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

Tomohiro ICHITSUKA
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

TABLE OF CONTENTS

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

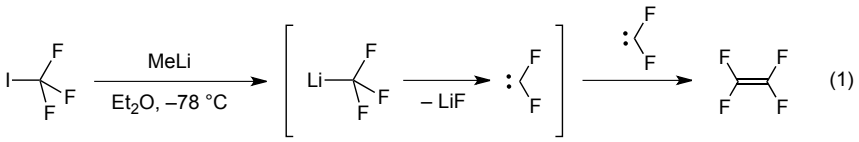
(A) Fluorinated Organolithium and Magnesium Reagents

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]

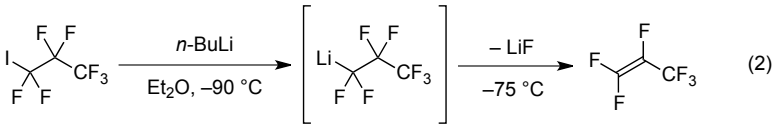
Scheme 1.

(a) α-fluorine elimination (b) β-fluorine elimination

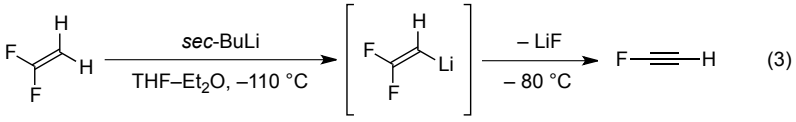
Fluorine elimination of alkyl lithium and alkyl magnesium reagents is extremely rapid even at low temperature, because of the highly polarized carbon–metal bond and the formation of highly stable metal fluoride salts (eqs 1 and 2). β-Fluorine elimination is generally more preferable than α-fluorine elimination 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.

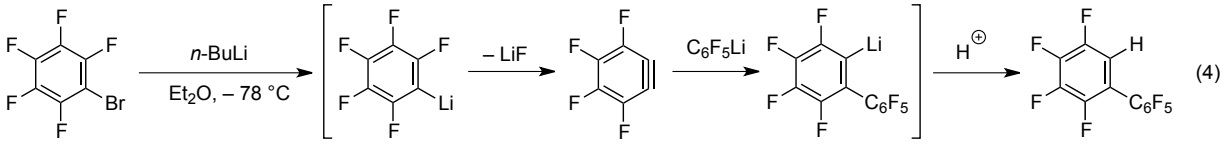


α-Fluorine Elimination



β-Fluorine Elimination



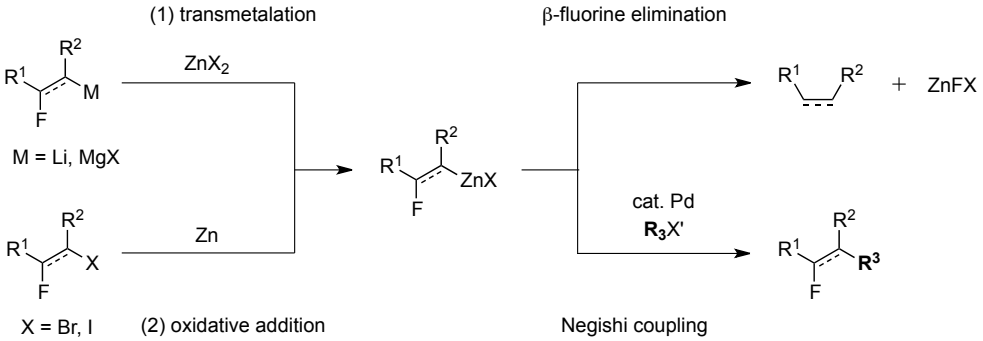


(B) Other Fluorinated Organometal Reagents (M = B, Si, Zn, Sn)

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.

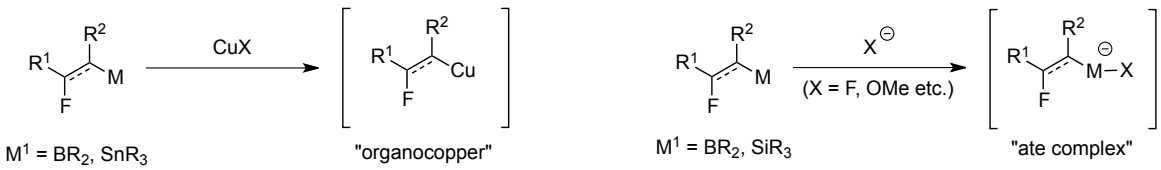
Organozinc reagents bearing β-fluorine substituents have moderate thermal stability.[7] When such organozinc reagents are used in the palladium-catalyzed Negishi cross-coupling reactions, the β-fluorine elimination may proceed at room temperature or above (Scheme 2).

Scheme 2.



On the other hand, fluorinated organoborane, organosilane, and organostannane compounds are particularly stable and less reactive compared to organozinc reagents.[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.



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

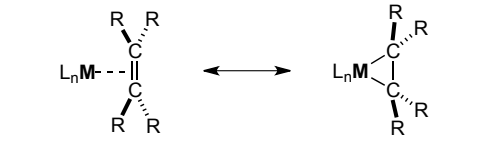


Figure 2.

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-dackdonation.

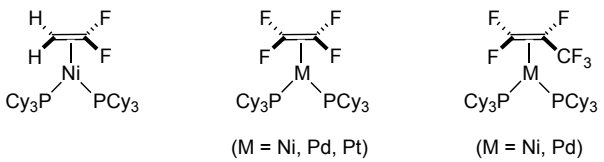
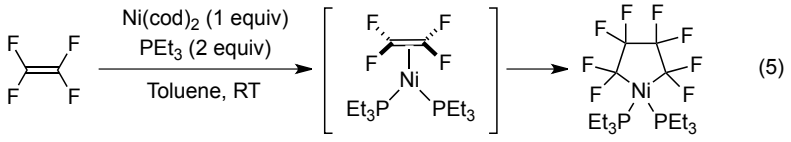
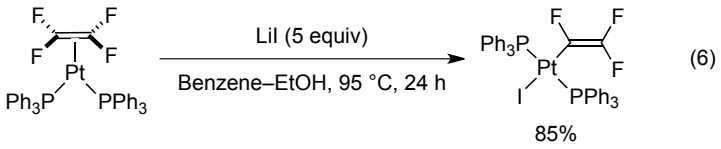
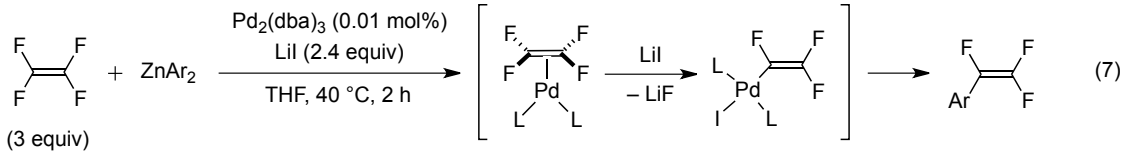


Figure 3. Transition metal–fluoroalkens complex

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 PtI(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 arylzinc reagents as coupling partners (eq 7).[15b] 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

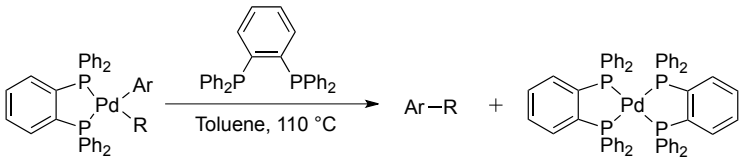
Alkyl transition metal complexes have played a vital role in various transition metal-catalyzed synthetic organic reactions.[9] Although, they are recognized as key intermediates in the fluoroalkylation of arenes and the hydrodefluorination of fluorocarbon pollutants, the reaction of fluoroalkyl complexes 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 of fluorine substituents exhibiting the highest electronegativity of all elements (Figure 4).[16] In particular, the fluoroalkyl complexes having multi-fluorine atoms on the α- and β-carbons are amazingly stable, and thus perfluoroalkyl ligand is often used as unreactive ancillary one.

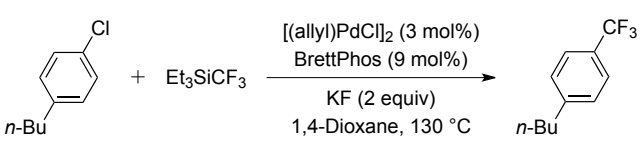
Figure 4. Carbon–metal bond stabilization with –I effect

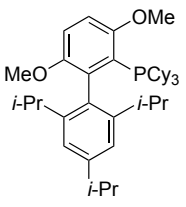
The inertness of fluoroalkyl ligands inhibits elementary processes involving cleavage of its carbon–metal bonds in transition metal-mediated reactions. For instance, the late transition metal–CF_3 bond is particularly strong and inert.[17] Hartwig disclosed that the reductive elimination of Ar–CF_3 from the corresponding trifluoromethyl–Pd(II) complex can not proceed even at 110 °C (Scheme 4).[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).[17c,d]

Scheme 4.



R	Ar	K_{rel}
CH_3	2-MeC_6H_4	> 600
CH_2CF_3	4-MeC_6H_4	1.7
CH_2CN	4-$^tBuC_6H_4$	1
CF_3	2-MeC_6H_4	no reaction



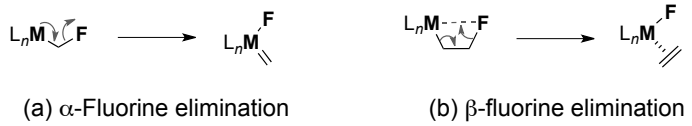


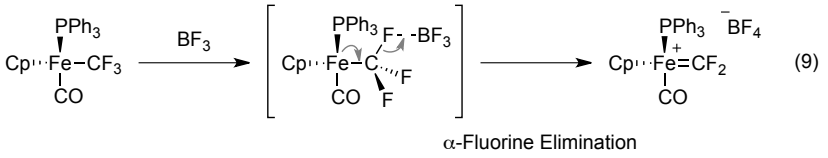
BrettPhos

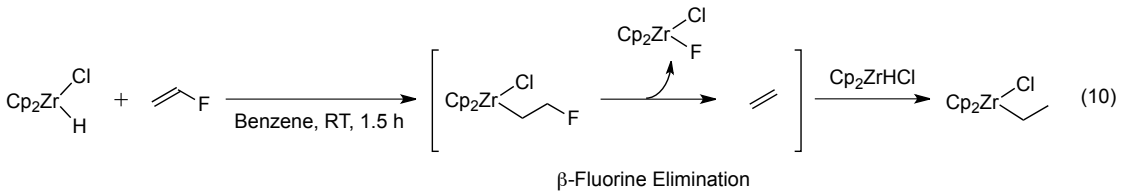
(8)

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).[18] In a similar manner, β-fluorine elimination from β-fluoroalkyl transition metal complexes provides the corresponding alkene ligands and a fluoride ligand (Scheme 5b).[19] Shriver reported that the iron trifluoromethyl complex reacts with BF_3 to give the cationic iron–difluorocarbene complex through α-fluorine elimination (eq 9).[18b] Caulton achieved β-fluorine elimination of the intermediary β-fluoroethyl zirconium complex generated by hydrozirconation of vinyl fluoride (eq 10).[19b] Surprisingly, these processes of fluorine elimination proceed spontaneously even at room temperature to provide the corresponding defluorinated product.

Scheme 5.

