Carbon Carbon Bond Forming Reactions by Controlling ƒÀ-Fluorine Elimination from Fluorinated Organometallic Complexes

著者 | 市塚 知宏
発行年 | 2015
その他のタイトル | 仮フッ素脱離の制御に基づく含フッ素有機金属錯体による炭素 炭素結合形成
学位授与大学 | 筑波大学
学位授与年度 | 2014
報告番号 | 仮

URL | http://hdl.handle.net/2241/00132022
Carbon–Carbon Bond Forming Reactions
by Controlling β-Fluorine Elimination
from Fluorinated Organometallic Complexes

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Doctoral Program in Chemistry

Submitted to the Graduate School of
Pure and Applied Sciences
in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy in
Science

at the
University of Tsukuba
Acknowledgement

The studies described in this thesis have been carried out under the supervision of Professor Dr. Junji Ichikawa at the Department of Chemistry, Graduate School of Pure and Applied Sciences, University of Tsukuba. I would like to express my sincere gratitude to Professor Dr. Junji Ichikawa for his continuing guidance, valuable suggestions and discussions, hearty encouragement, and enthusiasm throughout this study.

I would like to extend my heartfelt gratitude to Assistant Professor Dr. Takeshi Fujita for his kind guidance, valuable discussions and continuously developing my skills for a professional scientist for 4 years. I also appreciate to Associate Professor Dr. Kohei Fuchibe for his guidance, discussions, suggestions, and encouragement.

The author also wishes to express his appreciation to Professors Hideo Kigoshi and Akira Sekiguchi for their nice guidance and helpful discussions during the course of study.

I would like to give thanks to the past and present members of the Ichikawa Laboratory for their kind assistance throughout this work. Especially, I wish to thank Dr. Hiroyuki Tanabe, Mr. Yosuke Chiba, Mr. Toshiyuki Morikawa, Mr. Masahiko Shinjo, Mr. Tsuyoshi Takanohashi, Mr. Naoto Suzuki, Mr. Yota Watabe, and Mr. Tomohiro Arita for their helpful and daily discussions. I also thank the JSPS Young Scientist Fellow Ship for financial support.

I would like to thank Associate Professor Dr. Shunsuke Chiba of Nanyang Technological University for giving me a chance to join his research group from February to March in 2012.

Finally, I wish to express my deepest gratitude to my family for their kindly continuous encouragement and for providing a very comfortable environment, which allows me to concentrate on research.

Tomohiro Ichitsuka

February 2015
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CHAPTER 1

1. General Introduction

Fluorinated organic compounds have received considerable attention in the fields of medicinal and materials sciences, because of their unique properties derived from fluorine atoms.\[^{1}\] Therefore, the development of methodologies for introducing fluorine substituents or fluorinated functional groups into complex organic molecules is significant research area.\[^{2}\] Functionalization of fluorinated small molecules is one of the practical approaches to value-added organofluorine compounds. In particular, hydrofluorocarbons and its derivatives are ideal starting materials because they are commercially available, industrial materials.

Organometallic reactions have enabled efficient and various transformations that are not easily achieved by non-metal-mediated reactions. Thus, these reactions have been attempted to establish the powerful methodologies for transformation of fluorinated small organic molecules over the years. Organometal-mediated functionalizations of fluorinated organic compounds are classified into two categories: (1) main group metal-mediated reactions and (2) transition metal-catalyzed reactions. In both reactions, organometallic complexes bearing fluorinated ligands serve as the key intermediates. Intriguingly, the property and reactivity of fluorinated organometallic complexes can be dramatically changed by the fluorine substituents.
1.1 Main Group Fluorinated Organometallics

(A) Fluorinated Organolithium and Magnesium Reagents

Organolithium and organomagnesium compounds have been incredibly important reagents in organic synthesis.[3] Thus, a number of fluorinated organometallics (M = Li, Mg) have been prepared and utilized as the corresponding fluorinated organic anions for carbon–carbon and carbon–heteroatom bond forming reactions to produce fluorine-containing organic compounds by reactions with various electrophiles. However, the organometallics having fluorine atoms on the α- or β-carbon are readily decomposed to the metal fluorides and the corresponding carbenes or alkenes, respectively, through fluorine elimination (Scheme 1).[4]

![Scheme 1](image)

Fluorine elimination of alkyl lithium and alkyl magnesium reagents is extremely rapid even at low temperature, because of the highly polarized carbon–metal bond and the formation of highly stable metal fluoride salts (eqs 1 and 2). β-Fluorine elimination is generally more preferable than α-fluorine elimination as an elementary step from organometallics with both α- and β-fluorine atoms (eq 2).[5] The β-fluorine elimination form alkenyl metals and aryl metals typically proceed under mild conditions to generate the corresponding alkynes and arynes (eqs 3 and 4).[6] Despite its potential use in synthetic chemistry, fluorine elimination is widely recognized as one of major decomposition processes of main-group fluorinated organometallics.
(B) Other Fluorinated Organometal Reagents (M = B, Si, Zn, Sn)

Fluorinated organometallics of 12–14 group metals (B, Si, Zn, Sn, etc) are widely used to suppress the fluorine elimination and overcome the difficulty in the use of lithium and magnesium reagents.[7, 8] The fluorine-containing organometallics such as organoboranes and organozincs are much more thermally-stable than the corresponding lithium and magnesium reagents, because their carbon–metal bonds have higher covalent character compared to polar carbon–lithium and carbon–magnesium bonds. Their stability and moderate reactivity enables various organic synthetic reactions. In particular, its cross-coupling reactions with organic halides open up new synthetic routes to a variety of functionalized organofluorine compounds. Despite such usefulness, their reactions still have several limitations as described below.
Organozinc reagents bearing β-fluorine substituents have moderate thermal stability.\cite{7} When such organozinc reagents are used in the palladium-catalyzed Negishi cross-coupling reactions, the β-fluorine elimination may proceed at room temperature or above (Scheme 2).

![Scheme 2](image)

On the other hand, fluorinated organoborane, organosilane, and organostannane compounds are particularly stable and less reactive compared to organozinc reagents.\cite{8} To utilize these compounds for palladium-catalyzed cross-coupling, the stoichiometric additives for activation of the organometallics are generally required. The coupling reactions are effected in the following two ways: (1) the generation of organocopper by transmetalation with copper salt and (2) the formation of ate complex using an additive such as alkoxide or fluoride anions (Scheme 3). The organocoppers, organoborates and organosilicates thus generated are also less-stable and decomposed through β-fluorine elimination.

![Scheme 3](image)
1.2. Fluorinated Organo Transition Metal Complex

(A) Fluoroalkene Ligand

Alkene complexes serve as key intermediates in many transition metal-catalyzed reactions such as the Heck reaction, the Wacker reaction, alkene hydrogenation, cycloaddition and so on.\[^{[9]}\]

As shown in Figure 1, alkenes coordinate to transition metal centers through σ-donation and π-backdonation (Figure 1).\[^{[10]}\] In the case of the coordination of electron-deficient alkenes to electron-rich low-valent transition metals, π-backdonation is dominant (Figure 2).\[^{[11]}\]

![Figure 1. Transition metal–alkene bond: Dewar–Chatt–Duncanson bonding model](image)

Fluoroalkenes are known as electron-deficient alkenes because of the electron-withdrawing inductive effect of fluorine atoms. They coordinate strongly to low-valent transition metal centers through significant π-backdonation to form the thermally-stable transition metal–fluoroalkene complexes (Figure 3).\[^{[12]}\] Furthermore, these complexes often have the character of metalacyclopropanes (Figure 2, B) because of the strong π-backdonation.

![Figure 2.](image)

![Figure 3. Transition metal–fluoroalkene complex](image)
Reactions via the selective formation of these complexes have been reported. In 1970, Cundy et al. reported that oxidative cyclization of two tetrafluoroethylene molecules (CF$_2$=CF$_2$) on nickel(0) afforded the corresponding octafluoronickelacyclpentane (eq 5).$^{[13]}$ Hacker et al. revealed that the Pt(CF$_2$=CF$_2$)(PPh$_3$)$_2$ complex reacted with lithium iodide to give the Ptl(CF=CF$_2$)(PPh$_3$)$_2$ complex (eq 6).$^{[14]}$ On the basis of Hacker’s pioneering work, Ogoshi recently achieved the palladium-catalyzed carbon–fluorine bond arylation of teterafluoroethylene using arylzine reagents as coupling partners (eq 7).$^{[15]}$ Despite such potential advantages of fluoroalkene–transition metal complexes, there have been only a few reactions using them as key intermediates.$^{[15,19a,21]}

(B) Fluoroalkyl Ligand

Alkyl transition metal complexes have played a vital role in various transition metal-catalyzed synthetic organic reactions.$^{[9]}$ Although, they are recognized as key intermediates in the fluoroalkylation of arenes and the hydrodefluorination of fluorocarbon pollutants, the reaction of fluoroalkyl complexes has been extremely limited. This is mainly because the carbon–metal bond of fluoroalkyl transition metal complexes is strengthened by the electron-withdrawing inductive effect.
effect of fluorine substituents exhibiting the highest electronegativity of all elements (Figure 4).\textsuperscript{[16]} In particular, the fluoroalkyl complexes having multi-fluorine atoms on the $\alpha$- and $\beta$-carbons are amazingly stable, and thus perfluoroalkyl ligand is often used as unreactive ancillary one.

\[
\text{Figure 4. Carbon–metal bond stabilization with } -I \text{ effect}
\]

The inertness of fluoroalkyl ligands inhibits elementary processes involving cleavage of its carbon–metal bonds in transition metal-mediated reactions. For instance, the late transition metal–CF$_3$ bond is particularly strong and inert.\textsuperscript{[17]} Hartwig disclosed that the reductive elimination of Ar–CF$_3$ from the corresponding trifluoromethyl–Pd(II) complex can not proceed even at 110 °C (Scheme 4).\textsuperscript{[17a]} While the palladium-catalyzed cross-coupling reactions of haloarenes with trifluoromethyl metal reagents has been considered as an efficient approach to benzotrifluoride derivatives, the first example was reported by Buchwald only quite recently (eq 8).\textsuperscript{[17c,d]}

\[
\text{Scheme 4.}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>Ar</th>
<th>$K_{rel}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$</td>
<td>2-MeC$_6$H$_4$</td>
<td>&gt; 600</td>
</tr>
<tr>
<td>CH$_2$CF$_3$</td>
<td>4-MeC$_6$H$_4$</td>
<td>1.7</td>
</tr>
<tr>
<td>CH$_2$CN</td>
<td>4'-BuC$_6$H$_4$</td>
<td>1</td>
</tr>
<tr>
<td>CF$_3$</td>
<td>2-MeC$_6$H$_4$</td>
<td>no reaction</td>
</tr>
</tbody>
</table>
In contrast, fluorine elimination is one of the most reasonable processes for the transformation of inert fluoroalkyl transition metal complexes. α-Fluorine elimination from α-fluoroalkyl transition metal complexes gives the corresponding carbene ligands and a fluoride ligand (Scheme 5a). In a similar manner, β-fluorine elimination from β-fluoroalkyl transition metal complexes provides the corresponding alkene ligands and a fluoride ligand (Scheme 5b). Shriver reported that the iron trifluoromethyl complex reacts with BF₃ to give the cationic iron–difluorocarbene complex through α-fluorine elimination (eq 9). Caulton achieved β-fluorine elimination of the intermediary β-fluoroethyl zirconium complex generated by hydrozirconation of vinyl fluoride (eq 10). Surprisingly, these processes of fluorine elimination proceed spontaneously even at room temperature to provide the corresponding defluorinated product.

Furthermore, fluorine elimination can be utilized for the defluorinative substitution of fluoroalkyl metals with nucleophiles (eq 11 and 12). In these reactions, Brønsted or Lewis acid activates the leaving fluoride to accelerate carbon–fluorine bond cleavage. Subsequently,
nucleophiles such as phosphine and water attack the carbocation centers to afford the corresponding transition metal complexes bearing the functionalized ligands.

\[
\begin{align*}
L &= \text{Pyridine} \\
\text{L} &\text{Pt} - \text{CF}_3 \\
\text{CF}_3 &\text{OH}_2 \\
\rightarrow &\text{L} \text{Pt} - \text{CF}_3 \\
\text{CF}_3 &\rightarrow \text{L} \text{Pt} - \text{CF}_3 \\
\end{align*}
\]

\(\text{α-Fluorine Elimination}\)

Utilizing fluorine elimination as key elementary step, several catalytic reactions have been developed. In 1991, Heitz et al. developed the palladium-catalyzed vinylic carbon–fluorine bond arylation of 1,1-difluoroethylene with aryl iodides via regioselective alkene insertion–β-fluorine elimination sequence (eq 13).\(^{[20a]}\) The Ichikawa group to which I belong reported the palladium-catalyzed cyclization of oximes bearing a difluorovinyl group via 5-endo alkene insertion (eq 14).\(^{[20b]}\) In these reactions, the carbon–fluorine bond activation was achieved via β-fluorine elimination from the intermediary alkyl palladium species generated by iminopalladation of the alkene moiety. In a similar manner, the allylic carbon–fluorine bond activation was also achieved (eq 15).\(^{[20c]}\) Murakami et al. also reported the rhodium-catalyzed intermolecular reaction (eq 16).\(^{[20d]}\) Remarkably, this reaction involves the sp\(^3\) carbon–fluorine bond cleavage of the trifluoromethyl group, which is recognized as one of the most inert functional group. Recently, Chatani achieved the nickel-catalyzed synthesis of fluorocyclobutenes using α-fluorine elimination (eq 17).\(^{[21]}\) In my master’s study, I developed the nickel-catalyzed [2+2+2] cycloaddition of 1,1-difluoroethylene with alkynes using α-fluorine elimination from the intermediary
Therefore, fluorine elimination leads to alternative and powerful methodology for cleavage and functionalization of carbon–fluorine bond. Furthermore, the selective functionalization of
perfluoroalkyl compounds would be possible, because the fluorine elimination of the perfluoroalkyl ligands also proceed under mild conditions.

1.3. Survey of this thesis

As mentioned above, several unique interactions are observed between organometallics and fluorine atoms in this ligands. Particularly, fluorine elimination is one of the most important elementary processes in fluorinated organometallic-related chemistry. Considering such unique interactions throughout this thesis, I challenged to develop new carbon–carbon bond forming reactions by controlling β-fluorine elimination from fluorinated organometallics.

In main group organometal-mediated reactions, β-fluorine elimination step has been widely recognized as the decomposition process of fluorinated organometallic reagents. Therefore, the development of new fluorinated organometallic reagents possessing both substantial reactivity and stability has been one of the most important tasks to date. Typically, organozinc complexes are known to be stabilized by coordination of two amine ligands.\textsuperscript{[22]} On the Basis of this effect, I considered that 2,2-difluorovinylzinc complex would be stabilized by an bidentate amine ligand to avoid the β-fluorine elimination and could be thus utilized for its cross coupling reactions (Scheme 6). Chapter 2 described the results and discussions on the zinc complex.

![Scheme 6](image-url)

\textbf{Scheme 6.}

\[ \text{H} \quad \text{F} \quad \text{F} \quad \text{ZnCl(Amine)}_2 \]

\[ \text{F} \quad \text{F} \quad \text{R} \quad \text{X} \]

\[ \text{cat. Pd(0) or Cu(I)} \]

\[ \text{R} = \text{aryl, alkenyl, alkynyl, benzyl, allyl} \]
In chapter 3, I developed the transition metal mediated carbon–fluorine bond activation taking advantage of \( \beta \)-fluorine elimination. As mentioned in the previous section, \( \beta \)-fluorine elimination from fluorinated transition metal complexes would be considered as key for the attractive transformation of the multi-fluorinated alkyl ligands, even though they are generally less reactive. Although fluorine elimination is potentially advantageous, the literature contains only a few reports on its practical application to transition metal-mediated reactions, which could be due to little understanding about the importance of \( \beta \)-fluorine elimination as the synthetic tool. To add a approach to \( \beta \)-fluoroalkyl transition metals, I selected oxidative cyclization of trifluoromethylated alkenes and alkynes on nickel(0), because highly electron-deficient trifluoromethylated alkenes would coordinate strongly to nickel(0) complex as described in the previous section (Scheme 7).\textsuperscript{[23]}

Utilizing \( \beta \)-fluorine elimination from the intermediary nickelacycles, I herein demonstrated the nickel-mediated cycloaddition, which produced 2-fluorinated 1,3-cyclopentadienes (Scheme 7a). Chapter 3 described the results and discussions on this reaction.

In chapter 4, on the basis of the results of chapter 3, I developed the nickel-catalyzed synthesis of various fluoroalkene derivatives via allylic carbon–fluorine bond activation using \( \beta \)-fluorine elimination. By the choice of reductants for the intermediary Ni(II) species, the product selectivity was controlled (Scheme 7)

\textit{Scheme 7.}
1.4 References


[9] Hartwig, J. F. *Organotransition Metal Chemistry–From Bonding to Catalysis*; University


CHAPTER 2

Difluorovinylation via Cross Coupling of Zinc–TMEDA Complex Suppressing β-Fluorine Elimination

Abstract

A thermally stable 2,2-difluorovinylzinc–TMEDA complex was prepared via a deprotonation–transmetalation sequence starting from commercially available 1,1-difluoroethylene. The complex thus formed was successfully applied to transition metal-catalyzed coupling reactions with a wide range of organic halides, which led to the syntheses of 2,2-difluorovinyl compounds. On treatment with the difluorovinylzinc–TMEDA complex in the presence of an appropriate palladium or copper catalyst, aryl, alkenyl, alkynyl, allyl, and benzyl halides effectively underwent difluorovinylation to afford β,β-difluorostyrenes, 1,1-difluoro-1,3-dienes, 1,1-difluoro-1,3-enynes, 1,1-difluoro-1,4-dienes, and (3,3-difluoroallyl)arenes, respectively.
2.1. Introduction

2,2-Difluorovinyl compounds are an important class of compounds because they exhibit unique properties due to the steric and electronic effects of fluorine. They serve as not only building blocks for fluorine-containing organic molecules but also monomers for functional polymers.\textsuperscript{[1,2]} In addition, 2,2-difluorovinyl compounds often show substantial bioactivities. For example, they act as anti-herpes simplex virus type 1 (anti-HSV-1) agents and as squalene epoxidase inhibitors in antilipemic drugs.\textsuperscript{[3,4]} Further pharmaceutical applications of difluorovinyl compounds have been of great interest, since the difluorovinylidene moiety is considered to be a bioisostere of a carbonyl group.\textsuperscript{[5]}

Despite the usefulness of 2,2-difluorovinyl compounds, their availability is still limited. Typical synthetic methodologies are mostly classified into two categories: (i) difluoromethylenation of aldehydes and (ii) metal-mediated difluorovinyl coupling. The former protocol involves the Wittig reaction (Scheme 1, Route a), the Horner–Wadsworth–Emmons reaction (Route b), and the Julia–Kocienski reaction (Route c) with aldehyde substrates (Scheme 1).\textsuperscript{[6–8]} Although these reactions are widely used in common alkene synthesis, the Wittig reaction requires excess amounts of intermediary ylides, and the Horner–Wadsworth–Emmons and Julia–Kocienski reactions show narrow substrate scopes due to the necessity of highly basic conditions. Alternatively, the latter metal-mediated coupling has been considered to be a more straightforward approach to difluorovinyl compounds (Scheme 2). This protocol is achieved via the reaction between 2,2-difluorovinyl halides and organometallic species (Route a) or the reaction between 2,2-difluorovinylmetals and organic halides.\textsuperscript{[9,10]} Both types of reactions require starting difluorovinyl halides (Route b), which are expensive or rarely available from commercial sources.
Normant et al. reported the synthesis of a 2,2-difluorovinyl compound starting from 1,1-difluoroethylene (1), a commercially available, industrial material (eq 1).[11] In the study, a difluorovinylzinc complex, prepared via the deprotonation of 1 and subsequent transmetalation, was subjected to a palladium-catalyzed coupling reaction with 2-iodopyridine. This is the only one reported example of the coupling reaction with the difluorovinylzinc complex derived from 1,1-difluoroethylene monomer, and the product yield was no more than 50%, which was presumably due to the thermal instability of the intermediary zinc complex in the presence of a lithium salts (eq 2).[12,13] Thus, difluorovinylation via coupling reaction remains to be developed in terms of both generality and efficiency. Typically, organozinc reagents are unstable (not isolable)
and are prepared in situ just before use, because they are highly sensitive to moisture, air and heat. In addition, difluorovinylzinc regents are readily decomposed to fluoroacetylene and zinc fluoride via β-fluorine elimination.

\[
\begin{align*}
\text{H} & \text{F}_2\text{C} \quad 1) \text{sec-BuLi} \quad \text{H} \\
\text{F}_2\text{C} & \quad 2) \text{ZnCl}_2 \quad \text{H} \\
\text{F}_2\text{C} & \quad \text{ZnCl} \quad \text{cat. Pd} \quad \text{H} \\
\text{F}_2\text{C} & \quad \text{ZnCl} \quad \beta\text{-Fluorine Elimination} \\
\text{H} & \quad \text{F} \quad \text{=H} + \text{ZnClF} \quad (2)
\end{align*}
\]

It has been reported that organozinc reagents are often stabilized by coordination of two amine molecules.\textsuperscript{[14,15]} Although several organozinc complexes described below are stable enough to isolate, some of them still have reactivity to react with electrophiles such as aldehydes (Figure 1). On the basis of these facts, I assumed that the fluorinated organozinc reagents with two coordinating amine ligands would possess both substantial stability and reactivity for cross-coupling reactions.

![Figure 1. Stable Organozinc–Diamine Complexes](image)

This motivated me to seek an appropriate amine to produce the thermally stable 2,2-difluorovinylzinc complexing suppressing β-fluorine elimination. Section 2.2 described the preparation of the 2,2-difluorovinylzinc reagent by complexation with
Furthermore, I developed the palladium- or copper-catalyzed cross-coupling reactions of the prepared zinc–TMEDA complex with various organic halides. Section 2.3 described the details of facile synthesis of difluorovinyl compounds via cross-coupling.

2.2. Preparation of Thermally Stable 2,2-Difluorovinylzinc Complex

As mentioned above, I predicted that the 2,2-difluorovinylzinc complex could be stabilized with coordination of two amine ligands. To prove my hypothesis, I sought for the appropriate amine to afford a thermally stable 2,2-difluorovinylzinc complex. I first reviewed the previously reported conditions in which no ligands were employed. The conditions furnished 2,2-difluorovinylzinc chloride in 50% yield (Table 1, Entry 1). The main reason for the low yield might be due to decomposition of 2,2-difluorovinylzinc chloride to fluoroacetylene via β-fluorine elimination.

Next, I screened monodentate amine ligands (2.6 equiv) as additives. Use of N-methyl pyrrolidone (NMP) and pyridine decreased the corresponding complexes 2 (Entries 2 and 3), whereas NEt₃ marginally enhanced the formation of 2 (Entry 4). While 1,4-diazabicyclo[2.2.2]octane (DABCO), which can act as an exo-bidentate ligand, prevented the process (Entry 5), addition of N,N,N′,N′-tetramethylethlenediamine (TMEDA) turned out to be highly effective for the formation of 2 (Entries 6–8). The best result (95% yield of 2a) was obtained when sec-BuLi was added to the mixture of 1 and TMEDA, followed by addition of ZnCl₂ (Entry 7). The obtained 2,2-difluorovinylzinc–TMEDA complex 2a is thermally stable and thus storable.
Table 1. Screening of Amine Ligands for Preparation of the Zinc Reagent 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>ZnX₂ (x equiv)</th>
<th>Amine (y equiv)</th>
<th>Yield / %\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ZnCl₂ (1.0)</td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>ZnCl₂ (1.0)</td>
<td>NMP (2.6)</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>ZnCl₂ (1.0)</td>
<td>Pyridine (2.6)</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>ZnCl₂ (1.0)</td>
<td>NEt\textsubscript{3} (2.6)</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>ZnCl₂ (1.0)</td>
<td>DABCO (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>ZnCl₂ (1.0)</td>
<td>TMEDA (1.3)</td>
<td>90</td>
</tr>
<tr>
<td>7\textsuperscript{b}</td>
<td>ZnCl₂ (1.0)</td>
<td>TMEDA (1.3)</td>
<td>95</td>
</tr>
<tr>
<td>8\textsuperscript{b}</td>
<td>ZnI₂ (1.0)</td>
<td>TMEDA (1.3)</td>
<td>70</td>
</tr>
<tr>
<td>9</td>
<td>ZnCl₂·TMEDA (1.0)</td>
<td></td>
<td>62</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Yields are determined by \textsuperscript{19}F NMR using PhCF\textsubscript{3} as an internal standard.
\textsuperscript{b} Lithiation was carried out in the presence of TMEDA.

Removal of the solvents from the solution of 2a under reduced pressure afforded a white powder of 2a containing LiCl.\textsuperscript{[19]} The solid-state 2a was found to be more thermally stable than 2a in solution. While 2a in solution was storable for a week at –20 °C under argon, solid-state 2a was unchanged after being stored for more than a month at 0 °C under argon.
2.3. Palladium- or Copper-Catalyzed Cross-Coupling Reactions of 2 with Organic Halides and Pseudohalides

2.3.1. Cross-Coupling Reaction with Aryl Halides and Triflates: Synthesis of β,β-Difluorostyrenes

Having prepared thermally stable 2,2-difluorovinylzinc–TMEDA complex 2a, its palladium-catalyzed Negishi coupling was examined using a wide variety of aryl halides and pseudohalides (Table 2). Aryl iodides 3a–3d, aryl bromide 3e, and aryl triflate 3f participated in the coupling reaction to produce difluorostyrenes 4a–4f, respectively, in high yield (Entries 1–6). In the reactions of 3g–3k, PEPPSI-IPr was used as an electron-rich palladium catalyst or Cy-JohnPhos as an electron-rich ligand (Entries 7–11). Sterically hindered ortho-monosubstituted substrate 3g (Entry 7) and ortho-disubstituted substrates 3h and 3i (Entries 8 and 9) successfully underwent the coupling reaction. Even the reaction of aryl chloride 3j efficiently proceeded to give 4g in good yield (Entry 10). Intriguingly, even a boronate ester moiety was tolerated in this coupling reaction. Boronate ester 3k bearing a chlorine substituent reacted with the difluorovinylzinc–TMEDA complex 2a to give the corresponding difluorostyrene 4k in high yield without the formation of any self-Suzuki–Miyaura coupling products (Entry 11).
Table 2. Difluorostyrene Synthesis: Pd-Catalyzed Coupling of 2a with Aryl Halides and Triflates

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar−X</th>
<th>Pd catalyst (mol%)</th>
<th>Time / h</th>
<th>Yield / %a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(p-Me) 3a</td>
<td>Pd(PPh₃)$_4$ (2)</td>
<td>6</td>
<td>59 (86), 4a</td>
</tr>
<tr>
<td>2</td>
<td>(p-OMe) 3b</td>
<td>Pd(PPh₃)$_4$ (2)</td>
<td>6</td>
<td>87, 4b</td>
</tr>
<tr>
<td>3</td>
<td>(o-NH₂) 3c</td>
<td>Pd(PPh₃)$_4$ (2)</td>
<td>1</td>
<td>87, 4c</td>
</tr>
<tr>
<td>4b</td>
<td>(p-NO₂) 3d</td>
<td>Pd$_2$(dba)$_3$·CHCl$_3$ (2), PPh$_3$ (8)</td>
<td>12</td>
<td>84, 4d</td>
</tr>
<tr>
<td>5</td>
<td>Br 3e</td>
<td>Pd(PPh₃)$_4$ (2)</td>
<td>10</td>
<td>87, 4e</td>
</tr>
<tr>
<td>6</td>
<td>TfO 3f</td>
<td>Pd(PPh₃)$_4$ (2)</td>
<td>6</td>
<td>90, 4f</td>
</tr>
<tr>
<td>7</td>
<td>TfO Ph 3g</td>
<td>PEPSSI-IPr (5)</td>
<td>10</td>
<td>82, 4g</td>
</tr>
<tr>
<td>8</td>
<td>I OMe 3h</td>
<td>PEPSSI-IPr (4)</td>
<td>12</td>
<td>79, 4h</td>
</tr>
<tr>
<td>9</td>
<td>Me I Me 3i</td>
<td>Pd$_2$(dba)$_3$·CHCl$_3$ (2.5)/ Cy-JohnPhos (10)</td>
<td>24</td>
<td>(59), 4i</td>
</tr>
<tr>
<td>10</td>
<td>Cl Ph 3j</td>
<td>PEPSSI-IPr (5)</td>
<td>8</td>
<td>(71), 4g</td>
</tr>
<tr>
<td>11</td>
<td>B O 3k</td>
<td>PEPSSI-IPr (5)</td>
<td>6</td>
<td>73, 4k</td>
</tr>
</tbody>
</table>

a Isolated yield. In parentheses is shown yield determined by $^{19}$F NMR using PhCF$_3$ as an internal standard.
b Room temperature.

It is noteworthy that the reaction exhibited complete chemoselectivity (Table 3). Both 3-iodophenyl triflate (3l) and 3-bromo-4-iodobiphenyl (3m) showed thorough chemoselective
substitution of the iodo group (Entries 1 and 2). Likewise, the triflyloxy groups of 3n and 3o were exclusively substituted over the chlorine atoms (Entries 3 and 4). In the case of 3-bromophenyl triflate (3p), the triflyloxy group reacted preferentially (>85% selectivity), although triflates and bromides generally show similar reactivity toward transition-metal-catalyzed coupling reactions (Entry 5). As a result, the relative reactivity of aryl halides and pseudohalides was found to be in the order of I > OTf > Br > Cl.

Table 3. Chemoselectivity in the Coupling Reaction of 2a

| Entry | Ar−X | Pd catalyst (mol%) | Conditions | Yield / %
|-------|------|-------------------|------------|-------
| 1 I | O Tf | Pd₂dba (2.5) CHCl₃ (10) | RT, 4 h | 92, 4l |
| 2 Br | Ph | Pd₂dba (2.5) CHCl₃ (10) | 55 °C, 4 h | 96, 4m |
| 3 I | OTf | PdCl₂(dpp) (5) LiCl (375) | reflux, 23 h | 73, 4n |
| 4 Cl | O Tf | PdCl₂(dpff) (4) | reflux, 12 h | 87, 4o |
| 5 Cl | Br | Pd₂dba (2.5) CHCl₃ (10) | 45 °C, 24 h | 69 (71), 4p |

* Isolated yield. In parentheses is shown yield determined by ¹⁹F NMR using PhCF₃ as an internal standard.
* By-products formed by the reaction of the bromo group were observed by ¹⁹F NMR (10% in total).
2.3.2. Cross-Coupling reaction with alkenyl halides: Synthesis of 1,1-difluoro-1,3-dienes

The optimized conditions for the reactions of the difluorovinylzinc complex 2a with aryl halides 3 were successfully applied to the reactions with alkenyl halides 5 (eqs 4–6). On treatment with 1.3 equiv. of 2a in the presence of 2 mol% of Pd(PPh\textsubscript{3})\textsubscript{4}, (E)-β-iodo-p-methylstyrene (5a) smoothly underwent a coupling reaction to afford 1,1-difluoro-1,3-dienes 6a in 91% yield (eq 4). In this reaction, the E configuration of the alkenyl moiety was definitely retained. β-Bromostyrenes 5b and 5c, bearing electron-donating and electron-withdrawing substituents, also participated in the coupling reaction to afford the corresponding 1,1-difluoro-1,3-dienes 6b and 6c, respectively, in high yields with the retention of the E configuration (eq 5). Note that the double difluorovinylation of 1,1-dibromo-1-alkene 5d effectively proceeded to afford the tetrafluorinated, cross-conjugated triene ([3]dendralene) 6d in 70% yield (eq. 6).

![Chemical Structures](image)

2.3.3. Coupling reaction with alkynyl halides: Synthesis of 1,1-difluoro-1,3-enynes

When coupling the difluorovinylzinc complex 2a with alkynyl halides 7, the choice of ligand for palladium was critical (Table 4). The use of Pd(PPh\textsubscript{3})\textsubscript{4} as a catalyst in the reaction of 2a with
alkynyl iodide 7a gave 1,1-difluoro-1,3-enyne 8a as the expected product, albeit in a moderate yield of 59% (entry 1). Some bidentate phosphine ligands were found to improve the yield of 8a (entries 3–7). Among the bidentate ligands examined, 1,3-bis(diphenylphosphino)propane (dppp) afforded the highest yield of 8a, 96% (entry 5), while 1,1'-bis(diphenylphosphino)ferrocene (dpff) also gave a satisfactory yield of 86% (entry 7).

Table 4. Effect of ligands for Pd-catalyzed coupling of 2a with alkynyl halide 7a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd catalyst (mol%)</th>
<th>Time (h)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt; (4)</td>
<td>3</td>
<td>59</td>
</tr>
<tr>
<td>2</td>
<td>Pd&lt;sub&gt;2&lt;/sub&gt;(dba)&lt;sub&gt;3&lt;/sub&gt;·CHCl&lt;sub&gt;3&lt;/sub&gt; (2) PPh&lt;sub&gt;3&lt;/sub&gt; (8)</td>
<td>4</td>
<td>66</td>
</tr>
<tr>
<td>3</td>
<td>Pd&lt;sub&gt;2&lt;/sub&gt;(dba)&lt;sub&gt;3&lt;/sub&gt;·CHCl&lt;sub&gt;3&lt;/sub&gt; (2.5) dppe (5)</td>
<td>5</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>Pd&lt;sub&gt;2&lt;/sub&gt;(dba)&lt;sub&gt;3&lt;/sub&gt;·CHCl&lt;sub&gt;3&lt;/sub&gt; (2.5) dppe (5)</td>
<td>2</td>
<td>67</td>
</tr>
<tr>
<td>5</td>
<td>Pd&lt;sub&gt;2&lt;/sub&gt;(dba)&lt;sub&gt;3&lt;/sub&gt;·CHCl&lt;sub&gt;3&lt;/sub&gt; (2.5) dppp (5)</td>
<td>5</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>Pd&lt;sub&gt;2&lt;/sub&gt;(dba)&lt;sub&gt;3&lt;/sub&gt;·CHCl&lt;sub&gt;3&lt;/sub&gt; (2.5) dppb (5)</td>
<td>5</td>
<td>68</td>
</tr>
<tr>
<td>7</td>
<td>Pd&lt;sub&gt;2&lt;/sub&gt;(dba)&lt;sub&gt;3&lt;/sub&gt;·CHCl&lt;sub&gt;3&lt;/sub&gt; (2.5) dpff (5)</td>
<td>5</td>
<td>86</td>
</tr>
</tbody>
</table>

<sup>a</sup> <sup>19</sup>F NMR yield using PhCF<sub>3</sub> as an internal standard.

