver-catalyzed coupling reaction of alkyl bromides with alkylmagnesium reagents

The reaction of 1a with 3-phenylpropylmagnesium bromide (Table 2, entry 1) is representative. Silver bromide (9.4 mg, 0.05 mmol) and potassium fluoride (2.9 mg, 0.05 mmol) were placed in a 20-mL reaction flask. Dichloromethane (2 mL) and substrate 1a (96.6 mg, 0.50 mmol) were added under argon at −10 °C. 3-Phenylpropylmagnesium bromide (2.0 M diethyl ether solution, 0.45 mL, 0.90 mmol) was then added to the reaction mixture at −10 °C. After being stirred for 15 h at −10 °C, the reaction mixture was poured into a saturated ammonium chloride solution (20 mL). The products were extracted with hexane (20 mL × 3). The combined organic layer was dried over Na₂SO₄ and concentrated. Silica gel column purification (hexane) of the crude product provided the corresponding alkylated product 2a (72.1 mg, 0.31 mmol) in 62% isolated yield.

General procedure for a silver-catalyzed coupling reaction of alkyl bromides with arylmagnesium reagents

The reaction of 1c with phenylmagnesium bromide (Table 3, entry 2) is representative. Silver bromide (9.4 mg, 0.05 mmol) and triphenylphosphite (0.01 mL, 0.05 mmol) were placed in a 20-mL reaction flask. Hexane (2 mL) and substrate 1c (81.5 mg, 0.50 mmol) were added under argon. Phenylmagnesium bromide (1.0 M diethyl ether solution, 0.80 mL, 0.80 mmol) was then added to the reaction mixture at 25 °C. After being stirred for 5 h in refluxing hexane, the reaction mixture was poured into a saturated ammonium chloride solution (20 mL). The products were extracted with hexane (20 mL × 3). The combined organic layer was dried over Na₂SO₄ and concentrated. Silica gel column purification (hexane) of the crude product provided the corresponding phenylated product 3c (65.2 mg, 0.41 mmol) in 81% isolated yield.

Characterization Data

Compounds 1a–1d, 1f, 1i, and 3i were commercially available. Compound 1e, 16 2c, 17 2d, 18 3a, 19 3c, 20 3f, 21 and 4 were found in the literature.

**10-Bromo-1-(2-oxacyclohexyloxy)undecane (1g)**
oil. IR (neat) 2928, 1442, 1201, 1034, 869 cm⁻¹; ¹H NMR (CDCl₃) δ 1.25–1.44 (m, 11H), 1.45–1.62 (m, 7H), 1.17 (d, J = 7.0 Hz, 3H), 1.71–1.87 (m, 4H), 3.38 (dt, J = 9.5, 6.5 Hz, 1H), 3.50 (m, 1H), 3.73 (dt, J = 9.5, 7.0 Hz, 1H), 3.88 (m, 1H), 4.14 (m, 1H), 4.58 (dd, J = 4.5, 3.0 Hz, 1H); ¹³C NMR (CDCl₃) δ 19.93, 25.72, 26.43, 26.68, 27.97, 29.18, 29.63, 29.65, 29.69, 29.96, 31.00, 41.39, 52.28, 62.59, 67.91, 99.08;  Found: C, 57.50; H, 9.44%.  Calcd for C₁₆H₃₁BrO₂: C, 57.31; H, 9.32%.

N-Benzyl-N-(10-bromoundecyl)-p-toluenesulfonamide (1h)

oil. IR (neat) 2927, 2855, 1600, 1496, 1456, 1340, 1159, 1092, 933, 720 cm⁻¹; ¹H NMR (CDCl₃) δ 1.04–1.50 (m, 14H), 1.70 (d, J = 7.0 Hz, 3H), 1.70–1.85 (m, 2H), 2.44 (s, 3H), 3.07 (dd, J = 7.5, 7.5 Hz, 2H), 4.13 (m, 1H), 4.31 (s, 2H), 7.26–7.32 (m, 7H), 7.73 (d, J = 8.0 Hz, 2H); ¹³C NMR (CDCl₃) δ 21.74, 26.69, 26.78, 27.94, 28.12, 29.12, 29.18, 29.48, 29.50, 41.38, 48.31, 52.09, 52.22, 127.42, 127.91, 128.49, 128.72, 129.88, 136.85, 137.42, 143.33;  Found: C, 60.95; H, 7.50%.  Calcd for C₂₅H₃₆BrNO₂: C, 60.72; H, 7.34%.

1,10-Dibromoundecane (1j)

oil. IR (neat) 2927, 2360, 1444, 1429, 1378, 1223, 722 cm⁻¹; ¹H NMR (CDCl₃) δ 1.04–1.50 (m, 14H), 1.70 (d, J = 7.0 Hz, 3H), 1.70–1.85 (m, 2H), 2.44 (s, 3H), 3.07 (dd, J = 7.5, 7.5 Hz, 2H), 4.13 (m, 1H), 4.31 (s, 2H), 7.26–7.32 (m, 7H), 7.73 (d, J = 8.0 Hz, 2H); ¹³C NMR (CDCl₃) δ 21.74, 26.69, 26.78, 27.94, 28.12, 29.12, 29.18, 29.48, 29.50, 41.38, 48.31, 52.09, 52.22, 127.42, 127.91, 128.49, 128.72, 129.88, 136.85, 137.42, 143.33;  Found: C, 42.26; H, 6.96%.  Calcd for C₁₁H₂₂Br₂: C, 42.06; H, 7.06%.

4-Methyl-1-phenyldecane (2a)

oil. IR (neat) 2928, 2857, 1605, 1496, 1456, 1378, 747 cm⁻¹; ¹H NMR (CDCl₃) δ 0.85 (d, J =
6.5 Hz, 3H), 0.88 (t, J = 7.0 Hz, 3H), 1.06–1.45 (m, 13H), 1.53–1.67 (m, 2H), 2.53–2.63 (m, 2H), 7.16–7.19 (m, 3H), 7.26–7.30 (m, 2H); $^{13}$C NMR (CDCl$_3$) δ 14.35, 19.87, 22.91, 27.24, 29.29, 29.89, 32.16, 32.87, 36.55, 36.98, 37.21, 125.76, 128.43, 128.59, 143.21; Found: C, 88.05; H, 12.13%. Calcd for C$_{17}$H$_{28}$: C, 87.86; H, 12.14%.

(3-Cyclopentylpropyl)benzene (2b)

oil. IR (neat) 2946, 2857, 1605, 1497, 746 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 1.02–1.10 (m, 2H), 1.32–1.37 (m, 2H), 1.45–1.54 (m, 2H), 1.56–1.66 (m, 4H), 1.71–1.80 (m, 3H), 2.60 (t, J = 7.5 Hz, 2H), 7.15–7.20 (m, 3H), 7.25–7.29 (m, 2H); $^{13}$C NMR (CDCl$_3$) δ 25.40, 30.94, 32.90, 36.12, 36.48, 40.28, 125.75, 128.43, 128.61, 143.21; Found: C, 89.51; H, 10.97%. Calcd for C$_{14}$H$_{20}$: C, 89.29; H, 10.71%.

4,4-Dimethyl-1-phenyldodecane (2e)

oil. IR (neat) 2928, 2855, 1605, 1496, 1454, 1365, 747 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 0.81 (s, 6H), 0.88 (t, J = 6.5 Hz, 3H), 1.20–1.32 (m, 16H), 1.52–1.58 (m, 2H), 2.56 (t, J = 8.0 Hz, 2H), 7.15–7.19 (m, 3H), 7.26–7.29 (m, 2H); $^{13}$C NMR (CDCl$_3$) δ 14.34, 22.91, 24.20, 26.40, 27.50, 29.59, 29.90, 30.87, 32.16, 32.85, 37.15, 41.93, 42.16, 125.79, 128.44, 128.59, 143.22; Found: C, 87.38; H, 12.25%. Calcd for C$_{20}$H$_{34}$: C, 87.51; H, 12.49%.

[3-(1-Adamantyl)propyl]benzene (2f)
oil. IR (neat) 2900, 2846, 1604, 1496, 1452, 747 cm\(^{-1}\); \(^1^H\) NMR (CDCl\(_3\)) \(\delta\) 1.10 (dt, \(J = 8.5, 4.5\) Hz, 2H), 1.45 (s, 3H), 1.46 (s, 3H), 1.53–1.61 (m, 5H), 1.68 (dm, 3H), 1.92 (br-s, 3H), 2.55 (t, \(J = 7.5\) Hz, 2H), 7.16–7.19 (m, 3H), 7.26–7.29 (m, 2H); \(^1^H\) NMR (CDCl\(_3\)) \(\delta\) 19.87, 19.93, 25.72, 26.46, 27.26, 29.29, 29.72, 29.83, 29.87, 29.98, 30.19, 31.01, 32.87, 36.54, 36.97, 37.20, 62.57, 67.93, 99.06, 125.76, 128.43, 128.59, 143.20; Found: C, 79.94; H, 11.24%. Calcd for C\(_{34}\)H\(_{47}\)NO\(_2\)S: C, 80.16; H, 11.30%.