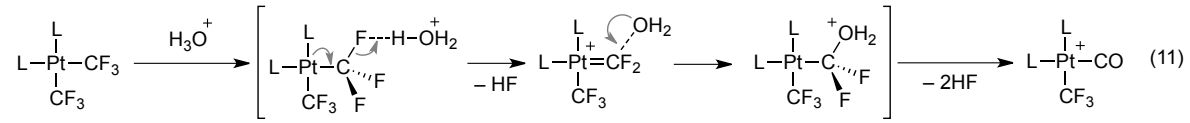


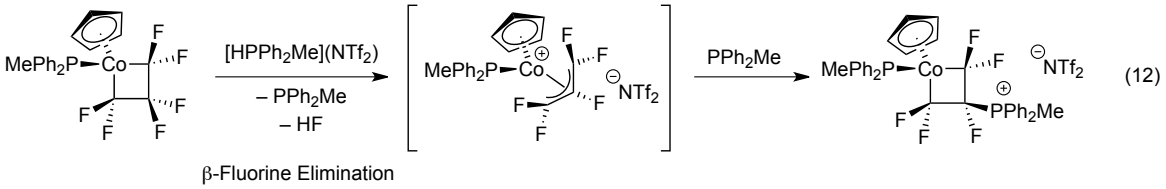




Furthermore, fluorine elimination can be utilized for the defluorinative substitution of fluoroalkyl metals with nucleophiles (eq 11 and 12).[18a, 19d] In these reactions, Brønsted or Lewis acid activates the leaving fluoride to accelerate carbon–fluorine bond cleavage. Subsequently,

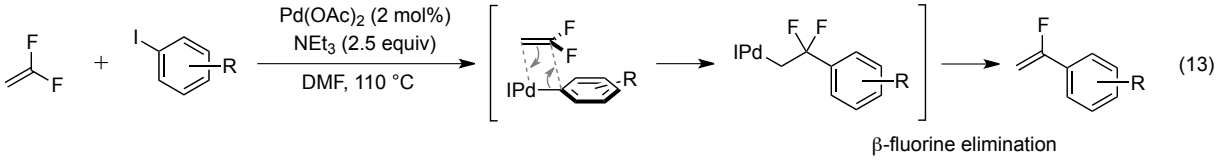
nucleophiles such as phosphine and water attack the carbocation centers to afford the corresponding transition metal complexes bearing the functionalized ligands.



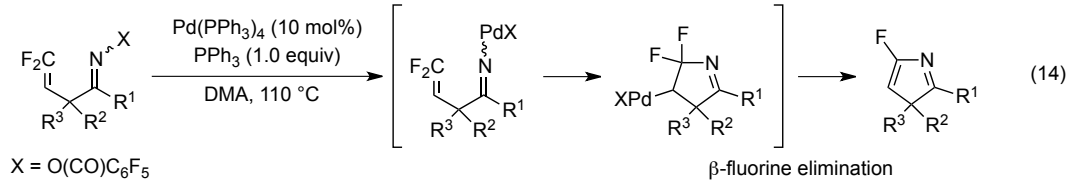


Utilizing fluorine elimination as key elementary step, several catalytic reactions have been developed. In 1991, Heitz et al. developed the palladium-catalyzed vinylic carbon–fluorine bond arylation of 1,1-difluoroethylene with aryl iodides via regioselective alkene insertion–β-fluorine elimination sequence (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

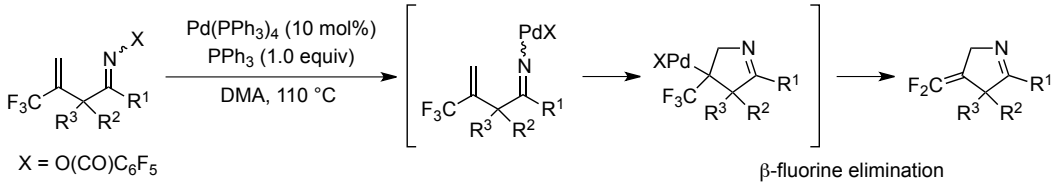
nickelacycloheptadienes (eq 18).



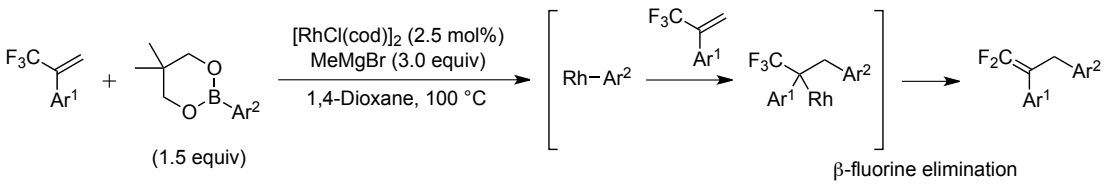
(13)



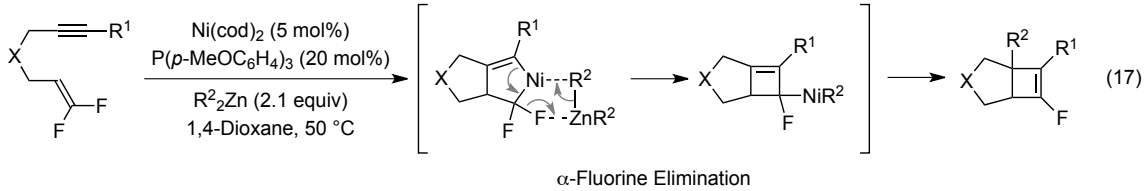
(14)



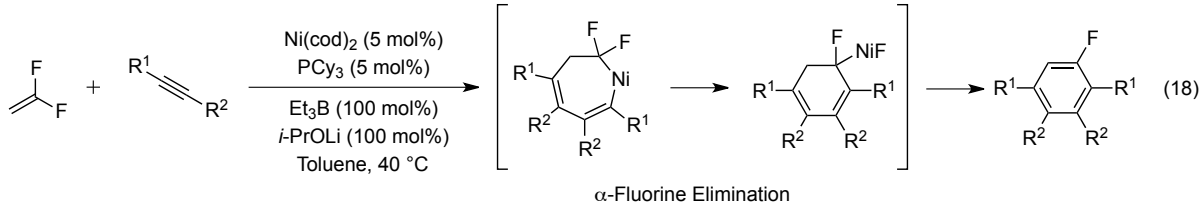
(15)



(16)



(17)



(18)

Therefore, fluorine elimination leads to alternative and powerful methodology for cleavage and functionalization of carbon–fluorine bond. Furthermore, the selective functionalization of

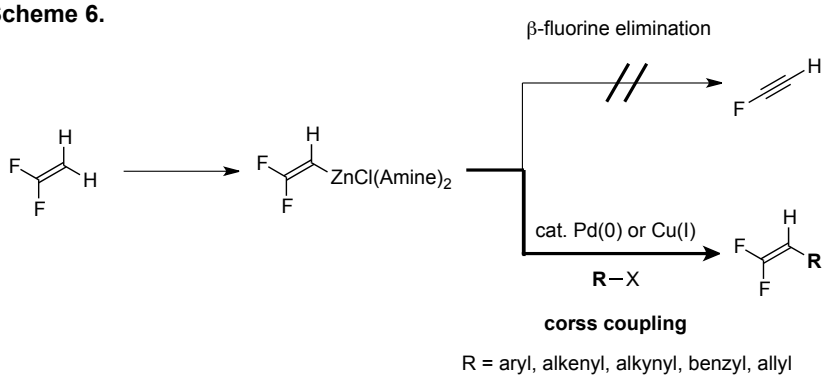
perfluoroalkyl compounds would be possible, because the fluorine elimination of the perfluoroalkyl ligands also proceed under mild conditions.

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.[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.

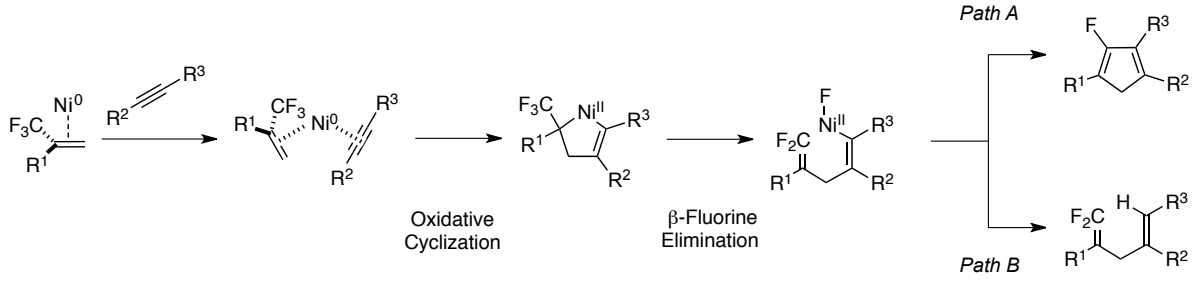
Scheme 6.



In chapter 3, I developed the transition metal mediated carbon–fluorine bond activation taking advantage of β-fluorine elimination. As mentioned in the previous section, β-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 β-fluorine elimination as the synthetic tool. To add a approach to β-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).[23] Utilizing β-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 β-fluorine elimination. By the choice of reductants for the intermediary Ni(II) species, the product selectivity was controlled (Scheme 7)

Scheme 7.



1.4 References

[1] (a) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH Verlag GmbH & Co.: Weinheim, Germany, **2004**. (b) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley-Backwell: Chichester, UK, **2009**.

[2] (a) Uneyama, K. *Organofluorine Chemistry*; Backwell Publishing: Oxford, UK. **2006**. (b) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264.

[3] (a) Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon Press: Oxford, UK, **1974**. (b) Richey, H. G. Jr. *Grignard Reagents: Novel Developments*; Wiley-VCH: Chichester, UK, **2000**.

[4] For selected reviews on fluorinated organometallics, see: (a) Burton, D. J.; Yang, Z.-Y. *Tetrahedron* **1992**, *48*, 189–275. (b) Burton, D. J.; Yang, Z.-Y.; Morken, P. A. *Tetrahedron* **1994**, *50*, 2993–3063.

[5] (a) Pierce, O. R.; McBee, E. T.; Judo, G. F. *J. Am. Chem. Soc.* **1954**, *76*, 474–478. (b) Johncock, P. *J. Organomet. Chem.* **1969**, *19*, 257–265.

[6] (a) Sauvetre, R.; Normant, J. F. *Tetrahedron Lett.* **1981**, *22*, 957–958. (b) Coe, P. L.; Stephens, R.; Tatlow, J. C. *J. Chem. Soc.* **1962**, 3227–3231.

[7] Davis, C. R.; Burton, D, J. in Knochel, P.; Jones, P. *Organozinc Reagents: A Practical Approach*; Oxford University Press: Oxford, UK, **1999**. Chap. 4, pp. 57–75.

[8] (a) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, 757–786. (b) Xue, L.; Lu, L.; Pedersen, S. D.; Liu, Q.; Narske, R. M.; Burton, D. J. *J. Org. Chem.* **1997**, *62*, 1064–1971. (c) Ichikawa, J. *J. Fluorine Chem.* **2000**, *105*, 257–263. (d) Ichikawa, J.; Fukui, H.; Ishibashi, Y. *J. Org. Chem.* **2003**, *68*, 7800–7805. (e) Levin, V. V.; Dilman, A. D.; Belyakov, P. A.; Struchkova, M. I.; Tartakovsky, V. A. *Tetrahedron Lett.* **2011**, *52*, 281–284.

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

Science Books: California, USA, **2010**.

[10] (a) Dewar, M. J. S. *Bull. Soc. Chim. Fr.* **1951**, *18*, C79. (b) Chatt, J.; Duncanson, L. A. *J. Chem. Soc.* **1953**, 2939–2947.

[11] (a) Yamamoto, T.; Yamamoto, A.; Ikeda, S. *J. Am. Chem. Soc*. **1971**, *93*, 3360–3364. (b) Tolman. C. A.; Seidel, W. C. *J. Am. Chem. Soc.* **1974**, *96*, 2774–2780. (c) Tolman, C. A. *J. Am. Chem. Soc.* **1974**, *96*, 2780–2789. (d) Komiya, S.; Ishizu, J.; Yamamoto, A.; Yamamoto, T.; Takenaka, A.; Sasada, Y. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1283–1287.