With optimized conditions in hand, the substrate scope was investigated (Table 5). Along with alkyl-substituted ethynyl iodides 7a and 7b (entries 1 and 2), aryl-substituted ethynyl iodide 7c effectively underwent the Pd(0)/dppp-catalyzed coupling reaction with 2a to afford the corresponding 1,1-difluoro-1,3-enyne 8c (entry 3). Difluorovinylation of alkynyl bromides was also
successfully achieved under similar conditions (entries 4 and 5). The reaction of arylethynyl bromide 7d, bearing an electron-donating methoxy group, effectively afforded 1,1-difluoro-1,3-ene 8d in 94% yield (entry 4), while the coupling of alkynyl bromide 7e, with an electron-withdrawing nitro group, afforded enyne 8e in 63% yield (entry 5).

Table 5. Synthesis of 1,1-difluoro-1,3-enynes 8 by coupling of 2a with alkynyl halides 7

<table>
<thead>
<tr>
<th>Entry</th>
<th>7</th>
<th>Time (h)</th>
<th>Yield (%)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1^b</td>
<td>7a</td>
<td>5</td>
<td>8a 85</td>
</tr>
<tr>
<td>2</td>
<td>7b</td>
<td>2</td>
<td>8b 94</td>
</tr>
<tr>
<td>3^c</td>
<td>7c</td>
<td>5</td>
<td>8c 90</td>
</tr>
<tr>
<td>4</td>
<td>7d</td>
<td>5</td>
<td>8d 94</td>
</tr>
<tr>
<td>5</td>
<td>7e</td>
<td>1</td>
<td>8e 63</td>
</tr>
</tbody>
</table>

^a Isolated yield. ^b 2a (1.3 equiv). ^c 2a (1.2 equiv).

2.3.4. Coupling reaction with benzyl halides: Synthesis of (3,3-difluoroallyl)arenes

Coupling reactions of the difluorovinylzinc complex 2a with benzyl bromides were troublesome because unavoidable self-coupling led to dibenzyls (Table 6). In the presence of 5 mol% of Pd(PPh₃)₄, the reaction of 2a with 4-phenylbenzyl bromide (9a) afforded a 27% yield of 4-(3,3-difluoroallyl)biphenyl 10a, where the rest of 9a was mostly converted to its homocoupling...
product (entry 1). Addition of sodium iodide provided a slightly better result, a 39% yield of 10a (entry 2). No effective catalyst was found on screening the ligands (entries 3–7). These results indicated that benzyl bromide 9a was too reactive to be used as a substrate for palladium-catalyzed coupling with 2a. Eventually, I found that the use of 1.0 equiv. of 4-phenylbenzyl chloride (9'a) drastically improved the yield of 10a, up to 92%, by suppressing the formation of the homocoupling product (entry 8).

![Chemical structure](image)

**Table 6.** Effect of conditions for Pd-catalyzed coupling of 2a with benzyl halides 9a and 9'a

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Pd catalyst (mol%)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>Pd[PPh₃]₄ (5)</td>
<td>1</td>
<td>27</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>Pd₂(dbaa)₂·CHCl₃ (2.5) NaI (130)</td>
<td>1</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>Pd₂(dbaa)₂·CHCl₃ (2.5) PPh₃ (10)</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>Pd₂(dbaa)₂·CHCl₃ (2.5) PCy₃ (10)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>Br</td>
<td>Pd₂(dbaa)₂·CHCl₃ (2.5) P(nBu)₂ (5)</td>
<td>2</td>
<td>33</td>
</tr>
<tr>
<td>6</td>
<td>Br</td>
<td>Pd₂(dbaa)₂·CHCl₃ (2.5) dppe (6)</td>
<td>2</td>
<td>N.D.</td>
</tr>
<tr>
<td>7</td>
<td>Br</td>
<td>PEPPSI·IPr (5)</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>8ᵇ</td>
<td>Cl</td>
<td>Pd[PPh₃]₄ (5)</td>
<td>2</td>
<td>92</td>
</tr>
</tbody>
</table>

*ᵃ ¹⁹F NMR yield using PhCF₃ as an internal standard. ᵇ 2a (1.0 equiv).

The synthesis of several (3,3-difluoroallyl)arenes 10 was examined via the coupling of 2a with benzyl chlorides 9' (Table 7). Benzyl chlorides 9'b–9'd bearing electron-donating (entries 2 and 3) and electron-withdrawing substituents (entry 4) successfully underwent palladium-catalyzed difluorovinylation using 2a to afford the corresponding (3,3-difluoroallyl)arenes 10b–10d, respectively.
Table 7. Synthesis of (3,3-difluoroallyl)benzenes 10 by coupling of 2a with benzyl chlorides 9′

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Time (h)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R = Ph</td>
<td>9′a</td>
<td>2</td>
</tr>
<tr>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>R = Bu</td>
<td>9′b</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>R = OMe</td>
<td>9′c</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>R = CF₃</td>
<td>9′d</td>
<td>6</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield. <sup>19</sup>F NMR yield using PhCF₃ as an internal standard is indicated in parentheses. <sup>b</sup> 2a (1.3 equiv).

2.3.5. Coupling reaction with allyl halides: Synthesis of 1,1-difluoro-1,4-dienes

We finally investigated the coupling of the difluoroallylzinc complex 2a with allyl halides, which have two possible reaction sites, namely, carbons α and γ to the leaving halo group (Table 8). In the difluoroallylation using allyl halide E-11a as a model substrate, the palladium catalyst Pd(PPh₃)₄ exhibited poor reactivity (entry 1). Addition of more than a stoichiometric amount of CuI instead of the Pd(0) catalyst significantly improved the yield of difluoroallylated products, with the S<sub>N</sub>2-type product E-12a preferentially obtained along with S<sub>N</sub>2′-type product 13a (entries 2 and 3). Among the Cu(I) species examined, a catalytic amount of CuBr·SMe₂ afforded the highest yield of difluoroallylated products and the highest selectivity in the formation of E-12a (E-12a/13a = 92:8, entry 6).
Table 8. Effect of conditions for Cu-catalyzed coupling of 2a with allyl halide E-11a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Conditions</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>E-12a/E-13a&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh₃)&lt;sub&gt;4&lt;/sub&gt; (2 mol%)</td>
<td>reflux, 3 h</td>
<td>5</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>CuI (1.3 equiv)</td>
<td>RT, 2 h</td>
<td>93</td>
<td>76:24</td>
</tr>
<tr>
<td>3</td>
<td>CuI (1.3 equiv)</td>
<td>0 °C, 2 h then RT, 2 h</td>
<td>83</td>
<td>86:14</td>
</tr>
<tr>
<td>4</td>
<td>CuI (10 mol%)</td>
<td>RT, 2 h</td>
<td>39</td>
<td>83:17</td>
</tr>
<tr>
<td>5</td>
<td>CuCN (10 mol%)</td>
<td>RT, 2 h</td>
<td>39</td>
<td>82:18</td>
</tr>
<tr>
<td>6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>CuBr•SMe₂ (10 mol%)</td>
<td>0 °C, 2 h</td>
<td>87</td>
<td>92:8</td>
</tr>
</tbody>
</table>

<sup>a</sup> ¹⁹F NMR yield using PhCF<sub>3</sub> as an internal standard. <sup>b</sup> The ratio of E-12a and 13a was determined by ¹⁹F NMR measurement. <sup>c</sup> 2a (1.2 equiv).

Other allyl bromides were difluorovinylated with 2a in the presence of Cu(I) catalysts. Allyl bromide Z-11a, a stereoisomer of E-11a, successfully reacted with 2a under the same conditions as those used in the reaction of E-11a to afford the difluorovinylated products Z-12a, E-12a, and 13a in 86% total yield (Z-12a/E-12a/13a = 90:2:8, eq. 8). In this reaction, difluorovinylation mainly proceeded on the carbon α to the bromine substituent with retention of stereochemistry. Furthermore, difluorovinylation of allyl bromide 11b was readily effected in the presence of 10 mol% of CuI to provide the corresponding 1,1-difluoro-1,4-diene 12b in 90% yield (eq. 6).
2.4. Conclusion

I have developed a versatile method for accessing 2,2-difluorovinyl compounds via palladium- or copper-catalyzed coupling with the difluorovinylzinc–TMEDA complex derived from 1,1-difluoroethylene, an industrial material. Difluorovinylation of aryl alkenyl, alkynyl, allyl, and benzyl halides was thus successfully achieved. As a powder, the difluorovinylzinc–TMEDA complex is storable for a longer duration than its solution and can be used as an easily-handled difluorovinylation reagent.
2.5. Reference and Notes


[13] Without any lithium salts, fluoroacetylenes are hardly produced from 2,2-difluorovinylzinc species. See ref. 10b.


[17] An equimolar amount of TMEDA could not complete the complexation.

[18] The formation of \(2a\) was supported by the \(^{19}\)FNMR (470 MHz) spectra of the reaction mixture. The data are shown below (\(\delta\): parts per million from hexafluorobenzene). \(2a\): \(\delta\) 87.9 (dd, \(J_{FF} = 58\) Hz, \(J_{FH} = 58\) Hz, 1F), 98.7 (dd, \(J_{FF} = 58\) Hz, \(J_{FH} = 15\) Hz, 1F). cf. 2,2-Difluorovinylzinc chloride: \(\delta\) 86.2 (dd, \(J_{FF} = 55\) Hz, \(J_{FH} = 55\) Hz, 1F), 98.5 (dd, \(J_{FF} = 55\) Hz, \(J_{FH} = 14\) Hz, 1F). 1,1-Difluoroethylene: \(\delta\) 80.0–80.2 (m, 2F).


[20] Difluorostyrene \(4a\) was difficult to isolate in high yield because of its volatility. Difluorostyrene \(4i\) and unreacted iodide \(3i\) were inseparable by distillation and column chromatography.

Cy-JohnPhos is a Buchwald ligand, which is used for various coupling reactions of sterically hindered substrates. For a review, see: Martin, R.; Buchwald, S. L. Acc. Chem. Res. 2008, 41, 1461–1473.


2.6. Experimental Section

2.6.1. General

$^1$H NMR, $^{13}$C NMR, and $^{19}$F NMR spectra were recorded on a Bruker Avance 500. Chemical shift values are given in ppm relative to internal Me$_2$Si (for $^1$H NMR: δ = 0.00 ppm), CDCl$_3$ (for $^{13}$C NMR: δ = 77.0 ppm), and C$_6$F$_6$ (for $^{19}$F NMR: δ = 0.00 ppm). IR spectra were recorded on a Horiba FT-300S spectrometer by the attenuated total reflectance (ATR) method. Mass spectra were measured on a JEOL JMS-T100GCV. Elemental analyses were carried out at the Elemental Analysis Laboratory, Division of Chemistry, Faculty of Pure and Applied Sciences, University of Tsukuba. All reactions were carried out under argon. Column chromatography was performed on silica gel (Kanto Chemical Co. Inc., Silica Gel 60). Tetrahydrofuran (THF) and diethyl ether were purified by a solvent-purification system (GlassContour) equipped with columns of activated alumina and supported-copper catalyst (Q-5) before use. $N,N,N',N'$-Tetramethylethylenediamine (TMEDA) was distilled from KOH.

2.6.2. Preparation of 2,2-difluorovinylzinc chloride–TMEDA (2a)

To a solution of TMEDA (98 µL, 0.65 mmol) in THF (2.0 mL) and diethyl ether (0.50 mL) at –110 °C was slowly added gaseous 1,1-difluoroethylene (14.5 mL, 0.60 mmol) via syringe, and the mixture was stirred at the same temperature for 5 min. sec-BuLi (0.96 M in hexane, 0.52 mL, 0.50 mmol) was added dropwise to the solution at –110 °C, and then the mixture was stirred at the same temperature for 20 min. To the reaction mixture at –110 °C was added a THF solution of anhydrous ZnCl$_2$ (1.00 M, 0.50 mL, 0.50 mmol). After the reaction mixture was stirred at –100 °C for 30 min, a THF–diethyl ether solution of 2a was obtained as a colorless solution (0.48 mmol, 95%: The yield and the concentration were determined by $^{19}$F NMR using PhCF$_3$ as an internal standard): $^{19}$F NMR (470 MHz, C$_6$D$_6$) δ 87.9 (1F, dd, $J_{FF} = 58$ Hz, $J_{FH} = 58$ Hz), 98.7 (1F, dd, $J_{FF} = 58$ Hz, $J_{FH} = 15$ Hz).

2.6.3. Synthesis of β,β-difluorostyrenes 4 by Pd-catalyzed coupling of 2a with aryl halides 3

(A) Typical procedure for the synthesis of β,β-difluorostyrenes 4

To the solution of 2a (0.125 M in THF and diethyl ether, 7.6 mL, 0.95 mmol) were added a solution of 4-iodoanisole (3b, 189 mg, 0.81 mmol) in THF (1.5 mL) and Pd(PPh$_3$)$_4$ (17 mg, 15 µmol). After being refluxed for 6 h, the reaction mixture was filtered through a pad of silica gel
(diethyl ether). The filtrate was concentrated under reduced pressure and purified by preparative thin layer chromatography on silica gel (pentane/diethyl ether = 20:1) to give 4b (119 mg, 87%).

(B) Spectral data of β,β-difluorostyrenes 4
1-(2,2-Difluorovinyl)-4-methylbenzene (4a)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.33 (s, 3H), 5.23 (dd, $J_{HF}$ = 26.4, 3.8 Hz, 1H), 7.14 (d, $J$ = 8.0 Hz, 2H), 7.22 (d, $J$ = 8.0 Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 21.1, 81.9 (dd, $J_{CF}$ = 29, 14 Hz), 127.3–127.5 (2C, m), 129.3, 136.7, 156.0 (dd, $J_{CF}$ = 298, 288 Hz). $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ 77.9 (dd, $J_{FF}$ = 33 Hz, $J_{FH}$ = 4 Hz, 1F), 79.9 (dd, $J_{FF}$ = 33 Hz, $J_{FH}$ = 26 Hz, 1F). The NMR spectral data described above showed good agreement with the literature data (ref 10b).

1-(2,2-Difluorovinyl)-4-methoxybenzene (4b)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.80 (s, 3H), 5.23 (dd, $J_{HF}$ = 26.4, 3.8 Hz, 1H), 6.87 (d, $J$ = 8.7 Hz, 2H), 7.25 (d, $J$ = 8.7 Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 55.2, 81.5 (dd, $J_{CF}$ = 29, 14 Hz), 114.1, 122.7 (dd, $J_{CF}$ = 6, 6 Hz), 128.7 (dd, $J_{CF}$ = 7, 4 Hz), 155.8 (dd, $J_{CF}$ = 297, 287 Hz), 158.5. $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ 76.5 (dd, $J_{FF}$ = 37 Hz, $J_{FH}$ = 4 Hz, 1F), 78.3 (dd, $J_{FF}$ = 37 Hz, $J_{FH}$ = 26 Hz, 1F). The NMR spectral data described above showed good agreement with the literature data (ref 24).

2-(2,2-Difluorovinyl)aniline (4c)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.80 (s, 2H), 5.21 (dd, $J_{HF}$ = 25.2, 2.9 Hz, 1H), 6.73 (d, $J$ = 7.9 Hz, 1H), 6.80 (dd, $J$ = 7.6, 7.5 Hz, 1H), 7.10 (dd, $J$ = 7.9, 7.5, Hz, 1H), 7.24 (d, $J$ = 7.6, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 77.0 (dd, $J_{CF}$ = 29, 16 Hz), 115.8, 116.2, 119.4, 128.6, 129.4 (dd, $J_{CF}$ = 6, 2 Hz), 143.2, 156.6 (dd, $J_{CF}$ = 297, 289 Hz). $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ 78.1 (dd, $J_{FF}$ = 29 Hz, $J_{FH}$ = 25 Hz, 1F), 79.3 (dd, $J_{FF}$ = 29 Hz, $J_{FH}$ = 3 Hz, 1F). IR (neat): 3384, 1732, 1236, 935, 771 cm$^{-1}$. HRMS (EI): m/z calcd. for C$_8$H$_7$F$_2$N ([M$^+$]): 155.0547; Found: 155.0548.

1-(2,2-Difluorovinyl)-4-nitrobenzene (4d)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.41 (dd, $J_{HF}$ = 25.5, 3.3 Hz, 1H), 7.49 (d, $J$ = 8.9 Hz, 2H), 8.21 (d, $J$ = 8.9 Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 81.6 (dd, $J_{CF}$ = 31, 13 Hz), 124.0, 128.1 (dd, $J_{CF}$ = 7,
4 Hz), 137.3 (dd, $J_{CF} = 7, 7$ Hz), 146.4, 157.1 (dd, $J_{CF} = 302, 293$ Hz). $^{19}$F NMR (470 MHz, CDCl$_3$): δ 83.4 (dd, $J_{FF} = 18$ Hz, $J_{FH} = 3$ Hz, 1F), 84.9 (dd, $J_{FH} = 26$ Hz, $J_{FF} = 18$ Hz, 1F). The NMR spectral data described above showed good agreement with the literature data (ref 10b).

1-(2,2-Difluorovinyl)naphthalene (4e)

$^1$H NMR (500 MHz, CDCl$_3$): δ 5.85 (dd, $J_{HF} = 24.4, 3.3$ Hz, 1H), 7.45 (dd, $J = 7.7, 7.7$ Hz, 1H), 7.47–7.53 (m, 2H), 7.57 (d, $J = 7.2$ Hz, 1H), 7.77 (d, $J = 8.2$ Hz, 1H), 7.83–7.85 (m, 1H), 7.93 (d, $J = 8.2$ Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$): δ 78.6 (dd, $J_{CF} = 29, 16$ Hz), 123.7, 125.4, 125.9, 126.3, 126.4–126.5 (overlapped dd), 126.5 (dd, $J_{CF} = 7, 2$ Hz), 127.9, 128.7, 131.4 (d, $J_{CF} = 3$ Hz), 133.6, 156.7 (dd, $J_{CF} = 297, 289$ Hz). $^{19}$F NMR (470 MHz, CDCl$_3$): δ 77.8 (dd, $J_{FF} = 29$ Hz, $J_{FH} = 24$ Hz, 1F), 79.7 (dd, $J_{FF} = 29$ Hz, $J_{FH} = 3$ Hz, 1F). The NMR spectral data described above showed good agreement with the literature data (ref 25).

2-(2,2-Difluorovinyl)naphthalene (4f)

$^1$H NMR (500 MHz, CDCl$_3$): δ 5.39 (dd, $J_{HF} = 26.2, 3.6$ Hz, 1H), 7.41–7.47 (m, 3H), 7.71 (s, 1H), 7.73–7.79 (m, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$): δ 82.4 (dd, $J_{CF} = 29, 14$ Hz), 125.3 (dd, $J_{CF} = 7, 2$ Hz), 126.0, 126.4, 126.6 (dd, $J_{CF} = 6, 6$ Hz), 127.6, 127.7, 127.8 (dd, $J_{CF} = 7, 7$ Hz), 128.3, 132.2, 133.4, 156.4 (dd, $J_{CF} = 299, 289$ Hz). $^{19}$F NMR (470 MHz, CDCl$_3$): δ 79.2 (dd, $J_{FF} = 31$ Hz, $J_{FH} = 4$ Hz, 1F), 80.9 (dd, $J_{FF} = 31$ Hz, $J_{FH} = 26$ Hz, 1F). The NMR spectral data described above showed good agreement with the literature data (ref 25).

2-(2,2-Difluorovinyl)biphenyl (4g)

$^1$H NMR (500 MHz, CDCl$_3$): δ 5.25 (dd, $J_{HF} = 26.1, 4.0$ Hz, 1H), 7.33–7.37 (m, 4H), 7.38–7.41 (m, 2H), 7.44–7.47 (m, 2H), 7.64 (d, $J = 7.4$ Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$): δ 80.6 (dd, $J_{CF} = 30, 13$ Hz), 127.1, 127.3, 127.5, 127.9 (d, $J_{CF} = 6$ Hz), 128.1 (d, $J_{CF} = 10$ Hz), 128.3, 129.5, 130.1, 140.7, 141.2 (d, $J_{CF} = 4$ Hz), 156.2 (dd, $J_{CF} = 288$ Hz). $^{19}$F NMR (470 MHz, CDCl$_3$): δ 78.1 (dd, $J_{FF} = 32$ Hz, $J_{FH} = 26$ Hz, 1F), 79.9 (dd, $J_{FF} = 32$ Hz, $J_{FH} = 4$ Hz, 1F). The NMR spectral data described above showed good agreement with the literature data (ref 26).
2-(2,2-Difluorovinyl)-1,3-dimethoxybenzene (4h)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.83 (s, 6H), 5.18 (dd, $J_{HF}$ = 27.7, 2.6 Hz, 1H), 6.56 (d, $J = 8.4$ Hz, 2H), 7.22 (t, $J = 8.4$ Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 55.8, 72.1 (dd, $J_{CF}$ = 27.7, 2.6 Hz), 103.6, 107.3 (dd, $J_{CF} = 7$, 4 Hz), 128.9, 155.4 (dd, $J_{CF} = 297$, 285 Hz), 157.9. $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ 77.9 (dd, $J_{FF} = 26$ Hz, $J_{FH} = 3$ Hz, 1F), 84.4 (dd, $J_{FF} = 28$ Hz, $J_{FH} = 26$ Hz, 1F). IR (neat): 2941, 1738, 1473, 1254, 1109 cm$^{-1}$. Anal. calcd. for C$_{10}$H$_{10}$F$_2$O$_2$: C, 60.00; H, 5.04; Found: C, 59.92; H, 5.09.

2-[2-(2,2-Difluorovinyl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4k)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 1.35 (s, 12H), 6.25 (dd, $J_{HF}$ = 26.8, 5.1 Hz, 1H), 7.22 (ddd, $J = 7$, 6, 1H), 7.36–7.47 (m, 1H), 7.55 (dd, $J = 8.0$, 1.0 Hz, 1H), 7.84 (dd, $J = 7$, 6, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 24.8, 82.4 (dd, $J_{CF}$ = 30, 11 Hz), 83.8, 126.1, 127.5 (d, $J_{CF} = 10$ Hz), 131.2, 136.2 (dd, $J_{CF} = 7$, 6, 1H), 136.4, 156.2 (dd, $J_{CF} = 299$, 287 Hz), (One aromatic carbon signal was not detected due to $^{13}$C–10B and $^{13}$C–11B coupling and overlapping with other signals). $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ 79.2 (dd, $J_{FF} = 26$ Hz, $J_{FH} = 5$ Hz, 1F), 79.6 (dd, $J_{FF} = 28$ Hz, $J_{FH} = 25$ Hz, 1F). IR (neat): 2979, 1724, 1346, 1146, 912, 743 cm$^{-1}$. HRMS (EI): $m/z$ calcd. for C$_{14}$H$_{17}$BF$_2$O$_2$ ([M]$^+$): 266.1290; Found: 266.1288.

3-(2,2-Difluorovinyl)phenyl trifluoromethanesulfonate (4l)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.32 (dd, $J_{HF} = 25.3$, 3.3 Hz, 1H), 7.16 (dd, $J = 8.2$, 2.3 Hz, 1H), 7.25 (dd, $J = 2.3$, 1.5 Hz, 1H), 7.34 (d, $J = 8.0$, 1H), 7.42 (dd, $J = 8.2$, 8.0 Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 81.3 (dd, $J_{CF} = 31$, 13 Hz), 118.7 (q, $J_{CF} = 321$ Hz), 119.7, 120.2 (dd, $J_{CF} = 7$, 3 Hz), 127.5 (dd, $J_{CF} = 6$, 4 Hz), 130.4, 133.1 (dd, $J_{CF} = 7$, 7 Hz), 149.8, 156.8 (dd, $J_{CF} = 300$, 292 Hz). $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ 81.6 (dd, $J_{FF} = 25$ Hz, $J_{FH} = 3$ Hz, 1F), 83.4 (dd, $J_{FF} = 25$ Hz, $J_{FH} = 25$ Hz, 1F), 90.0 (s, 3F). IR (neat): 1728, 1423, 1213, 1140, 906, 845, 771 cm$^{-1}$. HRMS (EI): $m/z$ calcd. for C$_9$H$_5$F$_3$O$_2$S ([M]$^+$): 287.9880; Found: 287.9879.

3-Bromo-4-(2,2-difluorovinyl)biphenyl (4m)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.72 (dd, $J_{HF} = 25.6$, 3.6 Hz, 1H), 7.37 (tt, $J = 7.4$, 1.3 Hz, 1H), 7.43–7.47 (m, 2H), 7.50–7.62 (m, 4H), 7.82 (d, $J = 1.9$ Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 81.4 (dd, $J_{CF} = 33$, 12 Hz), 123.6 (dd, $J_{CF} = 6$, 2 Hz), 126.2, 126.9, 128.0, 128.9, 129.16, 129.23,
131.3, 139.0, 141.6, 156.7 (dd, \(^{13}J_{CF} = 299, 290\) Hz). \(^{19}F\) NMR (470 MHz, CDCl\(_3\)): \(\delta 77.7\) (dd, \(^{19}J_{FF} = 30\) Hz, \(^{19}J_{FH} = 26\) Hz, 1F), 79.6 (dd, \(^{19}J_{FF} = 30\) Hz, \(^{19}J_{FH} = 4\) Hz, 1F). IR (neat): 1726, 1477, 1248, 1178, 945, 758 cm\(^{-1}\). HRMS (EI): \(m/z\) calcd. for C\(_{14}\)H\(_9\)BrF\(_2\) ([M]+): 293.9856; Found: 293.9849.

3,5-Dichloro-4-(2,2-difluorovinyl)biphenyl (4n)

\(^1H\) NMR (500 MHz, CDCl\(_3\)): \(\delta 5.34\) (d, \(^1J_{HF} = 25.9\) Hz, 1H), 7.39 (t, \(J = 7.5\) Hz, 1H), 7.44 (dd, \(J = 7.5, 7.1\) Hz, 2H), 7.52 (d, \(J = 7.1\) Hz, 2H), 7.55 (s, 2H). \(^{13}C\) NMR (126 MHz, CDCl\(_3\)): \(\delta 76.6–76.9\) (overlapped dd), 126.2 (dd, \(^{13}J_{CF} = 9, 4\) Hz), 126.5, 126.9, 128.6, 129.1, 135.9, 138.0, 142.9, 155.8 (dd, \(^{13}J_{CF} = 297, 290\) Hz). \(^{19}F\) NMR (470 MHz, CDCl\(_3\)): \(\delta 79.6\) (d, \(^{19}J_{FF} = 20\) Hz, 1F), 85.9 (dd, \(^{19}J_{FH} = 26, {^{19}J_{FF}} = 20\) Hz, 1F). IR (neat): 1738, 1535, 1248, 1173, 914, 758 cm\(^{-1}\). HRMS (EI): \(m/z\) calcd. for C\(_{14}\)H\(_9\)BrF\(_2\) ([M]+): 283.9971; Found: 283.9964.

3'-Chloro-2-(2,2-difluorovinyl)biphenyl (4o)

\(^1H\) NMR (500 MHz, CDCl\(_3\)): \(\delta 5.17\) (dd, \(^1J_{HF} = 25.8, 4.1\) Hz, 1H), 7.17–7.22 (m, 1H), 7.25–7.40 (m, 6H), 7.60 (d, \(J = 7.8\) Hz, 1H). \(^{13}C\) NMR (126 MHz, CDCl\(_3\)): \(\delta 80.3\) (dd, \(^{13}J_{CF} = 30, 13\) Hz), 127.2, 127.5, 127.8, 127.9 (dd, \(^{13}J_{CF} = 7, 6\) Hz), 128.0, 128.2 (dd, \(^{13}J_{CF} = 9, 1\) Hz), 129.49, 129.51, 130.0, 134.2, 139.7 (d, \(^{13}J_{CF} = 3.5\) Hz), 142.5, 156.3 (dd, \(^{13}J_{CF} = 299, 288\) Hz). \(^{19}F\) NMR (470 MHz, CDCl\(_3\)): \(\delta 77.7\) (dd, \(^{19}J_{FF} = 30\) Hz, \(^{19}J_{FH} = 26\) Hz, 1F), 79.6 (dd, \(^{19}J_{FF} = 30\) Hz, \(^{19}J_{FH} = 4\) Hz, 1F). IR (neat): 3062, 1724, 1232, 1173, 939, 756 cm\(^{-1}\). Anal. calcd. for C\(_{14}\)H\(_9\)ClF\(_2\): C, 67.08; H, 3.62; Found: C, 67.12; H, 3.72.

1-Bromo-3-(2,2-difluorovinyl)benzene (4p)

\(^1H\) NMR (500 MHz, CDCl\(_3\)): \(\delta 5.23\) (dd, \(^1J_{HF} = 25.8, 3.5\) Hz, 1H), 7.20 (dd, \(J = 7.8, 7.8\) Hz, 1H), 7.22–7.27 (m, 1H), 7.37 (d, \(J = 7.8\) Hz, 1H), 7.48 (s, 1H). \(^{13}C\) NMR (126 MHz, CDCl\(_3\)): \(\delta 81.3\) (dd, \(^{13}J_{CF} = 30, 14\) Hz), 122.7, 126.1 (dd, \(^{13}J_{CF} = 6, 4\) Hz), 130.0, 130.1, 130.4 (dd, \(^{13}J_{CF} = 7, 4\) Hz), 132.4 (dd, \(^{13}J_{CF} = 7, 7\) Hz), 156.5 (dd, \(^{13}J_{CF} = 300, 255\) Hz). \(^{19}F\) NMR (470 MHz, CDCl\(_3\)): \(\delta 80.4\) (dd, \(^{19}J_{FF} = 27, {^{19}J_{FH}} = 3\) Hz, 1F), 82.4 (dd, \(^{19}J_{FF} = 27\) Hz, \(^{19}J_{FH} = 26\) Hz, 1F). The NMR spectral data described above showed good agreement with the literature data (ref 6c).
2.6.4. Synthesis of 1,1-difluoro-1,3-dienes 6 by Pd-catalyzed coupling of 2a with alkenyl halides 5

(A) Typical procedure for the synthesis of 1,1-difluoro-1,3-dienes 6

To the solution of 2a (0.11 M in THF and diethyl ether, 2.5 mL, 0.27 mmol) were added a solution of (E)-1-(2-bromovinyl)-4-(trifluoromethyl)benzene (5c, 68 mg, 0.27 mmol) in THF (0.5 mL) and Pd(PPh₃)₄ (6 mg, 5 µmol). After being refluxed refluxing for 2 h, the reaction mixture was filtered through a pad of silica gel (diethyl ether). The filtrate was concentrated under reduced pressure and purified by preparative thin layer chromatography on silica gel (pentane) to give 6c (55 mg, 86%).

(B) Spectral data of 1,1-difluoro-1,3-dienes 6

(E)-1-(4,4-Difluorobuta-1,3-dienyl)-4-methylbenzene (6a)

1H NMR (500 MHz, CDCl₃): δ 2.33 (s, 3H), 5.10 (dddd, J_HF = 24.6 Hz, J = 10.9 Hz, 1H), 6.43 (d, J = 15.9 Hz, 1H), 6.60 (dd, J = 15.9, 10.9 Hz, 1H), 7.11 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H).

13C NMR (126 MHz, CDCl₃): δ 21.2, 82.9 (dd, J_CF = 30, 18 Hz), 114.1, 115.7 (d, J_CF = 4 Hz), 127.4, 129.8, 130.6 (dd, J_CF = 11, 3 Hz), 156.6 (dd, J_CF = 297, 292 Hz), 159.3.

19F NMR (470 MHz, CDCl₃): δ 74.8 (d, J_FF = 29 Hz, 1F), 76.6 (dd, J_FF = 29 Hz, J_FH = 24 Hz, 1F). IR (neat): 2923, 2852, 1716, 1510, 1458, 1377, 1254, 1178, 1124, 1034, 910, 737 cm⁻¹. HRMS (EI): m/z calcd. for C₁₁H₁₀F₂ ([M]+): 180.0751; Found: 180.0748.

(E)-1-(4,4-Difluorobuta-1,3-dienyl)-4-methoxybenzene (6b)

1H NMR (500 MHz, CDCl₃): δ 3.81 (s, 3H), 5.10 (dddd, J_HF = 24.3 Hz, J = 10.6 Hz, J_HF = 1.5 Hz, 1H), 6.42 (d, J = 15.9 Hz, 1H), 6.51 (dd, J = 15.9, 10.6 Hz, 1H), 6.85 (d, J = 8.8 Hz, 2H).

13C NMR (126 MHz, CDCl₃): δ 55.3, 82.9 (dd, J_CF = 30, 18 Hz), 114.1, 115.7 (d, J_CF = 4 Hz), 127.4, 129.8, 130.6 (dd, J_CF = 11, 3 Hz), 156.6 (dd, J_CF = 297, 292 Hz), 159.3. 19F NMR (470 MHz, CDCl₃): δ 74.8 (d, J_FF = 29 Hz, 1F), 76.6 (dd, J_FF = 29 Hz, J_FH = 24 Hz, 1F). IR (neat): 2923, 2852, 1716, 1606, 1510, 1458, 1377, 1254, 1178, 1124, 1034, 910, 737 cm⁻¹. HRMS (EI): m/z calcd. for C₁₁H₁₀F₂O ([M]+): 196.0700; Found: 196.0703.
(E)-1-(4,4-Difluorobuta-1,3-dienyl)-4-(trifluoromethyl)benzene (6e)

$^1$H NMR (500 MHz, CDCl$_3$): δ 5.17 (dd, $J_{HF} = 23.8$ Hz, $J = 11.0$ Hz, 1H), 6.50 (d, $J = 15.9$ Hz, 1H), 6.75 (dd, $J = 15.9$, 11.0 Hz, 1H), 7.47 (d, $J = 8.3$ Hz, 2H), 7.56 (d, $J = 8.3$ Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): δ 82.7 (dd, $J_{CF} = 28$, 17 Hz), 120.4 (dd, $J_{CF} = 4$, 2 Hz), 124.1 (q, $J_{CF} = 272$ Hz), 125.6 (q, $J_{CF} = 4$ Hz), 126.2, 129.3 (q, $J_{CF} = 33$ Hz), 129.5 (dd, $J_{CF} = 12$, 3 Hz), 140.3, 157.2 (dd, $J_{CF} = 299$, 293 Hz). $^{19}$F NMR (470 MHz, CDCl$_3$): δ 77.7 (d, $J_{FF} = 23$ Hz, 1F), 79.2 (dd, $J_{FH} = 24$ Hz, $J_{FF} = 23$ Hz, 1F), 100.3 (s, 3F). IR (neat): 1714, 1616, 1323, 1281, 1167, 1124, 1068, 937, 810 cm$^{-1}$. HRMS (EI): m/z calcd. for C$_{11}$H$_7$F$_5$ ([M]+): 234.0468; Found: 234.0466.

2.6.5. Synthesis of 1,1-difluoro-1,3-enynes 8 by Pd-catalyzed coupling of 2a with alkynyl halides 7

(A) Typical procedure for the synthesis of 1,1-difluoro-1,3-enynes 8

In a two-necked flask were placed Pd$_2$(dba)$_3$·CHCl$_3$ (8 mg, 8 µmol), dppp (6 mg, 0.02 mmol), and 2a (0.12 M in THF and diethyl ether, 3.2 mL, 0.38 mmol). After stirring for 10 min, 2-(4-iodobut-3-ynyl)naphthalene (7b, 77 mg, 0.30 mmol) was added to the mixture. After refluxing for 2 h, the reaction mixture was filtered through a pad of silica gel (diethyl ether). The filtrate was concentrated under reduced pressure and purified by silica gel column chromatography (hexane) to give 8b (68 mg, 94%).