\section*{4-Methyl-13-(2-oxacyclohexyloxy)-1-phenytridecane (2g)}

\begin{center}
\begin{tikzpicture}
\end{tikzpicture}
\end{center}

oil. IR (neat) 2926, 2854, 1456, 1352, 1121, 1078, 747, 698 cm\(^{-1}\); \(^1^H\) NMR (CDCl\(_3\)) \(\delta\) 0.85 (d, \(J = 6.5\) Hz, 3H), 1.05–1.44 (m, 16H), 1.50–1.67 (m, 9H), 1.71 (m, 1H), 1.84 (m, 1H), 2.58 (dt, \(J = 9.0, 6.0\) Hz, 2H), 3.38 (dt, \(J = 9.5, 6.5\) Hz, 1H), 3.50 (m, 1H), 3.73 (dt, \(J = 9.5, 7.0\) Hz, 1H), 3.87 (m, 1H), 4.58 (dd, \(J = 4.5, 3.0\) Hz, 1H), 7.15–7.19 (m, 3H), 7.26–7.29 (m, 2H); \(^1^C\) NMR (CDCl\(_3\)) \(\delta\) 19.87, 19.93, 25.72, 26.46, 27.26, 29.29, 29.72, 29.83, 29.87, 29.98, 30.19, 31.01, 32.87, 36.54, 36.97, 37.20, 62.57, 67.93, 99.06, 125.76, 128.42, 128.59, 143.20; Found: C, 79.94; H, 11.24%. Calcd for C\(_{32}\)H\(_{42}\)O\(_2\): C, 80.16; H, 11.30%.

\section*{N-Benzyl-N-(10-methyl-13-phenyltridecyl)-p-toluenesulfonamide (2h)}

\begin{center}
\begin{tikzpicture}
\end{tikzpicture}
\end{center}

oil. IR (neat) 2926, 2854, 1600, 1496, 1456, 1340, 1160, 1092, 698 cm\(^{-1}\); \(^1^H\) NMR (CDCl\(_3\)) \(\delta\) 0.84 (d, \(J = 6.5\) Hz, 3H), 1.06–1.44 (m, 19H), 1.54–1.68 (m, 2H), 2.44 (s, 3H), 2.53–6.63 (m, 2H), 3.07 (dd, \(J = 7.5, 7.5\) Hz, 2H), 4.31 (s, 2H), 7.15–7.19 (m, 3H), 7.26–7.32 (m, 9H), 7.73 (d, \(J = 8.0\) Hz, 2H); \(^1^C\) NMR (CDCl\(_3\)) \(\delta\) 19.87, 21.73, 26.82, 27.25, 28.08, 29.26, 29.27, 29.62, 29.74, 30.15, 32.88, 36.54, 36.98, 37.20, 48.27, 52.02, 125.77, 127.41, 127.89, 128.43, 128.48, 128.59, 128.71, 129.87, 136.84, 137.45, 143.19, 143.30; Found: C, 76.76; H, 8.69%. Calcd for C\(_{34}\)H\(_{47}\)NO\(_2\)S: C, 76.50; H, 8.87%.
5-Cycloheptyl-1-pentene (2j)

oil. IR (neat) 2924, 2854, 1641, 1460, 1446, 993, 909 cm\(^{-1}\); \(^1^H\) NMR (CDCl\(_3\)) \(\delta\) 1.12–1.70 (m, 17H), 2.02 (dd, \(J = 7.0, 7.0\) Hz, 2H), 4.91–5.01 (m, 2H), 5.82 (ddt, \(J = 17.5, 10.5, 7.0\) Hz, 1H); \(^1^3^C\) NMR (CDCl\(_3\)) \(\delta\) 26.78, 27.00, 28.79, 34.36, 34.85, 37.93, 39.40, 114.29, 139.54; Found: C, 86.90; H, 13.47%. Calcd for C\(_{12}\)H\(_{22}\): C, 86.67; H, 13.33%.

tert-Butyl(6-cycloheptylhexyloxy)dimethylsilane (2k)

oil. IR (neat) 2927, 2855, 1464, 1256, 1104, 836, 774 cm\(^{-1}\); \(^1^H\) NMR (CDCl\(_3\)) \(\delta\) 0.05 (s, 6H), 0.89 (s, 9H), 1.11–1.19 (m, 4H), 1.27–1.33 (m, 6H), 1.37–1.70 (m, 13H), 3.59 (t, \(J = 6.5\) Hz, 2H); \(^1^3^C\) NMR (CDCl\(_3\)) \(\delta\) –5.01, 18.61, 26.07, 26.22, 26.82, 27.62, 28.80, 30.01, 33.13, 34.91, 38.41, 39.49, 63.58; Found: C, 73.12; H, 12.62%. Calcd for C\(_{19}\)H\(_{40}\)OSi: C, 73.00; H, 12.90%.

1-Bromo-10-methylpentadecane (5a)

oil. IR (neat) 2925, 2855, 1457, 1377, 1249, 647 cm\(^{-1}\); \(^1^H\) NMR (CDCl\(_3\)) \(\delta\) 0.84 (d, \(J = 6.5\) Hz, 3H), 0.88 (t, \(J = 7.0\) Hz, 3H), 1.05–1.11 (m, 2H), 1.21–1.44 (m, 21H), 1.86 (quint, \(J = 7.0\) Hz, 2H), 3.41 (t, \(J = 7.0\) Hz, 2H); \(^1^3^C\) NMR (CDCl\(_3\)) \(\delta\) 14.34, 19.94, 22.94, 26.97, 27.28, 28.42, 29.00, 29.68, 29.80, 30.19, 32.48, 32.98, 33.08, 34.27, 37.28, 37.31; Found: C, 63.11; H, 10.99%. Calcd for C\(_{16}\)H\(_{33}\)Br: C, 62.94; H, 10.89%.
1-Bromo-10-phenylnonadecane (6a)

![Chemical Structure](image)

Oil. IR (neat) 2926, 2854, 1603, 1494, 1452, 1247, 762, 699 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.12–1.33 (m, 14H), 1.36–1.46 (m, 2H), 1.48–1.62 (m, 2H), 1.84 (dt, \(J = 14.0, 7.0\) Hz, 2H), 2.66 (tq, \(J = 7.0, 7.0\) Hz, 1H), 3.40 (t, \(J = 7.0\) Hz, 1H), 7.16–7.19 (m, 3H), 7.26–7.30 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 22.55, 27.88, 28.36, 29.59, 29.63, 29.86, 33.03, 34.30, 38.63, 40.14, 125.95, 127.20, 128.46, 148.16; Found: C, 65.64; H, 8.62%. Calcd for C\(_{15}\)H\(_{27}\)Br: C, 65.59; H, 8.74%.

1,10-Diphenylnonadecane (6b)

![Chemical Structure](image)

Oil. IR (neat) 2926, 2854, 1604, 1494, 1452, 1030, 761, 698 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.09–1.34 (m, 15H), 1.49–1.62 (m, 4H), 2.58 (t, \(J = 8.0\) Hz, 2H), 2.66 (tq, \(J = 7.0, 7.0\) Hz, 1H), 7.15–7.19 (m, 6H), 7.25–7.30 (m, 4H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 22.54, 27.92, 29.53, 29.69, 29.76, 29.76, 29.92, 31.73, 36.20, 38.65, 40.15, 125.75, 125.93, 127.20, 128.42, 128.45, 128.61, 143.17, 148.20; Found: C, 89.33; H, 10.65%. Calcd for C\(_{23}\)H\(_{32}\): C, 89.54; H, 10.46%.
References and Notes


(6) Silver is an effective catalyst for the coupling reaction of alkylmagnesium reagent R^1MgX with alkyl halide R^2MgX when the alkyl groups are the same (R^1 = R^2). (a) Kochi, J. K. J. Organomet. Chem. 2002, 653, 11–19. (b) Tamura, M.; Kochi, J. K. Synthesis 1971, 303–305.

(7) The reactions in hexane, toluene, Pr_3O, and THF resulted in lower yields (10–30%).


(9) Alkylsilver intermediates would be generated from alkyl halides and/or alkylmagnesium reagents.


(12) The author also detected alkenes and alkanes in these reactions. The alkanes were the main byproducts.
(13) The reactions of 3-bromo-1-phenylbutane with cyclopentylmagnesium bromide and with \textit{tert}-butylmagnesium bromide afforded the corresponding coupling products in 13\% and 5\% yields, respectively.

(14) The reactions in CH\textsubscript{2}Cl\textsubscript{2}, Et\textsubscript{2}O, and THF resulted in lower yields. The reaction in pentane resulted in a similar yield with a prolonged reaction time of 11 h.