[12] (a) Hoberg, H.; Guhl, D.; *J. Organomet. Chem.* **1989**, *373*, C27–C30. (b) Ohashi, M.; Shibata, M.; Saijo, H.; Kambara, T.; Ogoshi, S. *Organometallics* **2013**, *32*, 3631–3639. (c) Xu, W.; Sun, H.; Xiong, Z.; Li, X. *Organometallics* **2013**, *32*, 7122–7132. (d) Ohashi, M.; Shibata, M.; Ogoshi, S. *Angew. Chem. Int. Ed.* **2014**, *53*, 13578–13582.

[13] Cundy, C. S.; Green, M.; Stone, F. G. A. *J. Chem. Soc. A* **1970**, 1647–1653.

[14] Hacker, M. J.; Littlecott, G. W.; Kemmitt, R. D. W. *J. Organomet. Chem.* **1973**, *47*, 189–193.

[15] (a) Saeki, T.; Takashima, Y.; Tamao, K. *Synlett* **2005**, 1771–1774. (b) Ohashi, M.; Kambara, T.; Hatanaka, T.; Saijo, H.; Doi, R.; Ogoshi, S. *J. Am. Chem. Soc.* **2011**, *133*, 3256–3259. (c) Ohashi, M.; Saijo, H.; Shibata, M.; Ogoshi, S. *Eur. J. Org. Chem.* **2013**, 443–447. (d) Saijo, H.; Sakaguchi, H.; Ohashi, M.; Ogoshi, S. *Organometallics* **2014**, *33*, 3369–3672.

[16] (a) Kirker, G. W.; Bakac, A.; Espenson, J. H. *J. Am. Chem. Soc.* **1982**, *104*, 1249–1255. (b) Blau, R. J.; Espenson, J. H.; Bakac, A. *Inorg. Chem.* **1984**, *23*, 3526–3528.

[17] (a) Culkin, D. A.; Hartwig, J. F. *Organometallics* **2004**, *23*, 3398–3416. (b) Grushin, V. V. *Acc. Chem. Rec*. **2010**, *43*, 160–171. (c) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679–1681. (d) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470–477.

[18] For α-fluorine elimination of transition metal complex, see: (a) Reger, D. L.; Dukes, M. D. *J. Organomet. Chem.* **1978**, *153*, 67–72. (b) Crespi, A. M.; Shriver, D. F. *Organometallics* **1985**, *4*, 1830–1835. (c) Burch, R. R.; Calabrese, J. C.; Ittel, S. D. *Organometallics* **1988**, *7*, 1642–1648. (d) Appleton, T. G.; Berry, R. D.; Hall, J. R.; Neale, D. W. *J. Organomet. Chem.* **1989**, 364, 249–273. (e) Koola, J. D.; Roddick, D. M. *Organometallics* **1991**, 10, 591–597.

[19] For β-fluorine elimination of transition metal complex, see: (a) Fujiwara, M.; Ichikawa, J.; Okauchi, T.; Minami, T. *Tetrahedron Lett.* **1999**, *40*, 7261–7265. (b) Watson, L. A.; Yandulov, D. V.; Caulton, K. G. *J. Am. Chem. Soc.* **2001**, 123, 603–611. (c) Anderson, D. J.; McDonald, R.; Cowie, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 3741–3744. (d) Harrison, D. J.; Lee, G. M.; Leclerc, M. C.; Korobkov, I.; Baker, R. T. *J. Am. Chem. Soc.* **2013**, *135*, 18296–18299.

[20] For transition-metal catalyzed reactions by β-fluorine elimination, see: [alkene insertion–β-fluorine elimination sequence] (a) Heitz, W.; Knebelkamp, A. *Makromol. Chem., Rapid Commun.* **1991**, *12*, 69–75. (b) Sakoda, K.; Mihara, J.; Ichikawa, J. *Chem. Commun.* **2005**, 4684–4686. (c) Ichikawa, J.; Nadano, R.; Ito, N. *Chem. Commun.* **2006**, 4425–4427. (d) Miura, T.; Ito, Y.; Murakami, M. *Chem. Lett.* **2008**, *37*, 1006–1007. (e) Corberan, R.; Mszar, N. W.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2011**, *50*, 7079–7082. [Wacker-type nucleophilic addition–β-fluorine elimination sequence] (f) Yokota, M.; Fujita, D.; Ichikawa, J. *Org. Lett.* **2007**, *9*, 4639–4642. (g) Tanabe, H.; Ichikawa, J. *Chem. Lett.* **2010**, *39*, 248–249. See also: (h) Hu, M.; He, Z.; Gao, B.; Li, L.; Ni, C.; Hu J. *J. Am. Chem. Soc.* **2013**, *135*, 17302–17305.

[21] For transition-metal catalyzed reactions by α-fluorine elimination, see: Takachi, M.; Kita, Y.; Tobisu, M.; Fukumoto, Y.; Chatani, N. *Angew. Chem. Int. Ed.* **2010**, *49*, 8717–8720.

[22] Schumann, H.; Freitag, S.; Girgsdies, F.; Hemling, H.; Kociok-Köhn, G. *Eur. J. Inorg.*

Chem. **1998**, 245.

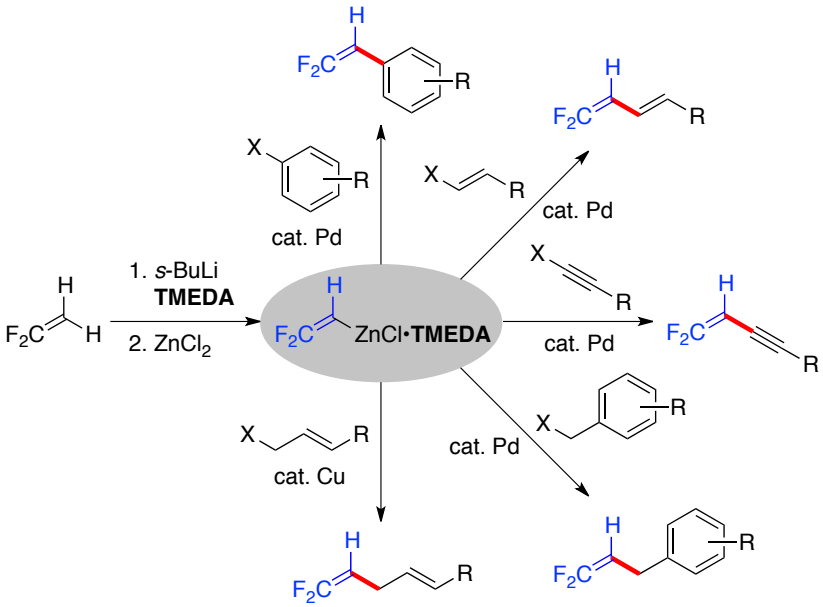
[23] Hoberg, H.; Guhl, D. *J. Organomet. Chem.* **1989**, *378*, 279–292.

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.

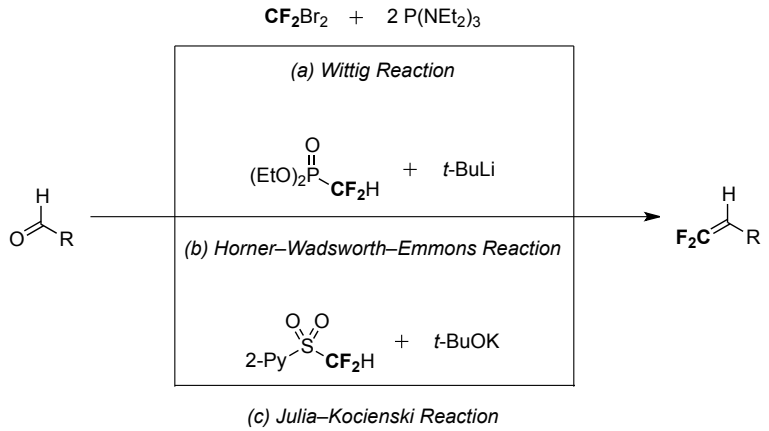


2.1. Introduction

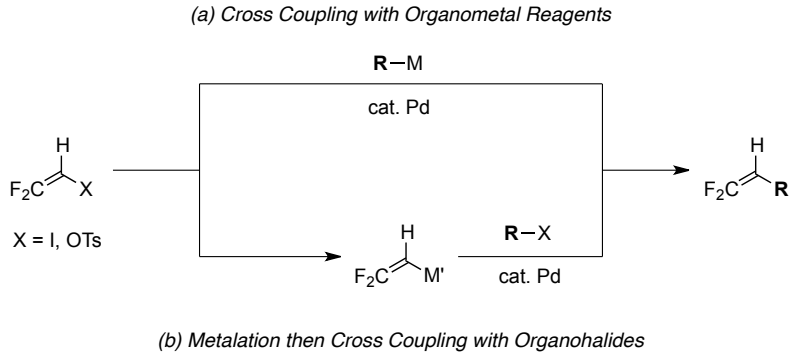
2,2-Difluorovinyl compounds are an important class of compounds because they exhibit unique properties due to the steric and electronic effects of fluorine. They serve as not only building blocks for fluorine-containing organic molecules but also monomers for functional polymers.[1,2] In addition, 2,2-difluorovinyl 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.[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.[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).[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.[9,10] Both types of reactions require starting difluorovinyl halides (Route b), which are expensive or rarely available from commercial sources.

Scheme 1. Difluoromethylation of Aldehydes

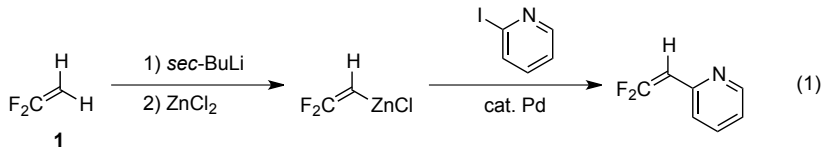


Scheme 2. Metal-Mediated Difluorovinylation

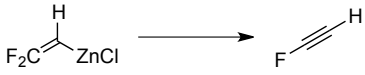


Normant *et al*. reported the synthesis of a 2,2-difluorovinyl compound starting from 1,1-difluoroethylene (**1**), a commercially available, industrial material (eq 1).[11] In the study, a difluorovinylzinc complex, prepared via the deprotonation of **1** and subsequent transmetalation, was subjected 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.



(1)



+ ZnClF (2)

β-Fluorine Elimination

It has been reported that organozinc reagents are often stabilized by coordination of two amine molecules.[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.

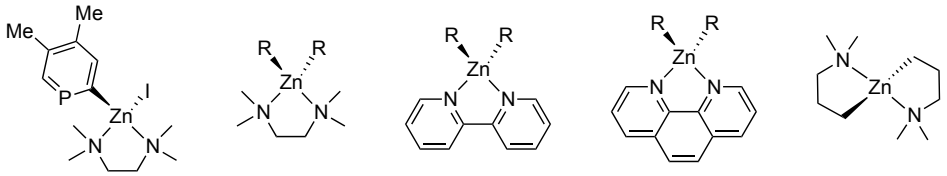
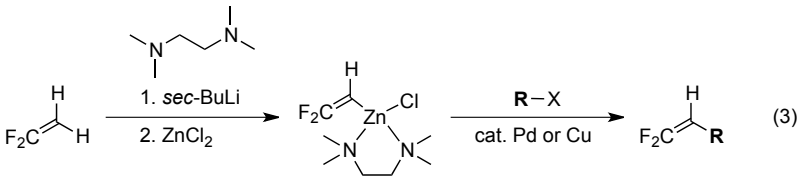


Figure 1. Stable Organozinc–Diamine Complexes

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

N,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA, eq 3). Furthermore, I developed the palladium- or copper-catalyzed cross-coupling reactions of the prepared zinc–TMEDA complex with various organic halides.[16] Section 2.3 described the details of facile synthesis of difluorovinyl compounds via cross-coupling.