[4-(2,2-Difluorovinyl)-6,6-difluorohepta-3,3-dienyl]benzene (6d)

$^1$H NMR (500 MHz, CDCl$_3$): δ 2.39 (td, $J = 7.6$, 7.5 Hz, 2H), 2.69 (t, $J = 7.6$ Hz, 2H), 4.87 (dd, $J_{HF} = 24.4$ Hz, 2H), 5.60 (t, $J = 7.5$ Hz, 1H), 7.16–7.22 (m, 3H), 7.28 (dd, $J_{HF} = 7.6$, 7.6 Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): δ 30.7, 35.1, 77.2 (dd, $J_{CF} = 29$, 16 Hz), 82.3 (dd, $J_{CF} = 29$, 13 Hz), 119.2 (dd, $J_{CF} = 9$, 5 Hz), 126.1, 128.40, 128.40, 133.7 (dddd, $J_{CF} = 17$, 11, 6, 2 Hz), 141.2, 155.7 (dd, $J_{CF} = 297$, 287), 155.8 (dd, $J_{CF} = 297$, 288). $^{19}$F NMR (470 MHz, CDCl$_3$): δ 75.5 (dd, $J_{FF} = 34$ Hz, $J_{FH} = 4$ Hz, 1F), 76.76 (ddd, $J_{FF} = 34$ Hz, $J_{FH} = 24$, 3 Hz, 1F), 76.77 (d, $J_{FF} = 30$ Hz, 1F), 79.9 (ddd, $J_{FF} = 30$ Hz, $J_{FH} = 24$, 4 Hz, 1F). IR (neat): 2927, 2850, 1541, 1508, 1219, 771 cm$^{-1}$. HRMS (EI): m/z calcd. for C$_{14}$H$_{12}$F$_4$ ([M]+): 256.0875; Found: 256.0876.
(B) Spectral data of 1,1-difluoro-1,3-enynes 8

(6,6-Difluorohex-5-en-3-ynyl)benzene (8a)

$^1$H NMR (500 MHz, CDCl$_3$): δ 2.58 (tdd, $J = 7.5$, 1.7 Hz, $J_{HF} = 1.1$ Hz, 2H), 2.84 (t, $J = 7.5$ Hz, 2H), 4.52 (ddt, $J_{HF} = 23.3$ Hz, $J = 1.7$ Hz, $J_{HF} = 0.6$ Hz, 1H), 7.20–7.22 (m, 3H), 7.29 (dd, $J = 7.5$, 7.5 Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): δ 21.6, 34.9, 65.4 (dd, $J_{CF} = 42$, 19 Hz), 69.2 (dd, $J_{CF} = 13$, 3 Hz), 93.5 (dd, $J_{CF} = 9$, 4 Hz), 126.3, 128.38, 128.43, 140.4, 162.0 (dd, $J_{CF} = 300$, 293 Hz).

$^{19}$F NMR (470 MHz, CDCl$_3$): δ 81.1 (d, $J_{FF} = 10$ Hz, 1F), 86.3 (dd, $J_{FH} = 23$ Hz, $J_{FF} = 10$ Hz, 1F). IR (neat): 2956, 2931, 1722, 1346, 1238, 914, 773, 698 cm$^{-1}$. HRMS (EI): $m/z$ calcd. for C$_{12}$H$_{10}$F$_2$ ([M]$^+$): 192.0751; Found: 192.0749.

2-(6,6-Difluorohex-5-en-3-ynyl)naphthalene (8b)

$^1$H NMR (500 MHz, CDCl$_3$): δ 2.68 (t, $J = 7.5$ Hz, 2H), 3.01 (t, $J = 7.5$ Hz, 2H), 4.53 (d, $J_{HF} = 23.4$ Hz, 1H), 7.35 (dd, $J = 8.4$, 1.8 Hz, 1H), 7.43 (dd, $J = 8.4$, 6.9, 1.1 Hz, 1H), 7.46 (ddd, $J = 8.4$, 6.9, 1.1 Hz, 1H), 7.67 (s, 1H), 7.77–7.82 (m, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$): δ 21.6, 35.0, 65.4 (dd, $J_{CF} = 42$, 19 Hz), 69.4 (dd, $J_{CF} = 12$, 5 Hz), 93.5 (dd, $J_{CF} = 9$, 4 Hz), 125.4, 126.0, 126.7, 127.1, 127.5, 127.6, 128.0, 132.2, 133.5, 137.9, 162.0 (dd, $J_{CF} = 299$, 293 Hz).

$^{19}$F NMR (470 MHz, CDCl$_3$): δ 80.0 (d, $J_{FF} = 10$ Hz, 1F), 86.3 (dd, $J_{FH} = 23$ Hz, $J_{FF} = 10$ Hz, 1F). IR (neat): 3055, 1720, 1508, 1344, 1234, 1165, 1124, 910, 814, 744 cm$^{-1}$. HRMS (EI): $m/z$ calcd. for C$_{16}$H$_{12}$F$_2$ ([M]$^+$): 242.0911; Found: 242.0911.

2-(4,4-Difluorobut-3-en-1-ynyl)biphenyl (8c)

$^1$H NMR (500 MHz, CDCl$_3$): δ 4.67 (d, $J_{HF} = 23.3$ Hz, 1H), 7.27–7.31 (m, 1H), 7.34–7.43 (m, 5H), 7.54–7.58 (m, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$): δ 65.8 (dd, $J_{CF} = 42$, 19 Hz), 80.4 (dd, $J_{CF} = 12$, 5 Hz), 92.9 (dd, $J_{CF} = 9$, 4 Hz), 121.1, 127.0, 127.5, 127.9, 128.7, 129.1, 129.5, 132.9, 140.2, 143.6, 161.7 (dd, $J_{CF} = 302$, 295 Hz). $^{19}$F NMR (470 MHz, CDCl$_3$): δ 83.5 (d, $J_{FF} = 3$ Hz, 1F), 88.9 (dd, $J_{FH} = 23$ Hz, $J_{FF} = 3$ Hz, 1F). IR (neat): 3053, 2960, 2920, 1728, 1281, 1173, 958, 827, 767 cm$^{-1}$. HRMS (EI): $m/z$ calcd. for C$_{16}$H$_{10}$F$_2$ ([M]$^+$): 240.0911; Found: 240.0911.

1-(4,4-Difluorobut-3-en-1-ynyl)-4-methoxybenzene (8d)

$^1$H NMR (500 MHz, CDCl$_3$): δ 3.81 (s, 3H), 4.78 (d, $J_{HF} = 23.1$ Hz, 1H), 6.84 (d, $J = 8.8$ Hz, 2H), 7.37 (d, $J = 8.8$ Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): δ 55.3, 65.8 (dd, $J_{CF} = 42$, 19 Hz), 76.1 (dd,
$J_{CF} = 12.5$ Hz), 93.1 (dd, $J_{FF} = 6$ Hz, 1F), 86.5 (dd, $J_{FH} = 23$ Hz, $J_{FF} = 6$ Hz, 1F). IR (neat): 2960, 2837, 1714, 1604, 1508, 1464, 1348, 1282, 1246, 1207, 1170, 1051, 1030, 908, 831, 771 cm$^{-1}$. HRMS (EI): $m/z$ calcd. for $C_{11}H_8F_2O ([M]^+)$: 194.0543; Found: 194.0547.

1-(4,4-Difluorobut-3-en-1-ynyl)-4-nitrobenzene (8e)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 4.86 (dd, $J_{HF} = 22.9$, 1.0 Hz, 1H), 6.84 (d, $J = 8.8$ Hz, 2H), 8.19 (d, $J = 8.8$ Hz, 2H). $^1^3$C NMR (126 MHz, CDCl$_3$): $\delta$ 65.4 (dd, $J_{CF} = 43$, 19 Hz), 83.0 (dd, $J_{CF} = 12$, 5 Hz), 91.4 (dd, $J_{CF} = 9$, 4 Hz), 123.6, 129.6, 132.0, 147.1, 162.2 (dd, $J_{CF} = 303$, 297 Hz). $^1^9$F NMR (470 MHz, CDCl$_3$): $\delta$ 85.1 (d, $J_{FF} = 2$ Hz, 1F), 90.0 (dd, $J_{FH} = 23$ Hz, $J_{FF} = 2$ Hz, 1F). IR (neat): 1716, 1593, 1522, 1344, 1296, 1201, 914, 854, 744 cm$^{-1}$. HRMS (EI): $m/z$ calcd. for $C_{10}H_5F_2NO_2 ([M]^+)$: 209.0288; Found: 209.0294.

2.6.6. Synthesis of (3,3-difluoroallyl)arenes 10 by Pd-catalyzed coupling of 2a with benzyl halides 9'

(A) Typical procedure for the synthesis of (3,3-difluoroallyl)arenes 10

In a two-necked flask was placed 2a (0.11 M in THF and diethyl ether, 9.1 mL, 1.0 mmol). To the solution were added a solution of 1-butyl-4-(chloromethyl)benzene (9'b, 146 mg, 0.80 mmol) in THF (0.5 mL) and Pd(PPh$_3$)$_4$ (46 mg, 4.0 µmol). After refluxing for 2 h, the reaction mixture was filtered through a pad of silica gel (diethyl ether). The filtrate was concentrated under reduced pressure and purified by preparative thin layer chromatography on silica gel (pentane) to give 10b (157 mg, 93%).

(B) Spectral data of (3,3-difluoroallyl)arenes 10

4-(3,3-Difluoroallyl)biphenyl (10a)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.37 (d, $J = 8.1$ Hz, 2H), 4.43 (dtd, $J_{HF} = 24.8$ Hz, $J = 8.1$ Hz, $J_{HF} = 2.2$ Hz, 1H), 7.27 (d, $J = 8.2$ Hz, 2H), 7.34 (tt, $J = 7.5$, 1.3 Hz, 1H), 7.43 (dd, $J = 7.5$, 7.5 Hz, 2H), 7.53 (d, $J = 8.2$ Hz, 2H), 7.57 (dd, $J = 7.5$, 1.3 Hz, 2H). $^{1^3}$C NMR (126 MHz, CDCl$_3$): $\delta$ 28.0 (d, $J_{CF} = 5$ Hz), 77.6 (dd, $J_{CF} = 23$, 20 Hz), 127.0, 127.2, 127.3, 128.5, 128.7, 138.5 (dd, $J_{CF} = 2$, 2 Hz), 139.5, 140.9, 156.6 (dd, $J_{CF} = 289$, 288 Hz). $^{1^9}$F NMR (470 MHz, CDCl$_3$): $\delta$ 71.3 (dd, $J_{FF} = 45$ Hz,
$J_{HF} = 25 \text{ Hz}, 1F), 74.2 (d, J_{FF} = 45 \text{ Hz}, 1F)$. IR (neat): 3030, 1747, 1489, 1294, 1230, 1173, 964, 758, 694 cm$^{-1}$. HRMS (EI): $m/z$ calcd. for C$_{15}$H$_{13}$F$_2$ ([M]$^+$): 230.0907; Found: 230.0904.

1-Butyl-4-(3,3-difluoroallyl)benzene (10b)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 0.92 (t, $J = 7.4$ Hz, 3H), 1.34 (qt, $J = 7.4, 7.4$ Hz, 2H), 1.58 (tt, $J = 7.8, 7.4$ Hz, 2H), 2.57 (t, $J = 7.8$ Hz, 2H), 3.27 (d, $J = 8.0$ Hz, 2H), 4.36 (dtd, $J_{HF} = 24.8$ Hz, $J = 8.0$ Hz, $J_{HF} = 2.3$ Hz, 1H), 7.08 (d, $J = 8.2$ Hz, 2H), 7.11 (d, $J = 8.2$ Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 13.9, 22.4, 28.0 (d, $J_{CF} = 5$ Hz), 33.7, 35.2, 77.8 (dd, $J_{CF} = 23, 20$ Hz), 127.9, 128.6, 136.6 (d, $J_{CF} = 2$ Hz), 141.1, 156.6 (dd, $J_{CF} = 288, 286$ Hz).

$^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ 69.9 (dd, $J_{FF} = 46$ Hz, $J_{FH} = 25$ Hz, 1F), 72.8 (d, $J_{FF} = 46$ Hz, 1F). HRMS (EI): $m/z$ calcd. for C$_{13}$H$_{16}$F$_2$ ([M]$^+$): 210.1220; Found: 210.1222.

1-(3,3-Difluoroallyl)-4-methoxybenzene (10c)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.19 (d, $J = 8.0$ Hz, 2H), 3.71 (s, 3H), 4.28 (dtd, $J_{HF} = 24.9$ Hz, $J = 8.0$ Hz, $J_{HF} = 2.3$ Hz, 1H), 6.77 (d, $J = 8.6$ Hz, 2H), 7.03 (d, $J = 8.6$ Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 27.5 (d, $J_{CF} = 5$ Hz), 55.3, 78.0 (dd, $J_{CF} = 23, 20$ Hz), 114.0, 129.0, 131.5, 156.5 (dd, $J_{CF} = 288, 287$ Hz), 158.2. $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ 69.0 (dd, $J_{FF} = 49$ Hz, $J_{FH} = 25$ Hz, 1F), 72.8 (d, $J_{FF} = 49$ Hz, 1F). IR (neat): 2958, 2929, 2858, 1745, 1514, 1288, 1230, 1171, 958, 802, 758 cm$^{-1}$. HRMS (EI): $m/z$ calcd. for C$_{10}$H$_{10}$F$_2$O ([M]$^+$): 184.0700; Found: 184.0698.

1-(3,3-Difluoroallyl)-4-(trifluoromethyl)benzene (10d)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.39 (d, $J = 8.1$ Hz, 2H), 4.39 (dtd, $J_{HF} = 24.5$ Hz, $J = 8.1$ Hz, $J_{HF} = 2.1$ Hz, 1H), 7.31 (d, $J = 8.0$ Hz, 2H), 7.56 (d, $J = 8.0$ Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 28.3 (d, $J_{CF} = 5$ Hz), 76.9 (dd, $J_{CF} = 24, 20$ Hz), 124.2 (q, $J_{CF} = 272$ Hz), 125.5 (q, $J_{CF} = 4$ Hz), 128.4, 128.9 (q, $J_{CF} = 32$ Hz), 143.5, 156.8 (dd, $J_{CF} = 289, 288$ Hz). $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ 72.1 (dd, $J_{FF} = 43$ Hz, $J_{FH} = 25$ Hz, 1F), 75.0 (dd, $J_{FF} = 43$ Hz, $J_{FH} = 2$ Hz, 1F), 100.4 (s, 3F). IR (neat): 2924, 2854, 1743, 1714, 1541, 1508, 1458, 1325, 1128, 1068, 760 cm$^{-1}$. HRMS (EI): $m/z$ calcd. for C$_{10}$H$_7$F$_5$ ([M]$^+$): 222.0468; Found: 222.0461.
2.6.7. Synthesis of 1,1-difluoro-1,4-dienes 12 by Cu-catalyzed coupling of 2a with allyl halides

(A) Typical procedure for the synthesis of 1,1-difluoro-1,4-dienes 12

To the solution of 2a (0.10 M in THF and diethyl ether, 6.0 mL, 0.60 mmol) was added CuBr·SMe₂ (10 mg, 50 µmol) at 0 °C. After being stirred for 5 min at the same temperature, a solution of (E)-(3-bromoprop-1-enyl)benzene (E-11a, 99 mg, 0.50 mmol) in THF (0.5 mL) was added. After being stirred for 2 h at 0 °C, the reaction mixture was filtered through a pad of silica gel (diethyl ether). The filtrate was concentrated under reduced pressure and purified by preparative thin layer chromatography on silica gel (pentane) to give 12a (77 mg, 86%, E/Z = 92:8).

(B) Spectral data of 1,1-difluoro-1,4-dienes 12

(E)-(5,5-Difluoropenta-1,4-dienyl)benzene (E-12a)

\(^1\text{H NMR}\) (500 MHz, CDCl₃): δ 2.90–2.94 (m, 2H), 4.31 (dtd, \(J_{HF} = 25.1\) Hz, \(J = 7.9\) Hz, \(J_{HF} = 2.3\) Hz, 1H), 6.19 (dt, \(J = 15.8, 6.4\) Hz, 1H), 6.46 (d, \(J = 15.8\) Hz, 1H), 7.25 (t, \(J = 7.3\) Hz, 1H), 7.34 (dd, \(J = 7.8, 7.3\) Hz, 2H), 7.38 (d, \(J = 7.8\) Hz, 2H). \(^{13}\text{C NMR}\) (126 MHz, CDCl₃): δ 25.6 (d, \(J_{CF} = 5\) Hz), 76.3 (dd, \(J_{CF} = 22, 20\) Hz), 126.1, 127.1, 127.2, 128.5, 130.7, 137.2, 156.5 (dd, \(J_{CF} = 288, 286\) Hz).

\(^{19}\text{F NMR}\) (470 MHz, CDCl₃): δ 71.8 (dd, \(J_{FF} = 45\) Hz, \(J_{FH} = 25\) Hz, 1F), 74.5 (d, \(J_{FF} = 45\) Hz, 1F). IR (neat): 3030, 2925, 2854, 1745, 1720, 1496, 1454, 1346, 1290, 1232, 1173, 958, 912, 742, 696 cm⁻¹. HRMS (EI): \(m/z\) calcd. for C_{11}H_{10}F_{2} ([M]⁺): 180.0751; Found: 180.0745.

(Z)-(5,5-Difluoropenta-1,4-dienyl)benzene (Z-12a)

\(^1\text{H NMR}\) (500 MHz, CDCl₃): δ 2.96–3.00 (m, 2H), 4.22 (dtd, \(J_{HF} = 25.2\) Hz, \(J = 7.7\) Hz, \(J_{HF} = 2.3\) Hz, 1H), 5.59 (dt, \(J = 11.5, 7.4\) Hz, 1H), 6.49 (d, \(J = 11.5\) Hz, 1H), 7.23–7.26 (m, 3H), 7.34 (dd, \(J = 7.6, 7.6\) Hz, 2H). \(^{13}\text{C NMR}\) (126 MHz, CDCl₃): δ 21.7 (d, \(J_{CF} = 5\) Hz), 77.1 (dd, \(J_{CF} = 23, 20\) Hz), 126.9, 128.3, 128.7, 129.0 (dd, \(J_{CF} = 2, 2\) Hz), 130.2, 136.9, 156.4 (dd, \(J_{CF} = 288, 286\) Hz). \(^{19}\text{F NMR}\) (470 MHz, CDCl₃): δ 72.2 (dd, \(J_{FF} = 46\) Hz, \(J_{FH} = 25\) Hz, 1F), 73.9 (dd, \(J_{FF} = 46\) Hz, \(J_{FH} = 2\) Hz, 1F). IR (neat): 3022, 2914, 1495, 1446, 1338, 1284, 1230, 1174, 945, 914, 806, 698 cm⁻¹. HRMS (EI): \(m/z\) calcd. for C_{11}H_{10}F_{2} ([M]⁺): 180.0751; Found: 180.0750.
(5,5-Difluoropenta-1,4-dien-2-yl)benzene (12b)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.17 (d, $J = 7.8$ Hz, 2H), 4.27 (dtd, $J_{HF} = 25.0$ Hz, $J = 7.8$ Hz, $J_{HF} = 2.3$ Hz, 1H), 5.12 (d, $J = 1.1$ Hz, 1H), 5.36 (d, $J = 1.1$ Hz, 1H), 7.28 (tt, $J = 7.3$, 1.4 Hz, 1H), 7.32–7.35 (m, 2H), 7.39–7.41 (m, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 28.1 (d, $J_{CF} = 5$ Hz), 76.4 (dd, $J_{CF} = 23$, 20 Hz), 113.0, 125.9, 127.7, 128.4, 140.3, 145.6, 156.5 (dd, $J_{CF} = 289$, 286 Hz). $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ 71.3 (dd, $J_{FF} = 48$ Hz, $J_{FH} = 25$ Hz, 1F), 74.1 (dd, $J_{FF} = 48$ Hz, $J_{FH} = 2$ Hz, 1F). IR (neat): 2958, 2927, 1749, 1541, 1257, 1215, 769 cm$^{-1}$. HRMS (EI): $m/z$ calcd. for C$_{11}$H$_{10}$F$_2$ ([M$^+$]): 180.0751; Found: 180.0752.
CHAPTER 3


Abstract

The nickel-mediated [3+2] cycloaddition of 2-trifluoromethyl-1-alkenes with alkynes afforded fluorine-containing multi-substituted cyclopentadienes in a regioselective manner. This reaction involves the consecutive two C–F bond cleavage of a trifluoromethyl or a pentafluoroethyl group via β-fluorine elimination.
3.1 Introduction

The carbon–fluorine bond is the strongest chemical bond among the single bonds involving a carbon atom. Thus, activation of C–F bond has been a challenging task to date. In particular, the defluorinative functionalizations of multi- and poly-fluorinated compounds is one of the most attractive approaches for highly functionalized organofluorine compounds.[1]

One of the powerful methods for C–F bond activation is the transition metal-mediated reaction. Especially, cross-coupling reactions via C–F bond cleavage of aryl, vinyl, and allyl fluorides has been intensively studied in this decade (eq 1).[2–4] In most cases, cleavage of a C–F bond was achieved via its oxidative addition to low-valent transition metal complexes. However, oxidative addition of a C–F bond is not necessarily possible because of its high bond energy.

\[
\begin{align*}
R_1'F & \xrightarrow{\text{M}^n} R_1'M^{n+2}F & M' - R & \xrightarrow{\text{M}^n} R_1'M^{n+2} - R & M' - \cancel{F} & \xrightarrow{\text{M}^n} R_1' - \cancel{R} & (1)
\end{align*}
\]

\text{Oxidative Addition}

In contrast, C–F bond cleavage via β-fluorine elimination has been considered to be a much more reasonable process compared to oxidative addition, because transition metal-mediated β-heteroatom elimination typically proceeds under milder conditions (Scheme 1).[5] Furthermore, β-fluorine elimination is sometimes even more preferable than β-hydrogen elimination as an elementary step from complexes with both fluorine and hydrogen atoms on the carbon β to the metal center.[5,6] Although β-fluorine elimination is potentially advantageous, the literature contains only a few reports on its practical application to transition metal-mediated reactions. For example, allylic C–F bond activation of 2-trifluoromethyl-1-alkenes proceeded via sequential imino- or carbometalation and β-fluorine elimination to give 1,1-difluoro-1-alkenes (Scheme 1A).[5f,g] In a similar manner, vinylic C–F bond activation of 1,1-difluoro-1-alkenes via an
imino- or carbometalation–β-fluorine elimination process provided monofluorinated alkenes (Scheme 1B).{[sc,d]}

**Scheme 1. C–F Bond Activation via β-Fluorine Elimination**

(A) Allylic C–F bond activation

(B) Vinylic C–F bond activation

To take complete advantage of these processes, I attempted the double C–F bond activation of 2-trifluoromethyl-1-alkenes through the sequential use of β-fluorine elimination (Scheme 2). As mentioned in Chapter 1, the highly electron-deficient trifluoromethylated alkenes can coordinate strongly to nickel(0) complexes.[7] On the basis of this interaction, I assumed that this alkene complex would be the new platform to construct the β-fluoroalkyl transition metal complexes as the key intermediates for β-fluorine elimination (Scheme 2). Because electron-deficient alkenes readily undergo oxidative cyclization,[8–10] I envisioned that oxidative cyclization of a 2-trifluoromethyl-1-alkene and an alkyne on a Ni(0) complex would generate a nickelacyclopentene bearing a trifluoromethyl group. β-Fluorine elimination of this type of nickelacycle would generate organonickel complexes having both a vinylnickel moiety and a difluoroalkene moiety. Subsequently, intramolecular vinylic C–F bond activation of the intermediary difluoroalkene might occur via normally disfavored 5-endo insertion{[sc,d]} to afford 2-fluoro-1,3-cyclopentadienes. Herein I demonstrate the nickel-mediated [3+2] cycloaddition of 2-trifluoromethyl-1-alkenes with alkynes.
via double C–F bond activation of a trifluoromethyl group by sequential β-fluorine elimination, which allowed the efficient synthesis of highly substituted 2-fluoro-1,3-cyclopentadines.

**Scheme 2. Double C–F Bond Activation of a CF$_3$ Group: This Work**

3.2 Nickel-Mediated [3+2] Cycloaddition of 2-Trifluoromethyl-1-Alkenes with Alkynes

3.2.1 Optimization of Reaction Conditions on Nickel-mediated [3+2] Cycloaddition

I selected 2-(4-acetyl)phenyl-3,3,3-trifluoropropene (14a) and 4-octyne (15a) as model substrates for optimization of the reaction conditions (Table 1). Upon treatment of 14a with 15a in the presence of an equimolar amount of Ni(cod)$_2$ (cod = 1,5-cyclooctadiene) and PPh$_3$ or 1,10-phenanthroline, no cyclization products were obtained (Table 1, Entries 1 and 2). However, when IMes possessing a strong σ-donating ability was employed as a ligand, the expected [3+2] cycloaddition proceeded to afford 2-fluoro-1,3-cyclopentadiene 16aa in 26% yield via cleavage of two C–F bonds in the trifluoromethyl group and formation of two C–C bonds (Table 1, Entry 3). In the case where PCy$_3$ was used, the yield of 16aa was improved to 66% (Entry 4). These results suggest that highly electron-rich Ni(0) species derived from strong σ-donating ligands promoted oxidative cyclization between 14a and 15a in the initial step. Next I screened reaction solvents.
Both THF and DME (1,2-dimethoxyethane) gave the product, albeit in low yields (Entries 5 and 6). The best result (74% yield of 16aa) was obtained using 1,4-dioxane (Entry 7).

Table 1. Optimization of reaction conditions in Ni-mediated [3+2] cycloaddition

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
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<tr>
<td>1</td>
<td>PPh₃</td>
<td>Toluene</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1,10-phen</td>
<td>Toluene</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>IMes·HClᵇ</td>
<td>Toluene</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>PCy₃</td>
<td>Toluene</td>
<td>66ᶜ</td>
</tr>
<tr>
<td>5</td>
<td>PCy₃</td>
<td>THF</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>PCy₃</td>
<td>DME</td>
<td>56</td>
</tr>
<tr>
<td>7</td>
<td>PCy₃</td>
<td>1,4-Dioxane</td>
<td>74ᶜ</td>
</tr>
</tbody>
</table>

ᵃ ¹⁹F NMR yield using PhCF₃ as an internal standard.ᵇ t-BuOK (1.0 equiv) was used as a base.ᶜ Isolated yield.

3.2.2. Synthesis of 2-Fluoro-1,3-cyclopentadienes by Nickel-Mediated [3+2] Cycloaddition

The scope of the [3+2] cycloaddition was examined using a wide variety of 2-trifluoromethyl-1-alkenes 14a–g and alkynes 15a–e under the previously described optimal reaction conditions (Figure 1, Table 2). The use of diphenylacetylene (15b) resulted in the formation of the corresponding cycloaddition product 16ab in 86% yield (Table 2, Entry 2). Unsymmetrical 4-methyl-2-pentyne (15c), 1-phenyl-1-propyne (15d), and 1-(4-methoxyphenyl)-1-pentyne (15e) also participated in this reaction to afford the corresponding 2-fluoro-1,3-cyclopentadienes 16ac, 16ad, and 16ae in 77%, 48%, and 64% yields, respectively,
with complete regioselectivity (Entries 3–5).\textsuperscript{[11]} $\alpha$-Trifluoromethylstyrenes 14b–d bearing electron-withdrawing cyano, trifluoromethyl, and ethoxycarbonyl groups further provided cyclopentadienes 16ba–da in good to high yields (Entries 6–8). Non-substituted $\alpha$-trifluoromethylstyrene (14e) and $\alpha$-trifluoromethylstyrene 14f bearing an electron-donating methoxy group successfully underwent cycloaddition with 15c or 15b (Entries 9 and 10). The reaction of $t$-butyl $\alpha$-trifluoromethacrylate (14g) with alkynes 15a and 15c readily proceeded to give 2-fluoro-1,3-cyclopentadiene-1-carboxylates 16ga and 16gc in 88% and 93% yields, respectively (Entries 11 and 12).

\begin{center}
\begin{tabular}{c c c c}
  & CF$_3$ & \multicolumn{2}{c}{R$^2$} \\
R$^1$ & \multicolumn{1}{c}{C$_6$H$_4$(p-Ac), 14a} & R$^2$ & \multicolumn{1}{c}{n-Pr, 15a} \\
R$^1$ & \multicolumn{1}{c}{C$_6$H$_4$(p-CN), 14b} & R$^2$ & \multicolumn{1}{c}{Ph, 15b} \\
R$^1$ & \multicolumn{1}{c}{C$_6$H$_4$(p-CF$_3$), 14c} & R$^2$ & \multicolumn{1}{c}{i-Pr, Me, 15c} \\
R$^1$ & \multicolumn{1}{c}{C$_6$H$_4$(p-CO$_2$Et), 14d} & R$^2$ & \multicolumn{1}{c}{Me, Ph, 15d} \\
R$^1$ & \multicolumn{1}{c}{Ph, 14e} & R$^2$ & \multicolumn{1}{c}{n-Pr, C$_6$H$_4$(p-OMe), 15e} \\
R$^1$ & \multicolumn{1}{c}{C$_6$H$_4$(p-OMe), 14f} & \multicolumn{2}{c}{} \\
R$^1$ & \multicolumn{1}{c}{CO$_2$t-Bu, 14g} & \multicolumn{2}{c}{}
\end{tabular}
\end{center}

\textbf{Figure 1.} List of substrates.
Table 2. Synthesis of 2-Fluoro-1,3-cyclopentadienes 16 by Ni-Mediated [3+2] Cycloaddition of 14 with 15

<table>
<thead>
<tr>
<th>Entry</th>
<th>14</th>
<th>15</th>
<th>Solvent</th>
<th>Conditions</th>
<th>16</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
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</thead>
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<td>1</td>
<td>14a</td>
<td>15a</td>
<td>1,4-Dioxane</td>
<td>RT, 3 h</td>
<td>16aa</td>
<td>74</td>
</tr>
<tr>
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<td>14a</td>
<td>15c</td>
<td>1,4-Dioxane</td>
<td>RT, 10.5 h</td>
<td>16ac</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>14a</td>
<td>15d</td>
<td>1,4-Dioxane</td>
<td>60 °C, 19 h</td>
<td>16ad</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>14a</td>
<td>15b</td>
<td>1,4-Dioxane</td>
<td>100 °C, 3 h</td>
<td>16ab</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>14a</td>
<td>15e</td>
<td>Toluene</td>
<td>100 °C, 3 h</td>
<td>16ae</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>14b</td>
<td>15a</td>
<td>Toluene</td>
<td>RT, 1.5 h then 80 °C, 1.5 h</td>
<td>16ba</td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td>14c</td>
<td>15a</td>
<td>Toluene</td>
<td>RT, 9 h</td>
<td>16ca</td>
<td>86</td>
</tr>
<tr>
<td>8</td>
<td>14d</td>
<td>15a</td>
<td>Toluene</td>
<td>50 °C, 1 h</td>
<td>16da</td>
<td>78</td>
</tr>
<tr>
<td>9</td>
<td>14e</td>
<td>15c</td>
<td>1,4-Dioxane</td>
<td>60 °C, 6 h</td>
<td>16ec</td>
<td>57</td>
</tr>
<tr>
<td>10</td>
<td>14f</td>
<td>15b</td>
<td>Toluene</td>
<td>100 °C, 3 h</td>
<td>16fb</td>
<td>42</td>
</tr>
<tr>
<td>11</td>
<td>14g</td>
<td>15a</td>
<td>1,4-Dioxane</td>
<td>RT, 3 h</td>
<td>16ga</td>
<td>88</td>
</tr>
<tr>
<td>12</td>
<td>14g</td>
<td>15c</td>
<td>Toluene</td>
<td>RT, 2 h</td>
<td>16gc</td>
<td>93</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield.
3.3. Mechanistic Studies on Nickel-Mediated [3+2] Cycloaddition

3.3.1. C–F Bond Cleavage Process

Two plausible mechanisms for this reaction are shown in Scheme 3. Nickelacyclopentene A bearing a trifluoromethyl group was probably formed by oxidative cyclization of 2-trifluoromethyl-1-alkene 14 and alkyne 15 with Ni(0) (Scheme 3, path A). Ring-opening of nickelacycle A readily proceeded via β-fluorine elimination to generate alkenylnickel species B. Subsequent 5-endo insertion and the second β-fluorine elimination afforded 2-fluoro-1,3-cyclopentadiene 16 along with NiF₂ species. An alternative mechanism could be the oxidative addition pathway (Scheme 3, path B), in which 2-trifluoromethyl-1-alkene 14 initially might react with Ni(0) to generate π-allylnickel intermediate A’ via oxidative addition of a C–F bond to Ni(0). An alternative mechanism could be the oxidative addition pathway (Scheme 3, path B), in which 2-trifluoromethyl-1-alkene 14 initially might react with Ni(0) to generate π-allylnickel intermediate A’ via oxidative addition of a C–F bond to Ni(0).

To elucidate the mechanism, the stoichiometric reaction of 2-trifluoromethyl-1-alkene 14a with a Ni(0) complex was conducted in the absence of alkynes (Scheme 4). If the reaction starts with oxidative addition of the C–F bond to Ni(0), the corresponding π-allylnickel complex would
be observed. Treatment of 14a with stoichiometric Ni(cod)$_2$ and PCy$_3$ in toluene at room temperature, however, afforded nickelacyclopropane 17a as the sole product in 92% yield; this was confirmed by $^{19}$F and $^{31}$P NMR.[3a–d,4d] In this reaction, no π-allylnickel complexes were observed in the NMR spectra. Heating the toluene solution of 17a led to only the decomposition of 17a to 14a instead of oxidative addition of the C–F bond (Scheme 4a).[12] The formation of 17a was further supported by the conversion of 17a to 18a, the hydrogenated product of 14a and the protonolysis product of 17a in 55% yield upon treatment with an excess of acetic acid (Scheme 4b).[13] In addition, 17a readily reacted with 4-octyne to afford 2-fluoro-1,3-cyclopentadiene 16aa in 81% yield (Scheme 4c). Therefore, the cyclopentadiene formation probably proceeded through an oxidative cyclization–β-fluorine elimination sequence (Scheme 3, path A).