(15) When pyridine, DPPE, P(OMe)\textsubscript{3}, and KF were used as additives in refluxing hexane, \textit{3c} was obtained in 44\%, 16\%, 54\%, and 56\% yield, respectively. When no additive was used, \textit{3c} was obtained in 41\% yield.


Chapter 5

Silver-Catalyzed Coupling Reactions of Alkyl Halides with Indenyllithium

Coupling reactions of tertiary and secondary alkyl halides with indenyllithium proceeded effectively in the presence of a catalytic amount of silver bromide to provide tertiary- and secondary-alkyl-substituted indene derivatives in good yields.
Introduction

Owing to the high nucleophilicity and the ready availability of organolithium reagents, coupling reactions of alkyl halides with organolithium reagents have been widely used for carbon-carbon bond formations in organic synthesis. The reaction of primary alkyl halides can proceed smoothly without any catalyst. However, the use of sterically bulky secondary alkyl halides as substrates in the coupling reactions often results in affording the corresponding coupling products in low yields, which is due to competitive side reactions, such as elimination to alkenes and reduction to alkanes.

Recent progress of transition-metal-catalyzed coupling reactions of alkyl halides enables us to use secondary alkyl halides as well as primary ones as substrates in the coupling reactions. While there are many reports in which Mg, Zn, Sn, B, or Si is used as the metal of the organometallic reagent, the use of organolithium is less investigated. Moreover, the reactions of tertiary alkyl halides are still rare and have to be established.

In Chapters 3 and 4, the author has described silver-catalyzed coupling reactions of alkyl halides with organomagnesium reagents. In these reactions, tertiary and secondary alkyl halides can be employed as substrates. In Chapter 5, he presents silver-catalyzed coupling reactions of tertiary and secondary alkyl halides with indenyllithium derivatives (Scheme 1). Indene framework can be found both in a large number of drug candidates and in various metallocene complexes. Thus, the new efficient route to modified indenes is important.

Scheme 1.

\[
\text{R-X} + \text{Li} \rightarrow \text{R} \quad \text{cat. AgBr} \quad \text{Et}_2\text{O} \\
\text{R} = \text{secondary and tertiary alkyl; } X = \text{I, Br, Cl}
\]

Results and Discussion

Treatment of 3-bromo-3-methyl-1-phenylbutane (1a) with two equivalents of indenyllithium
in the presence of 5 mol% AgBr in 

\[ \text{Et}_2\text{O} \] afforded the corresponding alkylated indene \( 2\text{a} \) in 90% yield (Table 1, entry 1).\(^{13}\) The reaction afforded 1-alkylindenes selectively, and no isomerization to 3-alkylindene occurred despite the presence of basic indenyllithium. Indenyllithium was prepared through deprotonative lithiation of indene with \( \text{sec}-\text{butyllithium} \) in \( \text{Et}_2\text{O} \) at 0 °C for 30 min.\(^{14}\) When AgBr was not added, only a trace amount of \( 2\text{a} \) was detected.\(^{15,16}\) The reactions performed in other ethereal solvents, such as THF and cyclopentyl methyl ether (CPME), resulted in lower yields (entries 2 and 3). The reaction in hexane, which was the solvent of \( \text{sec}-\text{butyllithium} \), resulted in moderate yield (entry 4).\(^{17}\) Other silver halides, such as AgI and AgCl, were not effective (entries 5 and 6). When AgNO\(_3\) was used instead of AgBr, the reaction was sluggish (entry 7).\(^{18}\) The reaction with AgOTf resulted in slightly lower yield than that with AgBr (entry 8).

**Table 1. Effects of solvents and silver salts**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield of ( 2\text{a} )% (^b)</th>
<th>Entry</th>
<th>X</th>
<th>Yield of ( 2\text{a} )% (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^a)</td>
<td>( \text{Et}_2\text{O} )</td>
<td>90</td>
<td>5(^d)</td>
<td>I</td>
<td>2(^e)</td>
</tr>
<tr>
<td>2(^a)</td>
<td>THF</td>
<td>10</td>
<td>6(^d)</td>
<td>Cl</td>
<td>30(^f)</td>
</tr>
<tr>
<td>3(^a)</td>
<td>CPME</td>
<td>56</td>
<td>7(^d)</td>
<td>NO(_3)</td>
<td>26(^g)</td>
</tr>
<tr>
<td>4(^a, c)</td>
<td>Hexane</td>
<td>64</td>
<td>8(^d)</td>
<td>OTf</td>
<td>74</td>
</tr>
</tbody>
</table>

\(^a\) Performed with 2.0 equiv of indenyllithium in the presence of 5 mol% AgBr. \(^b\) Based on NMR analysis. \(^c\) Indenyllithium was prepared in hexane. \(^d\) Performed in \( \text{Et}_2\text{O} \). \(^e\) Compound \( 1\text{a} \) was recovered in 88% yield. \(^f\) Compound \( 1\text{a} \) was recovered in 62% yield. \(^g\) Compound \( 1\text{a} \) was recovered in 40% yield.

The silver-catalyzed coupling reactions of various alkyl halides are summarized in Table 2. Cyclic tertiary alkyl bromide \( 1\text{b} \) also underwent the reaction smoothly (entry 2). It should be noted that the reaction of \( 1\text{b} \) was not stereospecific, which is highly suggestive of the existence of an intermediate having an \( \text{sp}^2 \)-hybridized carbon center.\(^9\) Since the reaction of
1-bromoadamantane (1c) was slow, CPME was used as a co-solvent and the reaction was performed under refluxing conditions (entry 3). Tertiary alkyl iodides 1d was too reactive under the reaction conditions (entry 4). The reaction of tertiary alkyl chloride 1e required a prolonged reaction time and a high temperature in CPME/Et₂O, and the coupling product was a 88/12 mixture of 1-alkyl- and 3-alkylindene derivatives through deprotonation of 2a by indenyllithium under the reaction conditions (entry 5). Both cyclic and acyclic secondary alkyl bromides reacted smoothly in refluxing Et₂O (entries 6 and 7). The substrates having functional groups, such as THP ether and sulfonamide could be also employed (entries 8 and 9). The coupling reaction of dibromide 1j proceeded selectively at the sp³-hybridized brominated carbon, although palladium-catalyzed coupling reactions of aryl halides with organolithium reagents can proceed smoothly (entry 10). Secondary alkyl iodides 1k can be employed (entry 11). However, cyclohexyl chloride resisted the reaction, being converted to 2f in only 17% yield.

**Table 2.** Silver-catalyzed coupling reactions of various alkyl halides with indenyllithium

<table>
<thead>
<tr>
<th>entry</th>
<th>R–X</th>
<th>1</th>
<th>temp.</th>
<th>2</th>
<th>yield /%b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph–Br</td>
<td>1a</td>
<td>0 °C</td>
<td>2a</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>tBu–Br</td>
<td>1b</td>
<td>reflux</td>
<td>2b</td>
<td>74d,e</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>refl</td>
<td>2c</td>
<td>61f,g,h</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>0 °C</td>
<td>2d</td>
<td>31</td>
<td></td>
</tr>
</tbody>
</table>
precursors of syndiospecific catalysts for Ziegler are known to be converted into the corresponding indenyltitanium trichlorides, which are afforded the corresponding indenylsilane derivative

Treatment of 1.88 g of tertiary alkyl bromide 1l (8.0 mmol) with indenyllithium (16 mmol) under the silver-catalyzed conditions afforded 1.82 g of 2j (84% yield). The same reaction in a 0.50 mmol-scale afforded 2j in 73% yield.

Treatment of 2j with sec-butyllithium followed by the addition of chlorotrimethylsilane afforded the corresponding indenylsilane derivative 4 in high yield (Scheme 3). Indenylsilanes are known to be converted into the corresponding indenyltitanium trichlorides, which are the precursors of syndiospecific catalysts for Ziegler-Natta polymerization of styrene.12a
The silver-catalyzed conditions were applicable to other stabilized organolithium reagents (Scheme 4). The reactions of both tertiary and secondary alkyl bromides with fluorenyllithium provided the corresponding 9-alkylfluorenes in good yields. The coupling reaction can be a useful tool because fluorene frameworks are known to have attractive optical properties. The regiocontrolled synthesis of 1,3-dialkylnedene could be achieved by the silver-catalyzed coupling reaction with the organolithium reagent derived from 2j. The alkyl moiety, which resulted from the alkyl halides, was substituted at the 1-position of the 1,3-dialkylated indenes and the regioisomer was not detected.
The author proposed a draft mechanism shown in Scheme 5. Formation of electron-rich silver(0)-ate complex initially takes place through the reaction of AgBr with two equivalents of indenyllithium (A). The ate complex effects a single electron transfer to alkyl halide to form the corresponding alkyl radical as cobalt- and manganese-ate complexes do (B). The radical is trapped by indenylsilver(I) to yield an oxidative adduct (C). Reductive elimination gives the coupling product (D), and the initial silver-ate complex is regenerated by the action of the remaining indenyllithium (E).
The initial reduction of silver(I) salt to silver(0) is justified as follows. Treatment of AgBr (0.30 mmol) with indenyllithium (0.60 mmol) in Et₂O at 0 °C for 30 min afforded 1H,1'H-1,1'-biindene (7) (0.14 mmol, dr = 73/27) (Scheme 6). The formation of 7, the amount of which is roughly equal to a half of AgBr used, indicates that Ag(I) would be reduced to Ag(0).