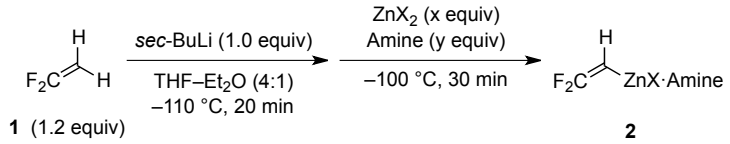


(3)

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.[11] 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.[12,13] 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 NEt_3 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'*-tetramethylethylenediamine (TMEDA) turned out to be highly effective for the formation of **2** (Entries 6–8).[17,18] 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 $ZnCl_2$ (Entry 7). The obtained 2,2-difluorovinylzinc–TMEDA complex **2a** is thermally stable and thus storable.

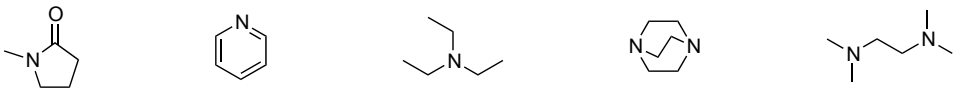
Table 1. Screening of Amine Ligands for Preparation of the Zinc Reagent **2**



1 (1.2 equiv) **2**

Entry	ZnX_2 (x equiv)	Amine (y equiv)	Yield / %[a]
1	$ZnCl_2$ (1.0)		50
2	$ZnCl_2$ (1.0)	NMP (2.6)	9
3	$ZnCl_2$ (1.0)	Pyridine (2.6)	36
4	$ZnCl_2$ (1.0)	NEt_3 (2.6)	70
5	$ZnCl_2$ (1.0)	DABCO (1.3)	0
6	$ZnCl_2$ (1.0)	TMEDA (1.3)	90
7[b]	$ZnCl_2$ (1.0)	TMEDA (1.3)	95
8[b]	ZnI_2 (1.0)	TMEDA (1.3)	70
9	$ZnCl_2$·TMEDA (1.0)		62

[a] Yields are determined by ^{19}F NMR using $PhCF_3$ as an internal standard.
[b] Lithiation was carried out in the presence of TMEDA.



NMP Pyridine NEt_3 DABCO TMEDA

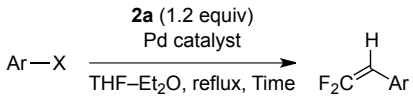
Removal of the solvents from the solution of **2a** under reduced pressure afforded a white powder of **2a** containing LiCl.[19] The solid-state **2a** was found to be more thermally stable than **2a** in solution. While **2a** in solution was storable for a week at –20 °C under argon, solid-state **2a** 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

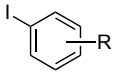
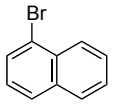
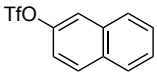
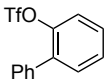
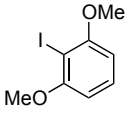
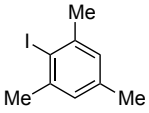
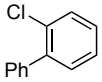
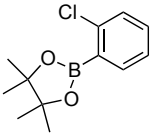
2.3.1. Cross-Coupling Reaction with Aryl Halides and Triflates: Synthesis of β,β-Difluorostyrenes

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).[20] 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).[21,22] 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).

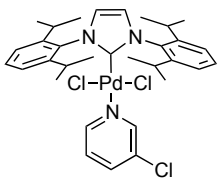
Table 2. Difluorostyrene Synthesis: Pd-Catalyzed Coupling of **2a** with Aryl Halides and Triflates



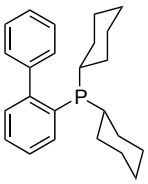
3a–j **4a–j**

Entry	Ar–X		Pd catalyst (mol%)	Time / h	Yield / %[a]
1		(*p*-Me) **3a**	$Pd(PPh_3)_4$ (2)	6	59 (86), **4a**
2		(*p*-OMe) **3b**	$Pd(PPh_3)_4$ (2)	6	87, **4b**
3		(*o*-NH_2) **3c**	$Pd(PPh_3)_4$ (2)	1	87, **4c**
4[b]		(*p*-NO_2) **3d**	$Pd_2(dba)_3{\cdot}CHCl_3$ (2), PPh_3 (8)	12	84, **4d**
5		**3e**	$Pd(PPh_3)_4$ (2)	10	87, **4e**
6		**3f**	$Pd(PPh_3)_4$ (2)	6	90, **4f**
7		**3g**	PEPPSI-IPr (5)	10	82, **4g**
8		**3h**	PEPPSI-IPr (4)	12	79, **4h**
9		**3i**	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5)/ Cy-JohnPhos (10)	24	(59), **4i**
10		**3j**	PEPPSI-IPr (5)	8	(71), **4g**
11		**3k**	PEPPSI-IPr (5)	6	73, **4k**

[a] Isolated yield. In parentheses is shown yield determined by ^{19}F NMR using $PhCF_3$ as an internal standard.
[b] Room temperature.



PEPPSI-IPr



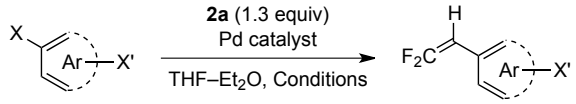
Cy-JohnPhos

It is noteworthy that the reaction exhibited complete chemoselectivity (Table 3).[23] Both 3-iodophenyl triflate (**3l**) and 3-bromo-4-iodobiphenyl (**3m**) showed thorough chemoselective

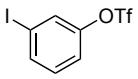
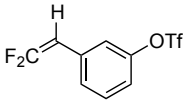
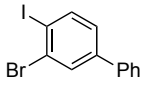
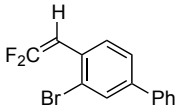
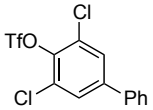
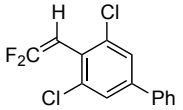
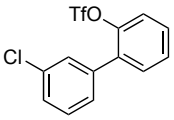
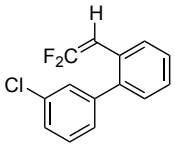
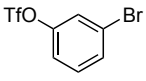
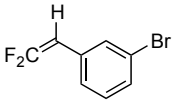
substitution of the iodo group (Entries 1 and 2). Likewise, the triflyloxy groups of **3n** and **3o** were exclusively substituted over the chlorine atoms (Entries 3 and 4). In the case of 3-bromophenyl triflate (**3p**), the triflyloxy group reacted preferentially (>85% selectivity), although triflates 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**

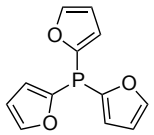
Table 3. Chemoselectivity in the coupling reaction of **2a**

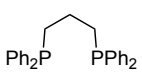


3l–p **4l–p**

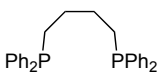
Entry	Ar−X		Pd catalyst (mol%)	Consitions	Yield / %[a]
1		**3l**	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5) $P(2\text{-furyl})_3$ (10)	RT, 4 h	 92, **4l**
2		**3m**	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5) $P(2\text{-furyl})_3$ (10)	55 °C, 4 h	 96, **4m**
3		**3n**	$PdCl_2$(dppp) (5) LiCl (375)	reflux, 23 h	 73, **4n**
4		**3o**	$PdCl_2$(dppf) (4)	reflux, 12 h	 87, **4o**
5[b]		**3p**	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5) dppb (5.0)	45 °C, 24 h	 69 (71), **4p**

[a] Isolated yield. In parentheses is shown yield determined by ^{19}F NMR using $PhCF_3$ as an internal standard.
[b] By-products formed by the reaction of the bromo group were observed by ^{19}F NMR (10% in total).

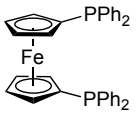

P(2-furyl)$_3$



dppp



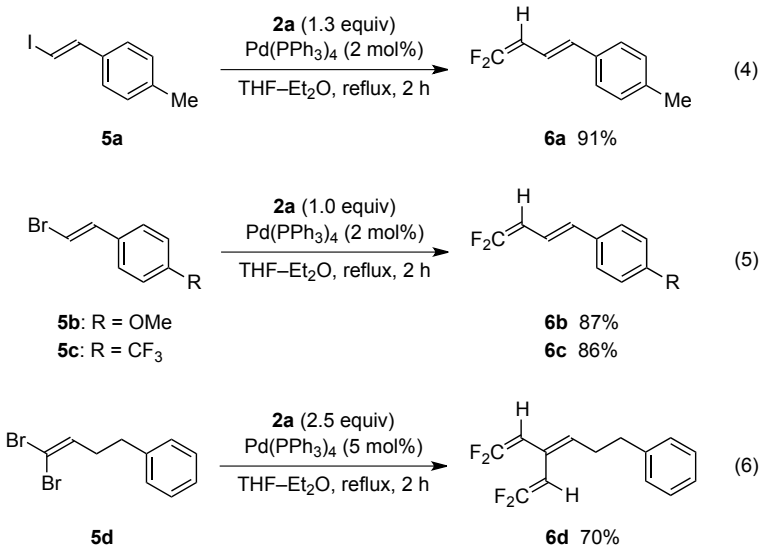
dppb



dppf

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 $Pd(PPh_3)_4$, (*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).

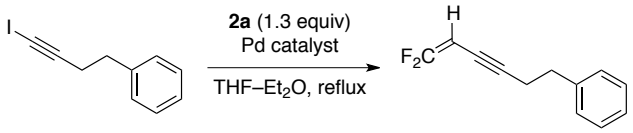


2.3.3. Coupling reaction with alkynyl halides: Synthesis of 1,1-difluoro-1,3-enynes

When coupling the difluorovinylzinc complex **2a** with alkynyl halides **7**, the choice of ligand for palladium was critical (Table 4). The use of $Pd(PPh_3)_4$ 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 (dppf) also gave a satisfactory yield of 86% (entry 7).

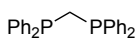
Table 4. Effect of ligands for Pd-catalyzed coupling of **2a** with alkynyl halide **7a**



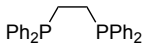
7a **8a**

Entry	Pd catalyst (mol%)	Time (h)	Yield (%)[a]
1	$Pd(PPh_3)_4$ (4)	3	59
2	$Pd_2(dba)_3{\cdot}CHCl_3$ (2) PPh_3 (8)	4	66
3	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5) dppm (5)	5	27
4	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5) dppe (5)	2	67
5	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5) dppp (5)	5	96
6	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5) dppb (5)	5	68
7	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5) dppf (5)	5	86

[a] ^{19}F NMR yield using $PhCF_3$ as an internal standard.



dppm

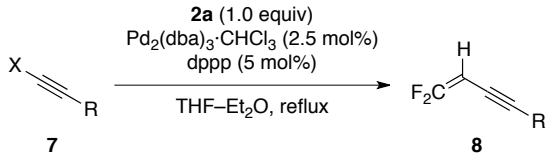


dppe

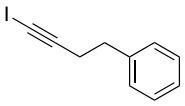
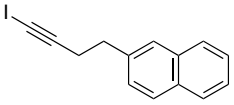
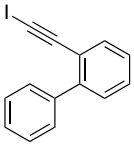
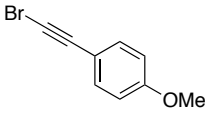
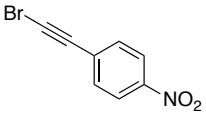
With optimized conditions in hand, the substrate scope was investigated (Table 5). Along with alkyl-substituted ethynyl iodides **7a** and **7b** (entries 1 and 2), aryl-substituted ethynyl iodide **7c** effectively underwent the Pd(0)/dppp-catalyzed coupling reaction with **2a** to afford the corresponding 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-enyne **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**



7 **8**

Entry	**7**		Time (h)	Yield (%)[a]
1[b]		**7a**	5	**8a** 85
2		**7b**	2	**8b** 94
3[c]		**7c**	5	**8c** 90
4		**7d**	5	**8d** 94
5		**7e**	1	**8e** 63

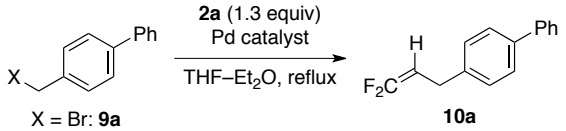
[a] Isolated yield. [b] **2a** (1.3 equiv). [c] **2a** (1.2 equiv).