**Scheme 4. Generation and Reactions of Nickelacyclopropane 17a**

3.3.2. Elimination of NiF$_2$ Species

To confirm the mechanism mentioned above, the existence of NiF$_2$(PCy)$_3$$_n$ (n = 1, 2) was investigated. First, I tried to observe the complex by $^{19}$F NMR measurement at the end of the reaction (eq 2). However, NiF$_2$ species was not detected, presumably due to the paramagnetic
property of tetrahedral Ni(II) complex. To present the experimental evidence on the formation of the NiF$_2$ complex, I treated the reaction mixture with 2 equiv of Ph$_3$SiCl after [3+2] cycloaddition (eq 3). As the result, violet crystallines of trans-NiCl$_2$(PCy$_3$)$_2$ and Ph$_3$SiF were obtained. I assumed that the generated NiF$_2$ species would react with the silyl chloride to lead to the elimination of highly stable silyl fluoride along with the formation of the NiCl$_2$ complex. This result supported the hypothesis that the NiF$_2$ complex was probably formed by the second β-fluorine elimination along with the generation of fluorocyclopentadienes 16.

\[ \text{15a (1.1 equiv)} \]
\[ \text{Ni(cod)$_2$ (1.0 equiv)} \]
\[ \text{PCy$_3$ (2.0 equiv)} \]
\[ \text{Toluene, RT, 2 h} \]
\[ \text{F} \]
\[ \text{Pr} \]
\[ \text{Pr} \]
\[ \text{Ar} \]
\[ \text{16aa 81\%} \]
\[ \text{not detected \{(\text{19F, 31P NMR)}\}} \]

\[ \text{15a (1.1 equiv)} \]
\[ \text{Ni(cod)$_2$ (1.0 equiv)} \]
\[ \text{PCy$_3$ (2.0 equiv)} \]
\[ \text{Toluene, RT, 2 h} \]
\[ \text{F} \]
\[ \text{Pr} \]
\[ \text{Pr} \]
\[ \text{Ar} \]
\[ \text{16aa} \]

3.3.3. Regioselectivity of Alkynes

As described in Section 3.2, the nickel-mediated [3+2] cycloaddition of unsymmetrical alkynes with 2-trifluoromethy-1-alkenes proceeded with complete regioselectivity. It is clear that the regioselectivity of alkynes was determined in the oxidative cyclization step, because the oxidative cyclization irreversibly proceeds in general. I assumed that the regioselectivity would be controlled by the two interactions between the nickel complex and alkynes: the steric effect and the extra coordinating ability (Schemes 5 and 6). In the case of unsymmetrical dialkyl alkyn 15c, the oxidative cyclization proceeds not via complex I-ac’ but via complex I-ac to avoid the steric
hindrance between the larger isopropyl group and the PCy$_3$ ligand, which affords 16ac exclusively. On the other hand, when aryl-substituted alkynes 15d and 15e were used, the selectivity of the oxidative cyclization was probably controlled by the coordination of $\pi$-electron-rich aryl groups to the nickel center. In addition, the regioselectivity of this reaction shows a good agreement with those of nickel-mediated reactions involving the oxidative cyclization of alkenes and unsymmetrical alkynes.$^{[9-11]}$

**Scheme 5.** Regioselectivity of Alkyne 15c

**Scheme 6.** Regioselectivity of Alkyne 15d
3.4. Synthesis of Trifluoromethylated Cyclopentadiene via Nickel-Mediated [3+2] cycloaddition

Furthermore, the sequential double C–F bond activation was successfully applied to pentafluoroethyl compounds under the same reaction conditions to give 5-trifluoromethyl-1,3-cyclopentadienes (Scheme 7). 2-Pentafluoroethyl-1-alkene 19a readily reacted with 4-octyne (15a) in the presence of the nickel complex to afford 5-trifluoromethyl-1,3-cyclopentadiene 20aa via isomerization in 77% yield. Thus, I also achieved the direct synthesis of a ring trifluoromethylated cyclopentadiene.

Scheme 7. Synthesis of 5-Trifluoromethyl-1,3-cyclopentadienes 20
3.5. Conclusion

In summary, I have developed a new methodology for allylic and vinylic C–F bond activation based on β-fluorine elimination from nickelacycles, generated by oxidative cyclization of 2-trifluoromethyl-1-alkenes with alkynes. The nickel-mediated [3+2] cycloaddition reaction involves the consecutive and regioselective cleavage of two C–F bonds of a trifluoromethyl and a pentafluoroethyl group. This methodology simultaneously enables the direct construction of a multisubstituted cyclopentadiene ring and the introduction of a fluorine substituent or a trifluoromethyl group in a regioselective manner.[14] Fluorine-containing, multisubstituted cyclopentadienes would be useful compounds as ligands of metallocene-type complexes[15] and as building blocks for further chemical transformations such as Diels–Alder reactions.[16]
3.5. References and Notes


[12] Ogoshi recently reported that the oxidative addition of tetrafluoroethylene and hexafluoropropene on nickel(0) complexes proceeds through nickelacyclop propane intermediates to generate the corresponding vinyl and allylnickel complexes, respectively. Moreover, the C–F bond activation was accelerated even at room temperature by using the appropriate Lewis-acidic metal halides. See: refs. 3b and 4d.


3.7. Experimental Section

3.7.1. General Statements

IR spectra were recorded on Horiba FT-300S spectrometers. NMR spectra were recorded on a Bruker advance 500 spectrometer in CDCl$_3$ at 500 MHz ($^1$H NMR), at 126 MHz ($^{13}$C NMR), and at 470 MHz ($^{19}$F NMR), and at 202 MHz ($^{31}$P NMR). Chemical shifts were given in ppm relative to internal Me$_4$Si (for $^1$H NMR: $\delta = 0.00$), CDCl$_3$ (for $^{13}$C NMR: $\delta = 77.0$), C$_6$F$_6$ (for $^{19}$F NMR: $\delta = 0.0$), and H$_3$PO$_4$ (for $^{31}$P NMR: $\delta = 0.0$). High resolution mass spectroscopy (HRMS) was conducted with a JMS-T100GCV spectrometer. Elemental analyses were performed with a YANAKO MT-3 CHN Corder apparatus.

Column chromatography and preparative thin-layer chromatography (PTLC) were conducted on silica gel (Silica Gel 60 N, Kanto Chemical Co., Inc. for column chromatography and Wakogel B-5F, Wako Pure Chemical Industries for PTLC, respectively). All the reactions were conducted under argon. Tetrahydrofuran (THF) and diethylether (Et$_2$O) were dried by passing over a column of activated alumina followed by a column of Q-5 scavenger (Engelhard). Toluene was distilled from sodium benzophenone ketyl, and stored over sodium chips. 1,4-Dioxane and C$_6$D$_6$ were distilled from CaH$_2$, and stored over activated molecular sieves 4A.

Ni(cod)$_2$ and PCy$_3$ were purchased from sigma-aldrich Co. and stored in a globe box under argon atmosphere. 4-Octyne and 4-methyl-1-pentyne were purchased from sigma-aldrich Co. and Tokyo Chemical Industry Co., Ltd., respectively. These compounds were used without further purification. Other liquid reagents were purified by distillation and solid reagents were purified by recrystallization.
3.7.2 Synthesis of Substrates

I. Synthesis of 2-Trifluoromethyl-1-alkenes 14

**General Procedure A**

![Diagram]

To a THF solution (0.3 M) of PdCl$_2$(PPh$_3$)$_2$ (1–3 mol%) and AsPh$_3$ (5–15 mol%) were added the arylboronic acid (1.0 equiv) and 2-bromo-3,3,3-trifluoropropene (1.5 equiv) at room temperature. Aqueous KOH (2.0 M, 4.0 equiv) was added, and the mixture was heated to reflux for the specified length of time. The reaction mixture was cooled to room temperature and quenched by addition of saturated aqueous NH$_4$Cl. Organic materials were extracted two times with Et$_2$O. The combined extracts were washed with brine and dried over Na$_2$SO$_4$. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography to give the corresponding α-(trifluoromethyl)styrenes 14.

**General Procedure B**

![Diagram]

To a THF solution (0.3 M) of PdCl$_2$(PPh$_3$)$_2$ (2–3 mol%) were added an aryl halide (1.0 equiv) and the α-(trifluoromethyl)ethenylboronic acid (4.0 equiv) at room temperature. Aqueous Na$_2$CO$_3$ (2.0 M, 8.0 equiv) was added, and the mixture was heated to reflux for the specified length of time. The reaction mixture was cooled to room temperature and quenched by addition of saturated aqueous NH$_4$Cl. Organic materials were extracted two times with Et$_2$O. The combined extracts were washed with brine and dried over Na$_2$SO$_4$. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography to give the corresponding α-(trifluoromethyl)styrenes 14.


1-(4-(3,3,3-Trifluoroprop-1-en-2-yl)phenyl)ethanone (14a)

Compound 14a was prepared according to General Procedure A using 4-ethanoylphenylboronic acid (796 mg, 4.85 mmol), 2-bromo-3,3,3-trifluoropropene (1.32 g, 7.52 mmol), PdCl$_2$(PPh$_3$)$_2$ (105 mg, 0.15 mmol), AsPh$_3$ (230 mg, 0.751 mmol), aqueous KOH (2.0 M, 10 mL, 20 mmol) and THF (15.0 mL) under reflux conditions for 18 h. Purification by silica gel column chromatography (hexane/EtOAc = 20:1~10:1) and further gave 14a (818 mg, 79%) as a pale yellow liquid. Spectral data for this compound showed good agreement with the literature data.3)

4-(3,3,3-Trifluoroprop-1-en-2-yl)benzonitrile (14b)

Compound 14b was prepared according to General Procedure B using 4-bromobenzonitrile (910 mg, 5.00 mmol), α-(trifluoromethyl)ethenyl boronic acid (2.90 g, 20.7 mmol), PdCl$_2$(PPh$_3$)$_2$ (105 mg, 0.15 mmol), aqueous Na$_2$CO$_3$ (2.0 M, 20 mL, 40 mmol), and THF (30 mL) under reflux conditions for 4.5 h. Purification by silica gel column chromatography (hexane/EtOAc = 15:1) and further distillation under reduced pressure gave 14b (890 mg, 90%) as a colorless liquid. 14b: IR (neat): ν = 2231, 1352, 1194, 1173, 1022, 1978, 845 cm$^{-1}$. $^1$H NMR: δ 5.89 (q, $J_{HF} = 1.6$ Hz, 1H), 6.11 (d, $J_{HF} = 1.3$ Hz, 1H), 7.57 (d, $J = 8.5$ Hz, 2H), 7.67–7.72 (m, 2H). $^{13}$C NMR: δ 112.9, 118.2, 122.8 (q, $J_{CF} = 275$ Hz), 122.8 (q, $J_{CF} = 6$ Hz), 128.1, 132.4, 137.7 (q, $J_{CF} = 31$ Hz), 137.9. $^{19}$F NMR: δ 98.4 (s, 3F). HRMS (EI+): Calcd for C$_{16}$H$_6$F$_3$N [M]$^+$ 197.0452, Found 197.0456.

1-(Trifluoromethyl)-4-(3,3,3-trifluoroprop-1-en-2-yl)benzene (14c)

Compound 14c was prepared according to General Procedure B using 4-bromobenzotrifluoride (1.12 g, 5.00 mmol), α-(trifluoromethyl)ethenyl boronic acid (2.89 g, 20.7 mmol), PdCl$_2$(PPh$_3$)$_2$ (151 mg, 0.215 mmol), aqueous Na$_2$CO$_3$ (2.0 M, 20 mL, 40 mmol), and THF (30 mL) under reflux conditions for 5.5 h. Purification by silica gel column chromatography (pentane) and further distillation under reduced pressure gave 14c (1.15 g, 96%) as a colorless liquid. Spectral data for this compound showed good agreement with the literature data.4)
Ethyl 4-[(3,3,3-trifluoroprop-1-en-2-yl)benzoate (14d)]

Compound 14d was prepared according to General Procedure B using ethyl 4-iodobenzoate (0.830 g, 3.01 mmol), α-(trifluoromethyl)ethenyl boronic acid (1.77 g, 12.7 mmol), PdCl₂(PPh₃)₂ (46 mg, 66 µmol), aqueous Na₂CO₃ (2.0 M, 12 mL, 24 mmol), and THF (24 mL) under reflux condition for 5.5 h. Purification by silica gel column chromatography (hexane/EtOAc = 10:1) and further distillation under reduced pressure gave 14d (660 mg, 90%) as a colorless liquid.

14d: IR (neat): ν = 2985, 1720, 1277, 1192, 1171, 1128 cm⁻¹. ¹H NMR: δ 1.40 (t, J = 7.2 Hz, 3H), 4.39 (q, J = 7.2 Hz, 2H), 5.86 (q, J₃HF = 1.6 Hz, 1H), 6.04 (q, J₅HF = 1.3 Hz, 1H), 7.53 (d, J = 8.2 Hz, 2H), 8.03–8.09 (m, 2H). ¹³C NMR: δ 14.3, 61.1, 121.8 (q, J₃CF = 6 Hz), 123.0 (q, J₅CF = 275 Hz), 127.3, 129.7, 130.9, 137.7, 138.3 (q, J₅CF = 31 Hz), 166.0. ¹⁹F NMR: δ 98.4 (s, 3F). Elemental analysis: Calcd for C₁₂H₁₁F₃O₂: C, 59.02; H, 4.54. Found: C, 59.25; H, 4.84.

α-(Trifluoromethyl)styrene (14e)

Compound 14e was prepared according to General Procedure A using phenyl boronic acid (3.66 g, 30.0 mmol), 2-bromo-3,3,3-trifluoropropene (7.92 g, 45.3 mmol), PdCl₂(PPh₃)₂ (0.211 g, 0.301 mmol), AsPh₃ (460 mg, 1.50 mmol) and aqueous KOH (2.0 M, 60 mL, 120 mmol), and THF (90 mL) under reflux conditions for 13 h. Purification by silica gel column chromatography (pentane) and further distillation under reduced pressure gave 14e (3.87 g, 75%) as a colorless liquid.
Spectral data for this compound showed good agreement with the literature data.¹)

1-Methoxy-4-[(3,3,3-trifluoroprop-1-en-2-yl)benzene (14f)]

Compound 14f was prepared according to General Procedure B using 4-bromoanisole (1.31 g, 6.98 mmol), α-(trifluoromethyl)ethenyl boronic acid (2.94 g, 21.0 mmol), PdCl₂(PPh₃)₂ (147 mg, 0.21 mmol), aqueous Na₂CO₃ (2.0 M, 20 mL, 40 mmol), and THF (30 mL) under reflux conditions for 9 h. Purification by silica gel column chromatography (hexane) and further distillation under reduced pressure gave 14f (968 mg, 69%) as a colorless liquid.
Spectral data for this compound showed good agreement with the literature data.\(^5\)


### II. Synthesis of Alkynes

1-Phenyl-2-propyne (15\(^d\))\(^6\), diphenylacetylene (15\(^b\))\(^7\), and 1-methoxy-4-(pent-1-ynyl)benzene (15\(^c\))\(^8\) were prepared by the literature procedures. Spectral data for these compounds showed good agreement with the literature data.


### III. Synthesis of 2-Pentafluoroethyl-1-alkene 19a

2,2,3,3,3-Pentafluoro-1-(naphthalene-2-yl)propan-1-one\(^9\)

\[
\text{CF}_3\text{CF}_2\text{CO}_2\text{Et (1.0 equiv) THF, –78 °C, 1 h} \quad \text{1M HCl aq. –70 °C then RT}
\]

To a THF solution (33 mL) of 2-bromonaphthalene (2.07 g, 10.0 mmol) was added \(n\)-BuLi (6.90 mL, 1.60 M in hexane, 11.0 mmol) at –78 °C over 10 min. After stirring for 30 min at –78 °C, this mixture was transferred by using a double-ended needle to a THF solution (33 mL) of ethyl 2,2,3,3,3-pentafluoropropionate (1.95 g, 10.2 mmol) at –78 °C over 15 min. After stirring for 1 h at that temperature, the mixture was then warmed to –70 °C, and aqueous HCl was added. Organic materials were extracted three times with Et\(_2\)O. The combined extracts were washed with brine and dried over anhydrous Na\(_2\)SO\(_4\). After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (hexane–EtOAc = 20:1) to give the title compound (2.26 g, 82%) as a colorless liquid.

2,2,3,3,3-Pentafluoro-1-(2’-naphthalenyl)propanone: IR (neat): \(\nu = 1701, 1211, 1157, 1126, 1066, 914, 735\) cm\(^{-1}\). \(^1\)H NMR: \(\delta = 7.62\) (ddd, \(J = 8.2\) Hz, 7.0 Hz, 1.1 Hz, 1H), 7.70 (ddd, \(J = 8.2\) Hz, 7.0 Hz, 1.1 Hz), 7.91 (d, \(J = 8.2\) Hz, 1H), 7.96 (d, \(J = 8.7\) Hz, 1H), 8.02 (d, \(J = 8.2\) Hz, 1H), 8.07 (dd, \(J = 8.7\) Hz, 1.1 Hz, 1H), 8.67 (s, 1H). \(^13\)C NMR: \(\delta = 108.9\) (tq, \(^1\)\(J_{CF} = 269\) Hz, \(^2\)\(J_{CF} = 37\) Hz), 118.1 (qt,
$^{1}J_{\text{CF}} = 288$ Hz, $^{2}J_{\text{CF}} = 34$ Hz), 124.2, 127.4, 127.9, 128.2, 129.0, 130.1, 130.3, 132.1, 133.2 (t, $J_{\text{CF}} = 5$ Hz), 136.4, 183.0 (t, $J_{\text{CF}} = 27$ Hz). $^{19}F$ NMR: $\delta$ 48.0 (s, 2F), 81.4 (s, 3F). HRMS (EI+): Calcd for C$_{13}$H$_{7}$F$_{5}$O [M]$^+$ 274.0417, Found 274.0420.

2-(3,3,4,4,4-Pentafluorobut-1-en-2-yl)naphthalene (19a)$^{10}$

![Chemical structure of 19a]

To a THF solution (30 mL) of Ph$_3$PCH$_3$I (2.73 g, 6.75 mmol) was added $t$-BuOK (0.756 g, 6.74 mmol) at 0 °C. The reaction mixture was stirred for 30 min at room temperature and then cooled to –78 °C. To the mixture was added slowly a THF solution (5 mL) of 2,2,3,3,3-pentafluoro-1-(naphthalene-2-yl)propan-1-one (1.68 g, 6.13 mmol) at –78 °C. After stirring for 3 h at room temperature, the reaction was quenched with saturated aqueous NH$_4$Cl at that temperature. The mixture was filtered through a pad of Celite (Et$_2$O), and then filtrate was extracted three times with Et$_2$O. The combined extracts were washed with brine and dried over anhydrous Na$_2$SO$_4$. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (hexane) to give 19a (1.44 g, 86%) as a colorless liquid.

19a: IR (neat): $\tilde{\nu}$ = 1333, 1200, 1153, 1126, 1014, 748 cm$^{-1}$. $^{1}H$ NMR: $\delta$ 5.90 (s, 1H), 6.09 (d, $J = 0.9$ Hz, 1H), 7.48 (d, $J = 8.5$ Hz, 1H), 7.50–7.55 (m, 2H), 7.81–7.89 (m, 4H). $^{13}C$ NMR: $\delta$ 113.1 (tq, $^{1}J_{\text{CF}} = 255$ Hz, $^{2}J_{\text{CF}} = 38$ Hz), 119.1 (qt, $^{1}J_{\text{CF}} = 287$ Hz, $^{2}J_{\text{CF}} = 38$ Hz), 125.0 (t, $J_{\text{CF}} = 8$ Hz), 125.9, 126.5, 126.8, 127.6, 128.0, 128.1, 128.3, 132.2, 132.9, 133.1, 138.6 (t, $J_{\text{CF}} = 21$ Hz). $^{19}F$ NMR: $\delta$ 49.9 (s, 2F), 80.1 (s, 3F). Elemental analysis: Calcd for C$_{14}$H$_{9}$F$_{5}$: C, 61.77; H, 3.33. Found: C, 62.07; H, 3.48.


3.7.3. Nickel-Mediated [3+2] Cycloaddition of 2-Trifluoromethyl-1-alkenes and Alkynes

(A) Typical Procedure for Synthesis of 2-Fluoro-1,3-cyclopentadienes (16)

**tert-Butyl 2-fluoro-3,4-dipropylcyclopenta-1,3-dienecarboxylate (16ga)**

![Reaction Scheme]

To a 1,4-dioxane solution (3.2 mL) of Ni(cod)₂ (86 mg, 0.31 mmol) and PCy₃ (88 mg, 0.31 mmol) were added 2-trifluoromethyl-1-alkene 14g (61 mg, 0.31 mmol) and 4-octyne (15a, 38 mg, 0.34 mmol) at room temperature. After stirring for 3 hours at the same temperature, the reaction mixture was filtered through a pad of silica gel (EtOAc). The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/EtOAc = 20:1) to give fluorocyclopentadiene 16ga (74 mg, 88%) as a colorless liquid.

16ga: IR (neat): ν ~ 2962, 2973, 1693, 1583, 1394, 1367, 1219, 1171, 771 cm⁻¹. ¹H NMR: δ 0.91 (t, J = 7.3 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H), 1.40–1.65 (m, 4H), 1.51 (s, 9H), 2.23 (t, J = 7.5 Hz, 2H), 2.32 (t, J = 7.7 Hz, 2H), 3.08 (d, J_HF = 7.4 Hz, 2H). ¹³C NMR: δ 13.9, 14.0, 22.2, 22.9, 25.8, 28.4, 30.9, 37.8 (d, J_CF = 5 Hz), 79.9, 108.1, 133.6 (d, J_CF = 23 Hz), 149.0 (d, J_CF = 6 Hz), 162.4 (d, J_CF = 4 Hz), 167.1 (d, J_CF = 294 Hz). ¹⁹F NMR: δ 56.5 (t, J_FH = 7.4 Hz, 1F). HRMS (EI⁺): Calcd for C_{16}H_{25}FO₂ [M]⁺ 268.1839, Found 268.1844.

(B) Synthesis of 2-Fluoro-1,3-cyclopentadienes

1-(4-(2-Fluoro-3,4-dipropylcyclopenta-1,3-dienyl)phenyl)ethanone (16aa)

Compound 16aa was synthesized according to the typical procedure using 1-(4-(3,3,3-Trifluoroprop-1-en-2-yl)phenyl)ethanone (14a, 50 mg, 0.23 mmol), 4-octyne (15a, 31 mg, 0.28 mmol), Ni(cod)₂ (72 mg, 0.26 mmol), PCy₃ (77 mg, 0.27 mmol), and 1,4-dioxane (2.0 mL) at room temperature for 3 h. Purification by preparative thin-layer chromatography (hexane/EtOAc = 50:1) gave 16aa (50 mg, 74%) as a yellow solid.

16aa: IR (neat): ν ~ 2960, 2870, 1670, 1585, 1273, 912, 742 cm⁻¹. ¹H NMR: δ 0.95 (t, J = 7.4 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H), 1.48–1.63 (m, 4H), 2.29 (t, J =7.6 Hz, 2H), 2.36 (t, J = 7.7 Hz, 2H), 2.58 (s, 3H), 3.20 (d, J_HF = 6.5 Hz, 2H), 7.57 (d, J = 8.5 Hz, 2H), 7.91 (d, J = 8.5 Hz, 2H). ¹³C NMR: δ 13.9, 14.1, 22.3, 23.1, 26.0, 26.4, 30.8, 37.8 (d, J_CF = 8 Hz), 112.8 (d, J_CF = 2 Hz), 125.1 (d,
\[ J_{CF} = 7 \text{ Hz}, 128.8, 133.8, 134.6 \text{ (d, } J_{CF} = 25 \text{ Hz}), 138.6 \text{ (d, } J_{CF} = 5 \text{ Hz}), 143.2 \text{ (d, } J_{CF} = 6 \text{ Hz}), 161.2 \text{ (d, } J_{CF} = 285 \text{ Hz}), 197.4. \]

\[ {^19}\text{F NMR: } \delta 43.9 \text{ (t, } J_{FH} = 6.5 \text{ Hz, 1F), HRMS (EI+): Calcd for C}_{19}\text{H}_{23}\text{FO [M] }^{+} 286.1733, \text{ Found 286.1730.} \]

1-(4-(2-Fluoro-3,4-diphenyclopenta-1,3-dienyl)phenyl)ethanone (16ab)

Compound 16ab was synthesized according to the typical procedure using 1-(4-(3,3,3-Trifluoroprop-1-en-2-yl)phenyl)ethanone (14a, 62 mg, 0.29 mmol), diphenylacetylene (15b, 57 mg, 0.32 mmol), Ni(cod)_2 (81 mg, 0.29 mmol), PCy_3 (82 mg, 0.29 mmol), and 1,4-dioxane (3.0 mL) at 100 °C for 3 h. Purification by silica gel column chromatography (hexane/EtOAc = 10:1) and further recrystallization from dichloromethane and hexane to give 16ab (89 mg, 86%) as yellow crystals.

16ab: IR (neat): \( \nu \approx 1678, 1601, 1362, 1269, 758, 696 \text{ cm}^{-1} \). \(^1\text{H NMR: } \delta 2.61 \text{ (s, 3H), 3.81 (d, } J_{HF} = 6.3 \text{ Hz, 2H), 7.12–7.30 \text{ (m, 5H), 7.31–7.50 \text{ (m, 5H), 7.71 (d, } J = 8.4 \text{ Hz, 2H).} \)

\[ {^13}\text{C NMR: } \delta 26.5, 38.4 \text{ (d, } J_{CF} = 7 \text{ Hz), 115.3, 125.7 \text{ (d, } J_{CF} = 7 \text{ Hz), 127.5, 127.7, 128.1, 128.5, 128.6, 128.9, 129.3, 132.3, 134.6, 135.4, 137.8, 137.9, 140.7 \text{ (d, } J_{CF} = 4 \text{ Hz), 159.4 \text{ (d, } J_{CF} = 283 \text{ Hz), 197.4. } {^19}\text{F NMR: } \delta 45.5 \text{ (t, } J_{FH} = 6.3 \text{ Hz, 1F), Elemental analysis: Calcd for C}_{25}\text{H}_{19}\text{FO: C, 84.72; H, 5.40. Found: C, 84.71; H, 5.54.} \]

1-(4-(2-Fluoro-4-isopropyl-3-methylcyclopenta-1,3-dienyl)phenyl)ethanone (16ac)

Compound 16ac was synthesized according to the typical procedure using 1-(4-(3,3,3-Trifluoroprop-1-en-2-yl)phenyl)ethanone (14a, 65 mg, 0.31 mmol), 4-methyl-1-pentyne (15c, 30 mg, 0.37 mmol), Ni(cod)_2 (87 mg, 0.32 mmol), PCy_3 (89 mg, 0.32 mmol), and 1,4-dioxane (3.2 mL) at room temperature for 10.5 h. Purification by silica gel column chromatography (hexane/EtOAc = 20:1) gave 16ac (60 mg, 77%) as a pale yellow solid.

16ac: IR (neat): \( \nu \approx 2962, 2870, 1670, 1601, 1585, 1362, 1272, 1109, 825, 592 \text{ cm}^{-1} \). \(^1\text{H NMR: } \delta 1.14 \text{ (d, } J = 6.9 \text{ Hz, 2H), 1.89 (s, 3H), 2.58 (s, 3H), 2.94 (sept, } J = 6.9 \text{ Hz, 1H), 3.18 (d, } J_{HF} = 6.5 \text{ Hz, 2H), 7.58 (d, } J = 8.4 \text{ Hz, 2H), 7.90 (d, } J = 8.4 \text{ Hz, 2H).} \)

\[ {^13}\text{C NMR: } \delta 8.6, 22.5, 26.4, 27.6 \text{ (d, } J_{CF} = 2 \text{ Hz), 34.1 (d, } J_{CF} = 8 \text{ Hz), 112.3 (d, } J_{CF} = 3 \text{ Hz), 125.1 (d, } J_{CF} = 7 \text{ Hz), 128.3 (d, } J_{CF} = 26 \text{ Hz),} \]

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128.8, 133.8, 138.5 (d, $J_{CF} = 6$ Hz), 148.8 (d, $J_{CF} = 5$ Hz), 160.9 (d, $J_{CF} = 284$ Hz), 197.4. $^{19}$F NMR: $\delta$ 42.1 (t, $J_{FH} = 6.5$ Hz, 1F). HRMS (EI+): Calcd for C$_{17}$H$_{19}$FO $[M]$ $^{+}$ 258.1420, Found 258.1409.

1-(4-(2-Fluoro-4-methyl-3-phenylcyclopenta-1,3-dienyl)phenyl)ethanone (16ad)

Compound 16ad was synthesized according to the typical procedure using 1-(4-(3,3,3-Trifluoroprop-1-en-2-yl)phenyl)ethanone (14a, 66 mg, 0.31 mmol), 1-phenyl-2-propyne (15d, 40 mg, 0.34 mmol), Ni(cod)$_2$ (84 mg, 0.31 mmol), PCy$_3$ (86 mg, 0.31 mmol), and 1,4-dioxane (3.1 mL) at 60 °C for 19 h. Purification by silica gel column chromatography (hexane/EtOAc = 20:1) and further recrystallization gave 16ad (43 mg, 48%) as pale yellow crystals.

16ad: IR (neat): $\nu$ = 1676, 1601, 1583, 1362, 1271, 1188, 700 cm$^{-1}$. $^1$H NMR: $\delta$ 2.18 (s, 3H), 2.59 (s, 3H), 3.36 (d, $J_{HF} = 6.5$ Hz, 2H), 7.32–7.51 (m, 5H), 7.62 (d, $J = 8.6$ Hz, 2H), 7.93 (d, $J = 8.6$ Hz, 2H).

13C NMR: $\delta$ 15.4, 26.4, 40.6 (d, $J_{CF} = 8$ Hz), 113.4 (d, $J_{CF} = 3$ Hz), 125.4 (d, $J_{CF} = 7$ Hz), 127.5, 128.3, 128.8, 132.1 (d, $J_{CF} = 3$ Hz), 134.2, 134.7 (d, $J_{CF} = 24$ Hz), 138.2 (d, $J_{CF} = 5$ Hz), 140.6 (d, $J_{CF} = 5$ Hz), 159.2 (d, $J_{CF} = 284$ Hz), 197.4. $^{19}$F NMR: $\delta$ 45.7 (t, $J_{FH} = 6.5$ Hz, 1F).

Elemental analysis: Calcd for C$_{20}$H$_{17}$FO: C, 82.17; H, 5.86. Found: C, 82.18; H, 6.08.

1-(4-(2-Fluoro-3-(4-methoxyphenyl)-4-propylcyclopenta-1,3-dienyl)phenyl)ethanone (16ae)

Compound 16ae was synthesized according to the typical procedure using 1-(4-(3,3,3-Trifluoroprop-1-en-2-yl)phenyl)ethanone (14a, 32 mg, 0.15 mmol), 1-methoxy-4-(pent-1-ynyl)benzene (15e, 30 mg, 0.17 mmol), Ni(cod)$_2$ (44 mg, 0.16 mmol), PCy$_3$ (45 mg, 0.16 mmol), and toluene (1.6 mL) at 100 °C for 3 h. Purification by silica gel column chromatography (hexane/EtOAc = 15:1) and further recrystallization from dichloromethane and hexane gave 16ae (34 mg, 64%) as pale yellow crystals.

16ae: IR (neat): $\nu$ = 2958, 1678, 1601, 1510, 1360, 1271, 1250, 1178, 771 cm$^{-1}$. $^1$H NMR: $\delta$ 0.94 (t, $J = 7.2$ Hz, 3H), 1.55–1.65 (m, 2H), 2.48 (t, $J = 7.7$ Hz, 2H), 2.59 (s, 3H), 3.35 (d, $J_{HF} = 6.2$ Hz, 2H), 3.85 (s, 3H), 6.97 (d, $J = 8.2$ Hz, 2H), 7.29 (d, $J = 8.0$ Hz, 2H), 7.62 (d, $J = 8.2$ Hz, 2H), 7.93 (d, $J = 8.0$ Hz, 2H). 13C NMR: $\delta$ 14.1, 23.2, 26.5, 31.3, 38.0 (d, $J_{CF} = 8$ Hz), 55.3, 113.4 (d, $J_{CF} = 2$
Hz), 113.8, 124.5 (d, J_{CF} = 3 Hz), 125.3 (d, J_{CF} = 7 Hz), 128.8, 130.1, 134.1, 134.5 (d, J_{CF} = 24 Hz), 138.3 (d, J_{CF} = 5 Hz), 144.6 (d, J_{CF} = 4 Hz), 159.0, 159.3 (d, J_{CF} = 284 Hz), 197.4. 19F NMR: δ 45.4 (t, J_{FH} = 6.2 Hz, 1F). HRMS (EI+): Calcd for C_{23}H_{23}FO_2 [M]^+ 350.1682, Found 350.1678.

4-(2-Fluoro-3,4-dipropylcyclopenta-1,3-dienyl)benzonitrile (16ba)

Compound 16ba was synthesized according to the typical procedure using 4-(3,3,3-trifluoroprop-1-yl)benzonitrile (14b, 43 mg, 0.22 mmol), 4-octyne (15a, 25 mg, 0.23 mmol), Ni(cod)₂ (57 mg, 0.21 mmol), PCy₃ (59 mg, 0.21 mmol), and toluene (2.1 mL) at room temperature for 1.5 h (then 80 °C for 1.5 h). Purification by silica gel column chromatography (hexane/EtOAc = 30:1) gave 16ba (46 mg, 82%) as a white solid.

16ba: IR (neat): ν = 2960, 2873, 2224, 1585, 912, 742 cm⁻¹. ¹H NMR: δ 0.95 (t, J = 7.4 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H), 1.47–1.60 (m, 4H), 2.28 (t, J = 7.6 Hz, 2H), 2.36 (t, J = 7.7 Hz, 2H), 3.17 (d, J_{HF} = 6.6 Hz, 2H), 7.56 (s, 4H). ¹³C NMR: δ 13.9, 14.1, 22.3, 23.1, 26.1, 30.7 (d, J_{CF} = 1 Hz), 37.8 (d, J_{CF} = 8 Hz), 112.3 (d, J_{CF} = 2 Hz), 123.3, 125.3 (d, J_{CF} = 7 Hz), 125.3–125.5 (m), 127.0 (qd, J_{CF} = 33 Hz, 3 Hz), 134.4 (d, J_{CF} = 25 Hz), 137.3 (d, J_{CF} = 5 Hz) 142.6 (d, J_{CF} = 6 Hz), 160.7 (d, J_{CF} = 283 Hz). 19F NMR: δ 45.4 (t, J_{FH} = 6.6 Hz, 1F). HRMS (EI+): Calcd for C_{18}H_{20}FN [M]^+ 269.1580, Found 269.1586.

1-(2-Fluoro-3,4-dipropylcyclopenta-1,3-dienyl)-4-(trifluoromethyl)benzene (16ca)

Compound 16ca was synthesized according to the typical procedure using 1-(trifluoromethyl)-4-(3,3,3-trifluoroprop-1-yl)benzene (14c, 98 mg, 0.41 mmol), 4-octyne (15a, 50 mg, 0.45 mmol), Ni(cod)₂ (115 mg, 0.42 mmol), PCy₃ (116 mg, 0.41 mmol), and toluene (4.1 mL) at room temperature for 9 h. Purification by silica gel column chromatography (hexane) gave 16ca (109 mg, 86%) as a colorless liquid.