The following experiments revealed that monoindenylsilver(0)-ate complex²⁵,²⁶ is reactive enough to effect the coupling reaction (Table 3). A reaction mixture prepared from equimolar amounts of AgBr and indenyllithium failed to promote the reaction of 1a (entry 1). In contrast, a 1:2 mixture of AgBr and indenyllithium was highly reactive to yield 2a in 90% yield (entry 2). Three equivalents of the indenyllithium based on AgBr did not improve the efficiency.
significantly (entry 3). Although the exact feature of the catalytically active species is not clear, these results support the proposed mechanism shown in Scheme 5.

Table 3. Reactions with stoichiometric silver bromide

![Reaction Scheme]

<table>
<thead>
<tr>
<th>entry</th>
<th>X /mmol</th>
<th>yield of 2a /%&lt;sup&gt;a&lt;/sup&gt;</th>
<th>recovery of 1a /%&lt;sup&gt;a&lt;/sup&gt;</th>
<th>yield of 7 /mmol&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.30</td>
<td>&lt;5</td>
<td>96</td>
<td>0.14</td>
</tr>
<tr>
<td>2</td>
<td>0.60</td>
<td>90</td>
<td>0</td>
<td>0.15</td>
</tr>
<tr>
<td>3</td>
<td>0.90</td>
<td>93</td>
<td>0</td>
<td>0.14</td>
</tr>
</tbody>
</table>

<sup>a</sup> Based on NMR analysis.

Conclusion

The author has developed silver-catalyzed coupling reactions of alkyl halides with indenyllithium. The silver-catalyzed coupling reactions can afford tertiary- and secondary-alkyl-substituted indenes and fluorenes in good yields.
Experimental Section

Instrumentation and Chemicals

$^1$H NMR (500 MHz) and $^{13}$C NMR (125.7 MHz) spectra were taken on a Varian UNITY INOVA 500 spectrometer and were recorded in CDCl$_3$. Chemical shifts (δ) are in parts per million relative to tetramethylsilane at 0.00 ppm for $^1$H and relative to CDCl$_3$ at 77.23 ppm for $^{13}$C unless otherwise noted. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. TLC analyses were performed on commercial glass plates bearing a 0.25-mm layer of Merck Silica gel 60F$_{254}$. Florisil (75–150 µm, 100–200 mesh) was used for filtration. Silica gel (Wakogel 200 mesh) was used for column chromatography. Mass spectra were determined on a JEOL Mstation 700 spectrometer. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Silver bromide, silver chloride, silver nitrate, $^1$H-indene, and cyclopentyl methyl ether were purchased from Wako Pure Chemicals. Silver iodide, butyllithium (1.6 M in hexane solution), 9$^1$H-fluorene, and hexane were purchased from Nacalai Tesque. Diethyl ether and tetrahydrofuran were purchased from Kanto Chemical Co., stored under nitrogen, and used as it is. Secondary butyllithium (1.0 M in cyclohexane/hexane solution) was also purchased from Kanto Chemical Co. Silver trifluoromethanesulfonate was purchased from Aldrich. All reactions were carried out under argon atmosphere.

Synthesis of 3-bromo-3-methyl-1-phenylbutane (1a)

2-Methyl-4-phenyl-2-butanol (4.1 g, 25 mmol) was placed in a 100-mL reaction flask. Then hydrobromic acid (47% solution, 12.9 g, 75 mmol) was added dropwise to the reaction mixture. After being stirred for 1 day at 25 °C, the reaction mixture was poured into ethylene glycol (20 mL). The products were extracted with hexane (30 mL × 2). The combined organic layer was dried over Na$_2$SO$_4$ and concentrated. Distillation of the crude oil (1 Torr, 110 °C) afforded tertiary alkyl bromide 1a (4.2 g 18.4 mmol) in 74% isolated yield.
Synthesis of 3-chloro-3-methyl-1-phenylbutane (1e)

2-Methyl-4-phenyl-2-butanol (4.9 g, 30 mmol) was placed in a 100-mL reaction flask. Hydrochloric acid (11 M solution, 11 mL, 121 mmol) was then added dropwise to the reaction mixture. After being stirred for 1 day at 25 °C, the reaction mixture was poured into ethylene glycol (20 mL). The products were extracted with hexane (30 mL × 2). The combined organic layer was dried over Na$_2$SO$_4$ and concentrated. Silica gel column purification (hexane) of the crude oil afforded tertiary alkyl chloride 1e (3.3 g, 17.8 mmol) in 93% isolated yield.

Synthesis of 3-bromo-1-(4-bromophenyl)butane (1j)

Magnesium (turnings, 0.36 g, 15 mmol) and Et$_2$O (5 mL) were placed in a 100-mL reaction flask. 4-Bromobenzyl bromide (2.5 g, 10 mmol) in Et$_2$O (10 mL) was added dropwise to the reaction mixture at 0 °C. After the mixture was stirred for 2 h, THF (10 mL) and 1,2-epoxypropane (1.4 mL, 20 mmol) were successively added at 0 °C. The reaction mixture was stirred for 2 h at room temperature. Then, the reaction mixture was poured into a saturated ammonium chloride solution. The products were extracted with ethyl acetate (20 mL × 2). The combined organic layer was dried over Na$_2$SO$_4$ and concentrated. Silica gel column purification (hexane/ethyl acetate = 2/1) of the crude oil afforded 4-(4-bromophenyl)-2-butanol (0.84 g, 3.7 mmol) in 37% isolated yield. This alcohol and dichloromethane (4 mL) were placed in a 30-mL reaction flask. Then, triethylamine (1.0 mL, 7.4 mmol), methanesulfonyl chloride (0.43 mL, 5.6 mmol), and 4-(dimethylamino)pyridine (0.01 mmol, 1.2 mg) were successively added to the reaction mixture. After being stirred for 4 h at room temperature, the reaction mixture was poured into a saturated ammonium chloride solution. The products were extracted with ethyl acetate (20 mL × 2). The combined organic layer was dried over Na$_2$SO$_4$ and concentrated. The crude oil in acetone (4 mL) was placed in a 30-mL reaction flask. Lithium bromide (0.96 g, 11 mmol) was then added to the reaction mixture. After being stirred for 12 h in refluxing acetone, the reaction mixture was poured into water. The products were extracted
with hexane (20 mL × 2). The combined organic layer was dried over Na₂SO₄ and concentrated. Silica gel column purification (hexane) of the crude oil afforded 1j (0.66 g, 2.3 mmol) in 61% isolated yield.

**General procedure for a silver-catalyzed coupling reaction of alkyl halides with indenyllithium**

The reaction of 1a with indenyllithium (Table 2, entry 1) is representative. Silver bromide (4.7 mg, 0.025 mmol) in Et₂O (1 mL) was placed in a 30-mL reaction flask. Indenyllithium, which was prepared by treatment of 1H-indene (0.13 mL, 1.1 mmol) with sec-butyllithium (1.0 M in cyclohexane/hexane solution, 1.0 mL, 1.0 mmol) in Et₂O (3 mL) at 0 °C for 1 h, was added to the reaction mixture at 0 °C. Then, substrate 1a (113.6 mg, 0.50 mmol) in Et₂O (2 mL) was added. After being stirred vigorously for 10 h at 0 °C, the reaction mixture was poured into a saturated ammonium chloride solution (30 mL). The products were extracted with ethyl acetate (30 mL × 3). The combined organic layer was passed through Florisil, dried over Na₂SO₄ and concentrated. Silica gel column purification (hexane/ethyl acetate = 80/1) of the crude product provided the corresponding coupling product 2a (112.8 mg, 0.43 mmol) in 86% isolated yield.

**A silver-catalyzed coupling reaction in a gram-scale**

Silver bromide (75.1 mg, 0.40 mmol) in Et₂O (8 mL) was placed in a 100-mL reaction flask. Indenyllithium prepared by treatment of 1H-indene (2.1 mL, 17.6 mmol) with sec-butyllithium (1.0 M in cyclohexane/hexane solution, 16 mL, 16 mmol) in Et₂O (16 mL) at 0 °C for 1 h, was added to the mixture at room temperature. Substrate 1l (1.88 g, 8.0 mmol) in Et₂O (16 mL) was then added to the reaction mixture. After being stirred vigorously for 10 h at room temperature, the reaction mixture was poured into a saturated ammonium chloride solution (30 mL). The products were extracted with ethyl acetate (30 mL × 3). The combined organic layer was passed through Florisil, dried over Na₂SO₄ and concentrated. Silica gel column purification (hexane) of the crude product provided the corresponding coupling product 2j (1.82 g, 6.7 mmol) in 84%
isolated yield.