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 $Pd(PPh_3)_4$, 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).

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



X = Br: **9a**
X = Cl: **9'a**

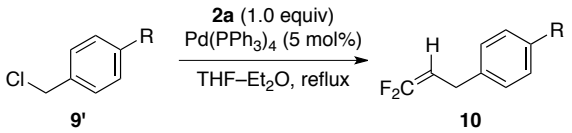
10a

Entry	X	Pd catalyst (mol%)	Time (h)	Yield (%)[a]
1	Br	$Pd(PPh_3)_4$ (5)	1	27
2	Br	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5) NaI (130)	1	39
3	Br	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5) PPh_3 (10)	2	19
4	Br	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5) PCy_3 (10)	1	3
5	Br	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5) $P(t\text{-}Bu)_3$ (5)	2	33
6	Br	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5) dppe (5)	2	N.D.
7	Br	PEPPSI-IPr (5)	1	14
8[b]	Cl	$Pd(PPh_3)_4$ (5)	2	92

[a] ^{19}F NMR yield using $PhCF_3$ 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'**



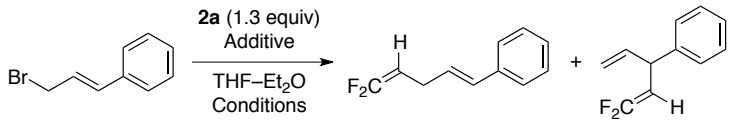
Entry	R		Time (h)	Yield (%)[a]
1	R = Ph	**9'a**	2	**10a** 92
2[b]	R = Bu	**9'b**	2	**10b** 93
3	R = OMe	**9'c**	2	**10c** 82
4	R = CF_3	**9'd**	6	**10d** 63 (73)

[a] Isolated yield. ^{19}F NMR yield using $PhCF_3$ as an internal standard is indicated in parentheses. [b] **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 difluorovinylzinc 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 difluorovinylation using allyl halide *E*-**11a** as a model substrate, the palladium catalyst $Pd(PPh_3)_4$ 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 difluorovinylated products, with the S_N2-type product *E*-**12a** preferentially obtained along with S_N2'-type product **13a** (entries 2 and 3). Among the Cu(I) species examined, a catalytic amount of $CuBr{\cdot}SMe_2$ afforded the highest yield of difluorovinylated 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**

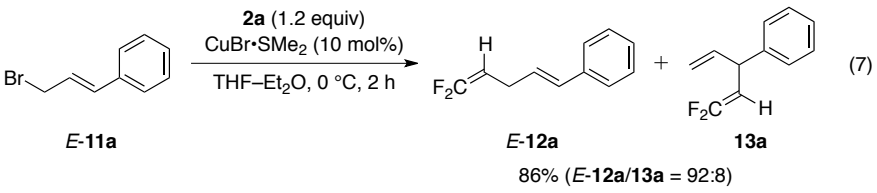


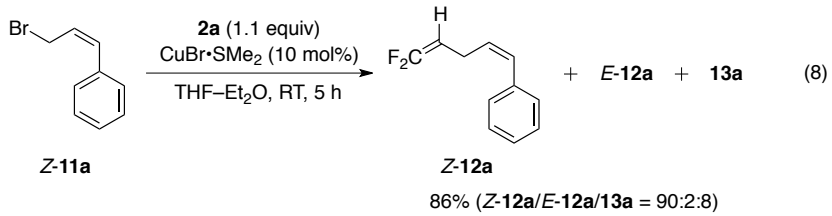
11a *E*-**12a** **13a**

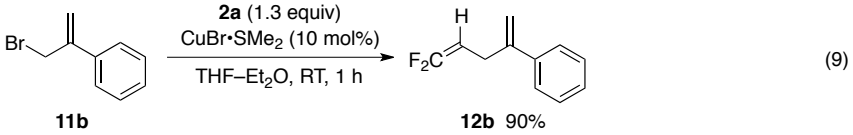
Entry	Additive	Conditions	Yield (%)[a]	*E*-**12a**/**13a**[b]
1	$Pd(PPh_3)_4$ (2 mol%)	reflux, 3 h	5	–
2	CuI (1.3 equiv)	RT, 2 h	93	76:24
3	CuI (1.3 equiv)	0 °C, 2 h then RT, 2 h	83	86:14
4	CuI (10 mol%)	RT, 2 h	39	83:17
5	CuCN (10 mol%)	RT, 2 h	39	82:18
6[c]	$CuBr•SMe_2$ (10 mol%)	0 °C, 2 h	87	92:8

[a] ^{19}F NMR yield using $PhCF_3$ as an internal standard. [b] The ratio of *E*-**12a** and **13a** was determined by ^{19}F NMR measurement. [c] **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

[1] (a) Uneyama, K. *Organofluorine Chemistry*; Blackwell Publishing: Oxford, UK, **2006**. (b) Ichikawa, J. *Chim. Oggi* **2007**, *25*, 54–57. (c) Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119–2183. (d) Ahrens, T.; Kohlmann, J.; Ahrens, M.; Braun, T. *Chem. Rev.* DOI: 10.1021/cr500257c.

[2] Souzy, R.; Ameduri, B.; Boutevin, B. *Prog. Polym. Sci.* **2004**, *29*, 75–106.

[3] Bobek, M.; Kavai, I.; De Clercq, E. *J. Med. Chem.* **1987**, *30*, 1494–1497.

[4] Moore, W. R.; Schatzman, G. L.; Jarvi, E. T.; Gross, R. S.; McCarthy, J. R. *J. Am. Chem. Soc.* **1992**, *114*, 360–361.

[5] (a) Magueur, G.; Crousse, B.; Ourévitch, M.; Bonnet-Delpon, D.; Bégué, J.-P. *J. Fluorine Chem.* **2006**, *127*, 637–642. (b) Ichikawa, J. *J. Synth. Org. Chem. Jpn.* **2010**, *68*, 1175–1184. (c) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529–2591.

[6] For recent reports on the Wittig-type difluoromethylenation, see: (a) Zheng, J.; Cai, J.; Lin, J.-H.; Guo, Y.; Xiao, J.-C. *Chem. Commun.* **2013**, *49*, 7513–7515. (b) Loska, R.; Szachowicz, K.; Szydlik, D. *Org. Lett.* **2013**, *15*, 5706–5709. (c) Zheng, J.; Lin, J.-H.; Cai, J.; Xiao, J.-C. *Chem. Eur. J.* **2013**, *19*, 15261–15266. (d) Li, Q.; Lin, J.-H.; Deng, Z.-Y.; Zheng, J.; Cai, J.; Xiao, J.-C. *J. Fluorine Chem.* **2014**, *163*, 38–41. (e) Wang, F.; Li, L.; Ni, C.; Hu, J. Beilstein *J. Org. Chem.* **2014**, *10*, 344–351. (f) Qiao, Y.; Si, T.; Yang, M.-H.; Altman, R. A. *J. Org. Chem.* **2014**, *79*, 7122–7131.

[7] Piettre, S. R.; Cabanas, L. *Tetrahedron Lett.* **1996**, *37*, 5881–5884.

[8] (a) Prakash, G. K. S.; Wang, Y.; Hu, J.; Olah, G. A. *J. Fluorine Chem.* **2005**, *126*, 1361–1367. (b) Zhao, Y.; Huang, W.; Zhu, L.; Hu, J. *Org. Lett.* **2010**, *12*, 1444–1447. (c) Wang, X.-P.; Lin, J.-H.; Xiao, J.-C.; Zheng, X. *Eur. J. Org. Chem.* **2014**, 928–932.

[9] (a) Gøgsig, T. M.; Søbjerg, L. S.; Lindhardt, A. T.; Jensen, K. L.; Skrydstrup, T. *J. Org. Chem.* **2008**, *73*, 3404–3410. (b) Ehm, C.; Akkerman, F. A.; Lentz, D. *J. Fluorine Chem.* **2010**. *131*, 1173–1181.

[10] (a) Ichikawa, J.; Fujiwara, M.; Nawata, H.; Okauchi, T.; Minami, T. *Tetrahedron Lett.* **1996**, *37*, 8799–8802. (b) Nguyen, B. V.; Burton, D. J. *J. Org. Chem.* **1997**, 62, 7758–7764. (c) Ichikawa, J.; *J. Fluorine Chem.* **2000**, *105*, 257–263. (d) Raghavanpillai, A.; Burton, D. J. *J. Org. Chem.* **2006**, *71*, 194–201. (e) Choi, J. H.; Jeong, I. H. *Tetrahedron Lett.* **2008**, *49*, 952–955. (f) Akkerman, F. A.; Kickbusch, R.; Lentz, D. *Chem. Asian J.* **2008**, *3*, 719–731. (g) Han, S. Y.; Jeong, I. H. *Org. Lett.* **2010**, *12*, 5518–5521. (h) Lu, L.; Burton, D. J. *J. Fluorine Chem.* **2012**, *133*, 16–19.

[11] (a) Gillet, J.-P.; Sauvetre, R.; Normant, J.-F. *Tetrahedron Lett.* **1985**, *26*, 3999–4002. (b) Gillet, J. P.; Sauvêtre, R.; Normant, J. F. *Synthesis* **1986**, 538–543.

[12] Fluoroacetylenes have been prepared by lithiation of 1,1-difluoroethylene. See: Hanamoto, T.; Koga, Y.; Kawanami, T.; Furuno, H.; Inanaga, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3582–3584.

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

[14] (a) Noltes, J. G.; van den Hurk, J. W. G. *J. Organomet. Chem.* **1964**, *3*, 222–228. (b) Dekker, J.; Boersma, J.; Fernholt, L.; Haaland, A.; Spek, A. L. *Organometallics* **1987**, *6*, 1202–1206. (c) Motevalli, M.; O'Brien, P.; Robinson, A. J.; Walsh J. R.; Wyatt P. B.; Jones, A. C. *J. Organomet. Chem.* **1993**, *461*, 5–7. (d) Teunissen, H. T.; Bickelhaupt, F. *Organometallics* **1996**, **15**, 794–801. (d) Schumann, H.; Freitag, S.; Girgsdies, F.; Hemling, H.; Kociok-Köhn, G. *Eur. J. Inorg. Chem.* **1998**, 245–252.

[15] For fluoroalkenylzinc reagents stabilized by TMEDA, see: (a) Jiang, B.; Xu, Y. *J. Org. Chem.* **1991**, *56*, 7336–7340. (b) Raghavanpillai, A.; Burton, D. J. *J. Org. Chem.* **2004**, *69*, 7083–7091.

[16] For a recent review on the Negishi coupling, see: Negishi, E.-i.; Hu, Q.; Huang, Z.; Qian, M.; Wang, G. *Aldrichimica Acta* **2005**, *38*, 71–88.

[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 (δ: parts per million from hexafluorobenzene). **2a**: δ 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: δ 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: δ 80.0–80.2 (m, 2F).

[19] Powdered organozinc reagents have been prepared. see: (a) S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9205–9209. (b) Manolikakes, S. M.; Ellwart, M.; Stathakis, C. I.; Knochel P. *Chem. Eur. J.* **2014**, *20*, 12289–12297.

[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.

[21] PEPPSI-IPr is known as an efficient catalyst for the Negishi coupling. For reviews, see: a) Organ, M. G.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Valente, C. *Chem. Eur. J.* **2006**, *12*, 4749–4755. (b) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Angew. Chem. Int. Ed.* **2007**, *46*, 2768–2813. (c) Valente, C.; Belowich, M. E.; Hadei, N.; Organ, M. G. *Eur. J. Org. Chem.* **2010**, 4343–4354.

[22] 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.