16ca: IR (neat): ν = 2960, 2873, 1591, 1321, 1163, 1111, 1066, 835 cm⁻¹. ¹H NMR: δ 0.95 (t, J = 7.4 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H), 1.49–1.59 (m, 4H), 2.28 (t, J = 7.6 Hz, 2H), 2.36 (t, J = 7.7 Hz, 2H), 3.17 (d, J_{HF} = 6.6 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H). ¹³C NMR: δ 13.9, 14.1, 22.3, 23.1, 26.1, 30.7 (d, J_{CF} = 1 Hz), 37.8 (d, J_{CF} = 8 Hz), 112.3 (d, J_{CF} = 2 Hz), 123.3, 125.3 (d, J_{CF} = 7 Hz), 125.3–125.5 (m), 127.0 (qd, J_{CF} = 33 Hz, 3 Hz), 134.4 (d, J_{CF} = 25 Hz), 137.3 (d, J_{CF} = 5 Hz) 142.6 (d, J_{CF} = 6 Hz), 160.7 (d, J_{CF} = 283 Hz). 19F NMR: δ 42.6 (t, J_{FH} = 6.6 Hz, 1F),
Compound 16da was synthesized according to the typical procedure using ethyl 4-(3,3,3-trifluoroprop-1-en-2-yl)benzoate (14d, 46 mg, 0.19 mmol), 4-octyne (15a, 22 mg, 0.20 mmol), Ni(cod)₂ (52 mg, 0.19 mmol), PCy₃ (57 mg, 0.20 mmol), and toluene (2.9 mL) at 50 °C for 1 h. Purification by silica gel column chromatography (hexane/EtOAc = 30:1) gave 16da (47 mg, 78%) as a white solid.

16da: IR (neat): ν = 2960, 2870, 1705, 1583, 1277, 1184, 1105, 769 cm⁻¹. ¹H NMR: δ 0.95 (t, J = 7.3 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H), 1.39 (t, J = 7.1 Hz, 3H), 1.48–1.60 (m, 4H), 2.28 (t, J = 7.5 Hz, 2H), 2.35 (t, J = 7.7 Hz, 2H), 3.19 (d, JHF = 6.5 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 7.55 (d, J = 8.6 Hz, 2H), 7.97 (d, J = 8.6 Hz, 2H). ¹³C NMR: δ 13.9, 14.1, 14.4, 22.3, 23.1, 26.0, 30.8 (d, JCF = 1 Hz), 37.8 (d, JCF = 8 Hz), 60.7, 112.8 (d, JCF = 2 Hz), 124.9 (d, JCF = 7 Hz), 126.9, 129.8, 134.5 (d, JCF = 25 Hz), 138.2 (d, JCF = 5 Hz) 142.8 (d, JCF = 6 Hz), 160.9 (d, JCF = 284 Hz), 166.6. ¹⁹F NMR: δ 42.3 (t, JFH = 6.5 Hz, 1F). Elemental analysis: Calcd for C₂₀H₂₅F₂O: C, 75.92; H, 7.96. Found: C, 75.74; H, 8.10.

(2-Fluoro-4-isopropyl-3-methylcyclopenta-1,3-dienyl)benzene (16ec)

Compound 16ec was synthesized according to the typical procedure using α-(trifluoromethyl)styrene (14d, 49 mg, 0.29 mmol), 4-methyl-2-pentyne (15c, 26 mg, 0.32 mmol), Ni(cod)₂ (82 mg, 0.30 mmol), PCy₃ (84 mg, 0.30 mmol), and 1,4-dioxane (3.0 mL) at 60 °C for 6 h. Purification by silica gel column chromatography (hexane) gave 16ec (37 mg, 57%) as a white solid.

16ec: IR (neat): ν = 2960, 1653, 1597, 1367, 1192, 912, 742, 692 cm⁻¹. ¹H NMR: δ 1.12 (d, J = 6.9 Hz, 6H), 1.87 (s, 3H), 2.91 (septet, J = 6.9 Hz, 1H), 3.13 (dd, JHF = 6.4 Hz, J = 1.5 Hz, 2H), 7.13 (t, J = 7.4 Hz, 1H), 7.31 (dd, J = 8.3, 7.4 Hz, 2H), 7.52 (dd, J = 8.3, 1.2 Hz, 2H). ¹³C NMR: δ 8.7, 22.6, 27.4 (d, JCF = 2 Hz), 34.1 (d, JCF = 8 Hz), 112.7, 125.5 (d, JCF = 4 Hz), 125.8, 128.0 (d, JCF = 27 Hz), 128.5, 134.0 (d, JCF = 6 Hz), 146.2 (d, JCF = 4 Hz), 158.8 (d, JCF = 280 Hz). ¹⁹F NMR: δ 36.8 (t, JFH = 6.4 Hz, 1F). HRMS (EI+): Calcd for C₁₅H₁₇F [M]⁺ 216.1314, Found: 216.1306.
(3-Fluoro-4-(4-methoxyphenyl)cyclopenta-1,3-diene-1,2-diyl)dibenzene (16fb)

Compound 16fb was synthesized according to the typical procedure using 1-methoxy-4-[(1-Trifluoromethyl)ethenyl]benzene (14f, 43 mg, 0.21 mmol), diphenylacetylene (15b, 43 mg, 0.24 mmol), Ni(cod)₂ (61 mg, 0.22 mmol), PCy₃ (62 mg, 0.22 mmol), and toluene (2.1 mL) at 100 °C for 3 h. Purification by preparative thin-layer chromatography (hexane/EtOAc = 5:1) gave 16fb (30 mg, 42%) as a pale brown solid.

16fb: IR (neat): ν = 3055, 1606, 1508, 1290, 1248, 1180, 1034, 906, 827, 735, 696 cm⁻¹. ¹H NMR: δ 3.73 (d, J₉HF = 6.4 Hz, 2H), 3.84 (s, 3H), 6.93 (d, J = 8.9 Hz, 2H), 7.15–7.24 (m, 3H), 7.25–7.28 (m, 3H), 7.32–7.40 (m, 4H), 7.59 (d, J = 8.9 Hz, 2H). ¹³C NMR: δ 38.6 (d, J₂CF = 7 Hz), 55.3, 114.1, 115.9 (d, J₂CF = 3 Hz), 126.2 (d, J₂CF = 6 Hz), 127.0, 127.2 (d, J₂CF = 6 Hz), 127.4, 127.8, 128.3, 128.5, 129.3, 132.9 (d, J₂CF = 3 Hz), 135.6 (d, J₂CF = 6 Hz), 135.9 (d, J₂CF = 3 Hz), 137.6 (d, J₂CF = 4 Hz), 156.2 (d, J₂CF = 277 Hz), 158.2 (d, J₂CF = 3 Hz). ¹⁹F NMR: δ 38.2 (t, J₉FH = 6.4 Hz, 1F). HRMS (EI⁺): Calcd for C₂₄H₁₉FO [M]⁺ 342.1420, Found 342.1415.

tert-Butyl 2-fluoro-4-isopropyl-3-methylcyclopenta-1,3-dienecarboxylate (16gc)

Compound 16gc was synthesized according to the typical procedure using tert-butyl 2-(trifluoromethyl)acrylate (14g, 55 mg, 0.28 mmol), 4-methyl-2-pentyne (15c, 25 mg, 0.31 mmol), Ni(cod)₂ (79 mg, 0.29 mmol), PCy₃ (81 mg, 0.29 mmol), and toluene (2.9 mL) at room temperature for 2 h. Purification by silica gel column chromatography (pentane/Et₂O = 5:1) gave compound 16gc (62 mg, 93%) as a colorless liquid.

16gc: IR (neat): ν = 2966, 1693, 1585, 1392, 1173, 1122, 771 cm⁻¹. ¹H NMR: δ 1.09 (d, J = 6.9 Hz, 6H), 1.51 (s, 9H), 1.83 (s, 3H), 2.90 (septet, J = 6.9 Hz, 1H), 3.06 (dd, J₉HF = 7.5 Hz, J = 1.5 Hz, 2H). ¹³C NMR: δ 8.3, 22.2, 27.8 (d, J₂CF = 2 Hz), 28.3, 34.2 (d, J₂CF = 5 Hz), 79.8, 107.6, 127.4 (d, J₂CF = 25 Hz), 154.5 (d, J₂CF = 5 Hz) 162.4 (d, J₂CF = 4 Hz), 166.7 (d, J₂CF = 294 Hz). ¹⁹F NMR: δ 54.9 (t, J₉FH = 7.5 Hz, 1F). HRMS (EI⁺): Calcd for C₁₄H₂₁FO₂ [M]⁺ 240.1526, Found 240.1521.
3.7.4. Synthesis of 5-trifluoromethyl-1,3-cyclopentadiene by nickel-mediated [3+2] cycloaddition of 2-pentafluoroethyl-1-alkenes and alkynes

2-(3,4-Dipropyl-5-(trifluoromethyl)cyclopenta-1,3-dienyl)naphthalene (20aa)

To a toluene solution (2.9 mL) of Ni(cod)\(_2\) (80 mg, 0.29 mmol) and PCy\(_3\) (82 mg, 0.29 mmol) were added 2-(3,3,4,4-pentafluorobut-1-en-2-yl)naphthalene (19a, 75 mg, 0.28 mmol) and 4-octyne (15a, 35 mg, 0.32 mmol) at 50 °C. After stirring for 3 hours at the same temperature, the reaction mixture was filtered through a pad of silica gel (EtOAc). The filtrate was concentrated under reduced pressure, and the residue was purified by preparative thin-layer chromatography (hexane/EtOAc = 20:1) to give 20aa (77 mg, 77%) as a pale yellow oil.

20aa: IR (neat): \(\nu \approx 3057, 2960, 2871, 1248, 1165, 1138, 1093, 746 \text{ cm}^{-1}\). \(^1\)H NMR: \(\delta 0.95 (t, J = 7.4 \text{ Hz}, 3H), 0.97 (t, J = 7.4 \text{ Hz}, 3H), 1.43–1.75 (m, 4H), 2.33 (t, J = 7.5 \text{ Hz}, 2H), 2.35–2.52 (m, 2H), 4.35 (q, J\(_{HF} = 9.1 \text{ Hz}, 1H), 6.75 (s, 1H), 7.40–7.50 (m, 2H), 7.56 (dd, J = 8.5, 1.6 \text{ Hz}, 1H), 7.74–7.89 (m, 4H). \(^{13}\)C NMR: \(\delta 13.8, 14.1, 22.2, 23.6, 29.1, 29.1, 54.9 (q, J\(_{CF} = 27 \text{ Hz}), 125.3, 125.5 (q, J\(_{CF} = 282 \text{ Hz}), 125.7, 126.2, 127.6, 127.7, 128.0, 132.5, 132.9, 133.4, 136.4, 137.2, 140.8, 144.5. \(^{19}\)F NMR: \(\delta 96.6 (d, J_{HF} = 9.1 \text{ Hz}, 3F). \) HRMS (EI+): Calcd for C\(_{22}\)H\(_{23}\)F\(_3\) [M]\(^+\) 344.1752, Found 344.1749.

3.7.5. Preparation and Reaction of Nickelacyclop propane Complex

(A) Stoichiometric Reaction of 2-Trifluoromethyl-1-alkene with Ni(0) Complex

To a C\(_6\)D\(_6\) solution (0.55 mL) of Ni(cod)\(_2\) (14 mg, 0.051 mmol) and PCy\(_3\) (28 mg, 0.10 mmol) was added 2-trifluoromethyl-1-alkene 14a (11 mg, 0.050 mmol) at room temperature. After stirring for 2 h at room temperature, a C\(_6\)D\(_6\) solution of 17a was obtained as a dark red solution. The formation of complex 17a was confirmed by \(^{19}\)F and \(^{31}\)P NMR.

17a: \(^{19}\)F NMR (470 MHz, C\(_6\)D\(_6\)): \(\delta 108.6 (d, J_{FP} = 8.1 \text{ Hz}, 3F). \) \(^{31}\)P NMR (202 Hz, C\(_6\)D\(_6\)): \(\delta 30.4 (d, J_{PP} = 27 \text{ Hz}, 1P), 34.2 (dq, J_{PP} = 27 \text{ Hz}, J_{PF} = 8 \text{ Hz}, 1P)\).
(B) Protonation of Nickelacyclopropane Complex 17a

To a toluene solution (2.1 mL) of Ni(cod)₂ (59 mg, 0.21 mmol) and PCy₃ (60 mg, 0.21 mmol) was added 2-trifluoromethyl-1-alkene 14a (43 mg, 0.20 mmol) at room temperature. After stirring for 2 h at room temperature, a toluene solution of 17a was obtained as a dark red solution (0.18 mmol, 92%; The yield was determined by ¹⁹F NMR using PhCF₃ as an internal standard). To the toluene solution of 17a thus obtained was added acetic acid (60 µL, 1.1 mmol) at room temperature. After stirring for 1 h at room temperature, the reaction mixture was filtered through a pad of silica gel (EtOAc). The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to give 18a (22 mg, 55% from 17a) as a colorless liquid.

1-(4-(1,1,1-Trifluoropropan-2-yl)phenyl)ethanone (18a)

18a: IR (neat): ν = 1687, 1269, 1167, 1132, 771, 742 cm⁻¹. ¹H NMR: δ 1.53 (d, J = 7.3 Hz, 3H), 2.61 (s, 3H), 3.44–3.58 (m, 1H), 7.43 (d, J = 8.2 Hz, 2H), 7.95 (d, J = 8.2 Hz, 2H). ¹³C NMR: δ 14.5 (q, J_CF = 3 Hz), 26.6, 44.2 (q, J_CF = 28 Hz), 126.8 (q, J_CF = 281 Hz), 128.6, 128.8, 136.9, 141.5 (q, J_CF = 2 Hz), 197.5. ¹⁹F NMR: δ 91.8 (d, J_FH = 9.1 Hz, 3F). HRMS (EI⁺): Calcd for C₁₁H₁₁F₃O [M]⁺ 216.0762, Found 216.0755.

(C) Reaction of Nickelacyclopropane Complex 17a with 4-Octyne (15a)

To a toluene solution (2.1 mL) of Ni(cod)₂ (58 mg, 0.21 mmol) and PCy₃ (59 mg, 0.21 mmol) was added 2-trifluoromethyl-1-alkene 14a (46 mg, 0.21 mmol) at room temperature. After stirring for 2
h at room temperature, a toluene solution of 17a was obtained as a dark red solution (0.19 mmol, 88%; The yield was determined by 19F NMR using PhCF$_3$ as an internal standard). To the toluene solution of 17a thus obtained was added 4-octyne (15a, 23 mg, 0.20 mmol) at room temperature. The reaction mixture changed from dark red to red. After stirring for 1 h at room temperature, the reaction mixture was filtered through a pad of silica gel (EtOAc). The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to give fluorocyclopentadiene 16aa (42 mg, 81% from 17a) as a yellow solid.

3.7.6. Experimental Evidence on the formation of the NiF$_2$ complex

To a toluene solution (2.1 mL) of Ni(cod)$_2$ (14 mg, 0.051 mmol) and PCy$_3$ (28 mg, 0.10 mmol) was added 2-trifluoromethyl-1-alkene 14a (11 mg, 0.051 mmol) and 4-octyne (15a, 6.8 mg, 0.061 mmol) at room temperature. After 30 min at room temperature, the disappearance of nickelacyclopropane 17a and the generation of 16aa were confirmed by 19F NMR. Then, Et$_3$SiCl (12 mg, 0.11 mmol) or Ph$_3$SiCl (30 mg, 0.10 mmol) was added to the reaction mixture. Then the reaction solution changed from red to orange. After 1 h, violet crystallines and Ph$_3$SiF were obtained (The generation R$_3$SiF was confirmed by 19F NMR (16aa/R$_3$SiF = 1:2)). The obtained violet crystallines was washed with cold Et$_2$O to give trans-NiCl$_2$(PCy$_3$)$_2$ (The structure of trans-NiCl$_2$(PCy$_3$)$_2$ was confirmed by X-ray diffraction analysis.)

**Figure S1.** X-Ray Crystal Structure of trans-NiCl$_2$(PCy$_3$)$_2$
Table S1. Crystal Data Collection Parameters for \textit{trans}-NiCl\textsubscript{2}(PCy\textsubscript{3})\textsubscript{2}

<table>
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<th>Parameter</th>
<th>\textit{trans}-NiCl\textsubscript{2}(PCy\textsubscript{3})\textsubscript{2}</th>
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<tbody>
<tr>
<td><strong>formula</strong></td>
<td>C\textsubscript{18}H\textsubscript{22}Cl\textsubscript{2}NiP\textsubscript{2}</td>
</tr>
<tr>
<td><strong>crystal system</strong></td>
<td>brock</td>
</tr>
<tr>
<td><strong>space group</strong></td>
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<tr>
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<td>0.0279, 0.1080</td>
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<tr>
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<td>0.0306, 0.1121</td>
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<tr>
<td><strong>GOF on (F^2)</strong></td>
<td>0.954</td>
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<tr>
<td><strong>a (Å)</strong></td>
<td>9.891(2)</td>
</tr>
<tr>
<td><strong>b (Å)</strong></td>
<td>10.173(2)</td>
</tr>
<tr>
<td><strong>c (Å)</strong></td>
<td>10.510(2)</td>
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<tr>
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<td>112.255(2)</td>
</tr>
<tr>
<td><strong>(\beta) (deg)</strong></td>
<td>109.417(2)</td>
</tr>
<tr>
<td><strong>(\gamma) (deg)</strong></td>
<td>91.778(3)</td>
</tr>
<tr>
<td><strong>(V \ (Å^3))</strong></td>
<td>908.041</td>
</tr>
<tr>
<td><strong>Z</strong></td>
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<tr>
<td><strong>(T \ (K))</strong></td>
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<tr>
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</tr>
<tr>
<td>(2\theta_{\text{min}}, 2\theta_{\text{max}} \ (deg))</td>
<td>4.40, 55.12</td>
</tr>
<tr>
<td>no. refln measured (unique)</td>
<td>5139</td>
</tr>
<tr>
<td>no. refln measured ((I &gt; 2\sigma(I)))</td>
<td>3892</td>
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<td>no. parameters</td>
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CHAPTER 4

Nickel-Catalyzed Defluorinative Coupling via Allylic C–F Bond Activation Using β-Fluorine Elimination

Abstract

The nickel-catalyzed defluorinative coupling reactions of trifluoromethylated alkenes with alkynes have been developed. These reactions involve the allylic C–F bond activation via β-fluorine elimination from the intermediary nickelacyclopentenes. The product selectivity was controlled by the choice of appropriate reducing reagents. The reaction enables the regio- and stereoselective synthesis of multi-organo substituted fluoroalkenes.

Single C–F Bond Cleavage

Double C–F Bond Cleavage
4.1. Introduction

Difluorovinylidene compounds have attracted considerable attention in the realms of medicinal and materials sciences, because of their unique properties derived from fluorine atoms. Therefore, the development of synthetic methodologies for difluorovinylidene compounds is a significant research area. On the basis of high availability of trifluoromethyl-bearing compounds, defluorinative functionalization of the trifluoromethyl group is one of the most practical approaches to difluorovinylidene compounds.\[^1\] However, C(sp\(^3\))–F bond activation of the trifluoromethyl group is rarely achieved because of its high bond energy and the shielding effect by lone-pair electrons of fluorine atoms.\[^2,3\] Thus, harsh reaction conditions were typically required to cleave a C(sp\(^3\))–F bond in the trifluoromethyl group.

**Scheme 1. Nickel-Mediated Double C–F Bond Activation using β-Fluorine Elimination**

As shown in Chapter 3, I achieved the nickel-mediated [3+2] cycloaddition of 2-trifluoromethyl-1-alkenes and alkynes via double C–F bond cleavage of a trifluoromethyl group under mild reaction conditions (Scheme 1). In this reaction, ring-opening of nickelacycle \(A\), formed by oxidative cyclization of a 2-trifluoromethyl-1-alkene and an alkyne with Ni\(^0\), readily proceeded by β-fluorine elimination to generate alkenynickel species \(B\). Subsequent 5-endo insertion and the second β-fluorine elimination afforded a 2-fluoro-1,3-cyclopentadiene. Considering the potential
advantage of this methodology, I herein describe two types of nickel-catalyzed coupling reactions of 2-trifluoromethyl-1-alkenes and alkynes by the aid of reductants via C(sp³)–F bond activation.

To establish the catalytic synthesis of difluorovinylidene compounds, I hypothesized that the intermediary alkenylnickel fluoride B could be reduced with the appropriate metal hydride to afford the corresponding product, 1,1-difluoro-1,4-dienes 21, along with the regenerated Ni(0) (Scheme 2). Similarly, the transition metal-catalyzed hydrodefluorination of fluoroarenes was conducted with metal hydride reagents via transmetalation of the intermediary arylmetal fluorides and subsequent reductive elimination (eq 1). After screening metal hydride reagents, I found that the combination of the nickel catalyst and Et₃SiH enables the catalytic synthesis of 1,1-difluoro-1,4-dienes via allylic C–F bond activation. In addition, I applied this methodology to the allylic C–F bond activation of 3,3-difluoropropene derivatives, establishing the new synthetic route to various monofluoroalkenes, which is described in Section 4.2 and Section 4.3.

**Scheme 2. Ni-Catalyzed Synthesis of 1,1-Difluoro-1,4-dienes**

![Scheme 2](image)

Although the transition metal-catalyzed C–F bond activation has been considered to be the most effective approach to cleave the strong C–F bond, there are only a few reports on a C(sp³)–F bond activation of the trifluoromethyl group (eqs 2–4). The present method is the first example of
allylic C(sp³)–F bond activation by using a nickel catalyst, which is a much more inexpensive than palladium and rhodium ones.

\[
\begin{align*}
\text{F}_3\text{C}=\equiv&\text{Ar}^1 + \text{O} = \text{O}\text{-}\text{Ar}^2 \\
&\text{Ar}^2 \text{O}-\text{Ar}^1
\end{align*}
\]

(1.5 equiv)

\[
\begin{align*}
\text{F}_3\text{C} = \equiv&\text{Ar}^1 + \text{O} = \text{O}\text{-}\text{Ar}^2 \\
&\text{Ar}^2 \text{O}-\text{Ar}^1
\end{align*}
\]

(1.5 equiv)

\[
\begin{align*}
\text{Me}_3\text{Si} = \text{CF}_3 + \text{N}_2 \text{Ar}^1 \text{R}-\text{Ar}^2 \\
&\text{Cu} (5 \text{ mol}%) \text{ CaF} (5 \text{ mol}%) \\
&1,4\text{-Dioxane–NMP (10:1), RT}
\end{align*}
\]

(2.0 equiv)

\[
\begin{align*}
\text{N}_2 \text{Ar}^1 \text{R}-\text{Ar}^2 \\
&\text{Cu} \text{CF}_3
\end{align*}
\]

(4)

As described in Scheme 1, the nickel(0)-mediated [3+2] cycloaddition via double C–F bond activation is an efficient method for the synthesis of fluorocyclopentadienes, whereas a stoichiometric amount of Ni(0) complex was required due to the generation of the inert NiF₂ complex. In terms of the economical and environmental benefits, I tried to reduce the required amount of the Ni complex by using reducing reagent, which makes this reaction catalytic (Scheme 3). The most challenging point in developing the desired catalytic reaction is the selective reduction of the Ni(II)F₂ to Ni(0) without the unnecessary reduction of other organonickel(II) fluoride intermediates. To establish the nickel-catalyzed [3+2] cycloaddition, I sought for the appropriate reducing reagent for the inert NiF₂ complex. After screening reducing reagents, it was found that the diboron compound is most effective for the catalytic [3+2] cycloaddition, which is described in Section 4.3.
4.2. Defluorinative Coupling of Trifluoromethylated Alkenes with Alkynes

4.2.1. Optimization of Reaction Conditions

As mentioned in Section 4.1, the intermediary alkenynickel fluoride B, generated via an oxidative cyclization–β-fluorine elimination sequence, could be reduced by an appropriate metal hydride reagent, which leads to the catalytic synthesis of 1,1-difluoro-1,4-dienes 21 (Scheme 2).[5]

To prove my hypothesis, I sought for the appropriate metal hydride reagents for the coupling reaction of α-trifluoromethylstyrene (14e) and 4-octyne (15a) in the presence of a catalytic amount of Ni(cod)₂ and PCy₃ in toluene at 50 °C (Table 1). The use of i-PrONa as a hydride source afforded the desired coupling product, 1,1-difluoro-1,4-diene 21ea in 74% yield via cleavage of C–F bond in the trifluoromethyl group and formation of the C–C and C–H bonds (Table 1, Entry 2).[4a] In the absence of i-PrONa, the corresponding fluorocyclopentadiene 16ea was obtained as the sole product in 3% instead of 21ea (Entry 1). Other secondary alkoxides also gave the product, albeit in low yields (Entries 3–6). When 9-BBN and DIBAL-H were employed, 14e was decomposed to give a complex mixture, because of their high reactivity (Entries 7 and 8). Et₃SiH, recognized as a mild hydride reagent, was found to be highly effective to improve the product yield up to 92% (Entry 9).[4b] Even 5 mol% of Ni catalyst successfully promoted the coupling reaction to give 21ea in an excellent yield (Entry 10). Furthermore, decrease in the reaction temperature to room temperature hardly affected the efficiency of the reaction to afford 21ea in 95% yield (Entry 11).
Table 1. Optimization of reaction conditions in Ni-catalyzed defluorinative coupling of 14e with 15a

<table>
<thead>
<tr>
<th>Entry</th>
<th>x (mol%)</th>
<th>metal hydride</th>
<th>Time (h)</th>
<th>21ea (%)</th>
<th>16ea (%)</th>
<th>Recovery of 14e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>none</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>i-PrONa</td>
<td>12</td>
<td>74</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>(Et₂CH)ONa</td>
<td>36</td>
<td>17</td>
<td>0</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>CyONa</td>
<td>36</td>
<td>66</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>i-PrOLi</td>
<td>12</td>
<td>44</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>i-PrOK</td>
<td>12</td>
<td>trace</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>9-BBN</td>
<td>48</td>
<td>15</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>DIBAL-H</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>Et₃SiH</td>
<td>4</td>
<td>92</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>10ᵇ</td>
<td>5</td>
<td>Et₃SiH</td>
<td>3</td>
<td>96</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11ᵇ,c</td>
<td>5</td>
<td>Et₃SiH</td>
<td>3</td>
<td>95</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12ᵇ,d</td>
<td>5</td>
<td>Et₃SiH</td>
<td>3</td>
<td>84</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

ᵃ¹⁹F NMR yield using PhCF₃ as the internal standard. ᵇ 15a (1.1 equiv) was used. ᶜ Room temperature. ᵈ 80 °C.

4.2.2. Synthesis of 1,1-Difluoro-1,4-dienes by Nickel-Catalyzed Defluorinative Coupling

I carried out the synthesis of various 1,1-difluoro-1,4-dienes 21 via the nickel-catalyzed defluorinative coupling. First, the scope of trifluoromethylalkenes 14 for the coupling reaction was examined under the reaction conditions obtained above. α-Trifluoromethylstyrenes 14h and 14f bearing electron-donating methoxy group provided 1,1-difluoro-1,4-dienes 21ha and 21fa, respectively, in good yields (Table 2, Entries 2 and 3). Likewise, α-trifluoromethylstyrenes 14a and
bearing electron-withdrawing acetyl and ethoxycarbonyl group also provided 1,1-difluoro-1,4-dienes 21aa and 21da, respectively, in high yields (Entries 4 and 5). Intriguingly, α-trifluoromethylstyrene 14i bearing a chlorine substituent, which could be reduced with nickel(0) complex via oxidative addition, was applicable to this reaction without the losing the chlorine substituent (Entry 6).\[6\]

**Table 2. Synthesis of 1,1-Difluoro-1,4-dienes: Scope of α-Trifluoromethylstyrene derivatives 14**

<table>
<thead>
<tr>
<th>Entry</th>
<th>14</th>
<th>R</th>
<th>21</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14e</td>
<td>H</td>
<td>21ea</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>14h</td>
<td>o-OMe</td>
<td>21ha</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>14f</td>
<td>p-OMe</td>
<td>21fa</td>
<td>80</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield

The reaction of trifluoropropene (14j) with diphenylacetylene (15b) afforded the corresponding 1,1-difluoro-1,4-diene 21jb (56%) along with 1-trifluoromethy-1,3,5-triene 22jb (20%, Table 3, Entry 2). The triene 22jb was probably generated through the insertion of 14j into nickelacyclopentadiene A'-bb formed by oxidative cyclization of two molecules of alkyne 15b on nickel (0) (Scheme 4).\[7\] To prevent the generation of the triene 22jb, N-heterocyclic carbene ligands were used instead of PCy₃ for the coupling reaction (Entries 3–5). In the case of using SIMes, 21jb was obtained as the sole product in 77% yield without the formation of triene 22jb (Entry 4). The chemoselectivity could be controlled with the two characteristic properties of SIMes ligand: the highly bulky substituents on nitrogen atoms and the strong σ-donating ability.\[8\] The strong σ-donating ability of SIMes increased the electron density at the nickel center, increasing the
π-backdonation to electron-deficient 14j (Scheme 5). This could improve the chemoselectivity of the oxidative cyclization. In addition, the steric repulsive interaction between the bulky SIMes ligand and alkyne 15b prevented the coordination of two molecules of alkyne 15b to the nickel center, which would inhibit the formation of the nickelacyclopentadiene A'-bb.

Table 3. Defluorinative Coupling of Trifluoropropene 14j with 15b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand (mol%)</th>
<th>Time (h)</th>
<th>21jb (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>22jb (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPh&lt;sub&gt;3&lt;/sub&gt; (20)</td>
<td>17</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>PCy&lt;sub&gt;3&lt;/sub&gt; (20)</td>
<td>10</td>
<td>56</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>IMes·HCl (10) + t-BuOk (10)</td>
<td>17</td>
<td>54</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>SIMes·HCl (10), t-BuOk (10)</td>
<td>10</td>
<td>77&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>SiPr·HCl (10), t-BuOk (10)</td>
<td>17</td>
<td>30</td>
<td>0</td>
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</table>

<sup>a</sup> 19F NMR yield using PhCF<sub>3</sub> as the internal standard. <sup>b</sup> Isolated yield.

Scheme 4. Plausible Reaction Mechanism for Subgeneration of 22jb
Scheme 5. Ligand-Controlled Chemoselective Coupling Reaction

The defluorinative coupling of alkyl-substituted trifluoromethylalkene 14k gave the corresponding product 21ka, albeit in 15% yield (Table 4, Entry 1). The electron donating alkyl group could increase the electron density of the alkene moiety of 14k, inhibiting the coordination of 14k to the nickel(0) center by less π-backdonation (Scheme 6).\(^9\) This might prevent the oxidative cyclization toward the nickelacyclopetene A-ka. I assumed that the electrophilic activation of the alkene moiety of 14k by the coordination of the trifluoromethyl group to a Lewis acid would promote both the coordination step and the oxidative cyclization.\(^10,11\) To prove my hypothesis, I sought for the appropriate Lewis acid for the coupling of alkyl-substituted trifluoromethylalkene 14k with 4-octyne (15a) in the presence of a nickel catalyst. As the result, the use of only 10 mol% of ZrF\(_4\) improved the yield of 21ka to 85% (Entry 7).\(^10\) Moreover, the reactions of silyl-substituted trifluoromethylalkene 14l and trisubstituted one 14m also proceeded smoothly to afford the coupling products 21la and 21ma, respectively, in good yields when ZrF\(_4\) was added as a co-catalyst (eqs 5 and 6). Thus, I succeeded in expanding the substrate scope of trifluoromethylalkenes 14 for the defluorinative coupling by using the co-catalyst ZrF\(_4\).
Table 4. Defluorinative Coupling of 14k with 15b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Yield 21ka (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Recover of 14k (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Entry</th>
<th>Lewis acid</th>
<th>Yield 21ka (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Recover of 14k (%)&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
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<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>74</td>
<td>5</td>
<td>TiF&lt;sub&gt;4&lt;/sub&gt;</td>
<td>44</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>MgF&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0</td>
<td>96</td>
<td>6</td>
<td>ZrF&lt;sub&gt;4&lt;/sub&gt;</td>
<td>77</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>BF&lt;sub&gt;3&lt;/sub&gt;·OEt&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0</td>
<td>98</td>
<td>7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>ZrF&lt;sub&gt;4&lt;/sub&gt;</td>
<td>85&lt;sup&gt;d&lt;/sup&gt;</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>AlF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>70</td>
<td>23</td>
<td>8</td>
<td>ZrCl&lt;sub&gt;4&lt;/sub&gt;</td>
<td>0</td>
<td>93</td>
</tr>
</tbody>
</table>

<sup>a</sup> <sup>19F</sup>NMR yield using PhCF<sub>3</sub> as the internal standard. <sup>b</sup> 5 h. <sup>c</sup> Ni(cod)<sub>2</sub> (10 mol%), PCy<sub>3</sub> (20 mol%). <sup>d</sup>Isolated yield.

Scheme 6. Lewis Acid-Promoted Defluorinative Coupling
Next, I examined the scope of alkynes 15 (Table 5). The use of diphenylacetylene (15b) resulted in the formation of the corresponding coupling product 21eb in 73% yield. Unsymmetrical 4-methyl-2-pentyne (15c), 1-phenyl-1-propyne (15d), 1-(4’-methoxyphenyl)-1-pentyne (15e), 1-phenyl-1-pentyne (15f), and 1-(4’-ethoxycarbonylphenyl)-1-pentyne (15g) also participated in this reaction to afford the corresponding 1,1-difluoro-1,4-dienes 21ac–ag in good to excellent yields with good to complete regioselectivities. The obtained regioselectivities were in agreement with literature on nickel-catalyzed coupling reactions of alkenes and alkynes via oxidative cyclization.\textsuperscript{[12]}

**Table 5. Nickel-Catalyzed Synthesis of 1,1-difluoro-1,4-dienes 21: Scope of Alkynes 15\textsuperscript{a}**

| \( \text{CF}_3 \text{Ph} = \) | \( \text{R}^2 \text{R}^3 \text{Ni(cod)}_2 \text{ (5 mol%)} \) | \| \( \text{SIMes·HCl} \text{ (5 mol%)} \) | \| \( \text{t-BuOK} \text{ (5 mol%)} \) | \| \( \text{Et}_3\text{SiH} \text{ (2.0 equiv)} \) | \| \( \text{Toluene, RT, 3 h} \) | \| \( \text{F}_2\text{CPh} \text{H} \text{R}^3 \text{R}^2 \) |
|---|---|---|---|---|---|---|---|
| \( \text{21eb} \) | 73%\textsuperscript{b} | | | | | | |
| \( \text{21ee} \) | 99% | | | | | | |
| \( \text{21ef} \) | 99% | | | | | | |
| \( \text{21eg} \) | 68% | | | | | | |
| \( \text{21ed} \) | 61% \((21\text{ed}/21\text{ed} = 85:15)\textsuperscript{c}\) | | | | | | |
| | 91%\textsuperscript{d} \((21\text{ec}/21\text{ec} = 100:0)\textsuperscript{c}\) | | | | | | |
| \( \text{21ec} \) | 88%\textsuperscript{e} \((21\text{ec}/21\text{ec} = 95:5)\textsuperscript{c}\) | | | | | | |

\textsuperscript{a} Isolated yield. \textsuperscript{b} 8 h. \textsuperscript{c} Regio isomer ratio was determined by \( ^{19}\text{F} \) NMR measurement. \textsuperscript{d} \( \text{PCy}_3 \) (10 mol%) was used instead of \( \text{SIMes} \). \( \text{Ni(cod)}_2 \) (10 mol%), \( \text{PCy}_3 \) (20 mol%) were used as catalyst.
4.2.3. Mechanistic Studies on Nickel-Catalyzed Defluorinative Coupling of 14 with 15

There are three plausible mechanisms for this reaction as shown in Scheme 7 as follows:

**Path A: Oxidative Cyclization–β-Fluorine Elimination**

Nickelacyclopentene A is initially formed by oxidative cyclization of 2-trifluoromethyl-1-alkenes 14 and alkynes 15 with Ni(0) (Scheme 7, path A). β-Fluorine elimination from nickelacycle A proceeds to generate the corresponding alkenynickel fluoride B. Subsequent transmetalation of the intermediate B with Et₃SiH gives alkenynickel hydride D. Finally, reductive elimination affords the desired 1,1-difluoro-1,4-diene 21 along with Ni(0) complex, which completes the catalytic cycle.