**Synthesis of 3-(1,1-dimethylnonyl)-1-trimethylsilyl-1H-indene (4)**

Indene derivative 2j (0.41 g, 1.5 mmol) in Et₂O (1.5 mL) was placed in a 30-mL reaction flask. Then, sec-butyllithium (1.0 M in cyclohexane/hexane solution, 1.65 mL, 1.65 mmol) was added dropwise to the mixture at 0 °C. After the mixture was stirred at 0 °C for 1.5 h, chlorotrimethylsilane (0.29 mL, 2.25 mmol) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for 12 h. Then, the reaction mixture was poured into water (20 mL). The products were extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried over Na₂SO₄ and concentrated. Silica gel column purification (hexane) of the crude product provided the corresponding indenylsilane derivative 4 (0.50 g, 1.45 mmol) in 97% isolated yield. (Silica Gel 60 N (spherical, neutral) 40–100 µm, which was purchased from Kanto Chemical Co., was used for column chromatography in this case.)

**General procedure for a silver-catalyzed coupling reaction of alkyl halides with fluorenyllithium**

The synthesis of 5a (Scheme 4) is representative. Silver bromide (4.7 mg, 0.025 mmol) in Et₂O (1 mL) was placed in a 30-mL reaction flask. Fluorenyllithium, which was prepared through treatment of 9H-fluorene (182.8 mg, 1.1 mmol) with butyllithium (1.6 M in cyclohexane/hexane solution, 0.63 mL, 1.0 mmol) in Et₂O (3 mL) at 0 °C for 1 h, was added to the reaction mixture at −20 °C. Then, substrate 1a (113.6 mg, 0.50 mmol) in Et₂O (2 mL) was added at the same temperature. After being stirred vigorously for 10 h at −20 °C, the reaction mixture was poured into a saturated ammonium chloride solution (30 mL). The products were extracted with ethyl acetate (30 mL × 3). The combined organic layer was passed through Florisil, dried over Na₂SO₄ and concentrated. Silica gel column purification (hexane/ethyl acetate = 50/1) of the crude product provided the corresponding coupling product 5a (110.4 mg, 0.35 mmol) in 71% isolated yield.
General procedure for synthesis of 1,3-dialkylindenones

The synthesis of 6a (Scheme 4) is representative. Silver bromide (4.7 mg, 0.025 mmol) in Et₂O (1 mL) was placed in a 30-mL reaction flask. Indenyllithium derivative, which was prepared through treatment of 2j (297.5 mg, 1.1 mmol) with sec-butyllithium (1.0 M in cyclohexane/hexane solution, 1.0 mL, 1.0 mmol) in Et₂O (3 mL) at 0 °C for 1.5 h, was added to the reaction mixture at 0 °C. Then, substrate 1a (113.6 mg, 0.50 mmol) in Et₂O (2 mL) was added at the same temperature. After being stirred vigorously for 12 h at 0 °C, the reaction mixture was poured into a saturated ammonium chloride solution (30 mL). The products were extracted with ethyl acetate (30 mL × 3). The combined organic layer was passed through Florisil, dried over Na₂SO₄ and concentrated. Purification by silica gel column chromatography (hexane/ethyl acetate = 80/1), which was followed by gel permeation chromatography, of the crude product provided the corresponding coupling product 6a (84.6 mg, 0.20 mmol) in 41% isolated yield.

Characterization Data

Compounds 1c, 1d, 1g, 1k, 3a, and 3b were commercially available. Compound 1b, 27 1f, 28 1h, 9b 1i, 9b and 1l 3b were found in the literature.

3-Bromo-3-methyl-1-phenylbutane (1a)

\[
\begin{align*}
\text{Ph} & \quad \text{Br} \\
\end{align*}
\]

colorless oil. IR (neat) 3024, 2932, 1604, 1497, 1450, 1103, 740, 702 cm⁻¹; "H NMR (CDCl₃) δ 1.82 (s, 6H), 2.09 (ddd, J = 8.0, 4.5, 3.5 Hz, 2H), 2.84–2.87 (m, 2H), 7.18–7.22 (m, 3H), 7.27–7.31 (m, 2H); "C NMR (CDCl₃) δ 33.11, 34.49, 49.66, 67.69, 126.19, 128.63, 128.70, 141.81; Found: C, 58.33; H, 6.68%. Calcd for C₁₁H₁₂Br: C, 58.17; H, 6.66%.

3-Chloro-3-methyl-1-phenylbutane (1e)
colorless oil. IR (neat) 2932, 2893, 1604, 1458, 1373, 1110, 748, 702 cm⁻¹; ¹H NMR (CDCl₃) δ 1.64 (s, 6H), 2.04 (ddd, J = 8.0, 5.0, 4.5 Hz, 2H), 2.82 (dt, J = 8.0, 4.5 Hz, 2H), 7.18–7.22 (m, 3H), 7.27–7.31 (m, 2H); ¹³C NMR (CDCl₃) δ 31.87, 32.69, 48.17, 70.76, 126.15, 128.61, 128.68, 141.99; Found: C, 72.41; H, 8.19%. Calcd for C₁₁H₁₅Cl: C, 72.32; H, 8.28%.

3-Bromo-1-(4-bromophenyl)butane (1j)

yellow oil. IR (neat) 2924, 2862, 1489, 1450, 1072, 1001, 826 cm⁻¹; ¹H NMR (CDCl₃) δ 1.72 (d, J = 6.5 Hz, 3H), 2.00 (m, 1H), 2.10 (m, 1H), 2.71 (m, 1H), 2.82 (m, 1H), 4.04 (m, 1H), 7.09 (dt, J = 8.5, 2.0 Hz, 2H), 7.41 (dt, J = 8.5, 2.0 Hz, 2H); ¹³C NMR (CDCl₃) δ 26.74, 33.59, 42.62, 50.73, 120.08, 130.51, 131.76, 140.06; Found: C, 41.20; H, 4.19%. Calcd for C₁₀H₁₂Br₂: C, 41.13; H, 4.14%.

1-(1,1-Dimethyl-3-phenylpropyl)-1H-indene (2a)

yellow oil. IR (neat) 3024, 2963, 2862, 1605, 1458, 1366, 763, 702 cm⁻¹; ¹H NMR (CDCl₃) δ 1.05 (s, 3H), 1.07 (s, 3H), 1.66–1.77 (m, 2H), 2.69 (t, J = 8.5 Hz, 2H), 3.46 (t, J = 2.0 Hz, 1H), 6.57 (dd, J = 6.0, 2.0 Hz, 1H), 6.83 (dd, J = 6.0, 2.0 Hz, 1H), 7.13–7.19 (m, 4H), 7.22–7.29 (m, 3H), 7.32 (d, J = 7.0 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H); ¹³C NMR (CDCl₃) δ 26.22, 26.28, 31.10, 37.07, 43.96, 59.64, 121.24, 124.52, 124.98, 125.89, 126.65, 128.56, 128.62, 132.00, 137.74, 143.30, 145.69, 145.72; Found: C, 91.67; H, 8.51%. Calcd for C₂₀H₂₂: C, 91.55; H, 8.45%.
1-(1-Methyl-4-(1,1-dimethylethyl)cyclohexyl)-1H-indene (2b) (cis/trans = 35/65 mixture of diastereomers)²⁹

![Chemical structure of 1-(1-Methyl-4-(1,1-dimethylethyl)cyclohexyl)-1H-indene (2b)](image)

white solid. IR (nujol) 3063, 2939, 2862, 1458, 1366, 1227, 1150, 1103, 1026, 926, 756, 725 cm⁻¹; ¹H NMR (CDCl₃) δ 0.34 (s, 0.35×3H), 0.68 (s, 0.65×3H), 0.85 (s, 0.65×9H), 0.92 (s, 0.35×9H), 0.95 (m, 0.65×1H), 1.12–1.32 (m, 0.35×1H + 2H), 1.47–1.81 (m, 0.65×1H + 4H), 1.99 (m, 1H), 2.37 (m, 0.35×1H), 3.20 (br-s, 0.65×1H), 3.85 (br-s, 0.35×1H), 6.53 (dd, J = 5.5, 2.0 Hz, 0.35×1H), 6.58 (dd, J = 5.5, 2.0 Hz, 0.65×1H), 6.81(m, 1H), 7.13 (m, 1H), 7.23 (m, 1H), 7.32 (t, J = 7.0 Hz, 1H), 7.45 (d, J = 7.5 Hz, 0.35×1H), 7.54 (d, J = 7.5 Hz, 0.65×1H); ¹³C NMR (CDCl₃) δ 18.62, 22.84, 22.97, 23.09, 23.18, 23.96, 27.76, 27.87, 32.60, 32.80, 36.51, 37.06, 37.75, 38.15, 38.38, 40.20, 48.30, 48.32, 52.22, 63.58, 121.04, 121.17, 124.26, 124.30, 124.95, 125.41, 126.44, 126.55, 131.61, 131.77, 137.56, 138.10, 145.60, 145.78, 145.80, 146.06; Found: C, 89.20; H, 10.72%. Calcd for C₂₀H₂₈: C, 89.49; H, 10.51%. m.p. 54–55 °C.