[23] For several examples on chemoselective coupling reactions, see: a) Rottländer, M.; Palmer, N.; Knochel, P. *Synlett* **1996**, 573–575. (b) Kamikawa, T.; Hayashi, T. *Tetrahedron Lett.* **1997**, *38*, 7087–7090. (c) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.

[24] Pohmakotr, M.; Boonkitpattarakul, K.; Ieawsuwan, W.; Jarussophon, S.; Duangdee, N.; Tuchinda, P.; Reutrakul, V. *Tetrahedron* **2006**, *62*, 5973–5985.

[25] Nowak, I.; Robins, M. J. *Org. Lett.* **2005**, *7*, 721–724.

[26] Yokota, M.; Fujita, D.; Ichikawa, J. *Org. Lett.* **2007**, *9*, 4639–4642.

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_4Si (for ^{1}H NMR: δ = 0.00 ppm), $CDCl_3$ (for ^{13}C NMR: δ = 77.0 ppm), and C_6F_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_6D_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, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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 $C_8H_7F_2N$ ($[M]^+$): 155.0547; Found: 155.0548.

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

^{1}H NMR (500 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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 9a).

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, $CDCl_3$): δ 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, $CDCl_3$): δ 55.8, 72.1 (dd, J_{CF} = 34, 19 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, $CDCl_3$): δ 77.9 (dd, J_{FF} = 26 Hz, J_{FH} = 3 Hz, 1F), 84.4 (dd, J_{FH} = 28 Hz, J_{FF} = 26 Hz, 1F). IR (neat): 2941, 1738, 1473, 1254, 1109 cm^{-1}. Anal. calcd. for $C_{10}H_{10}F_2O_2$: 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, $CDCl_3$): δ 1.35 (s, 12H), 6.25 (dd, J_{HF} = 26.8, 5.1 Hz, 1H), 7.22 (ddd, J = 7.6, 7.4, 1.0 Hz, 1H), 7.36–7.47 (m, 1H), 7.55 (dd, J = 8.0, 1.0 Hz, 1H), 7.84 (dd, J = 7.6, 1.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 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 Hz), 136.4, 156.2 (dd, J_{CF} = 299, 287 Hz), (One aromatic carbon signal was not detected due to ^{13}C–^{10}B and ^{13}C–^{11}B coupling and overlapping with other signals). ^{19}F NMR (470 MHz, $CDCl_3$): δ 79.2 (dd, J_{FF} 32 Hz, J_{FH} = 5 Hz, 1F), 79.6 (dd, J_{FF} = 32 Hz, J_{FH} = 27 Hz, 1F). IR (neat): 2979, 1724, 1346, 1146, 912, 743 cm^{-1}. HRMS (EI): *m*/*z* calcd. for $C_{14}H_{17}BF_2O_2$ ([M]$^+$): 266.1290; Found: 266.1288.

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

^{1}H NMR (500 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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 $C_9H_5F_5O_3S$ ([M]$^+$): 287.9880; Found: 287.9879.

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

^{1}H NMR (500 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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, J_{CF} = 299, 290 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 77.7 (dd, J_{FF} = 30 Hz, J_{FH} = 26 Hz, 1F), 79.6 (dd, J_{FF} = 30 Hz, J_{FH} = 4 Hz, 1F). IR (neat): 1726, 1477, 1248, 1178, 945, 758 cm^{-1}. HRMS (EI): *m*/*z* calcd. for $C_{14}H_9BrF_2$ ([M]$^+$): 293.9856; Found: 293.9849.

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

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.34 (d, J_{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, $CDCl_3$): δ 76.6–76.9 (overlapped dd), 126.2 (dd, *J* = 9, 4 Hz), 126.5, 126.9, 128.6, 129.1, 135.9, 138.0, 142.9, 155.8 (dd, J_{CF} = 297, 290 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 79.6 (d, J_{FF} = 20 Hz, 1F), 85.9 (dd, J_{FH} = 26, J_{FF} = 20 Hz, 1F). IR (neat): 1738, 1535, 1248, 1173, 914, 758 cm^{-1}. HRMS (EI): *m*/*z* calcd. for $C_{14}H_8Cl_2F_2$ ([M]$^+$): 283.9971; Found: 283.9964.

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

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.17 (dd, J_{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, $CDCl_3$): δ 80.3 (dd, J_{CF} = 30, 13 Hz), 127.2, 127.5, 127.8, 127.9 (dd, J_{CF} = 7, 6 Hz), 128.0, 128.2 (dd, J_{CF} = 9, 1 Hz), 129.49, 129.51, 130.0, 134.2, 139.7 (d, J_{CF} = 3.5 Hz), 142.5, 156.3 (dd, J_{CF} = 299, 288 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 77.7 (dd, J_{FF} = 30 Hz, J_{FH} = 26 Hz, 1F), 79.6 (dd, J_{FF} = 30 Hz, J_{FH} = 4 Hz, 1F). IR (neat): 3062, 1724, 1232, 1173, 939, 756 cm^{-1}. Anal. calcd. for $C_{14}H_9ClF_2$: C, 67.08; H, 3.62; Found: C, 67.12; H, 3.72.

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

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.23 (dd, J_{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, $CDCl_3$): δ 81.3 (dd, J_{CF} = 30, 14 Hz), 122.7, 126.1 (dd, J_{CF} = 6, 4 Hz), 130.0, 130.1, 130.4 (dd, J_{CF} = 7, 4 Hz), 132.4 (dd, J_{CF} = 7, 7 Hz), 156.5 (dd, J_{CF} = 300, 255 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 80.4 (dd, J_{FF} = 27, J_{FH} = 3 Hz, 1F), 82.4 (dd, J_{FF} = 27 Hz, 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 $Pd(PPh_3)_4$ (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**)

^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.2, 82.9 (dd, J_{CF} = 30, 17 Hz), 116.8 (dd, J_{CF} = 4, 2 Hz), 126.0, 129.3, 131.0 (dd, J_{CF} = 13, 4 Hz), 134.1, 137.5, 156.7 (dd, J_{CF} = 321, 314 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 75.3 (d, J_{FF} = 28 Hz, 1F), 77.1 (dd, J_{FF} = 28 Hz, J_{FH} = 24 Hz, 1F). IR (neat): 2924, 2854, 1747, 1716, 1512, 1456, 1248, 1180, 1142, 796, 748 cm^{-1}. HRMS (EI): *m/z* calcd. for $C_{11}H_{10}F_2$ ($[M]^+$): 180.0751; Found: 180.0748.

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

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.81 (s, 3H), 5.10 (ddd, 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), 7.32 (d, J = 8.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): 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. ^{19}F NMR (470 MHz, $CDCl_3$): 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 $C_{11}H_{10}F_2O$ ($[M]^+$): 196.0700; Found: 196.0703.

(*E*)-1-(4,4-Difluorobuta-1,3-dienyl)-4-(trifluoromethyl)benzene (**6c**)

^{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 $C_{11}H_7F_5$ ([M]$^+$): 234.0468; Found: 234.0466.

[4-(2,2-Difluorovinyl)-6,6-difluorohexa-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 = 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.

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 $Pd_2(dba)_3{\cdot}CHCl_3$ (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%).

(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 (dtd, 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 (ddd, 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), 85.2 (dd, J_{FH} = 23 Hz, J_{FF} = 10 Hz, 1F). IR (neat): 3055, 1720, 1508, 1344, 1234, 1165, 1124, 928, 910, 814, 744 cm^{-1}. HRMS (EI): *m/z* calcd. for $C_{16}H_{12}F_2$ ([M]$^+$): 242.0907; 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]$^+$): 240.0751; Found: 240.0746.

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_{CF} = 8, 4 Hz), 114.0, 114.9, 132.9, 159.8, 161.6 (dd, J_{CF} = 300, 295 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 81.1 (d, 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, $CDCl_3$): δ 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). ^{13}C NMR (126 MHz, $CDCl_3$): δ 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). ^{19}F NMR (470 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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). ^{13}C NMR (126 MHz, $CDCl_3$): δ 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). ^{19}F NMR (470 MHz, $CDCl_3$): δ 71.3 (dd, J_{FF} = 45 Hz,

J_{FH} = 25 Hz, 1F), 74.2 (d, J_{FF} = 45 Hz, 1F). IR (neat): 3030, 1747, 1489, 1294, 1230, 1173, 964, 758, 694 cm^{-1}. HRMS (EI): *m/z* calcd. for $C_{15}H_{12}F_2$ ($[M]^+$): 230.0907; Found: 230.0904.

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

^1H NMR (500 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $CDCl_3$): δ 69.9 (dd, J_{FF} = 46 Hz, J_{FH} = 25 Hz, 1F), 72.8 (d, J_{FF} = 46 Hz, 1F). IR (neat): 2958, 2929, 2858, 1745, 1514, 1344, 1288, 1230, 1171, 958, 802, 758 cm^{-1}. 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**)

^1H NMR (500 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $CDCl_3$): δ 69.0 (dd, J_{FF} = 49 Hz, J_{FH} = 25 Hz, 1F), 71.9 (d, J_{FF} = 49 Hz, 1F). IR (neat): 2952, 1747, 1558, 1541, 1514, 1250, 1176, 1036, 741 cm^{-1}. HRMS (EI): *m/z* calcd. for $C_{10}H_{10}F_2O$ ($[M]^+$): 184.0700; Found: 184.0698.

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

^1H NMR (500 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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 $C_{10}H_7F_5$ ($[M]^+$): 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 11

(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 $CuBr{\cdot}SMe_2$ (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}H NMR (500 MHz, $CDCl_3$): 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}C NMR (126 MHz, $CDCl_3$): 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}F NMR (470 MHz, $CDCl_3$): 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}H NMR (500 MHz, $CDCl_3$): 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}C NMR (126 MHz, $CDCl_3$): 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}F NMR (470 MHz, $CDCl_3$): 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, 1741, 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**)

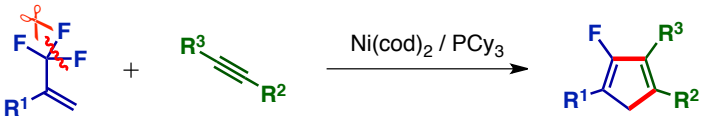
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.17 (d, J = 7.8 Hz, 2H), 4.27 (dtd, J_{HF} = 25.0 Hz, J = 7.8 Hz, J_{HF} = 2.3 Hz, 1H), 5.12 (d, J = 1.1 Hz, 1H), 5.36 (d, J = 1.1 Hz, 1H), 7.28 (tt, J = 7.3, 1.4 Hz, 1H), 7.32–7.35 (m, 2H), 7.39–7.41 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.1 (d, J_{CF} = 5 Hz), 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, $CDCl_3$): δ 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

Nickel-Mediated [3+2] Cycloaddition via Double C–F Bond Activation Using β-Fluorine Elimination

Abstract

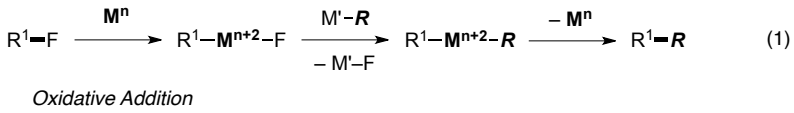
The nickel-mediated [3+2] cycloaddition of 2-trifluoromethyl-1-alkenes with alkynes afforded fluorine-containing multi-substituted cyclopentadienes in a regioselective manner. This reaction involves the consecutive two C–F bond cleavage of a trifluoromethyl or a pentafluoroethyl group via β-fluorine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

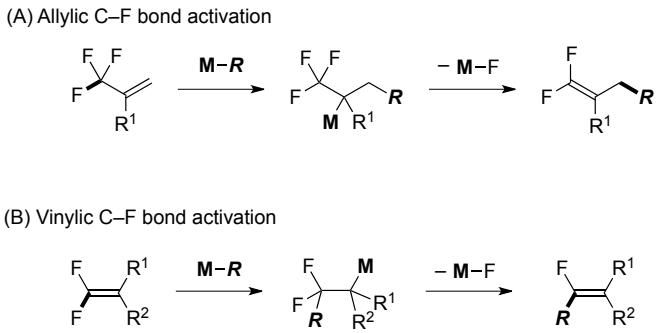


(1)