**Path B: Oxidative Addition–Alkyne Insertion**

2-Trifluoromethyl-1-alkene 14 initially reacts with Ni(0) to generate the corresponding π-allylnickel complex C by oxidative addition of C–F bond to Ni(0) (Scheme 7, path B). Alkyne insertion into the C–Ni bond of C leads to the formation of intermediate B, followed by transmetalation of B with Et₃SiH to afford the same coupling product 21.

**Path C: Alkyne Insertion–β-Fluorine Elimination**

Alkyne insertion initially proceeds into the Ni–H bond of silylnickel hydride E, generated by oxidative addition of the Si–H bond to Ni(0), which gives the alkenynickel complex F (Scheme 7, path C). Subsequent insertion of 14 into the C–Ni bond gave the alkenynickel complex G having a CF₃ group on the carbon α to the nickel center. Finally, β-fluorine elimination from G gives 21 along with the silylnickel fluoride complex, which would be reduced to Ni(0) by reductive elimination of the silyl fluoride.
To clarify the mechanism, several experiments were performed. First, to examine the possibility of path C, the stoichiometric reaction of Ni(0) complex with Et₃SiH in the presence of alkynes was conducted (eq 7). If the reaction involves the oxidative addition of Si–H bond to Ni(0), the consumption of the hydrosilane would be observed. On treatment of Et₃SiH and 15a with a stoichiometric amount of Ni(cod)₂ and PCy₃ in toluene-d₈ at 50 °C, no consumption of Et₃SiH and no generation of the corresponding organonickel species were observed by ¹H and ³¹P NMR measurements. Thus, the possibility of path C was ruled out.

\[
\begin{align*}
\text{Scheme 7. Plausible Reaction Mechanism} \\
\text{path A} & \\
\text{path B} & \\
\text{path C} & \\
\text{Et₃SiH} \quad \text{Ni(0)} \quad \text{Et₃Si-NiII-H} \quad \text{Et₃Si-NiII-H} \quad \text{Et₃Si-NiII-H} \quad \text{Et₃Si-NiII-H} \\
\text{Alkyne Insertion} & \\
\text{Alkyne Insertion} & \\
\text{Alkyne Insertion} & \\
\end{align*}
\]
As mentioned in Chapter 3, the stoichiometric reaction of 2-trifluoromethyl-1-alkene 14a with a Ni(0) complex afforded the corresponding nickelacyclopropane 17a as the sole product (eq 8). In this reaction, the allylnickel complex generated by oxidative addition of C–F bond was not observed. Moreover, the obtained nickel complex 17a reacted with alkyne 15a and Et3SiH to afford the coupling product 21aa in 64% yield. Therefore, in this reaction, the C–F bond activation probably proceeded by an oxidative addition–β-fluorine elimination sequence (Scheme 5, path A).

4.3. Defluorinative Coupling of 3,3-Difluoropropenes with Alkynes

Monofluoroalkenes have been widely recognized to be important such as the peptide bond isosteres, enzymatic inhibitors, liquid crystalline materials, and so on. One of the most straightforward approaches to monofluoroalkenes is defluorinative functionalization of 3,3-difluoropropene derivatives, which are easily prepared from commercially available bromodifluoromethyl compounds. However, previous methods have problems such as the narrow substrate scope, the strong basic conditions and the requirement of a stoichiometric amount of highly reactive organometallic reagents.\(^{[13c,16]}\)

To establish the catalytic synthesis of monofluoroalkenes, I applied the nickel-catalyzed defluorinative coupling to the allylic C–F bond activation of 3,3-difluoropropene derivatives 23. The reaction of α-difluoromethylstyrene (23a) with 4-octyne (15a) was promoted by the nickel catalyst in the presence of 2.0 equiv of Et3SiH via allylic C–F bond cleavage to afford the corresponding 1-fluoro-1,4-diene 24aa in 82% yield (Table 6).
Table 6. Nickel-Catalyzed Defluorinative Coupling of Acyclic 3,3-Difluoropropenes 23 with Alkynes 15

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield</th>
<th>Stereoselectivity</th>
</tr>
</thead>
</table>
| Table 6  | Ni(cod)$_2$ (5 mol%), PCy$_3$ (10 mol%), Et$_3$SiH (2.0 equiv) Toluene | 24a | 82% | (E/Z = 50:50)$^a$
|          | (50 °C, 2 h) | 24ba | 63%$^{c,d}$ | (E/Z = 11:89)$^b$
|          | (70 °C, 24 h) | 24cb | 86%$^{c,d}$ | (80 °C, 7 h) |
|          | (50 °C, 5 h) | 24'dh | 99% | (50 °C, 5 h) |
|          | (2.0 equiv) | 24'eh | 95% | (E/Z = 2.98)$^{b,e}$ |

$^a$ Isolated yield. $^b$ Isomer ratio was determined by $^{19}$F NMR. $^c$ Ni(cod)$_2$ (10 mol%), PCy$_3$ (20 mol%), $^d$ Et$_3$SiH (1.0 equiv). $^e$ 15h (2.0 equiv). $^{f,19}$F NMR yield using PhCF$_3$ as the internal standard.

Figure 1. List of Substrates

Next, the scope of 3,3-difluoropropenes was examined (Table 6, Figure 1). The reaction of 3,3-difluoropropenes 23b and 23c bearing bulky methoxybenzyl and heptafluoropropyl substituents on the carbon α to fluorine substituents proceeded smoothly to afford the products 24ba and 24cb in 63% and 86% yield, respectively, with good to complete stereoselectivities. 2,3-Disubstituted-3,3-difluoropropenes 23d and 23e also participated in this reaction to afford the corresponding 1-fluoro-1,4-dienes 24’dh, and 24’eh in 99%, and 95% yields, respectively, with excellent to complete stereoselectivities. Furthermore, cyclic difluoropropenes were applicable to
this reaction. The reaction of 5-membered carbocyclic difluoropropene 23f with 15a readily proceeded to give the corresponding 2-fluoroindene derivative 24fa and its isomer 24”fa in 88% and 9% yield, respectively. 5-Membered heterocyclic difluoropropenes 23g provided 2-fluoroindole derivatives 24ga in 75% yield.

As shown above, this reaction exhibited high stereoselectivity in the synthesis of acyclic monofluoroalkenes. It is clear that the stereoselectivity of products was determined in the step of β-fluorine elimination, which proceeds via syn-conformation I or syn-conformation II from the intermediary nickelacycle A (Scheme 8). I assumed that the stereoselectivity of the fluoroalkene moiety would be controlled by the steric effect. In the reaction of 23b or 23c, the β-fluorine elimination proceeds not via conformation II but via conformation I to avoid the steric hindrance between the R1 substituent and the methylene group of nickelacycle A to afford 24 selectively. On the other hand, when 23d or 23e was used as the substrate, the β-fluorine elimination proceeds not via conformation I but via conformation II to avoid the steric hindrance between the R1 substituent and the R2 substituent to afford 24’.

**Scheme 8. Stereoselectivity of Monofluoroalkenes 24**
4.4. Catalytic [3+2] Cycloaddition of Trifluoromethylated Alkenes with Alkynes

Here, I demonstrate the nickel-catalyzed [3+2] cycloaddition of 2-trifluoromethyl-1-alkenes 14 with alkynes 15 by using a reducing agent for the NiF₂. The most challenging point in developing the desired catalytic reaction is the selective reduction of the Ni(II)F₂ to Ni(0) without the reduction of other organonickel(II) fluoride intermediates, which cause side reactions.[17]

To establish the catalytic synthesis of 2-fluoro-1,3-cyclopentadines 16, I sought for the appropriate reducing agent for the [3+2] cycloaddition of 2-(4-acetylphenyl)-3,3,3-trifluoropropene (14a) and 4-octyne (15a) in the presence of a catalytic amount of Ni(cod)₂ and PCy₃ in 1,4-dioxane at 80 °C (Table 7). First, I attempted the direct reduction of the NiF₂ to Ni(0) with zero-valent metals, which serve as electron-transfer reductant (Scheme 9a). The use of metallic Na decomposed substrates to a complex mixture (Table 7, Entry 2). Although Mn and Zn metals have been typically used for the reduction of the NiX₂ (X = Cl, Br, I), the catalytic reaction was not achieved (Entries 3 and 4).[18] Next, I investigated the use of bismetal compounds bearing a metal–metal single bond as the reducing agents for this reaction.[19] I assumed that the appropriate bismetal compound would reduce the NiF₂ complex to Ni(0) through a transmetalation–reductive elimination sequence, which was accompanied by the elimination of highly stable metal fluoride (Scheme 9b). To prove my hypothesis, I screened several bismetal compounds such as disilane, silylboron and diboron compounds (Entries 5–9). Unfortunately, the use of bismetal reagents alone never realized the catalytic reaction probably due to their low reactivity. To activate the bismetal reagents, the additional base was used to generate the reactive ate complexes.[20] After screening several bismetal regents and bases, the combination of B₂(nep)₂ and t-BuOK was found to be effective for the reduction of the NiF₂ (Entry 10). Furthermore, the addition of MgF₂ with 10 mol% of the Ni catalyst improved the product yield up to 33% (Entry 11). Finally, increase of the catalyst amount to 20 mol% improved the product yield of 16aa to 60% (Entry 12).
Table 7. Optimization of Reaction Conditions in Nickel-Catalyzed [3+2] Cycloaddition

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reducing Reagent (equiv)</th>
<th>Yield (%)</th>
<th>Entry</th>
<th>Reducing Reagent (equiv)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>1</td>
<td>7</td>
<td>B_2(pin)_2 (1.1)</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>Na (3.0)</td>
<td>6</td>
<td>8</td>
<td>B_2(cat)_2 (1.1)</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>Mn (2.0)</td>
<td>5</td>
<td>9</td>
<td>B_2(nep)_2 (1.1)</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>Zn (2.0)</td>
<td>5</td>
<td>10</td>
<td>B_2(nep)_2 (1.1), t-BuOK (1.1)</td>
<td>21</td>
</tr>
<tr>
<td>5</td>
<td>Me_3SiSiMe_3 (1.1)</td>
<td>5</td>
<td>11</td>
<td>B_2(nep)_2 (1.1), t-BuOK (1.1), MgF_2 (1.0)</td>
<td>33</td>
</tr>
<tr>
<td>6</td>
<td>Me_2PhSiB(pin) (1.1)</td>
<td>7</td>
<td>12</td>
<td>B_2(nep)_2 (1.1), t-BuOK (1.1), MgF_2 (1.0)</td>
<td>60</td>
</tr>
</tbody>
</table>

*a 19F NMR yield using PhCF_3 as the internal standard. b Ni(cod)_2 (20 mol%), PCy_3 (40 mol%).

Scheme 9. Strategies for Regeneration of Ni(0) from the Ni(II)F_2

(a) electron-transfer reduction

(b) transmetalation–reductive elimination sequence

With the optimized reaction conditions in hand, I carried out the synthesis of various 2-fluoro-1,3-cyclopentadienes 16 via the nickel-catalyzed [3+2] cycloaddition (Figure 2, Table 8). Unsymmetrical 4-methyl-2-pentyne (15c) also participated in this catalytic reaction to afford the corresponding 2-fluoro-1,3-cyclopentadienes 16ac in 70% yield with a complete regioselectivity.
α-Trifluoromethylstyrenes 14b and 14n bearing electron-withdrawing cyano and fluorine groups also provided cyclopentadienes 16bc and 16nc in 48% and 50% yields, respectively. Non-substituted α-trifluoromethylstyrenes 14e successfully underwent cycloaddition with 15c. Furthermore, the catalytic reaction was applied to intramolecular reaction of 9-trifluoromethyl-2,8-enyne 15o under the same conditions to give the ring-fused fluorocyclopentadiene 16o in 47% yield (eq 9).

![Figure 2. List of Substrates](image)

### Table 8. Synthesis of Fluorocyclopentadienes 16 by Nickel-Catalyzed [3+2] Cycloaddition

<table>
<thead>
<tr>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;(p-Ac)</td>
<td>Me</td>
<td>i-Pr</td>
<td>53% (60%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;(p-CN)</td>
<td>Me</td>
<td>i-Pr</td>
<td>70%</td>
</tr>
<tr>
<td>Ph</td>
<td>Me</td>
<td>i-Pr</td>
<td>48% (60%)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;(m-F)</td>
<td>Me</td>
<td>i-Pr</td>
<td>50%</td>
</tr>
<tr>
<td>Ph</td>
<td>Me</td>
<td>i-Pr</td>
<td>48%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield.  <sup>b</sup> <sup>19</sup>F NMR yield using PhCF<sub>3</sub> as the internal standard.

![Ni(cod)<sub>2</sub> (20 mol%), PCy<sub>3</sub> (40 mol%), B<sub>2</sub>(nep)<sub>2</sub> (1.1 equiv), t-BuOK (1.1 equiv), MgF<sub>2</sub> (1.0 equiv), 1,4-Dioxane, 80 °C, 3 h](image)

* 14o (E/Z = 60:40)  
  Ni(cod)<sub>2</sub> (20 mol%), PCy<sub>3</sub> (40 mol%), B<sub>2</sub>(nep)<sub>2</sub> (1.1 equiv), t-BuOK (1.1 equiv), MgF<sub>2</sub> (1.0 equiv), 1,4-Dioxane, 40 °C, 20 min then 80 °C, 15 h
  16o 36% (47%)<sup>a</sup>  
  <sup>a</sup> <sup>19</sup>F NMR yield
The plausible reaction mechanism is shown in Scheme 10. Nickelacyclopentene A is initially formed by oxidative cyclization of 2-trifluoromethyl-1-alkenes 14 and alkynes 15 with Ni(0). β-Fluorine elimination from nickelacycle A proceeds to generate the corresponding alkenylnickel fluoride B. When Et₃SiH is used as the reducing regent, transmetalation of intermediate B with Et₃SiH would proceeds more preferentially than 5-endo insertion from intermediate B, which eventually gives the desired 1,1-difluoro-1,4-diene 21 after reductive elimination from alkenylnickel hydride F along with Ni(0) (Scheme 10, path A). On the other hand, transmetalation of intermediate B with the boron–ate complex G derived from B₂(nep)₂ and base would be slower than 5-endo insertion from intermediate B, probably due to the lower reactivity of G compared to Et₃SiH (Scheme 10, path B). In this reaction pathway, the second β-fluorine elimination from intermediate C gives the 2-fluoro-1,3-cyclopentadiene 16 along with NiF₂ complex D. Finally, the NiF₂ is reduced to Ni(0) with the boron–ate complex G through subsequent transmetalation and reductive elimination, which completes the catalytic cycle.
4.5 Conclusion

In summary, I have developed the new methodologies for catalytic C(sp$^3$)–F bond activation of the trifluoromethyl group by β-fluorine elimination from nickelacyclopentenes bearing a trifluoromethyl group, which were generated from oxidative cyclization of 2-trifluoromethyl-1-alkenes 14 and alkynes 15 with Ni(0). Utilizing the combination of these elementary processes, the choice of appropriate reducing reagents efficiently controlled the product selectivity in nickel-catalyzed defluorinative coupling reactions between 2-trifluoromethyl-1-alkene 14 and alkyne 15. This reaction enables the regio- and stereoselective synthesis of multiorgano-substituted mono- and difluoroalkenes, which have attracted considerable attentions in medicinal and material sciences.
4.6. References and Notes


4.7 Experimental Section

4.7.1. General Statements

IR spectra were recorded on Horiba FT-300S spectrometers. NMR spectra were recorded on a Bruker avance 500 spectrometer in CDCl$_3$ at 500 MHz ($^1$H NMR), at 126 MHz ($^{13}$C NMR), and at 470 MHz ($^{19}$F NMR), and at 202 MHz ($^{31}$P NMR). Chemical shifts were given in ppm relative to internal Me$_4$Si (for $^1$H NMR: $\delta = 0.00$), CDCl$_3$ (for $^{13}$C NMR: $\delta = 77.0$), C$_6$F$_6$ (for $^{19}$F NMR: $\delta = 0.0$), and H$_3$PO$_4$ (for $^{31}$P NMR: $\delta = 0.0$). High resolution mass spectroscopy (HRMS) was conducted with a JMS-T100GCV spectrometer. Elemental analyses were performed with a YANAKO MT-3 CHN Corder apparatus.

Column chromatography and preparative thin-layer chromatography (PTLC) were conducted on silica gel (Silica Gel 60 N, Kanto Chemical Co., Inc. for column chromatography and Wakogel B-5F, Wako Pure Chemical Industries for PTLC, respectively). All the reactions were conducted under argon. Tetrahydrofuran (THF) and diethylether (Et$_2$O) were dried by passing over a column of activated alumina followed by a column of Q-5 scavenger (Engelhard). Toluene was distilled from sodium benzophenone ketyl, and stored over sodium chips. 1,4-Dioxane and C$_6$D$_6$ were distilled from CaH$_2$, and stored over activated molecular sieves 4A.

Ni(cod)$_2$ and PCy$_3$ were purchased from sigma-aldrich Co. and stored in a globe box under argon atmosphere. 4-Octyne, 4-methyl-1-pentyne, Et$_3$SiH, B$_2$(nep)$_2$, $t$-BuOK, MgF$_2$ were purchased from sigma-aldrich Co. and Tokyo Chemical Industry Co., Ltd., respectively. These compounds were used without further purification. Other liquid reagents were purified by distillation and solid reagents were purified by recrystallization.
4.7.2. Synthesis of Substrates

[1] Synthesis of 2-Trifluoromethyl-1-alkenes 14

1-Methoxy-2-(3,3,3-trifluoroprop-1-en-2-yl)benzene (14h)

To a THF solution (16 mL, 0.3 M) of PdCl₂(PPh₃)₂ (108 mg, 0.154 mmol) and AsPh₃ (236 mg, 0.771 mmol) were added 2-methoxyphenyl boronic acid (779 mg, 5.13 mmol) and 2-bromo-3,3,3-trifluoropropene (1.35 g, 7.71 mmol) at room temperature. Aqueous KOH (2.0 M, 10.3 mL, 20.6 mmol) was added, and the mixture was heated to reflux for 11.5 h. The reaction mixture was cooled to room temperature and quenched by addition of saturated aqueous NH₄Cl. Organic materials were extracted two times with Et₂O. The combined extracts were washed with brine and dried over Na₂SO₄. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (Hexane) and further distillation under reduced pressure to give 14h (778 g, 75%) as a colorless liquid.

Spectral data for this compound showed good agreement with the literature data.

1-(4-chlorophenyl)-2,2,2-trifluoroethanone

To a THF solution (33 mL) of 4-chlorobromobenzene (2.87 g, 15.0 mmol) was added n-BuLi (10.0 mL, 1.61 M in hexane, 16.1 mmol) at −78 °C over 15 min. After stirring for 15 min at −78 °C, this mixture was transferred by using a double-ended needle to a THF solution (33 mL) of ethyl trifluoroacetate (2.34 g, 16.5 mmol) at between −78 °C and −67 °C over 75 min. Then, the mixture was warmed to room temperature over 10 h, and saturated aqueous NH₄Cl was added. Organic materials were extracted three times with Et₂O. The combined extracts were washed with brine and dried over anhydrous Na₂SO₄. After removal of the solvent under reduced pressure, the residue was purified by distillation under reduced pressure (55–58 °C/6.2 mmHg) to give the title compound (1.65 g, 53%) as a colorless liquid.
1-Chloro-4-(3,3,3-Trifluoroprop-1-en-2-yl)benzene (14i)

To a Et₂O solution (50 mL) of Ph₃PCH₃I (11.9 g, 29.3 mmol) was added t-BuONa (3.99 g, 41.6 mmol) at 0 °C. The reaction mixture was stirred for 10 min at room temperature and then cooled to –78 °C. To the mixture was added slowly a Et₂O solution (5.0 mL) of 1-(4-chlorophenyl)-2,2,2-trifluoroethanone (5.83 g, 28.0 mmol) at –78 °C over 10 min. Then, the mixture was warmed to room temperature over 11 h, the reaction was quenched with saturated aqueous NH₄Cl at that temperature. Organic materials were extracted three times with Et₂O. The combined extracts were washed with brine and dried over anhydrous Na₂SO₄. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (hexane) and further distillation under reduced pressure to give 14i (1.91 g, 33%) as a colorless liquid.

Spectral data for this compound showed good agreement with the literature data.²

1,1,1-Trifluoro-4-phenyl-2-butanone

To a Et₂O solution (100 mL) of ethyl trifluoroacetate (7.16 g, 50.0 mmol) was added phenethylmagnesium bromide (1.0 M in Et₂O, 50.0 mL, 50.0 mmol) prepared from phenethylbromide (9.25 g, 50.0 mmol) and magnesium turning (1.32 g, 55.0 mmol) at –78 °C over 30 min. After stirring for 30 min at that temperature, the mixture was warmed to –50 °C over 1 h, and saturated aqueous NH₄Cl was added at that temperature. Organic materials were extracted three times with Et₂O. The combined extracts were washed with brine and dried over anhydrous Na₂SO₄. After removal of the solvent under reduced pressure, the residue was purified by distillation under reduced pressure (89–91 °C/17–21 mmHg) to give the title compound (7.47 g, 74%) as a colorless liquid.

Spectral data for this compound showed good agreement with the literature data.³

[3-(Trifluoromethyl)-3-butenyl]benzene (14k)
To a Et₂O solution (64 mL) of Ph₃PCH₃I (7.11 g, 17.6 mmol) was added t-BuOK (1.97 g, 17.6 mmol) at room temperature. The reaction mixture was stirred for 30 min at room temperature and then cooled to −78 °C. To the mixture was added slowly a Et₂O solution (16 mL) of 1-(4-chlorophenyl)-2,2,2-trifluoroethanone (3.23 g, 16.0 mmol) at −78 °C over 10 min. Then, the mixture was warmed to room temperature over 10 h, the reaction was quenched with aqueous HCl (1.0 M) at that temperature. Organic materials were extracted three times with Et₂O. The combined extracts were washed with brine and dried over anhydrous Na₂SO₄. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (hexane) and further distillation under reduced pressure to give 1h (2.65 g, 77%) as a colorless liquid. Spectral data for this compound showed good agreement with the literature data.³

**Dimethylphenyl[1-(trifluoromethyl)ethenyl]silane (14l)**

\[
\begin{align*}
\text{Ph} & \text{SiCl} \quad \text{Br} \quad \text{CF₃} \\
(2.0 \text{ equiv}) & \quad \text{THF, −10 °C, 12 h then RT, 12 h} \\
\rightarrow & \quad \text{CF₃} \quad \text{Ph} \\
\text{Mg (1.2 equiv)} & \quad \text{14l 80%}
\end{align*}
\]

To a suspension of magnesium turnings (2.88 g, 120 mmol) and chlorodimethylphenylsilane (33.0 mL, 199 mmol) in THF (100 mL) was added 2-bromo-3,3,3-trifluoro-1-propene (10.4 mL, 100 mmol) over 8 h at −10 °C. The reaction mixture was stirred at −10 °C for 4 h and then at room temperature for an additional 12 h. The reaction mixture was quenched with phosphate buffer (pH 7), and organic materials were extracted with Et₂O. The combined extracts were washed with brine and then dried over Na₂SO₄. After removal of the solvent, the residue was purified by silica gel column chromatography (pentane) and distillation under reduced pressure to give 14l as a colorless oil. Spectral data for this compound showed good agreement with the literature data.⁴

Preparation methods for 1-(4-(3,3,3-Trifluoroprop-1-en-2-yl)phenyl)ethanone (14a), 4-(3,3,3-Trifluoroprop-1-en-2-yl)benzonitrile (14b), Ethyl 4-(3,3,3-trifluoroprop-1-en-2-yl)benzoate (14d), α-(Trifluoromethyl)styrene (14e), 1-Methoxy-4-(3,3,3-trifluoroprop-1-en-2-yl)benzene (14f) were shown in experimental section of Chapter 3 (page 67–70.).

---


[2] Synthesis of Alkynes

Ethyl 4-(pent-1-ynyl)benzoate (15g)

To a THF solution (20 mL) of PdCl₂(PPh₃)₂ (140 mg, 0.199 mmol) and CuI (76.0 mg, 0.399 mmol) were added the ethyl 4-iodobenzoate (5.38 g, 19.5 mmol) and NEt₃ (3.06 g, 30.2 mmol), 1-pentyne (1.52 g, 22.3 mmol). After stirring for 48 h at room temperature, the mixture was quenched with aqueous HCl (1.0 M). Organic materials were extracted three times with Et₂O. The combined extracts were washed with brine and dried over anhydrous Na₂SO₄. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (hexane–EtOAc = 20:1) and distilled under reduced pressure to give the title compound (3.84 g, 91%) as a pale yellow liquid.

15g: IR (neat): ν = 2964, 2933, 2237, 1712, 1606, 1265, 1174, 1103, 768 cm⁻¹. ¹H NMR: δ 1.06 (t, J = 7.4 Hz, 3H), 1.39 (t, J = 7.1 Hz, 3H), 1.65 (qt, J = 7.4, 7.1 Hz, 2H), 2.41 (t, J = 7.1 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 7.96 (d, J = 8.3 Hz, 2H). ¹³C NMR: δ 13.5, 14.2, 21.4, 22.0, 60.9, 80.2, 93.5, 128.7, 129.1, 129.3, 131.3, 166.1. HRMS (EI+): Calcd for C₁₄H₁₆O₂ [M⁺] 216.1150, Found 216.1141.

Diphenylacetylene (15b), and 1-phenyl-1-propyne (15d), 1-methoxy-4-(pent-1-ynyl)benzene (15e), 1-phenyl-1-pentyne (15f) were prepared by the literature procedures. Spectral data for these compounds showed good agreement with the literature data.


α-Difluoromethylstyrene (23a)

**Synthesis of ketone**: To a Et₂O solution (70 mL) of ethyl 2,2-difluoroacetate (2.33 g, 10.0 mmol) was added slowly a Bu₃O–Et₂O solution of PhLi (12.5 mL, 1.60 M in Bu₃O, 10.5 mmol and Et₂O 7.5 mL) at –78 °C over 50 min. After stirring for 1.5 h at that temperature, the reaction mixture was quenched with aqueous HCl (1.0 M). Organic materials were extracted two times with Et₂O. The combined extracts were washed with brine and dried over anhydrous Na₂SO₄. After removal of the solvent under reduced pressure, the residue was purified by distillation under reduced pressure (80–85 °C/28–30 mmHg) to give 2,2-difluorophenylethan-1-one (2.44 g, 78%) as a colorless liquid. Spectral data for this compound showed good agreement with the literature data.¹²

**Wittig Reaction**: To a Et₂O solution (70 mL) of Ph₃PCH₃I (6.95 g, 17.2 mmol) was added t-BuOK (1.93 g, 17.2 mmol) at 0 °C. The reaction mixture was stirred for 30 min at room temperature and then cooled to −78 °C. To the mixture was added slowly a Et₂O solution (16 mL) of 2,2-difluorophenylethan-1-one (2.44 g, 15.6 mmol) at −78 °C. The mixture was warmed to room temperature over 17 h, and then quenched with saturated aqueous NH₄Cl at that temperature. The mixture was filtered through a pad of Celite (Et₂O), and then filtrate was extracted three times with Et₂O. The combined extracts were washed with brine and dried over anhydrous Na₂SO₄. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (pentane) and distillation under reduced pressure to give α-difluoromethylstyrene (23a, 1.52 g, 63%) as a colorless liquid. Spectral data for this compound showed good agreement with the literature data.¹

(2,2-Difluoro-1-methoxybut-3-en-1-yl)benzene (23b)

**Zinc-mediated difluoroallylation**: To a suspension of zinc power (2.29 g, 35 mmol) in THF (25 mL) was added I₂ (2.54 g, 10.0 mmol) in several portions at 0 °C. After stirring for 30 min at room temperature, benzaldehyde (2.1 g, 20.0 mmol) was added to the mixture and then cooled to 0 °C. To
the mixture was added slowly a THF solution (10 mL) of 3-bromo-3,3-difluoropropene (2.54 mL, 25.0 mmol) over 10 min at 0 °C. After stirring for 18 h at room temperature, the reaction mixture was quenched with aqueous HCl (1.0 M), and organic materials were extracted with EtOAc. The combined extracts were washed with brine and then dried over Na₂SO₄. After removal of the solvent, the residue was purified by silicagel column chromatography (hexane:EtOAc = 20:1–5:1) to give 2,2-difluoro-1-phenylbut-3-en-1-ol (2.23 g, 88%) as a colorless liquid. Spectral data for this compound showed good agreement with the literature data.⁸

*Methylation of the alcohol:* To a suspension of sodium hydride (55 wt%, 436 mg, 10.0 mmol) in THF (8 mL) was added slowly a THF solution (2.0 mL) of 2,2-difluoro-1-phenylbut-3-en-1-ol (921 mg, 5.00 mmol) at 0 °C. After stirring for 30 min at 0 °C, iodomethane (0.623 mL, 10.0 mmol) was added to the reaction mixture at 0 °C. The mixture was stirred for 18 h at room temperature, and then quenched with cooled water, and organic materials were extracted with Et₂O. The combined extracts were washed with brine and then dried over Na₂SO₄. After removal of the solvent, the residue was purified by silicagel column chromatography (hexane:EtOAc = 10:1) and distillation under reduced pressure to give (2,2-difluoro-1-methoxybut-3-en-1-yl)benzene (23b, 892 mg, 90%) as a colorless liquid.

23b: ¹H NMR: δ 3.28 (s, 3H), 4.31 (dd, ²JHF = 9.6, 9.6 Hz, 1H), 5.37 (d, ²J = 11.1 Hz, 1H), 5.48 (ddd, ²J = 17.4, 2.5, 2.5 Hz, 1H), 5.78−5.93 (m, 1H), 7.24−7.33 (m, 5H). ¹³C NMR: δ 57.9, 85.0 (dd, ²JCF = 30, 30 Hz), 118.8 (dd, ²JCF = 245, 245 Hz), 120.9 (dd, ²JCF = 9, 9 Hz), 128.1, 128.4, 128.7, 129.9 (dd, ²JCF = 26, 26 Hz), 134.4 (d, ²JCF = 4 Hz). ¹⁹F NMR: δ 53.9 (ddd, ²JFF = 249 Hz, ²JFH = 10, 10 Hz, 1F), 58.1 (ddd, ²JFF = 249 Hz, ²JFH = 10, 10 Hz, 1F). Elemental analysis: Calcd for C₁₁H₁₂F₂O: C, 66.66; H, 6.10. Found: C, 66.60; H, 6.25.

(1,1-Difluoroprop-2-ene-1,2-diyl)dibenzene (23d)

23d was prepared by the literature procedures.⁹ Spectral data for this compound showed good agreement with the literature data.
4-(3,3,4,4-Pentafluorobut-1-en-2-yl)biphenyl (23e)\textsuperscript{10,11}

\begin{align*}
\text{Br} & \quad \text{n-BuLi (1.1 equiv)} \quad \text{THF, } –78 \, ^\circ\text{C}, 5 \text{ min} \quad \text{then to } –30 \, ^\circ\text{C}, 2 \text{ h} \\
\text{Ph} & \\
\text{n-CF}_2\text{CF}_2\text{CO}_2\text{Et (1.0 equiv)} \quad \text{–78 \, ^\circ\text{C}, 40 min} \quad \text{then to } 0 \, ^\circ\text{C}, 35 \text{ min} \\
\text{Ph} & \\
\text{Ph} & \quad \text{Ph}_3\text{PCH}_3\text{I (1.1 equiv)} \quad \text{t-BuOK (1.1 equiv)} \quad \text{THF, } –78 \, ^\circ\text{C} \quad \text{then to RT, 10 h} \\
\text{Ph} & \\
\text{Ph} & \\
\text{F} & \\
\text{F} & \quad \text{F} & \\
\text{F} & \quad \text{F} & \\
\text{23e} & \quad 81\% \\
\end{align*}

**Synthesis of ketone:** To a THF solution (30 mL) of 4-bromobiphenyl (2.33 g, 10.0 mmol) was added n-BuLi (6.60 mL, 1.59 M in hexane, 10.5 mmol) at –78 °C over 5 min. The mixture was warmed to –30 °C over 2 h, and then transferred by using a double-ended needle to a THF solution (30 mL) of ethyl 2,2,3,3,3-pentafluoropropionate (1.92 g, 10.0 mmol) at –78 °C over 10 min. After stirring for 30 min at that temperature, the mixture was then warmed to 0 °C over 35 min, and aqueous HCl (1.0 M) was added. Organic materials were extracted two times with Et\textsubscript{2}O. The combined extracts were washed with brine and dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (hexane–EtOAc = 20:1) to give 2,2,3,3,3-Pentafluoro-1-(biphenyl-4-yl)propanone (2.13 g, 71%) as a white solid.

2,2,3,3,3-Pentafluoro-1-(biphenyl-4-yl)propanone: IR (neat): \( \nu \approx 1705, 1605, 1228, 1171, 912, 870 \text{ cm}^{-1} \). \( ^1\text{H} \text{ NMR: } \delta = 7.45 (t, J = 7.4 \text{ Hz}, 1\text{H}), 7.50 (dd, J = 7.4, 7.1 \text{ Hz}, 2\text{H}), 7.65 (d, J = 7.1 \text{ Hz}, 2\text{H}), 7.77 (d, J = 8.3 \text{ Hz}, 2\text{H}), 8.17 (d, J = 8.3 \text{ Hz}, 2\text{H}). \)

\( ^{13}\text{C} \text{ NMR: } \delta = 108.8 (tq, J_{\text{CF}} = 270, 37 \text{ Hz}), 118.0 (qt, J_{\text{CF}} = 288, 38 \text{ Hz}), 127.4, 127.6, 128.9, 129.1, 129.6, 130.7, 139.1, 148.2, 182.7 (t, J_{\text{CF}} = 27 \text{ Hz}). \)

\( ^{19}\text{F} \text{ NMR: } \delta = 47.4 (s, 2\text{F}), 81.3 (s, 3\text{F}). \)

HRMS (EI\textsuperscript{+}): Calcd for C\textsubscript{15}H\textsubscript{9}F\textsubscript{5}O \[M\]\textsuperscript{+} 300.0574, Found 300.0574.