1-(1-Adamantyl)-1H-indene (2c)

white solid. IR (nujol) 2854, 1450, 1366, 1096, 756, 716 cm⁻¹; ¹H NMR (CDCl₃) δ 1.58–1.64 (m, 6H), 1.66–1.71 (dm, 3H), 1.82 (dm, 3H), 1.95 (br-s, 3H), 3.14 (s, 1H), 6.60 (d, J = 5.5 Hz, 1H), 6.80 (d, J = 5.5 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H); ¹³C NMR (CDCl₃) δ 29.03, 37.03, 37.28, 41.01, 62.02, 121.03, 124.17, 125.53, 126.53, 131.77, 137.09, 145.00, 145.72; Found: C, 91.22; H, 8.60%. Calcd for C₁₉H₂₅: C, 91.14; H, 8.86%. m.p. 64–65 °C.
Chapter 5

1-(1,1-Dimethylethyl)-1H-indene (2d)

1H NMR (CDCl₃) δ 1.03 (s, 9H), 3.27 (s, 1H), 6.55 (dd, J = 6.0, 2.0 Hz, 1H), 6.81 (dt, J = 6.0, 1.0 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 7.24 (t, J = 7.5 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H); ¹³C NMR (CDCl₃) δ 28.77, 34.35, 61.56, 121.06, 124.37, 125.04, 126.57, 131.70, 138.22, 145.61, 145.97; Found: C, 90.45; H, 9.63%. Calcd for C₁₃H₁₆: C, 90.64; H, 9.36%.

1-(1-Methyl-3-phenylpropyl)-1H-indene (2e) (56:44 mixture of diastereomers)

1H NMR (CDCl₃) δ 0.56 (d, J = 7.0 Hz, 0.44×3H), 1.08 (d, J = 7.0 Hz, 0.56×3H), 1.35 (m, 1H), 1.70 (m, 0.44×1H), 1.91 (m, 0.44×1H), 2.26 (m, 1H), 2.42 (m, 0.56×1H), 2.62 (m, 0.56×1H), 2.77 (m, 1H), 3.48 (br-s, 0.56×1H), 3.56 (br-s, 0.44×1H), 6.47 (dd, J = 6.0, 2.0 Hz, 0.44×1H), 6.50 (dd, J = 5.5, 2.0 Hz, 0.56×1H), 6.81 (dd, J = 5.5, 2.5 Hz, 0.56×1H), 6.85 (dd, J = 5.5, 2.5 Hz, 0.44×1H), 7.04 (d, J = 7.5 Hz, 1H), 7.13–7.19 (m, 0.44×1H + 1H), 7.21–7.25 (m, 4H), 7.30–7.36 (m, 0.56×1H + 2H); ¹³C NMR (CDCl₃) δ 14.88, 18.27, 34.20, 34.36, 34.39, 34.41, 34.67, 38.27, 55.48, 56.55, 121.12, 122.96, 123.38, 124.73, 124.84, 125.82, 126.00, 126.60, 126.64, 128.34, 128.49, 128.56, 128.62, 128.63, 131.82, 132.39, 136.54, 137.48, 142.66, 142.76, 145.12, 145.34, 146.46, 147.17; Found: C, 91.81; H, 8.15%. Calcd for C₁₉H₂₀: C, 91.88; H, 8.12%.

1-Cyclohexyl-1H-indene (2f)
colorless oil. IR (neat) 3063, 2924, 2855, 1450, 1366, 772, 718 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 0.90 (m, \(J = 1\) Hz), 1.05–1.18 (m, 2H), 1.20–1.35 (m, 3H), 1.61 (dm, 2H), 1.77 (m, 1H), 1.87–2.02 (m, 2H), 3.40 (t, \(J = 2.0\) Hz, 1H), 6.52 (dd, \(J = 5.5, 2.0\) Hz, 1H), 6.80 (dd, \(J = 5.5, 2.0\) Hz, 1H), 7.17 (td, \(J = 7.5, 1.0\) Hz, 1H), 7.23 (t, \(J = 7.5\) Hz, 1H), 7.33 (d, \(J = 7.5\) Hz, 1H), 7.41 (d, \(J = 7.5\) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 26.73, 26.73, 27.12, 28.54, 32.47, 40.53, 56.76, 121.03, 123.29, 124.66, 126.52, 131.53, 137.78, 145.15, 146.90; Found: C, 90.67; H, 9.22%. Calcd for C\(_{15}\)H\(_{18}\): C, 90.85; H, 9.15%.

2-[(10-(1H-Inden-1-yl)undecyl)oxy]tetrahydropyran (2g) (53:47 mixture of diastereomers)

green oil. IR (neat) 2924, 2855, 1458, 1072, 1034, 772, 725 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 0.46 (d, \(J = 6.5\) Hz, 0.53×3H), 0.98 (d, \(J = 6.5\) Hz, 0.47×3H), 1.03 (m, 1H), 1.09–1.47 (m, 14H), 1.49–1.64 (m, 6H), 1.72 (m, 1H), 1.84 (m, 1H), 2.19 (m, 1H), 3.38 (ddt, \(J = 10.5, 10.0, 6.5\) Hz, 1H), 3.49 (m, 1H), 3.73 (ddt, \(J = 10.5, 10.0, 6.5\) Hz, 1H), 3.87 (m, 1H), 4.57 (m, 1H), 6.47 (dd, \(J = 6.0, 2.0\) Hz, 0.53×1H), 6.49 (dd, \(J = 5.5, 2.0\) Hz, 0.53×1H), 6.81 (dd, \(J = 6.0, 2.0\) Hz, 0.57×1H), 6.84 (dd, \(J = 5.5, 2.0\) Hz, 0.53×1H), 7.17 (m, 1H), 7.24 (m, 1H), 7.33 (d, \(J = 7.5\) Hz, 1H), 7.39 (m, 1H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 14.86, 18.21, 19.94 (×2C), 25.74 (×2C), 26.45, 26.48, 27.97, 28.09, 29.67, 29.72, 29.75 (×2C), 29.83, 29.84, 29.87, 29.97, 30.00, 30.08, 31.02 (×2C), 32.85, 34.89, 35.13, 36.57, 55.62, 56.61, 62.56, 62.58, 67.91 (×2C), 99.07, 99.09, 121.03, 121.05, 122.91, 123.42, 124.63, 124.74, 126.47, 126.53, 131.49, 132.11, 136.83, 137.99, 145.14, 145.42, 146.69, 147.48; Found: C, 80.64; H, 10.30%. Calcd for C\(_{25}\)H\(_{38}\)O\(_2\): C, 81.03; H, 10.33%.

\(N\)-(10-(1H-Inden-1-yl)undecyl)-\(N\)-(phenylmethyl)-\(p\)-toluenesulfonamide (2h) (54:46 mixture
of diastereomers)

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\text{Ph} \quad \text{Ts} \quad \text{Br}
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colorless oil. IR (neat) 3063, 2924, 2855, 1458, 1342, 1157, 733 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 0.47 (d, \(J = 6.5\) Hz, 0.46\(\times\)3H), 0.98 (d, \(J = 6.5\) Hz, 0.54\(\times\)3H), 0.98–1.57 (m, 16H), 2.18 (m, 1H), 2.43 (s, 0.54\(\times\)3H), 2.44 (s, 0.46\(\times\)3H), 3.04–3.09 (m, 2H), 3.46 (br-s, 0.54\(\times\)1H), 3.50 (br-s, 0.46\(\times\)1H), 4.30 (s, 0.54\(\times\)2H), 4.31 (s, 0.46\(\times\)2H), 6.46 (dd, \(J = 6.0, 2.0\) Hz, 0.46\(\times\)1H), 6.49 (dd, \(J = 6.0, 2.0\) Hz, 0.54\(\times\)1H), 6.81 (dd, \(J = 6.0, 2.0\) Hz, 0.54\(\times\)1H), 6.84 (dd, \(J = 6.0, 2.0\) Hz, 0.46\(\times\)1H), 7.16 (m, 1H), 7.22–7.34 (m, 9H), 7.39 (t, \(J = 7.5\) Hz, 1H), 7.72 (dd, \(J = 8.5, 5.0\) Hz, 2H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 14.91, 18.26, 21.72 (\(\times\)2C), 26.80, 26.84, 27.95, 28.07, 28.09, 28.15, 29.20, 29.27, 29.53, 29.61, 29.62, 29.75, 29.79, 30.03, 32.82, 34.90, 35.14, 36.53, 48.27, 48.32, 52.05, 52.08, 55.63, 56.63, 121.06, 121.07, 122.92, 123.40, 124.64, 124.76, 126.50, 126.55, 127.42, 127.43, 127.90 (\(\times\)2C), 128.49, 128.50, 128.72 (\(\times\)2C), 129.87 (\(\times\)2C), 131.53, 132.14, 136.81, 136.86, 136.88, 137.51 (\(\times\)2C), 137.95, 143.30, 143.31, 145.15, 145.43, 146.70, 147.46; HRMS (m/z) obsd 529.3011 (\(\Delta = -0.6\) ppm), calcd for C\(_{34}\)H\(_{43}\)O\(_2\)NS 529.3015.