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). [5c,d]

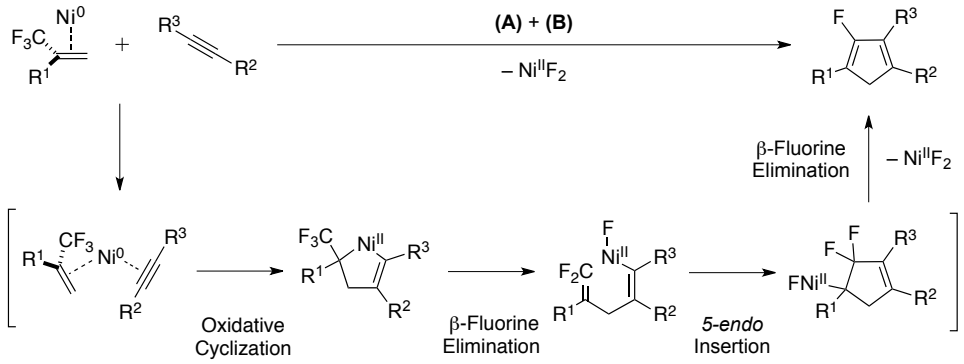
Scheme 1. C–F Bond Activation via β-Fluorine Elimination



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[5c,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



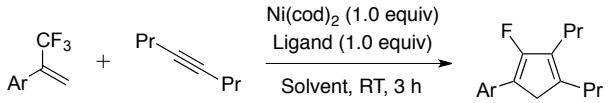
3.2 Nickel-Mediated [3+2] Cycloaddition of 2-Trifluoromethyl-1-Alkenes with Alkynes

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).

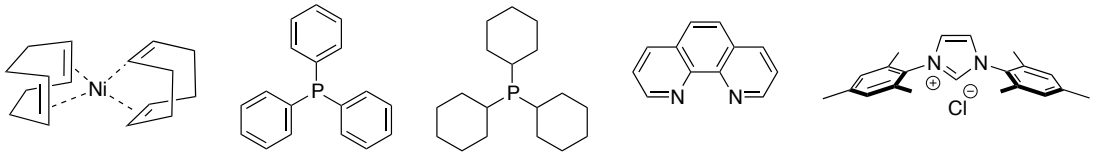
Table 1. Optimization of reaction conditions in Ni-mediated [3+2] cycloaddition



14a Ar = C_6H_4(*p*-Ac) **15a** (1.1 equiv) **16aa**

Entry	Ligand	Solvent	Yield (%)[a]
1	PPh_3	Toluene	0
2	1,10-phen	Toluene	0
3	IMes·HCl[b]	Toluene	26
4	PCy_3	Toluene	66[c]
5	PCy_3	THF	48
6	PCy_3	DME	56
7	PCy_3	1,4-Dioxane	74[c]

[a] ^{19}F NMR yield using $PhCF_3$ as an internal standard. [b] *t*-BuOK (1.0 equiv) was used as a base. [c] Isolated yield.



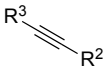
$Ni(cod)_2$ PPh_3 PCy_3 1,10-phen IMes·HCl

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).[11] α-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 α-trifluoromethylstyrene (**14e**) and α-trifluoromethylstyrene **14f** bearing an electron-donating methoxy group successfully underwent cycloaddition with **15c** or **15b** (Entries 9 and 10). The reaction of *t*-butyl α-trifluoromethyacrylate (**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).

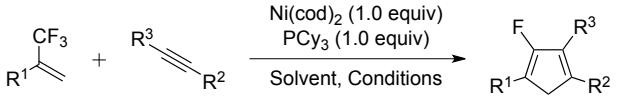
R^1 = C_6H_4(*p*-Ac), **14a**
R^1 = C_6H_4(*p*-CN), **14b**
R^1 = C_6H_4(*p*-CF_3), **14c**
R^1 = C_6H_4(*p*-CO_2Et), **14d**
R^1 = Ph, **14e**
R^1 = C_6H_4(*p*-OMe), **14f**
R^1 = CO_2*t*-Bu, **14g**



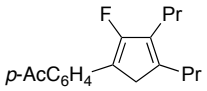
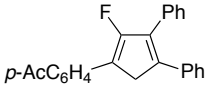
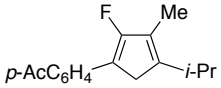
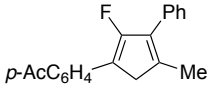
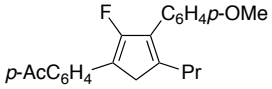
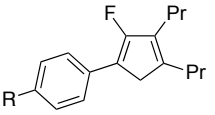
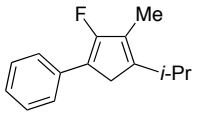
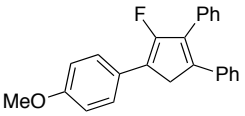
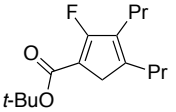
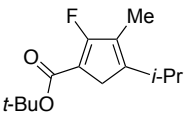
R^2, R^3 = *n*-Pr, **15a**
R^2, R^3 = Ph, **15b**
R^2 = *i*-Pr, R^3 = Me, **15c**
R^2 = Me, R^3 = Ph, **15d**
R^2 = *n*-Pr, R^3 = C_6H_4(*p*-OMe), **15e**

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**



14 **15** (1.1 equiv) **16**

Entry	14	15	Solvent	Conditions	16	Yield (%)[a]
1	**14a**	**15a**	1,4-Dioxane	RT, 3 h		**16aa** 74
4	**14a**	**15b**	1,4-Dioxane	100 °C, 3 h		**16ab** 86
2	**14a**	**15c**	1,4-Dioxane	RT, 10.5 h		**16ac** 77
3	**14a**	**15d**	1,4-Dioxane	60 °C, 19 h		**16ad** 48
5	**14a**	**15e**	Toluene	100 °C, 3 h		**16ae** 64
6	**14b**	**15a**	Toluene	RT, 1.5 h then 80 °C, 1.5 h	 R = CN	**16ba** 82
7	**14c**	**15a**	Toluene	RT, 9 h		CF_3 **16ca** 86
8	**14d**	**15a**	Toluene	50 °C, 1 h		CO_2Et **16da** 78
9	**14e**	**15c**	1,4-Dioxane	60 °C, 6 h		**16ec** 57
10	**14f**	**15b**	Toluene	100 °C, 3 h		**16fb** 42
11	**14g**	**15a**	1,4-Dioxane	RT, 3 h		**16ga** 88
12	**14g**	**15c**	Toluene	RT, 2 h		**16gc** 93

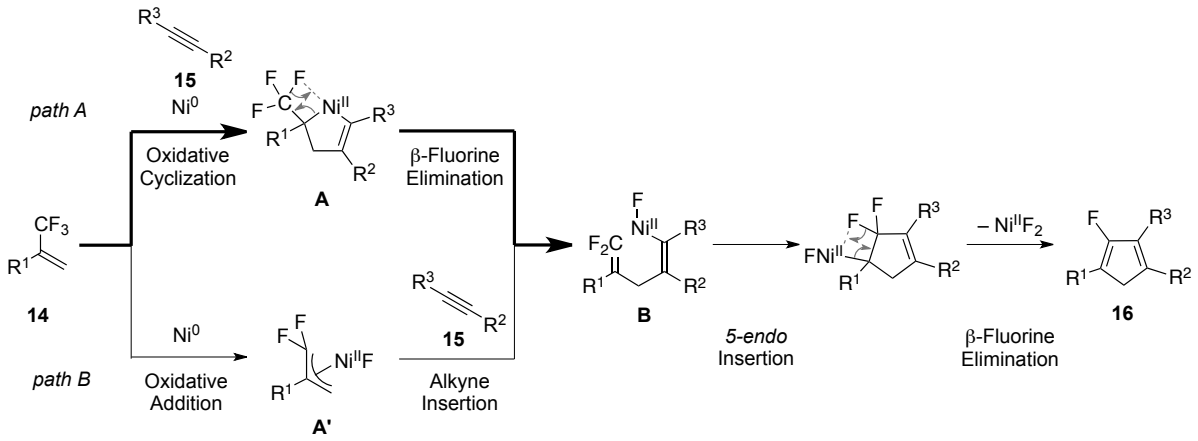
[a] Isolated yield.

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 NiF_2 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).[4] Alkyne insertion into the C–Ni bond of **A'** could lead to generation of **B**, followed by subsequent 5-*endo* insertion and β-fluorine elimination to give the same product **16**.

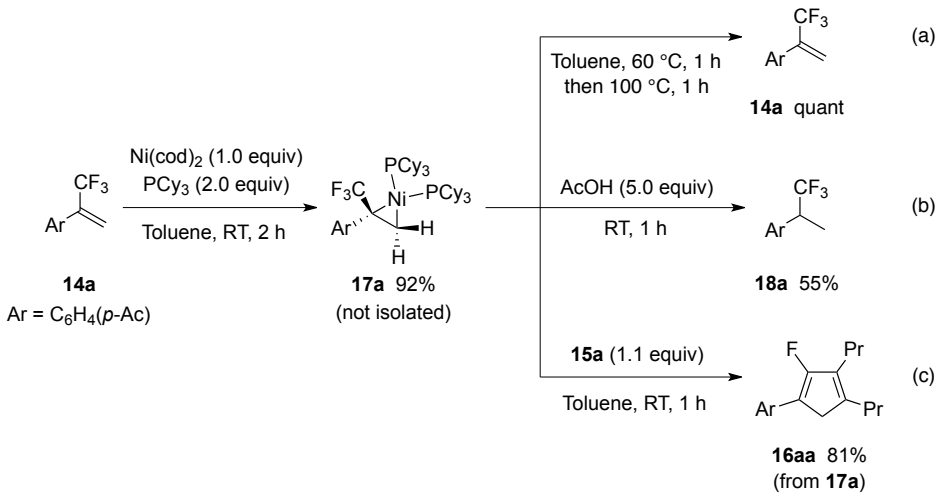
Scheme 3. Plausible Reaction Mechanisms for Ni-Mediated [3+2] Cycloaddition



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 starta 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).

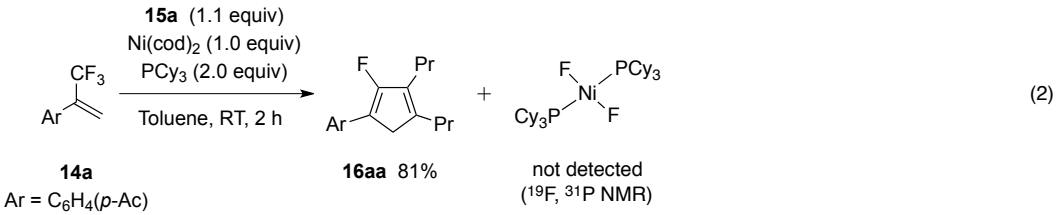
Scheme 4. Generation and Reactions of Nickelacyclopropane **17a**

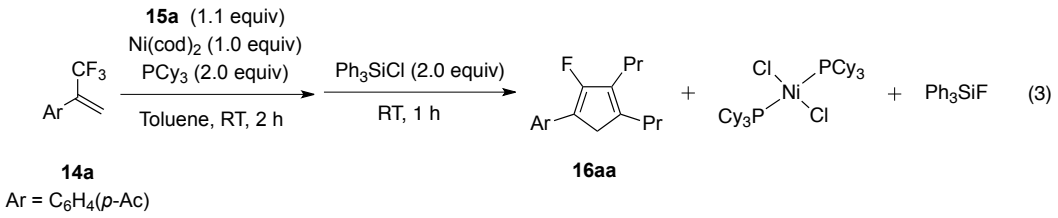


3.3.2. Elimination of NiF_2 Species

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_3SiCl after [3+2] cycloaddition (eq 3). As the result, violet crystallines of *trans*-$NiCl_2(PCy_3)_2$ and Ph_3SiF 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**.