**Wittig Reaction:** To a THF solution (33 mL) of Ph\textsubscript{3}PCH\textsubscript{3}I (2.92 g, 7.22 mmol) was added t-BuOK (0.810 g, 7.22 mmol) at 0 °C. The reaction mixture was stirred for 30 min at room temperature and then cooled to –78 °C. To the mixture was added slowly a THF solution (10 mL) of 2,2,3,3,3-pentafluoro-1-(biphenyl-4-yl)propan-1-one (1.90 g, 6.34 mmol) at –78 °C. The mixture was warmed to room temperature over 10 h, and then quenched with saturated aqueous NH\textsubscript{4}Cl at that temperature. The mixture was filtered through a pad of Celite (Et\textsubscript{2}O), and then filtrate was extracted three times with Et\textsubscript{2}O. The combined extracts were washed with brine and dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (hexane) to give 23e (1.53 g, 81%) as a white solid.

23e: IR (neat): \( \nu \approx 1333, 1205, 1165, 1140, 1086, 1018, 908, 739 \text{ cm}^{-1} \). \( ^1\text{H} \text{ NMR: } \delta = 5.84 (t, J = 1.3 \text{ Hz}, 1\text{H}), 6.03 (t, J = 1.6, 1\text{H}), 7.37 (tt, J = 7.3, 1.2 \text{ Hz}, 1\text{H}), 7.41–7.49 (m, 4\text{H}), 7.55–7.63 (m, 4\text{H}). \)

\( ^{13}\text{C} \text{ NMR: } \delta = 113.0 (tq, J_{\text{CF}} = 255, 38 \text{ Hz}), 119.1 (qt, J_{\text{CF}} = 288, 38 \text{ Hz}), 124.6 (t, J_{\text{CF}} = 8 \text{ Hz}), 127.0,
127.1, 127.7, 128.85, 128.90, 133.7, 138.2 (t, JCF = 22 Hz), 140.3, 141.7. £F NMR: δ 49.8 (s, 2F), 80.1 (s, 3F). Elemental analysis: Calcd for C$_{16}$H$_{11}$F$_5$: C, 64.43; H, 3.72. Found: C, 64.44; H, 3.68.

2,2-difluoro-1-methoxy-3-methylene-2,3-dihydro-1H-indene (23f)

\[
\begin{align*}
\text{Zinc-mediated difluoroallylation:} & \text{ To a suspension of zinc power (1.14 g, 17.5 mmol) in THF (15 mL) was added I$_2$ (1.27 g, 5.0 mmol) in several portions at 0 °C. After stirring for 30 min at room temperature, 2-bromobenzaldehyde (1.86 g, 10 mmol) was added to the mixture and then cooled to 0 °C. To the mixture was added slowly a THF solution (5 mL) of 3-bromo-3,3-difluoropropene (1.27 mL, 12.5 mmol) over 10 min at 0 °C. After stirring for 24 h at room temperature, the reaction mixture was quenched with aqueous HCl (1.0 M), and organic materials were extracted with EtOAc. The combined extracts were washed with brine and then dried over Na$_2$SO$_4$. After removal of the solvent, the residue was purified by silicagel column chromatography (hexane:EtOAc = 20:1~5:1) to give 2,2-difluoro-1-(4-bromophenyl)but-3-en-1-ol (2.35 g, 89%) as a colorless liquid.} \\
\text{Palladium-catalyzed Heck cyclization:} & \text{ To a DMF solution (2.0 mL) of 2,2-difluoro-1-(4-bromophenyl)but-3-en-1-ol (132 mg, 0.50 mmol) and palladium acetate (1.1 mg, 0.005 mmol) was added sodium acetate (205 mg, 2.5 mmol), and the mixture was heated to 110 °C. After stirring for 90 min at the same temperature, the reaction mixture was cooled to room temperature, and the reaction was quenched with phosphate buffer (pH 7). The organic materials were extracted three times with diethyl ether. The organic layers were combined and dried over Na$_2$SO$_4$. After removal of the solvent under the reduced pressure, the residue was purified by silica gel column chromatography (hexane:EtOAc = 10:1) to give 2,2-difluoro-3-methylene-2,3-dihydro-1H-inden-1-ol (77 mg, 85%) as a white solid.} \\
\text{Methylation of the alcohol:} & \text{ To a suspension of sodium hydride (55 wt%, 333 mg, 7.62 mmol) in THF (8 mL) was added slowly 2,2-difluoro-3-methylene-2,3-dihydro-1H-inden-1-ol (693 mg, 3.81 mmol) at 0 °C. After stirring for 30 min at 0 °C, iodomethane (0.475 mL, 7.62 mmol) was added to the reaction mixture at 0 °C. The mixture was stirred for 12 h at room temperature, and then quenched with cooled water, and organic materials were extracted with Et$_3$O. The combined extracts were washed with brine and then dried over Na$_2$SO$_4$. After removal of the solvent, the} \end{align*}
\]

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residue was purified by silicagel column chromatography (hexane:EtOAc = 20:1) and distillation under reduced pressure to give 2,2-difluoro-1-methoxy-3-methylene-2,3-dihydro-1H-indene (23f, 689 mg, 92%) as a colorless liquid.

23f: IR (neat): ν = 2935, 2835, 1223, 1093, 1059, 980, 912, 733 cm⁻¹. ¹H NMR: δ 3.68 (s, 3H), 4.76 (dd, J = 12.4, 4.9 Hz, 1H), 5.68 (dd, J = 3.0, 3.0 Hz, 1H), 5.82 (dd, J = 2.8, 2.8 Hz, 1H), 7.36–7.41 (m, 2H), 7.42–7.47 (m, 1H), 7.48–7.55 (m, 1H). ¹³C NMR: δ 58.8 (d, J = 2 Hz), 83.0 (dd, J = 31, 19 Hz), 109.7, 121.0, 123.8 (dd, J = 258, 252 Hz), 125.8, 129.8, 130.1, 135.9 (dd, J = 8, 8 Hz), 138.4, 142.4 (dd, J = 23, 23 Hz). ¹⁹F NMR: δ 49.7 (d, J = 251 Hz, 1F), 62.2 (dd, J = 251 Hz, J = 12 Hz, 1F). HRMS (EI+): Calcd for C₁₁H₁₀F₂O [M]⁺ 196.0700, Found 196.0697.

2,2-Difluoro-1-methylen-1,2-dihydronaphtho[2,1-b]furan (23g)

Palladium-catalyzed difluoroallylation: To a round-bottom flask containing sodium hydride (24 mg, 1.0 mmol) was placed a solution of 1-bromo-2-naphthol (223 mg, 1.0 mmol) in THF (2.0 mL). To the mixture were added palladium acetate (2.3 mg, 0.010 mmol), triphenylphosphine (11 mg, 0.041 mmol) and THF (6.7 mL). The mixture was cooled to 0 °C, and 3-bromo-3,3-difluoropropene (102 µL, 1.0 mmol) and THF (1.0 mL) were added to the mixture. After stirring for 30 min at 40 °C, phosphate buffer (pH 7) was added to the reaction mixture. The organic materials were extracted three times with dichloromethane. The organic layers were combined and dried over Na₂SO₄. The extracts were concentrated under the reduced pressure. The residue was purified by silica gel column chromatography (hexane) to give 1-Bromo-2-(1,1-difluoroprop-2-en-1-oxy)naphthalene (282 mg, 97%) as a white solid.

Palladium-catalyzed Heck cyclization: To a DMF solution (2.0 mL) of 1-Bromo-2-(1,1-difluoroprop-2-en-1-oxy)naphthalene (60 mg, 0.20 mmol) and palladium acetate (0.5 mg, 0.002 mmol) was added sodium acetate (82 mg, 1.0 mmol), and the mixture was heated to 110 °C. After stirring for 30 min at the same temperature, the reaction mixture was cooled to room temperature, and the reaction was quenched with phosphate buffer (pH 7). The organic materials were extracted three times with diethyl ether. The organic layers were combined and dried over
Na$_2$SO$_4$. After removal of the solvent under the reduced pressure, the residue was purified by silica gel column chromatography (hexane) to give 23g (42 mg, 96\%) as a white solid.

**23g**: IR (neat): $\nu = 3057, 1630, 1527, 1460, 1392, 1296, 1267, 1174, 1097, 978, 808, 742$ cm$^{-1}$. $^1$H NMR: $\delta$ 5.96 (td, $J_{HF} = 4.0$ Hz, $J = 1.7$ Hz, 1H), 6.26 (td, $J_{HF} = 4.0$ Hz, $J = 1.7$ Hz, 1H), 7.22 (d, $J = 8.6$ Hz, 1H), 7.44–7.47 (m, 1H), 7.60–7.63 (m, 1H), 7.85–7.87 (m, 2H), 8.09 (d, $J = 8.6$ Hz, 1H).

$^{13}$CNMR: $\delta$ 111.6, 113.3, 113.6 (t, $J_{CF} = 2$ Hz), 122.3, 124.8, 127.8 (t, $J_{CF} = 261$Hz), 128.6, 128.9, 129.7, 130.6, 133.2, 138.5 (t, $J_{CF} = 25$ Hz), 156.3. $^{19}$F NMR: $\delta$ 94.0 (s, 2F). HRMS (EI+) Calcd for C$_{13}$H$_8$F$_2$O [M]$^+$: 218.0543, Found 218.0534.

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4.7.5. Nickel-Catalyzed Defluorinative Coupling Reaction of 2-Trifluoromethyl-1-alkenes with Alkynes: Synthesis of 1,1-Difluoro-1,4-dienes

\((E)-(1,1\text{-Difluoro-4-propylocta-1,4-dien-2-yl})\text{benzene (21ea): Typical Procedure A}\)

![Diagram](image)

To a toluene solution (3.2 mL) of Ni\((\text{cod})_2\) (8.9 mg, 0.032 mmol) and PCy\(_3\) (15 mg, 0.055 mmol) were added \(\alpha\)-trifluoromethylstyrene (14e, 110 mg, 0.64 mmol) and Et\(_3\)SiH (149 mg, 1.3 mmol), 4-octyne (15a, 79 mg, 0.72 mmol) at room temperature. After stirring for 3 hours at 50 °C, the reaction mixture was filtered through a pad of silica gel (EtOAc). The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 1,1-difluoro-1,4-diene 21ea (157 mg, 93%) as a colorless liquid.

\[\text{21ea}: \text{IR (neat)}: \nu = 2958, 2931, 2871, 1724, 1446, 1234, 1124, 1005, 768, 696 \text{ cm}^{-1}. \text{H NMR: } \delta 0.76 \text{ (t, } J = 7.4 \text{ Hz, 3H), 0.88 \text{ (t, } J = 7.3 \text{ Hz, 3H), 1.24 \text{ (qt, } J = 7.3, 7.3 \text{ Hz, 2H), 1.40 \text{ (qt, } J = 7.4, 7.4 \text{ Hz, 2H), 1.87–2.00 \text{ (m, 4H), 3.05 \text{ (s, 2H), 5.13 \text{ (t, } J = 7.1 \text{ Hz, 1H), 7.19–7.26 \text{ (m, 1H), 7.27–7.35 \text{ (m, 4H). 13C NMR: } \delta 13.6, 14.0, 21.3, 22.9, 29.8, 32.0, 35.1, 90.7 \text{ (dd, } J_{CF} = 17, 17 \text{ Hz), 127.0, 127.4, 128.1, 128.2 \text{ (dd, } J_{CF} = 3, 3 \text{ Hz), 134.1, 135.0, 154.1 \text{ (dd, } J_{CF} = 290, 290 \text{ Hz). 19F NMR: } \delta 72.0 \text{ (s, 2F). Elemental analysis: Caled for } C_{17}H_{22}F_2: \text{ C, 77.24; H, 8.39. Found: C, 77.30; H, 8.46.}\]

\((E)-1-(1,1\text{-Difluoro-4-propylocta-1,4-dien-2-yl})\text{-2-methoxybenzene (21ha)}\)

![Diagram](image)

Compound 21ha was synthesized according to the typical procedure A using 1-Methoxy-2-(3,3,3-trifluoroprop-1-en-2-yl)benzene (14h, 99 mg, 0.49 mmol), 4-octyne (15a, 59 mg, 0.54 mmol), Et\(_3\)SiH (113 mg, 0.97 mmol), Ni\((\text{cod})_2\) (6.7 mg, 0.024 mmol), PCy\(_3\) (14 mg, 0.051 mmol), and Toluene (2.4 mL) at 50 °C for 3 h. Purification by silica gel column chromatography (hexane/EtOAc = 50:1) gave 21ha (119 mg, 84%) as a colorless liquid.

\[\text{21ha}: \text{IR (neat): } \nu = 2958, 2931, 2871, 1739, 1495, 1458, 1244, 1232, 771, 750 \text{ cm}^{-1}. \text{H NMR: } \delta 0.71 \text{ (t, } J = 7.4 \text{ Hz, 3H), 0.85 \text{ (t, } J = 7.4 \text{ Hz, 3H), 1.17 \text{ (qt, } J = 7.4, 7.4 \text{ Hz, 2H), 1.36 \text{ (qt, } J = 7.4, 7.3 \text{ Hz, 2H), 1.85 \text{ (dt, } J = 7.3, 7.3 \text{ Hz, 2H), 1.92 \text{ (t, } J = 7.4 \text{ Hz, 2H), 3.01 \text{ (s, 2H), 3.80 \text{ (s, 3H), 5.03 \text{ (t, } J = 7.3 \text{ Hz, 2H).}\]

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= 7.3 Hz, 1H), 6.83–6.92 (m, 2H), 7.07 (dd, J = 7.5, 1.7 Hz, 1H), 7.23 (ddd, J = 8.3, 7.5, 1.7 Hz, 1H). 13C NMR: δ 13.5, 14.0, 21.2, 22.9, 29.7, 31.6, 35.2, 55.3, 88.0 (dd, JCF = 23, 16 Hz), 110.8, 120.2, 122.7 (dd, JCF = 4, 2 Hz), 127.4, 128.8, 131.1, 135.2 (dd, JCF = 2, 2 Hz), 153.4 (dd, JCF = 288, 288 Hz), 157.1. 19F NMR: δ 69.0 (d, JFF = 42 Hz, 1F), 73.4 (d, JFF = 42 Hz, 1F). Elemental analysis: Calcd for C18H24F2O: C, 73.44; H, 8.22. Found: C, 73.41; H, 8.12.

(E)-1-(1,1-Difluoro-4-propylocta-1,4-dien-2-yl)-4-methoxybenzene (21fa)

Compound 21fa was synthesized according to the typical procedure A using 1-Methoxy-4-(3,3,3-trifluoroprop-1-en-2-yl)benzene (14f, 105 mg, 0.52 mmol), 4-octyne (15a, 62 mg, 0.56 mmol), Et3SiH (118 mg, 1.0 mmol), Ni(cod)2 (7.0 mg, 0.025 mmol), PCy3 (14 mg, 0.051 mmol), and Toluene (2.5 mL) at 50 °C for 3 h. Purification by silica gel column chromatography (hexane/EtOAc = 40:1) gave 21fa (122 mg, 80%) as a colorless liquid.

21fa: IR (neat): ν̇ = 2960, 2935, 2873, 1614, 1591, 1321, 1163, 1111, 1066, 835 cm⁻¹. 1H NMR: δ 0.78 (t, J = 7.4 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H), 1.26 (qt, J = 7.4, 7.4 Hz, 2H), 1.34–1.45 (m, 2H), 1.88–2.00 (m, 4H), 3.01 (s, 2H), 3.80 (s, 3H), 5.13 (t, J = 7.2 Hz, 1H), 6.81–6.88 (m, 2H), 7.19–7.28 (m, 2H). 13C NMR: δ 13.6, 14.1, 21.3, 22.9, 29.8, 32.0, 35.2, 55.2, 90.1 (dd, JCF = 20, 13 Hz), 113.6, 126.3 (dd, JCF = 6, 6 Hz), 127.3, 129.3 (dd, JCF = 4, 4 Hz), 135.1 (dd, JCF = 2, 2 Hz), 154.0 (dd, JCF = 291, 287 Hz), 158.5. 19F NMR: δ 71.0 (d, JFF = 44 Hz, 1F), 71.1 (d, JFF = 44 Hz, 1F). Elemental analysis: Calcd for C18H24F2O: C, 73.44; H, 8.22. Found: C, 73.55; H, 8.24.

(E)-1-Chloro-4-(1,1-difluoro-4-propylocta-1,4-dien-2-yl)benzene (21ia)

Compound 21ia was synthesized according to the typical procedure A using 1-Chloro-4-(3,3,3-trifluoroprop-1-en-2-yl)benzene (14i, 107 mg, 0.52 mmol), 4-octyne (15a, 59 mg, 0.54 mmol), Et3SiH (113 mg, 0.97 mmol), Ni(cod)2 (6.7 mg, 0.024 mmol), PCy3 (14 mg, 0.049 mmol), and Toluene (2.4 mL) at 50 °C for 2 h. Purification by silica gel column chromatography (hexane) gave 21ia (141 mg, 91%) as a colorless liquid.
**21ia:** IR (neat): $\nu = 2958, 2931, 2871, 1722, 1493, 1238, 1092, 999, 827, 771 \text{ cm}^{-1}$. $^1H$ NMR: $\delta$ 0.77 (t, $J = 7.4$ Hz, 3H), 0.88 (t, $J = 7.4$ Hz, 3H), 1.25 (qt, $J = 7.4, 7.4$ Hz, 2H), 1.39 (qt, $J = 7.4, 7.4$ Hz, 2H), 1.87–1.98 (m, 4H), 3.02 (s, 2H), 5.11 (t, $J = 7.3$ Hz, 1H), 7.23 (d, $J = 8.6$ Hz, 2H), 7.28 (d, $J = 8.6$ Hz, 2H). $^{13}C$ NMR: $\delta$ 13.6, 14.0, 21.3, 22.9, 29.7, 32.0, 35.0, 89.9 (dd, $J_{CF} = 21, 14$ Hz), 127.7, 128.3, 129.6 (dd, $J_{CF} = 3, 3$ Hz), 132.5, 132.8, 134.7, 154.1 (dd, $J_{CF} = 292, 289$ Hz). $^{19}F$ NMR: $\delta$ 71.1 (d, $J_{FF} = 44$ Hz, 1F), 71.2 (d, $J_{FF} = 44$ Hz, 1F). Elemental analysis: Calcd for C$_{17}$H$_{21}$ClF$_2$: C, 68.33; H, 7.08. Found: C, 68.46; H, 7.16.

**Compound 21aa** was synthesized according to the typical procedure A using 1-(4-(3,3,3-Trifluoroprop-1-en-2-yl)phenyl)ethanone (14a, 110 mg, 0.51 mmol), 4-octyne (15a, 63 mg, 0.57 mmol), Et$_3$SiH (121 mg, 1.0 mmol), Ni(cod)$_2$ (7.2 mg, 0.026 mmol), PCy$_3$ (14 mg, 0.051 mmol), and Toluene (2.6 mL) at 50 °C for 2 h. Purification by silica gel column chromatography (hexane/EtOAc = 20:1) gave 21aa (149 mg, 95%) as a colorless liquid.

**21aa:** IR (neat): $\nu = 2958, 2931, 2871, 1716, 1684, 1606, 1267, 1238, 1217, 771 \text{ cm}^{-1}$. $^1H$ NMR: $\delta$ 0.76 (t, $J = 7.4$ Hz, 3H), 0.89 (t, $J = 7.3$ Hz, 1H), 1.24 (qt, $J = 7.3, 7.3$ Hz, 2H), 1.40 (qt, $J = 7.4, 7.4$ Hz, 2H), 1.86–2.02 (m, 4H), 2.59 (s, 3H), 3.09 (s, 2H), 5.13 (t, $J = 7.2$ Hz, 1H), 7.42 (d, $J = 8.5$ Hz, 2H), 7.91 (d, $J = 8.5$ Hz, 2H). $^{13}C$ NMR: $\delta$ 13.6, 14.0, 21.3, 22.8, 26.5, 29.7, 32.0, 34.7, 90.4 (dd, $J_{CF} = 21, 12$ Hz), 127.6, 128.2, 128.3 (dd, $J_{CF} = 4, 4$ Hz), 134.6, 135.6, 139.1 (dd, $J_{CF} = 4, 4$ Hz), 154.4 (dd, $J_{CF} = 294, 290$ Hz), 197.5. $^{19}F$ NMR: $\delta$ 74.6 (d, $J_{FF} = 35$ Hz, 1F), 74.7 (d, $J_{FF} = 35$ Hz, 1F). Elemental analysis: Calcd for C$_{19}$H$_{24}$F$_2$O: C, 74.48; H, 7.90. Found: C, 74.47; H, 7.86.

**Compound 21da** was synthesized according to the typical procedure A using ethyl 4-(3,3,3-Trifluoroprop-1-en-2-yl)benzoate (1d, 143 mg, 0.58 mmol), 4-octyne (15a, 71 mg, 0.64 mmol), Et$_3$SiH (135 mg, 1.2 mmol), Ni(cod)$_2$ (8.0 mg, 0.029 mmol), PCy$_3$ (16 mg, 0.058 mmol), and Toluene (2.9 mL) at 50 °C for 4 h. Purification by silica gel column chromatography...
(hexane/EtOAc = 10:1) gave 21da (172 mg, 88%) as a colorless liquid.

**21da:** IR (neat): ν ~ 2960, 2931, 2871, 1716, 1610, 1273, 1238, 1107, 773 cm⁻¹. ¹H NMR: δ 0.76 (t, J = 7.4 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H), 1.24 (qt, J = 7.4, 7.4 Hz, 2H), 1.34–1.45 (m, 5H), 1.85–2.05 (m, 4H), 3.08 (s, 2H), 4.37 (q, J = 7.1 Hz, 2H), 5.12 (t, J = 7.6 Hz, 1H), 7.38 (d, J = 8.4 Hz, 2H), 7.99 (d, J = 8.4 Hz, 2H). ¹³C NMR: δ 13.6, 14.0, 14.3, 21.3, 22.9, 29.7, 32.0, 34.8, 60.9, 90.5 (dd, J_CF = 18, 16 Hz), 127.6, 128.1 (dd, J_CF = 3, 3 Hz), 129.0, 129.4, 134.6 (dd, J_CF = 2, 2 Hz), 138.8, 154.4 (dd, J_CF = 292, 292 Hz), 166.3. ¹⁹F NMR: δ 74.4 (s, 2F). HRMS (EI⁺): Calcd for C₂₀H₂₆F₂O₂ [M]+ 336.1901, Found 336.1898.

**Z-(5,5-Difluoropenta-1,4-diene-1,2-diyl)di benzene (21jb)**

![Chemical reaction diagram]

To a toluene solution (2.0 mL) of Ni(cod)₂ (10 mg, 0.037 mmol) and SIMes·HCl (13 mg, 0.037 mmol), t-BuOK (4.2 mg, 0.037 mmol) were added α-trifluoromethylstyrene (14j, 1.0 atm) and Et₃SiH (86 mg, 0.74 mmol), diphenylacetylene (15b, 66 mg, 0.37 mmol) at room temperature. After stirring for 10 hours at 80 °C, the reaction mixture was filtered through a pad of silica gel (EtOAc). The filtrate was concentrated under reduced pressure, and the residue was purified by preparative thin-layer chromatography (hexane/EtOAc = 5:1) to give 1,1-difluoro-1,4-diene 21jb (73 mg, 77%) as a colorless liquid.

**21jb:** IR (neat): ν ~ 3023, 1741, 1286, 1236, 1173, 912, 696 cm⁻¹. ¹H NMR: δ 3.16 (ddt, J = 7.9, 1.6, 1.6 Hz, 2H), 4.27 (ddt, J_HF = 25.0 Hz, J_HH = 7.9 Hz, J_HF = 2.3 Hz, 1H), 6.47 (s, 1H), 6.93 (dd, J = 7.4, 1.8 Hz, 2H), 7.04–7.18 (m, 4H), 7.22–7.35 (m, 4H). ¹³C NMR: δ 33.0 (d, J_CF = 5 Hz), 76.0 (dd, J_CF = 33, 20 Hz), 126.5, 126.9, 127.2, 127.9, 128.5, 128.6, 129.0, 136.9, 140.1, 140.4, 156.6 (dd, J_CF = 288, 288 Hz). ¹⁹F NMR: 71.0 (dd, J_FF = 44 Hz, J_FH = 24 Hz, 1F), 74.0 (d, J_FF = 44 Hz, 1F). HRMS (EI⁺): Calcd for C₁₇H₁₄F₂ [M]+ 256.1064, Found 256.1058.

**E-(3-(Difluoromethylene)-5-propynon-5-en-1-yl)benzene (21ka)**

![Chemical reaction diagram]
To a toluene solution (2.5 mL) of Ni(cod)₂ (14 mg, 0.051 mmol) and PCy₃ (28 mg, 0.10 mmol), ZrF₄ (8.6 mg, 0.051 mmol) were added [3-(trifluoromethyl)-3-buten-1-y1]benzene (14k, 103 mg, 0.51 mmol) and Et₃SiH (116 mg, 1.0 mmol), 4-octyne (15a, 64 mg, 0.58 mmol) at room temperature. After stirring for 15 hours at 80 °C, the reaction mixture was filtered through a pad of silica gel (EtOAc). The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 1,1-difluoro-1,4-diene 21ka (128 mg, 86%) as a colorless liquid.

21ka: IR (neat): ν ~ 2958, 2929, 2871, 1745, 1454, 1221, 1059, 737, 696 cm⁻¹. ¹H NMR: δ 0.89 (t, J = 7.5 Hz, 3H), 0.90 (t, J = 7.4 Hz, 3H), 1.32–1.43 (m, 4H), 1.92 (t, J = 7.7 Hz, 2H), 2.00 (dt, J = 7.3, 7.3 Hz, 2H), 2.19 (tt, J = 8.1, 2.1 Hz, 2H), 2.59–2.70 (m, 4H), 5.20 (t, J = 7.3 Hz, 1H), 7.11–7.20 (m, 3H), 7.23–7.31 (m, 2H). ¹³C NMR: δ 13.9, 14.1, 21.4, 23.1, 27.7, 29.9, 31.5, 33.8, 33.9, 87.2 (dd, J_CF = 17, 17 Hz), 126.0, 127.8, 128.34, 128.34, 135.4, 141.5, 153.8 (dd, J_CF = 285, 285 Hz). ¹⁹F NMR: δ 66.8 (d, J_FF = 54 Hz, 1F), 68.1 (d, J_FF = 54 Hz, 1F). HRMS (EI⁺): Calcd for C₁₉H₂₆F₂ [M]⁺ 292.2003, Found 292.2007.

(E)-(1,1-Difluoro-4-propyl)octa-1,4-dien-2-y1)dimethyl(phenyl)ilane (21la)

To a toluene solution (2.7 mL) of Ni(cod)₂ (15 mg, 0.054 mmol) and PCy₃ (30 mg, 0.11 mmol), ZrF₄ (9.0 mg, 0.054 mmol) were added dimethylphenyl[1-(trifluoromethyl)ethenyl]silane (14l, 125 mg, 0.54 mmol) and Et₃SiH (116 mg, 1.1 mmol), 4-octyne (15a, 65 mg, 0.59 mmol) at room temperature. After stirring for 2 hours at room temperature, the reaction mixture was quenched with saturated aqueous NaHCO₃. Organic materials were extracted three times with Et₂O. The combined extracts were washed with brine and dried over anhydrous Na₂SO₄. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (hexane) to give 1,1-difluoro-1,4-diene 21la (139 mg, 79%) as a colorless liquid.

21la: IR (neat): ν ~ 2958, 2929, 2871, 1685, 1213, 1111, 812, 777, 698 cm⁻¹. ¹H NMR: δ 0.40 (s, 6H), 0.84 (t, J = 7.3 Hz, 3H), 0.87 (t, J = 7.4 Hz, 3H), 1.22–1.36 (m, 4H), 1.85 (t, J = 7.8 Hz, 2H), 1.92 (td, J = 7.3, 7.2 Hz, 2H), 2.64 (s, 2H), 5.00 (t, J = 7.1 Hz, 1H), 7.30–7.39 (m, 3H), 7.45–7.54 (m, 2H). ¹³C NMR: δ –2.4, 13.9, 14.1, 21.4, 23.0, 30.0, 32.5, 32.6 (dd, J_CF = 6, 4 Hz), 79.2 (dd, J_CF = 27, 3 Hz), 126.0, 127.7, 129.1, 133.8, 136.3 (d, J_CF = 2 Hz), 137.4, 156.7 (dd, J_CF = 308, 284 Hz). ¹⁹F NMR: δ 87.5 (d, J_FF = 34 Hz, 1F), 89.5 (d, J_FF = 34 Hz, 1F). HRMS (EI⁺): Calcd for C₁₀H₂₆F₂Si ([M]⁺–PhH) 244.1459, Found 244.1453.
To a toluene solution (3.0 mL) of Ni(cod)$_2$ (8.2 mg, 0.030 mmol) and SIMes·HCl (11 mg, 0.030 mmol), t-BuOK (3.4 mg, 0.030 mmol) were added α-trifluoromethylstyrene (14e, 104 mg, 0.60 mmol) and Et$_3$SiH (139 mg, 1.2 mmol), diphenylacetylene (15b, 117 mg, 0.66 mmol) at room temperature. After stirring for 8 hours at room temperature, the reaction mixture was filtered through a pad of silica gel (EtOAc). The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 1,1-difluoro-1,4-diene 21eb (146 mg, 73%) as a colorless liquid.

21eb: IR (neat): $\nu = 3060, 3024, 1732, 1240, 912, 742, 696$ cm$^{-1}$. $^1$H NMR: $\delta 3.54$–$3.58$ (m, 2H), 6.41 (s, 1H), 6.84 (dd, $J = 7.7, 2.0$ Hz, 2H), 6.98–7.12 (m, 5H), 7.20–7.38 (m, 8H). $^{13}$C NMR: $\delta 38.5, 90.0$ (dd, $J_{CF} = 21, 14$ Hz), 126.4, 127.18, 127.21, 127.8, 127.9, 128.27 (dd, $J_{CF} = 3, 3$ Hz), 128.30, 128.49, 128.49, 129.0, 133.6 (dd, $J_{CF} = 4, 4$ Hz), 136.8, 138.8, 140.4, 154.3 (dd, $J_{CF} = 293, 289$ Hz). $^{19}$F NMR: $\delta 72.6$ (d, $J_{FF} = 38$ Hz, 1F), 73.5 (d, $J_{FF} = 38$ Hz, 1F). HRMS (EI+): Calcd for C$_{23}$H$_{18}$F$_2$ [M]$^+$ 332.1377, Found: 332.1366.

$^{(E)}$-(5,5-Difluoro-2-propylpenta-1,4-diene-1,4-diyldibenzene (21ef)

Compound 21ef was synthesized according to the typical procedure B using α-trifluoromethylstyrene (15e, 99 mg, 0.57 mmol), 1-phenyl-1-pentyne (15f, 89 mg, 0.62 mmol), Et$_3$SiH (130 mg, 1.1 mmol), Ni(cod)$_2$ (7.7 mg, 0.028 mmol), SIMes·HCl (9.6 mg, 0.028 mmol), t-BuOK (3.1 mg, 0.028 mmol), and Toluene (2.8 mL) at room temperature for 3 h. Purification by silica gel column chromatography (hexane) gave 21ef (169 mg, 99%) as a colorless liquid.

21ef: IR (neat): $\nu = 2960, 2871, 1724, 1495, 1446, 1236, 993, 771, 696$ cm$^{-1}$. $^1$H NMR: $\delta 0.89$ (t, $J = 7.4$ Hz, 3H), 1.47–1.57 (m, 2H), 2.12–2.19 (m, 2H), 3.24 (d, $J = 1.7$ Hz, 2H), 6.26 (s, 1H), 7.08 (d, $J = 7.2$ Hz, 2H), 7.16 (t, $J = 7.4$ Hz, 1H), 7.21–7.38 (m, 7H). $^{13}$C NMR: $\delta 14.1, 21.4, 32.8, 35.5, 90.5$ (dd, $J_{CF} = 17, 17$ Hz), 126.1, 127.0, 127.2, 128.0, 128.26 (dd, $J_{CF} = 3, 3$ Hz), 128.28, 128.5, 133.8, 138.1, 139.1 (dd, $J_{CF} = 4, 4$ Hz), 154.3 (dd, $J_{CF} = 290$ Hz). $^{19}$F NMR: $\delta 71.6$ (s, 2F). Elemental analysis: Calcd for C$_{20}$H$_{20}$F$_2$: C, 80.51; H, 6.76. Found: C, 80.35; H, 6.76.
(E)-1-(5,5-Difluoro-4-phenyl-2-propylpenta-1,4-dien-1-yl)-4-methoxybenzene (21ee)

Compound 21ee was synthesized according to the typical procedure B using α-trifluoromethylstyrene (14e, 110 mg, 0.64 mmol), 1-methoxy-4-(pent-1-ynyl)benzene (15e, 123 mg, 0.70 mmol), Et₃SiH (149 mg, 1.3 mmol), Ni(cod)₂ (8.8 mg, 0.032 mmol), SIMes·HCl (11 mg, 0.032 mmol), t-BuOK (3.7 mg, 0.033 mmol), and Toluene (3.2 mL) at room temperature for 3 h. Purification by silica gel column chromatography (hexane/EtOAc = 30:1) gave 21ee (209 mg, 99%) as a colorless liquid.

21ee: IR (neat): ν = 2958, 2871, 1726, 1608, 1510, 1246, 1176, 1038, 771 cm⁻¹. ¹H NMR: δ 0.90 (t, J = 7.3 Hz, 3H), 1.46–1.57 (m, 2H), 2.15 (t, J = 8.0 Hz, 2H), 3.20–3.34 (m, 2H), 3.79 (s, 3H), 6.19 (s, 1H), 6.82 (d, J = 8.6 Hz, 2H), 7.02 (d, J = 8.6 Hz, 2H), 7.20–7.28 (m, 1H), 7.29–7.38 (m, 4H). ¹³C NMR: δ 14.2, 21.4, 32.8, 35.5, 55.2, 90.5 (dd, J_CF = 18, 16 Hz), 113.5, 126.4, 127.2, 128.25, 128.25, 129.6, 130.6, 133.9, 137.8, 154.2 (dd, J_CF = 290, 290 Hz), 157.9. ¹⁹F NMR: δ 72.6 (s, 2F).