1-(3-(4-Bromophenyl)-1-methylpropyl)-1H-indene (2i) (54:46 mixture of diastereomers)

\[
\text{Br}
\]

eyellow oil. IR (neat) 3064, 2924, 2862, 1488, 1373, 1072, 1001, 764 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 0.56 (d, \(J = 7.0\) Hz, 0.46\(\times\)3H), 1.09 (d, \(J = 7.0\) Hz, 0.54\(\times\)3H), 1.28 (m, 1H), 1.66 (m, 0.46\(\times\)1H), 1.86 (m, 0.54\(\times\)1H), 2.22 (m, 1H), 2.35 (dt, \(J = 14.0, 8.0\) Hz, 0.54\(\times\)1H), 2.55 (m, 0.46\(\times\)1H), 2.72 (m, 1H), 3.46 (t, \(J = 2.0\) Hz, 0.46\(\times\)1H), 3.53 (t, \(J = 2.0\) Hz, 0.54\(\times\)1H), 6.45 (dd, \(J = 5.5, 2.0\) Hz, 0.54\(\times\)1H), 6.49 (dd, \(J = 5.5, 2.0\) Hz, 0.46\(\times\)1H), 6.82 (dd \(J = 5.5, 2.0\) Hz, 0.54\(\times\)1H), 6.85 (dd, \(J = 5.5, 2.0\) Hz, 0.46\(\times\)1H), 6.90 (d, \(J = 8.5\) Hz, 1H), 7.10 (d, \(J = 8.5\) Hz, 1H), 7.16 (m, 1H), 7.23–7.36
(m, 4H), 7.42 (d, \(J = 8.5\) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 14.90, 18.45, 33.52, 33.75, 33.98, 34.17, 34.52, 37.96, 55.42, 56.51, 119.50, 119.70, 121.16, 121.17, 122.96, 123.26, 124.79, 124.89, 126.66, 126.71, 130.33, 130.39, 131.44, 131.65, 131.95, 132.49, 136.38, 137.19, 141.54, 141.66, 145.08, 145.26, 146.39, 146.98; Found: C, 69.43; H, 5.83%. Calcd for C\(_{19}\)H\(_{19}\)Br: C, 69.73; H, 5.85%.

1-(1,1-Dimethylnonyl)-1H-indene (2j)

![Diagram of 1-(1,1-Dimethylnonyl)-1H-indene (2j)]

colorless oil. IR (neat) 2924, 2855, 1466, 1366, 763, 725 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 0.89 (t, \(J = 6.5\) Hz, 3H), 0.93 (s, 3H), 0.93 (s, 3H), 1.24–1.34 (m, 10H), 1.35–1.46 (m, 4H), 3.39 (br-s, 1H), 6.53 (dd, \(J = 5.5, 2.0\) Hz, 1H), 6.80 (dd, \(J = 5.5, 2.0\) Hz, 1H), 7.13 (td, \(J = 7.5, 1.0\) Hz, 1H), 7.23 (m, 1H), 7.32 (d, \(J = 8.0\) Hz, 1H), 7.48 (d, \(J = 7.5\) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 14.35, 22.91, 24.41, 26.03, 26.20, 29.59, 29.93, 30.77, 32.14, 36.88, 42.07, 59.52, 121.09, 124.34, 124.98, 126.48, 131.65, 138.17, 145.74, 145.94; Found: C, 88.82; H, 11.28%. Calcd for C\(_{20}\)H\(_{30}\): C, 88.82; H, 11.18%.

3-(1,1-Dimethylnonyl)-1-trimethylsilyl-1H-indene (4)

![Diagram of 3-(1,1-Dimethylnonyl)-1-trimethylsilyl-1H-indene (4)]
yellow oil. IR (neat) 2932, 2855, 1458, 1381, 1249, 1034, 841, 763 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) –0.06 (s, 9H), 0.84 (t, \(J = 7.5\) Hz, 3H), 1.09–1.14 (m, 2H), 1.15–1.27 (m, 10H), 1.33 (s, 6H), 1.71–1.82 (m, 2H), 3.33 (d, \(J = 2.0\) Hz, 1H), 6.26 (d, \(J = 2.0\) Hz, 1H), 7.14 (t, \(J = 7.5\) Hz, 1H), 7.22 (t, \(J = 7.5\) Hz, 1H), 7.41 (d, \(J = 7.5\) Hz, 1H), 7.66 (d, \(J = 7.5\) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) –2.11, 14.30, 22.86, 25.20, 28.44, 28.45, 29.51, 29.78, 30.63, 32.10, 36.72, 41.53, 44.10, 122.12,
123.13, 123.20, 124.26, 129.61, 143.33, 147.51, 149.67; HRMS (m/z) obsd 342.2740 (Δ = -0.8 ppm), calcd for C$_{23}$H$_{38}$Si 342.2743.

9-(1,1-Dimethyl-3-phenylpropyl)-9H-fluorene (5a)

white solid. IR (nujol) 2924, 2854, 1604, 1450, 1381, 1281, 1173, 741 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 1.02 (s, 6H), 1.73 (dt, $J$ = 9.0, 5.0 Hz, 2H), 2.76 (dt, $J$ = 9.0, 5.0 Hz, 2H), 3.97 (s, 1H), 7.17–7.24 (m, 5H), 7.28 (t, $J$ = 8.0 Hz, 2H), 7.34 (t, $J$ = 7.0 Hz, 2H), 7.59 (d, $J$ = 8.0 Hz, 2H), 7.72 (d, $J$ = 7.0 Hz, 2H); $^{13}$C NMR (CDCl$_3$) δ 26.40, 31.02, 37.96, 42.96, 56.29, 119.76, 125.92, 126.24, 126.61, 127.20, 128.54, 128.63, 142.42, 143.11, 145.97; Found: C, 91.97; H, 7.89%. Calcd for C$_{24}$H$_{24}$: C, 92.26; H, 7.74%. m.p. 67–68 °C.

9-(1-Methyl-3-phenylpropyl)-9H-fluorene (5b)

white solid. IR (nujol) 2924, 2731, 1458, 1373, 740, 702 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 0.72 (d, $J$ = 6.5 Hz, 3H), 1.61 (m, 1H), 1.77 (m, 1H), 2.41 (m, 1H), 2.65 (ddd, $J$ = 13.5, 10.0, 6.5 Hz, 1H), 2.75 (ddd, $J$ = 13.5, 10.0, 6.0 Hz, 1H), 4.02 (d, $J$ = 3.0 Hz, 1H), 7.14–7.20 (m, 3H), 7.24–7.30 (m, 4H), 7.33–7.37 (m, 2H), 7.46–7.48 (m, 2H), 7.74 (dd, $J$ = 7.0, 4.5 Hz, 2H); $^{13}$C NMR (CDCl$_3$) δ 16.07, 34.37, 36.24, 36.83, 52.69, 119.83, 119.91, 124.66, 125.23, 125.96, 126.84, 126.99, 127.08, 127.14, 128.55, 128.62, 141.77, 142.09, 142.58, 145.82, 146.90; Found: C, 92.60; H, 7.40%. Calcd for C$_{23}$H$_{22}$: C, 92.57; H, 7.43%. m.p. 72–73 °C.
3-(1,1-Dimethylnonyl)-1-(1,1-dimethyl-3-phenylpropyl)-1H-indene (6a)

![Structure of 6a]

colorless oil. IR (neat) 2932, 2855, 1605, 1458, 1366, 763 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 0.84 (t, \(J = 7.0\) Hz, 3H), 1.01 (s, 3H), 1.04 (s, 3H), 1.06–1.25 (m, 12H), 1.30 (s, 3H), 1.31 (s, 3H), 1.62–1.84 (m, 4H), 2.65–2.73 (m, 2H), 3.33 (d, \(J = 2.0\) Hz, 1H), 6.18 (d, \(J = 2.0\) Hz, 1H), 7.12 (t, \(J = 7.5\) Hz, 1H), 7.16–7.30 (m, 6H), 7.54 (dd, \(J = 11.5, 7.5\) Hz, 2H); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 14.30, 22.86, 25.15, 26.25, 26.37, 28.21, 28.27, 29.49, 29.68, 30.53, 31.10, 32.08, 36.67, 37.21, 41.11, 44.04, 56.92, 122.10, 123.83, 125.08, 125.85, 126.02, 128.53, 128.60, 131.38, 143.41, 145.02, 147.64, 151.63; Found: C, 89.58; H, 10.49%. Calcd for C\(_{31}\)H\(_{44}\): C, 89.36; H, 10.64%.