(E)-Ethyl 4-(5,5-difluoro-4-phenyl-2-propylpenta-1,4-dien-1-yl)benzoate (21eg)

Compound 21eg was synthesized according to the typical procedure B using α-trifluoromethylstyrene (14e, 92 mg, 0.53 mmol), ethyl 4-(pent-1-ynyl)benzoate (15g, 126 mg, 0.58 mmol), Et₃SiH (124 mg, 1.1 mmol), Ni(cod)₂ (7.3 mg, 0.027 mmol), SIMes·HCl (11 mg, 0.027 mmol), t-BuOK (3.0 mg, 0.027 mmol), and Toluene (2.6 mL) at room temperature for 3 h. Purification by preparative thin-layer chromatography (hexane/EtOAc = 5:1) gave 21eg (128 mg, 65%) as a pale yellow liquid.

21eg: IR (neat): ν = 2960, 2871, 1714, 1606, 1271, 1236, 1101, 766, 696 cm⁻¹. ¹H NMR: δ 0.89 (t, J = 7.3 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H), 1.45–1.59 (m, 2H), 2.16 (t, J = 8.0 Hz, 2H), 3.24–3.28 (m, 2H), 4.36 (q, J = 7.1 Hz, 2H), 6.28 (s, 1H), 7.14 (d, J = 8.3 Hz, 2H), 7.21–7.30 (m, 1H), 7.31–7.38 (m, 4H), 7.95 (d, J = 8.3 Hz, 2H). ¹³C NMR: δ 14.1, 14.3, 21.4, 33.0, 35.5, 60.8, 90.2 (dd, J_CF = 18, 16 Hz), 126.2, 127.3, 128.1, 128.2 (dd, J_CF = 3, 3 Hz), 128.3, 128.4, 129.3, 133.6, 141.3, 142.7, 154.3 (dd, J_CF = 291 291 Hz), 166.5. ¹⁹F NMR: δ 73.0 (d, J_FF = 39 Hz, 1F), 73.1 (d, J_FF = 39 Hz,
(E)-(5,5-Difluoro-2-methylpenta-1,4-diene-1,4-diyl)dibenzene (21ed)

Compound 21ed was synthesized according to the typical procedure A using α-trifluoromethylstyrene (14e, 108 mg, 0.63 mmol), 1-phenyl-propyne (15d, 84 mg, 0.72 mmol), Et₃SiH (149 mg, 1.3 mmol), Ni(cod)₂ (8.8 mg, 0.032 mmol), PCy₃ (18 mg, 0.064 mmol), and Toluene (3.2 mL) at room temperature for 3 h. Purification by silica gel column chromatography (hexane) gave 21ed (155 mg, 91%) as a colorless liquid.

21ed: IR (neat): ν ~ = 3024, 2912, 1722, 1446, 1236, 978, 743, 694 cm⁻¹. ¹H NMR: δ 1.83 (s, 3H), 3.24 (s, 2H), 6.28 (s, 1H), 7.10–7.20 (m, 3H), 7.21–7.39 (m, 7H). ¹³C NMR: δ 17.5, 38.5, 90.4 (dd, J₉CF = 20, 14 Hz), 126.1, 126.9, 127.2, 128.0, 128.2 (dd, J₉CF = 3, 3 Hz), 128.3, 128.8, 133.7, 134.9 (dd, J₉CF = 2, 2 Hz), 138.0, 154.3 (dd, J₉CF = 292, 289 Hz). ¹⁹F NMR: δ 72.6 (d, J₉FF = 40 Hz, 1F), 72.7 (d, J₉FF = 40 Hz, 1F). HRMS (EI+): Calcd for C₁₈H₁₆F₂ [M⁺] 270.1220, Found: 270.1210.

(Z)-(1,1-Difluoro-4-isopropylhexa-1,4-dien-2-yl)benzene (21ec)

Compound 21ec was synthesized according to the typical procedure A using α-trifluoromethylstyrene (14e, 91 mg, 0.53 mmol), 4-methyl-2-pentyne (15c, 54 mg, 0.66 mmol), Et₃SiH (140 mg, 1.2 mmol), Ni(cod)₂ (16.6 mg, 0.060 mmol), PCy₃ (34 mg, 0.12 mmol), and Toluene (3.0 mL) at room temperature for 4 h. Purification by silica gel column chromatography (hexane) gave 21ec (110 mg, 88%) as a colorless liquid.

21ec: IR (neat): ν ~ = 2962, 2912, 1722, 1446, 1236, 1126, 1005, 768, 694 cm⁻¹. ¹H NMR: δ 1.01 (d, J = 7.0 Hz, 6H), 1.56 (d, J = 6.9 Hz, 3H), 2.90 (sep, J = 7.0 Hz, 1H), 3.00 (s, 2H), 5.14 (q, J = 6.9 Hz, 1H), 7.19–7.25 (m, 1H), 7.28–7.35 (m, 4H). ¹³C NMR: δ 12.7, 20.5, 28.3, 29.3, 90.3 (dd, J₉CF = 21, 12 Hz), 118.1, 126.9, 127.9 (dd, J₉CF = 3, 3 Hz), 128.2, 134.4 (dd, J₉CF = 3, 3 Hz), 140.2, 154.1 (dd, J₉CF = 293, 288 Hz). ¹⁹F NMR: δ 72.7 (d, J₉FF = 40 Hz, 1F), 72.9 (d, J₉FF = 40 Hz, 1F). HRMS (EI+): Calcd for C₁₃H₁₈F₂ [M⁺] 236.1377, Found: 236.1377.
4.7.5. Nickel-Catalyzed Defluorinative Coupling Reaction of 3,3-Difluoropropenes with Alkynes: Synthesis of 1-Fluoro-1,4-dienes

Typical Procedure for Synthesis of 1-Fluoro-1,4-dienes 24 and 24’

4-((2Z,5E)-1,1,1,2-Tetrafluoro-5-methylhepta-2,5-dien-3-yl)-1,1'-biphenyl (24’eh)

To a toluene solution (3.1 mL) of Ni(cod)₂ (8.7 mg, 0.032 mmol) and PCy₃ (18 mg, 0.063 mmol) were added 4-(3,3,4,4,4-Pentafluorobut-1-en-2-yl)biphenyl (23e, 190 mg, 0.64 mmol), 2-butyne (15h, 69 mg, 1.3 mmol), Et₃SiH (149 mg, 1.3 mmol) at room temperature. After stirring for 3 hours at 50 °C, the reaction mixture was filtered through a pad of silica gel (EtOAc). The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 24’eh (207 mg, 93%) as a white solid.

24’eh: IR (neat): ν ~ 2922, 1333, 1304, 1184, 1132, 1080, 912, 737, 696 cm⁻¹. ¹H NMR: δ 1.51 (d, J = 6.7 Hz, 3H), 1.57 (s, 3H), 3.25 (s, 2H), 5.21 (q, J = 6.7 Hz), 7.31–7.40 (m, 3H), 7.45 (dd, J = 7.9, 7.4 Hz, 2H), 7.59 (d, J = 7.9 Hz, 2H), 7.61 (d, J = 7.2 Hz, 2H). ¹³C NMR: δ 13.4, 15.7, 39.9, 119.9 (qd, J_CF = 274, 43 Hz), 122.1, 125.4–125.7 (m), 126.8, 127.0, 127.6, 128.7 (d, J_CF = 3 Hz), 128.8, 130.7 (d, J_CF = 2 Hz), 133.6, 140.4, 141.1, 142.5 (dq, J_CF = 254, 38 Hz). ¹⁹F NMR: δ 35.0 (q, J_FF = 8 Hz, 1F), 98.2 (d, J_FF = 8 Hz, 3F). Elemental analysis: Calcd for C₂₀H₁₈F₄: C, 71.84; H, 5.43. Found: C, 71.69; H, 5.69.

The stereochemistry of 24’eh was determined by X-ray diffraction analysis.

Figure S1. X-Ray Crystal Structure of 24’eh
Table S1. Crystal Data Collection Parameters for 24’eh

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((2Z,5E)-2-Fluoro-1-methoxy-5-propynona-2,5-dien-1-yl)benzene (24ba)

Compound 24ba was synthesized according to the typical procedure using (2,2-difluoro-1-methoxybut-3-en-1-yl)benzene (23b, 100 mg, 0.51 mmol), 4-octyne (15a, 62 mg,
0.56 mmol), Et₃SiH (60 mg, 0.51 mmol), Ni(cod)₂ (14 mg, 0.052 mmol), PCy₃ (28 mg, 0.10 mmol), and Toluene (2.8 mL) at 70 °C for 24 h. Purification by silica gel column chromatography (hexane ~ hexane:EtOAc = 20:1) gave 24ba (194 mg, 86%) as a colorless liquid.

24ba: ¹H NMR: δ 0.86 (t, J = 7.4 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H), 1.27–1.41 (m, 4H), 1.92–2.01 (m, 4H), 2.70–2.88 (m, 2H), 3.41 (s, 3H), 4.67 (d, J = 16.0 Hz, 1H), 4.92 (dt, J = 36.4 Hz, 7.7 Hz), 5.16 (t, J = 7.2 Hz, 1H), 7.28–7.44 (m, 5H).

((1Z,4Z)-5,6,6,7,8,8-Octafluoroocta-1,4-diene-1,2-diyl)dibenzene (24cb)

Compound 24cb was synthesized according to the typical procedure using 3,3,4,4,5,5,6,6,6-nonafluoro-1-hexene (23c, 136 mg, 0.55 mmol), diphenylacetylene (15b, 99 mg, 0.55 mmol), Et₃SiH (149 mg, 0.55 mmol), Ni(cod)₂ (15 mg, 0.055 mmol), PCy₃ (31 mg, 0.11 mmol), and Toluene (2.8 mL) at 80 °C for 7 h. Purification by silica gel column chromatography (hexane) gave 24cb (194 mg, 86%) as a colorless liquid.

24cb: IR (neat): ν ~ = 1230, 1186, 1120, 912, 742 cm⁻¹. ¹H NMR: δ 3.43 (d, J = 7.8 Hz, 2H), 5.68 (dt, J_HF = 33.1, J_HH = 7.8 Hz, 1H), 6.49 (s, 1H), 6.90–6.97 (m, 2H), 7.06–7.19 (m, 5H), 7.24–7.35 (m, 3H). ¹³C NMR: δ 34.2 (d, J_CF = 3 Hz), 106.5–112.7 (m, 2C), 113.5 (dt, J_CF = 9, 4 Hz), 117.7 (qt, J_CF = 288, 34 Hz), 126.8, 127.6, 128.0, 128.3, 128.4, 128.8, 129.1, 136.6, 138.2, 139.9, 146.2 (dt, J_CF = 260, 29 Hz). ¹⁹F NMR: δ 31.5–31.9 (m, 1F), 35.5 (d, J_FF = 8 Hz, 2F), 44.3–44.7 (m, 2F), 82.2 (t, J_FF = 9 Hz, 3F). HRMS (EI+): Caled for C₂₀H₁₄F₈ [M⁺] 406.0968, Found: 406.0975.

((1Z,4E)-1-Fluoro-4-methylhexa-1,4-diene-1,2-diyl)dibenzene (24’dh)

Compound 24’dh was synthesized according to the typical procedure using (1,1-difluoroprop-2-ene-1,2-diyl)dibenzene (23d, 82 mg, 0.36 mmol), 2-butyne (15h, 38 mg, 0.70 mmol), Et₃SiH (82 mg, 0.70 mmol), Ni(cod)₂ (10 mg, 0.035 mmol), PCy₃ (19 mg, 0.069 mmol), and Toluene (1.8 mL) at 50 °C for 5 h. Purification by silica gel column chromatography (hexane) gave 24’dh (93 mg, 99%) as a white solid.

24’dh: IR (neat): ν ~ = 3059, 2916, 2860, 1496, 1444, 1261, 1061, 767, 696 cm⁻¹. ¹H NMR: δ 1.55 (d, J = 6.3 Hz, 3H), 1.56 (s, 3H), 3.15 (s, 2H), 5.32 (q, J = 6.3 Hz, 1H), 7.26 (t, J = 7.4 Hz, 1H),
7.32–7.43 (m, 5H), 7.45 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 7.2 Hz, 2H). $^{13}$C NMR: δ 13.5, 16.6, 40.9 (d, J$_{CF}$ = 3 Hz), 117.5 (d, J$_{CF}$ = 14 Hz), 120.4, 126.9, 127.94 (d, J$_{CF}$ = 4 Hz), 127.96, 128.2, 128.7 (d, J$_{CF}$ = 4 Hz), 129.0 132.8 (d, J$_{CF}$ = 3 Hz), 133.0 (d, J$_{CF}$ = 30 Hz), 137.6, 154.3 (d, J$_{CF}$ = 248 Hz). $^{19}$F NMR: δ 62.7 (s, 1F).

The stereochemistry of 24’dh was determined by 2D NMR studies.

(E)-2-Fluoro-1-methoxy-3-(2-propylhex-2-en-1-yl)-1H-indene (24fa)

Compound 24fa was synthesized according to the typical procedure using 2,2-difluoro-1-methoxy-3-methylene-2,3-dihydro-1H-indene (23f, 105 mg, 0.534 mmol), 4-octyne (15a, 65 mg, 0.59 mmol), Et$_3$SiH (123 mg, 1.06 mmol), Ni(cod)$_2$ (7 mg, 0.027 mmol), PCy$_3$ (15 mg, 0.053 mmol), and Toluene (2.7 mL) at room temperature for 2 h. Purification by silica gel column chromatography (hexane) gave 24fa (141 mg, 92%) as a colorless liquid.

24fa: IR (neat): ν ~ = 2958, 2929, 2871, 1674, 1458, 1340, 1109, 760, 731 cm$^{-1}$. $^1$H NMR: δ 0.86 (t, J = 7.4 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H), 1.33 (qt, J = 7.4, 7.4 Hz, 2H), 1.46 (qt, J = 7.4, 7.3 Hz, 2H), 1.94–2.05 (m, 4H), 3.12 (d, J = 15.4 Hz, 1H), 3.20 (d, J = 15.4 Hz, 1H), 3.26 (s, 3H), 5.02 (s, 1H), 7.15 (d, J = 7.6 Hz, 1H), 7.16 (dd, J = 7.3, 7.1 Hz, 1H), 7.24 (dd, J = 7.6, 7.3 Hz, 1H), 7.34 (d, J = 7.1 Hz, 1H). $^{13}$C NMR: δ 13.8, 14.1, 21.4, 23.0, 29.9, 30.3, 32.1, 53.3, 77.7 (d, J$_{CF}$ = 22 Hz), 119.0 (d, J$_{CF}$ = 10 Hz), 120.1 (d, J$_{CF}$ = 7 Hz), 123.5, 125.3 (d, J$_{CF}$ = 4 Hz), 127.4, 128.7, 134.6 (d, J$_{CF}$ = 2 Hz), 135.5 (d, J$_{CF}$ = 7 Hz), 141.5 (d, J$_{CF}$ = 7 Hz), 161.8 (d, J$_{CF}$ = 287 Hz). $^{19}$F NMR: δ 28.2 (s, 1F).

(E)-2-fluoro-(2-propylhex-2-en-1-yl)naphtho[2,1-b]furan (24ga)

Compound 24ga was synthesized according to the typical procedure using 2,2-difluoro-1-methoxy-1,2-dihyronaphtho[2,1-b]furan (23g, 27 mg, 0.12 mmol), 4-octyne (15a, 15 mg, 0.14 mmol), Et$_3$SiH (29 mg, 0.25 mmol), Ni(cod)$_2$ (3 mg, 0.012 mmol), PCy$_3$ (7 mg, 0.025 mmol), and Toluene (0.7 mL) at room temperature for 1.5 h. Purification by silica gel column chromatography (hexane) gave 24ga (29 mg, 77%) as a white solid.
**24ga**: IR (neat): ν = 2958, 2929, 2870, 1662, 1583, 1414, 1390, 1238, 798 cm⁻¹. ¹H NMR: δ 0.76 (t, J = 7.4 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H), 1.22 (qt, J = 7.4, 7.3 Hz, 2H), 1.48–1.62 (m, 2H), 1.97 (dt, J = 7.3, 7.3 Hz, 2H), 2.14 (t, J = 7.7 Hz, 2H), 3.59 (s, 2H), 5.21 (t, J = 7.3 Hz, 1H), 7.42–7.52 (m, 2H), 7.55 (d, J = 8.9 Hz, 1H), 7.68 (d, J = 8.9 Hz, 1H), 7.91 (d, J = 7.7 Hz, 1H), 8.16 (d, J = 8.2 Hz, 1H). ¹³C NMR: δ 13.8, 14.2, 21.5, 22.9, 29.9, 30.0, 32.9, 91.0 (d, J_CF = 11 Hz), 111.7, 123.1, 124.16, 124.21, 124.4, 125.8, 127.0, 128.2 (d, J_CF = 5 Hz), 128.8, 130.9, 135.4, 143.8, 157.3 (d, J_CF = 276 Hz). ¹⁹F NMR: δ 42.6 (s, 1F).


*Typical Procedure for Catalytic Synthesis of 2-Fluoro-1,3-cyclopentadienes*

1-(4-(2-Fluoro-3,4-dipropylcyclopenta-1,3-dienyl)phenyl)ethanone (16aa)

Ni(cod)₂ (14 mg, 0.051 mmol), PCy₃ (29 mg, 0.10 mmol), B₂(nep)₂ (62 mg, 0.27 mmol), t-BuOK (30 mg, 0.27 mmol), and MgF₂ (16 mg, 0.26 mmol) were dissolved in 1,4-dioxane (3 mL). After stirring at room temperature for 10 min, 2-trifluoromethyl-1-alkene 14a (53 mg, 0.25 mmol) and 4-octyne (15a, 30 mg, 0.28 mmol) were added to the mixture at room temperature. After stirring for 3 h at 80 °C, the reaction mixture was quenched by addition of 1 M HCl. Organic materials were extracted two times with Et₂O. The combined extracts were washed with brine and dried over Na₂SO₄. After removal of the solvent under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/EtOAc = 50:1) to give fluorocyclopentadiene 16aa (38 mg, 53%) as a yellow solid.

The spectral data of 16aa is shown in Chapter 3 (page 72).

1-(4-(2-Fluoro-4-isopropyl-3-methylcyclopenta-1,3-dienyl)phenyl)ethanone (16ac)

Fluorocyclopentadiene 16ac was synthesized according to the typical procedure. Purification by silica gel column chromatography (hexane/EtOAc = 50:1) gave 16ac (45 mg, 70%) as a yellow
The spectral data of 16ac is shown in Chapter 3 (page 73).

3-(2-Fluoro-4-isopropyl-3-methylocyclopenta-1,3-dienyl)fluorobenzene (16nc)

Fluorocyclopentadiene 16nc was synthesized according to the typical procedure. Purification by silica gel column chromatography (hexane) gave 16nc (27 mg, 50%) as a white solid.

16nc: IR (neat): \(\nu = 2962, 2868, 1651, 1610, 1595, 1365, 1269, 1176, 781, 686\) cm\(^{-1}\). \(^1\)H NMR: \(\delta 1.05\) (d, \(J = 7.0\) Hz, 6 H), 1.80 (s, 3 H), 2.84 (septet, 1H), 3.04 (dd, \(J_{CF} = 6.5\) Hz, \(J = 1.5\), 2H), 6.72–6.76 (m, 1H), 7.13–7.21 (m, 3H). \(^1^C\) NMR: \(\delta 8.6, 22.5, 27.4\) (d, \(J_{CF} = 2\) Hz), 34.1 (d, \(J_{CF} = 8\) Hz), 112.0 (d, \(J_{CF} = 7\) Hz), 112.2 (d, \(J_{CF} = 7\) Hz), 112.2 (dd, \(J_{CF} = 21\) Hz, \(J_{CF} = 2\) Hz), 121.0 (dd, \(J_{CF} = 7\) Hz, \(J_{CF} = 3\) Hz), 128.0 (d, \(J_{CF} = 26\) Hz), 129.8 (d, \(J_{CF} = 8\) Hz), 136.0 (dd, \(J_{CF} = 8\) Hz, \(J_{CF} = 5\) Hz), 147.1 (d, \(J_{CF} = 4\) Hz), 159.6 (d, \(J_{CF} = 281\) Hz). 163.1 (d, \(J_{CF} = 245\) Hz), \(^1^9\)F NMR: \(\delta 38.9\) (t, \(J_{FH} = 6.4\) Hz, 1F), 48.8 (m, 1H). HRMS (EI+): Calcd for C\(_{15}\)H\(_{16}\)F\(_2\) [M]+ 234.1220, Found 234.1209.

4-(2-Fluoro-4-isopropyl-3-methylocyclopenta-1,3-dienyl)benzonitrile (16bc)

Fluorocyclopentadiene 16bc was synthesized according to the typical procedure. Purification by silica gel column chromatography (hexane/EtOAc = 50:1) gave 16bc (27 mg, 48%) as a white solid.

16bc: IR (neat): \(\nu = 2958, 2868, 2222, 1585, 912, 742\) cm\(^{-1}\). \(^1\)H NMR: \(\delta 1.06\) (d, \(J = 6.9\) Hz, 6 H), 1.81 (s, 3 H), 2.87 (septet, \(J = 6.9\) Hz, 1H), 3.08 (dd, \(J_{CF} = 6.8\) Hz, \(J = 1.5\), 2H), 7.50 (m, 4H). \(^1^C\) NMR: \(\delta 8.5, 22.4, 27.5\) (d, \(J_{CF} = 2\) Hz), 33.9 (d, \(J_{CF} = 7\) Hz), 108.0 (d, \(J_{CF} = 3\) Hz), 111.6 (d, \(J_{CF} = 2\) Hz), 119.4, 125.4 (d, \(J_{CF} = 7\) Hz), 128.3 (d, \(J_{CF} = 26\) Hz), 132.2, 138.1 (d, \(J_{CF} = 5\) Hz), 149.3 (d, \(J_{CF} = 4\) Hz), 161.4 (d, \(J_{CF} = 285\) Hz). \(^1^9\)F NMR: \(\delta 43.4\) (t, \(J_{FH} = 7.0\) Hz, 1F). HRMS (EI+): Calcd for C\(_{15}\)H\(_{16}\)FN [M]+ 241.1267, Found 241.1270.

(2-Fluoro-4-isopropyl-3-methylocyclopenta-1,3-dienyl)benzene (16ec)
Fluorocyclopentadiene 16ec was synthesized according to the typical procedure. Purification by silica gel column chromatography (hexane/EtOAc = 50:1) gave 16ec (29 mg, 52%) as a white solid. 16ec: IR (neat): ν ~ 2960, 1653, 1597, 1367, 1192, 912, 742, 692 cm⁻¹. ¹H NMR: δ 1.12 (d, J = 6.9 Hz, 6H), 1.87 (s, 3H), 2.91 (septet, J = 6.9 Hz, 1H), 3.13 (dd, JHF = 6.4 Hz, J = 1.5 Hz, 2H), 7.13 (t, J = 7.4 Hz, 1H), 7.31 (dd, J = 8.3, 7.4 Hz, 2H), 7.52 (dd, J = 8.3, 1.2 Hz, 2H). ¹³C NMR: δ 8.7, 22.6, 27.4 (d, JCF = 2 Hz), 34.1 (d, JCF = 8 Hz), 112.7, 125.5 (d, JCF = 4 Hz), 125.5, 128.0 (d, JCF = 27 Hz), 128.5, 134.0 (d, JCF = 6 Hz), 146.2 (d, JCF = 4 Hz), 158.8 (d, JCF = 280 Hz). ¹⁹F NMR: δ 36.8 (t, JFH = 6.4 Hz, 1F). HRMS (EI+): Calcd for C15H17F [M]+ 216.1314, Found: 216.1306.

**Synthesis of Trifluoromethylated Enyne 14o**

(1,1,1-trifluoronon-2-en-8-yn-2-yl)benzene

To a solution of phosphonium salt (481 mg, 1.1 mmol) in tetrahydrofuran (5 mL) was added n-BuLi (1.60 M in hexane, 0.76 mL, 1.2 mmol) at −78 °C. After stirring for 5 min at −78 °C, the reaction solution was warmed to 0 °C, stirred for 1 h, and then cooled to −78 °C. A solution of 2,2,2-trifluoroacetophenone (174 mg, 1.0 mmol) in tetrahydrofuran (4 mL) was added via cannula over 3 min. The reaction mixture was maintained at −78 °C for 1 h. Then, the temperature was raised to 0 °C. After stirring for 1 h at 0 °C, the temperature was then raised to room temperature. After stirring for 1 h, the reaction mixture was quenched by addition of saturated aqueous NH₄Cl. Organic materials were extracted two times with Et₂O. The combined extracts were washed with brine and dried over Na₂SO₄. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography to give the titled compound (220 mg, 0.87 mmol, 87%, E/Z = 64:36) as a colorless liquid.

(E)-(1,1,1-trifluoronon-2-en-8-yn-2-yl)benzene: IR (neat): ν ~ 2941, 2864, 1302, 1169, 1113, 758, 700, 632 cm⁻¹. ¹H NMR: δ 1.35–1.47 (m, 4 H), 1.84 (t, J = 2.5 Hz, 1H), 1.91–1.94 (m, 2H), 2.04 (td, J = 6.5 Hz, J = 2.5 Hz, 2H), 6.34 (td, J = 6.8 Hz, JHF = 1.6 Hz, 1H), 7.14–7.16 (m, 2H), 7.28–7.33 (m, 3H). ¹³C NMR: δ 18.1, 27.7, 27.9, 28.2, 68.5, 83.9, 123.5 (q, JCF = 273 Hz), 128.2, 128.4, 129.7, 131.5 (q, JCF = 29 Hz), 132.3, 136.2 (q, JCF = 5 Hz). ¹⁹F NMR: δ 96.0 (s, 3F). HRMS (EI+): Calcd for C₁₅H₁₃F₃ [M⁺] 252.1126, Found: 252.1112.

(Z)-(1,1,1-trifluoronon-2-en-8-yn-2-yl)benzene: IR (neat): ν ~ 2941, 2864, 1302, 1169, 1113, 758, 700, 632 cm⁻¹. ¹H NMR: δ 1.49–1.58 (m, 4 H), 1.88 (t, J = 3.0 Hz, 1H), 2.15 (td, J = 6.0 Hz, J
= 3.0 Hz, 2H), 2.38 (m, 2H), 5.93 (t, J = 7.8 Hz, 1H), 7.20–7.22 (m, 2H), 7.25–7.28 (m, 3H). $^{13}$C NMR: δ 18.2, 27.7, 27.9, 28.2, 68.5, 84.0, 123.9 (q, $J_{CF} = 276$ Hz), 128.0, 128.2, 128.4, 131.9 (q, $J_{CF} = 30$ Hz), 136.6, 141.6 (q, $J_{CF} = 3$ Hz). $^{19}$F NMR: δ 104.6 (s, 3F). HRMS (EI+): Calcd for C$_{15}$H$_{15}$F$_3$ [M]$^+$ 252.1126, Found: 252.1112.

(1,1,1-trifluorodec-2-en-8-yn-2-yl)benzene (14o)

To a solution of (1,1,1-trifluoronon-2-en-8-yn-2-yl)benzene (251 mg, 0.994 mmol) in tetrahydrofuran (10 mL) was added n-BuLi (1.60 M in hexane, 0.68 mL, 1.1 mmol) at –78 ºC. After stirring for 1 h at –78 ºC, iodomethane (0.13 mL, 2.0 mmol) was added to the reaction solution. Then the reaction mixture was warmed to 40 ºC and stirred for 1 h. The reaction mixture was quenched by addition of 1 M HCl. Organic materials were extracted two times with Et$_2$O. The combined extracts were washed with brine and dried over Na$_2$SO$_4$. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography to give alkyne 14o (265 mg, quant, E/Z = 60:40) as a colorless liquid.

(E)-(1,1,1-trifluorodec-2-en-8-yn-2-yl)benzene (14o, (E)-isomer): IR (neat): $\nu^\prime =$ 2935, 2862, 1302, 1169, 912, 737, 702, 632 cm$^{-1}$. $^1$H NMR: δ 1.31–1.37 (m, 2 H), 1.39–1.45 (m, 2H), 1.69 (t, J = 2.5 Hz, 3H), 1.92–2.01 (m, 4H), 6.34 (tq, J = 7.5 Hz, $J_{HF} = 1.6$ Hz, 1H), 7.15–7.16 (m, 2H), 7.29–7.33 (m, 3H). $^{13}$C NMR: δ 3.4, 18.4, 27.8, 28.3, 28.5, 75.7, 78.6, 123.5 (q, $J_{CF} = 273$ Hz), 128.2, 128.3, 129.7, 131.3 (q, $J_{CF} = 29$ Hz), 132.4, 136.4 (q, $J_{CF} = 6$ Hz). $^{19}$F NMR: δ 96.0 (s, 3F). HRMS (EI+): Calcd for C$_{15}$H$_{14}$F$_3$ [M–CH$_3$]$^+$ 251.1048, Found: 251.1059.

(Z)-(1,1,1-trifluorodec-2-en-8-yn-2-yl)benzene (14o, (Z)-isomer): IR (neat): $\nu^\prime =$ 2935, 2862, 1302, 1169, 912, 737, 702, 632 cm$^{-1}$. $^1$H NMR: δ 1.46–1.56 (m, 4 H), 1.71 (t, J = 2.5 Hz, 3H), 2.08–2.12 (m, 2H), 2.35–2.41 (m, 2H), 5.95 (t, J = 7.8 Hz, 1H), 7.21–7.23 (m, 2H), 7.25–7.29 (m, 3H). $^{13}$C NMR: δ 3.4, 18.5, 27.8, 27.8, 28.4, 75.8, 78.7, 124.0 (q, $J_{CF} = 276$ Hz), 127.9, 128.2, 128.3, 131.7 (q, $J_{CF} = 30$ Hz), 136.6, 141.9 (q, $J_{CF} = 3$ Hz). $^{19}$F NMR: δ 104.6 (s, 3F). HRMS (EI+): Calcd for C$_{15}$H$_{14}$F$_3$ [M–CH$_3$]$^+$ 251.1048, Found: 251.1053.
**Ni-Catalyzed Intramolecular [3+2] Cycloaddition of Trifluoromethylated Enyne**

2-Fluoro-1-methyl-3-phenyl-4,5,6,7-tetrahydro-3aH-indene (16o)

Ni(cod)$_2$ (14 mg, 0.051 mmol), PCy$_3$ (29 mg, 0.10 mmol), B$_2$(nep)$_2$ (62 mg, 0.27 mmol), t-BuOK (30 mg, 0.27 mmol), and MgF$_2$ (16 mg, 0.26 mmol) were dissolved in 1,4-dioxane (3 mL). After stirring at room temperature for 10 min, enyne 14o (53 mg, 0.25 mmol) was added to the mixture at room temperature. The temperature of the reaction mixture was raised to 40 ºC and maintained at that temperature for 20 min. The temperature was then raised to 80 ºC, and the mixture was stirred for 15 h. Then the reaction mixture was filtered through a pad of silica gel (EtOAc). The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/EtOAc = 50:1) to give fluorocyclopentadiene 16o (21 mg, 36%) as a white solid.

16o: IR (neat): $\tilde{\nu}$ = 2933, 2856, 906, 731, 650 cm$^{-1}$. $^1$H NMR: $\delta$ 0.84 (dddd, $J = 13.2$ Hz, $J = 13.2$ Hz, $J = 3.3$ Hz, 1H), 1.16–1.25 (m, 1H), 1.45–1.54 (m, 1H), 1.77–1.83 (m, 1H), 1.87 (t, $J_{HF} = 1.5$ Hz, 3H), 1.97–2.03 (m, 1H), 2.09–2.16 (m, 1H), 2.37–2.42 (m, 1H), 2.69–2.73 (m, 1H), 2.96–3.01 (m, 1H), 7.14 (tt, $J = 7.5$ Hz, $J = 1.0$ Hz), 7.33 (dd, $J = 7.5$ Hz, $J = 7.5$ Hz, 2H), 7.46 (dd, $J = 7.5$ Hz, $J = 1.0$ Hz, 2H). $^{13}$C NMR: $\delta$ 8.5, 25.5, 26.2 (d, $J_{CF} = 2$ Hz), 29.1, 33.4 (d, $J_{CF} = 3$ Hz), 47.1 (d, $J_{CF} = 8$ Hz), 118.3, 124.6 (d, $J_{CF} = 28$ Hz), 125.4 (d, $J_{CF} = 2$ Hz), 126.3 (d, $J_{CF} = 6$ Hz), 128.4, 133.0 (d, $J_{CF} = 5$ Hz), 144.5 (d, $J_{CF} = 6$ Hz), 159.0 (d, $J_{CF} = 281$ Hz). $^{19}$F NMR: $\delta$ 33.8 (d, $J_{FH} = 6.1$ Hz, 1F). HRMS (EI+): Calcd for C$_{16}$H$_{17}$F [M]$^+$ 228.1314, Found: 228.1323.
CHAPTER 5

Conclusions

I demonstrated new carbon–carbon bond forming reactions by controlling β-fluorine elimination from fluorinated organometallics, which have unique interactions between their metal centers and the fluorine substituents on the ligand.

In Chapter 2, I showed the preparation of a thermally stable 2,2-difluorovinylzinc–TMEDA complex from 1,1-difluoroethylene, a commercially available industrial material. Stabilization of the zinc complex by coordination of the bidentate TMEDA ligand suppressed the β-fluorine elimination process. Moreover, I applied the zinc complex to the transition metal-catalyzed cross-coupling reactions with a wide variety of organic halides, establishing the versatile syntheses of 2,2-difluorovinyl compounds.

In Chapter 3, I developed a new methodology for allylic and vinylic C–F bond activation by β-fluorine elimination from the intermediary nickelacycles. The nickel-mediated [3+2] cycloaddition involves the consecutive cleavage of two C–F bonds of the trifluoromethyl and perfluoroalkyl groups, which are recognized as inert functional groups. Furthermore, this methodology enables the direct construction of a multisubstituted cyclopentadiene ring and the introduction of a fluorine substituent or a trifluoromethyl group in a regioselective manner.

In Chapter 4, I achieved catalytic C(sp³)–F bond activation of the trifluoromethyl group by employing appropriate reducing reagents in the nickel-mediated reaction developed in Chapter 3. The nickel-catalyzed defluorinative coupling reaction enables the regio- and stereoselective syntheses of multisubstituted fluoroalkenes.
Through these studies, I showed the usefulness of 2,2-difluorovinylzinc–TMEDA complex as a difluorovinylation reagent and potential advantages of β-fluorine elimination as a tool for the catalytic defluorinative functionalization of multi-fluorinated organic compounds.
List of Publications

1. “Facile Synthesis of β,β-Difluorostyrenes via the Negishi Coupling of Thermally Stable 2,2-Difluorovinyl Zinc–TMEDA Complex”
   T. Fujita, T. Ichitsuka, K. Fuchibe, J. Ichikawa

   T. Ichitsuka, T. Fujita, T. Arita, J. Ichikawa

3. “A Versatile Difluorovinylation Method: Cross-Coupling Reactions of the 2,2-Difluorovinylzinc–TMEDA Complex with Alkenyl, Alkynyl, Allyl and Benzyl Halides”
   T. Ichitsuka, T. Takanoashi, T. Fujita, J. Ichikawa