3-(1,1-Dimethylnonyl)-1-(1-methyl-3-phenylpropyl)-1H-indene (6b) (51:49 mixture of diastereomers)

![Structure of 6b]

colorless oil. IR (neat) 2924, 2855, 1605, 1458, 1381, 741, 694 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 0.50 (d, \(J = 7.0\) Hz, 0.49×3H), 0.84 (t, \(J = 7.0\) Hz, 0.49×3H), 0.84 (t, \(J = 7.0\) Hz, 0.51×3H), 1.06 (d, \(J = 7.0\) Hz, 0.51×3H), 1.06–1.25 (m, 12H), 1.30–1.35 (m, 7H), 1.64 (m, 1H), 1.71 (m, 0.49×1H), 1.80 (m, 1H), 1.91 (m, 0.51×1H), 2.21 (m, 1H), 2.39 (dt, \(J = 14.0, 8.5\) Hz, 0.49×1H), 2.59 (m, 0.51×1H), 2.78 (m, 1H), 3.36 (br-s, 0.51×1H), 3.44 (br-s, 0.49×1H), 6.06 (d, \(J = 2.0\) Hz, 0.49×1H), 6.10 (d, \(J = 2.0\) Hz, 0.51×1H), 7.03 (d, \(J = 6.5\) Hz, 1H), 7.11–7.16 (m, 2H), 7.19–7.24 (m, 3H), 7.32 (dd, \(J = 14.5, 7.0\) Hz, 2H), 7.54 (dd, \(J = 7.5, 2.5\) Hz, 1H); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 14.30, 14.31, 14.66, 18.42, 22.86, 22.87, 25.12 (× 2C), 28.14, 28.15, 28.25 (× 2C), 29.47, 29.51,
29.67, 29.71, 30.52, 30.53, 32.08 (∗ 2C), 34.05, 34.20, 34.45, 34.59, 34.94, 36.69, 36.79, 38.43, 41.08 (∗ 2C), 52.95, 54.14, 122.07, 122.09, 123.01, 123.46, 124.11, 124.23, 125.75, 125.97 (∗ 2C), 126.02, 128.38, 128.50, 128.59, 128.64, 129.78, 130.88, 142.72, 142.89, 144.51, 144.70, 148.45, 149.19, 151.81, 152.50; Found: C, 89.51; H, 10.79%. Calcd for C₃₀H₄₂: C, 89.49; H, 10.51%.

1H,1H'-1',1'-Biindene (7) (73:27 mixture of diastereomers)

[Diagram of 1H,1H'-1',1'-Biindene (7)]

white solid. IR (nujol) 2924, 2855, 1458, 1373, 964, 802, 756 cm⁻¹; ¹H NMR (CDCl₃) δ 4.16 (s, 0.27×2H), 4.19 (s, 0.73×2H), 5.85 (dd, J = 5.5, 1.0 Hz, 0.73×2H), 6.34 (dd, J = 6.0, 1.0 Hz, 0.27×2H), 6.70 (d, J = 5.5 Hz, 0.73×2H), 6.73 (d, J = 6.0 Hz, 0.27×2H), 6.88 (d, J = 7.5 Hz, 0.27×2H), 7.04 (t, J = 7.5 Hz, 0.27×2H), 7.21–7.32 (m, 4H), 7.34 (d, J = 7.0 Hz, 0.73×2H), 7.62 (d, J = 7.0 Hz, 0.73×2H); ¹³C NMR (CDCl₃) δ 50.92, 51.37, 121.27, 121.43, 122.87, 122.99, 124.89, 125.07, 127.08, 127.12, 132.13, 132.31, 136.25, 136.91, 144.72, 144.86, 145.20, 146.02; Found: C, 93.81; H, 6.04%. Calcd for C₁₈H₁₄: C, 93.87; H, 6.13%. m.p. 77–78 °C.
References and Notes


(8) For examples of transition-metal-catalyzed coupling reactions with organolithium reagents,


(13) When the catalytic amount of AgBr was reduced from 5 mol%, a prolonged reaction time was needed. Reoptimization of the reaction time should be required.

(14) The silver-catalyzed reactions with indenylmagnesium bromide-LiBr complex and with indenyllithium-TMEDA complex afforded 2a in 37% and 9% yields, respectively.

(16) The coupling reaction of 1a without AgBr was so slow that alkene rather than the desired coupling product was gradually produced by elimination.

(17) In the silver-catalyzed coupling reactions with organomagnesium reagents (Ref. 9), Et₂O was also the suitable solvent for the coupling reactions. This fact indicates that silver catalyst coordinated by Et₂O and/or indenyllithium the reactivity of which is controlled by Et₂O are important.

(18) In each case, indene was recovered by the protonation of the unreacted indenyllithium after the work-up.

(19) The reaction of 1f without AgBr afforded 2e in 28% yield.


(21) The position of the double bond of 6 was tentatively assigned by comparison of the 1H NMR spectrum of 6 with those of 2a, 2e, and 2j.


(24) The results of entries 4 and 5 in Table 2 indicate that a single electron process (B) is the rate-limiting step in this reaction.


(29) The stereochemistry of the products was tentatively assigned in analogy with the corresponding alkylated products. The alkylated products were reported in Ref. 3b and 27.
Publication List

I. Parts of the present thesis have been published in the following journals.

Chapter 1  N-Heterocyclic Carbene Ligands in Cobalt-Catalyzed Sequential Cyclization/Cross-Coupling Reactions of 6-Halo-1-hexene Derivatives with Grignard Reagents
Hidenori Someya, Hirohisa Ohmiya, Hideki Yorimitsu, and Koichiro Oshima

Chapter 2  A New Approach to 4-Aryl-1,3-butanediols by Cobalt-Catalyzed Sequential Radical Cyclization–Arylation Reaction of Silicon-Tethered 6-Iodo-1-hexene Derivatives
Hidenori Someya, Azusa Kondoh, Akinori Sato, Hirohisa Ohmiya, Hideki Yorimitsu, and Koichiro Oshima
Synlett 2006, 3061–3064.

Cobalt-catalyzed sequential cyclization/cross-coupling reactions of 6-halo-1-hexene derivatives with Grignard reagents and their application to the synthesis of 1,3-diols
Hidenori Someya, Hirohisa Ohmiya, Hideki Yorimitsu, and Koichiro Oshima

Chapter 3  Silver-Catalyzed Benzylation and Allylation Reactions of Tertiary and Secondary Alkyl Halides with Grignard Reagents
Hidenori Someya, Hirohisa Ohmiya, Hideki Yorimitsu, and Koichiro Oshima
Chapter 4 Silver-catalyzed cross-coupling reactions of alkyl bromides with alkyl or aryl Grignard reagents
Hidenori Someya, Hideki Yorimitsu, and Koichiro Oshima

Chapter 5 Silver-catalyzed coupling reactions of alkyl halides with indenyllithiums
Hidenori Someya, Hideki Yorimitsu, and Koichiro Oshima
II. Other Publications not included in this thesis.

(1) 1,2-Migration of Phosphorus-Centered Anions on Ate-type Copper Carbenoids and Its Application for the Synthesis of New Potent Phosphine Ligands
Junichi Kondo, Hidenori Someya, Hidenori Kinoshita, Hiroshi Shinokubo, Hideki Yorimitsu, and Koichiro Oshima

(2) Copper-Catalyzed Reaction of Alkyl Halides with Cyclopentadienylmagnesium Reagent
Masahiro Sai, Hidenori Someya, Hideki Yorimitsu, and Koichiro Oshima
*Org. Lett.* **2008**, *10*, 2545–2547.

(3) Silver-Catalyzed Diallylation and Dibenzylation of *gem*-Dibromoalkanes with Grignard Reagents
Yukihiro Mitamura, Hidenori Someya, Hideki Yorimitsu, and Koichiro Oshima

(4) Silver-Catalyzed Benzylation and Allylation of Tertiary Alkyl Bromides with Organozinc Reagents
Yukihiro Mitamura, Yoshihiro Asada, Kei Murakami, Hidenori Someya, Hideki Yorimitsu, and Koichiro Oshima
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