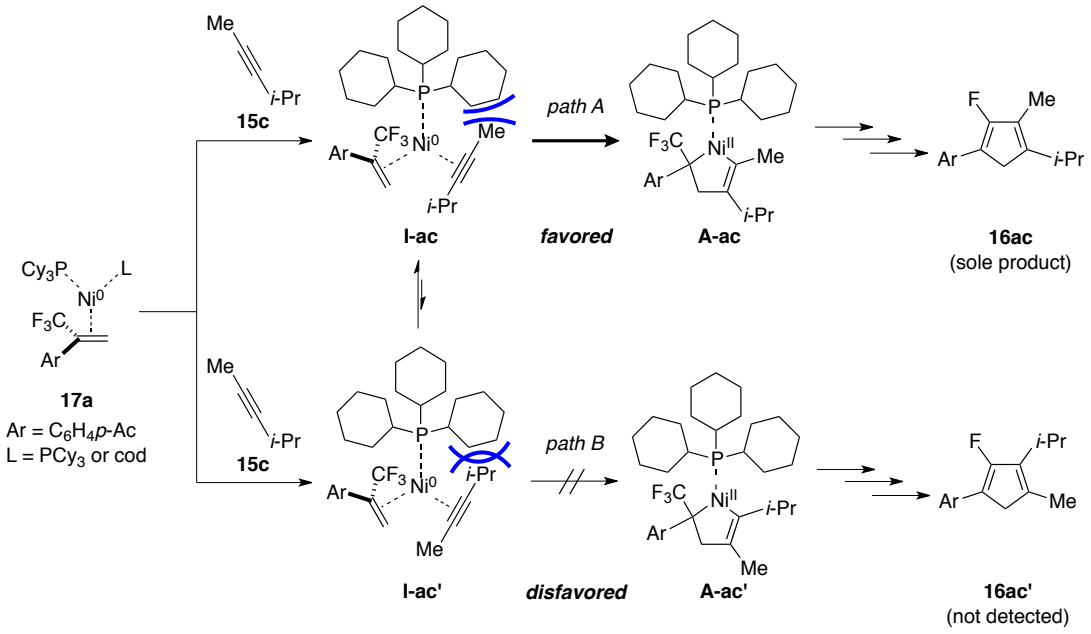


3.3.3. Regioselectivity of Alkynes

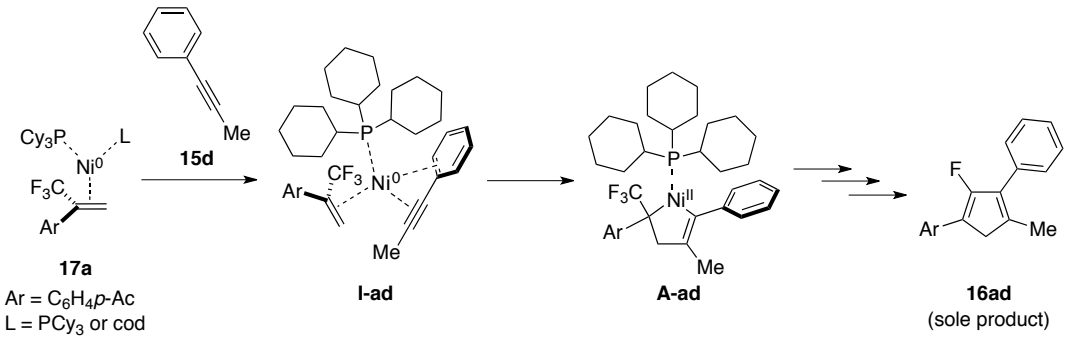
As described in Section 3.2, the nickel-mediated [3+2] cycloaddition of unsymmetrical alkynes with 2-trifluoromethy-1-alkenes proceeded with complete regioselectivity. It is clear that the regioselectivity of alkynes was determined in the oxidative cyclization step, because the oxidative cyclization 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 alkyne **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 π-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**



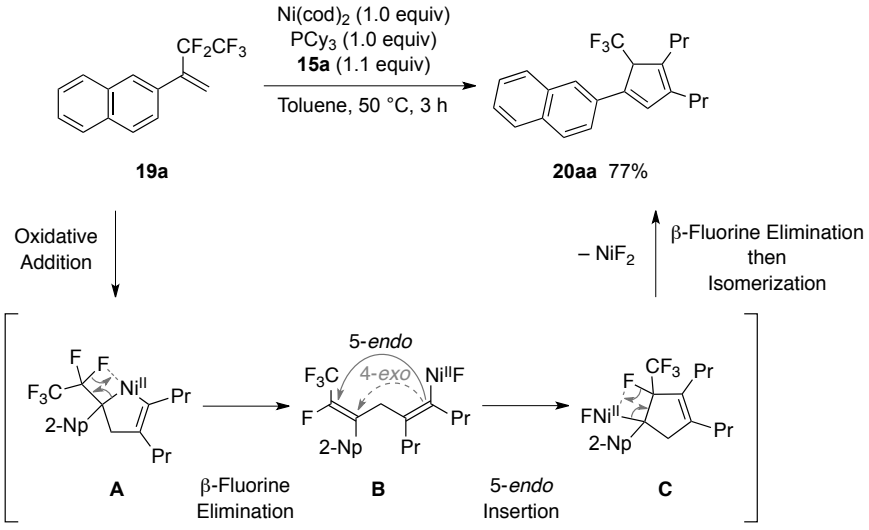
Scheme 6. Regioselectivity of Alkyne **15d**



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

[1] For selected reviews on C–F bond activation, see: (a) Amii, H.; Uneyama, K.; *Chem. Rev.* **2009**, *109*, 2119–2183. (b) Kuehnel, M. F.; Lentz, D.; Braun, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 3328–3348. (c) Ahrens, T.; Kohlmann, J.; Ahrens, M.; Braun, T. *Chem. Rev.* DOI: 10.1021/cr500257c.

[2] For recent reports on transition-metal-mediated reactions via aromatic C(sp^2)–F activation, see: (a) Cargill, M. R.; Sandford, G.; Tadeusiak, A. J.; Yufit, D. S.; Howard, J. A. K.; Kilickiran, P.; Nelles, G.; *J. Org. Chem.* **2010**, *75*, 5860–5866. (b) Tobisu, M.; Xu, T.; Shimasaki, T.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 19505–19511. (c) Jin, Z.; Li, Y.-J.; Ma, Y.-Q.; Qiu, L.-L.; Fang, J.-X. *Chem. Eur. J.* **2012**, *18*, 446–450 (d) Yu, D.; Shen, Q.; Lu, L.; *J. Org. Chem.* **2012**, *77*, 1798–1804. (e) Ohashi, M.; Doi, R.; Ogoshi, S. *Chem. Eur. J.* **2014**, *20*, 2040–2048.

[3] For recent reports on transition-metal-mediated reactions via vinylic C(sp^2)–F activation, see: [C–F bond cleavage via oxidative addition] (a) Ohashi, M.; Kambara, T.; Hatanaka, T.; Saijo, H.; Doi, R.; Ogoshi, S. *J. Am. Chem. Soc.* **2011**, *133*, 3256–3259. (b) Ohashi, M.; Shibata, M.; Saijo, H.; Kambara, T.; Ogoshi, S. *Organometallics* **2013**, *32*, 3631–3639. (c) Xu, W.; Sun, H.; Xiong, Z.; Li, X. *Organometallics* **2013**, 32, 7122–7132. (d) Saijo, H.; Sakaguchi, H.; Ohashi, M.; Ogoshi, S. *Organometallics* **2014**, *33*, 3369–3672. [C–F bond cleavage via other processes] (e) Takachi, M.; Kita, Y.; Tobisu, M.; Fukumoto, Y.; Chatani, N. *Angew. Chem. Int. Ed.* **2010**, *49*, 8717–8720. (f) Fuchibe, K.; Mayumi, Y.; Zhao, N.; Watanabe, S.; Yokota, M.; Ichikawa, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 7852–7828.

[4] For recent reports on transition-metal-mediated reactions via allylic C(sp^3)–F activation, see: (a) Narumi, T.; Tomita, K.; Inokuchi, E.; Kobayashi, K.; Oishi, S.; Ohno, H.; Fijii, N. *Org. Lett.* **2007**, *9*, 3465–3468. (b) Hazari, A.; Gouverneur, V.; Brown, J. M. *Angew. Chem. Int. Ed.*

2009, *48*, 1296–1299. (c) Pigeon, X.; Bergeon, M.; Barabé, F.; Dubé, P.; Frost, H. N.; Paquin, J.-F. *Angew. Chem. Int. Ed.* **2010**, *49*, 1123–1127. (d) Ohashi, M.; Shibara, M.; Ogoshi, S. *Angew. Chem. Int. Ed.* **2014**, *53*, 13578–13582.

[5] For transition-metal-mediated reactions via β-fluorine elimination, see: [vinylic C(sp^2)–F bond activation] (a) Heitz, W.; Knebelkamp, A. *Macromol. Chem. Rapid. Commun.* **1991**, 69–75. (b) Fujiwara, M.; Ichikawa, J.; Okauchi, T.; Minami, T. *Tetrahedron Lett.* **1999**, *40*, 7261–7265. (c) Sakoda, K.; Mihara, J.; Ichikawa, J. *Chem. Commum.* **2005**, 4684–4686. (d) Ichikawa, J.; Sakoda, K.; Mihara, J.; Ito, N. *J. Fluorine Chem.* **2006**, *127*, 489–504. (e) Harrison, D. J.; Lee, G. H.; Leclerc, M. C.; Lorobkov, I.; Baker, R. T. *J. Am. Chem. Soc.* **2013**, *135*, 18296–18299. [allylic C(sp^3)–F bond activation] (f) Ichikawa, J.; Nadano, R.; Ito, N. *Chem. Commum.* **2006**, 4425–4427. (g) Miura, T.; Ito, Y.; Murakami, M. *Chem. Lett.* **2008**, *37*, 1006–1007. See also: (h) Hu, M.; He, Z.; Gao, B.; Li, L.; Ni, C.; Hu J. *J. Am. Chem. Soc.* **2013**, *135*, 17302–17305.

[6] (a) Tolman, C. A. *J. Am. Chem. Soc.* **1974**, *96*, 2780–2789. (b) Hoberg, H.; Guhl, D.; *J. Organomet. Chem.* **1989**, *373*, C27–C30.

[7] For DFT study on β-fluorine elimination, see: Zhao, H.; Aliafard, A.; Lin, Z.; *Organometallics* **2006**, *25*, 812.

[8] For review, see: (a) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467–473. (b) Ikeda, S.; *Acc. Chem. Res.* **2000**, *33*, 511–519. (c) Montgomery, J. *Angew. Chem. Int. Ed.* **2004**, *43*, 3890–3908. (d) Moslin, R. M.; Miller-Moslin, K.; Jamison, T. F. *Chem. Commun.* **2007**, 4441–4449.

[9] For Ni-catalyzed reactions of electron-deficient alkenes with alkynes via oxidative cyclization, see: (a) Ikeda, S.; Sato, Y. *J. Am. Chem. Soc.* **1994**, 116, 5975–5976. (b) Montgomery, J.; Savchenko, A. V. *J. Am. Chem. Soc.* **1996**, *118*, 2099–2100. (c) Koyama, I.; Kurahashi, T.;

Matsubara, S. *J. Am. Chem. Soc.* **2009**, *131*, 1350–1351. (d) Ogoshi, S.; Nishimura, A.; Ohashi, M. *Org. Lett.* **2010**, *12*, 3450–3452.

[10] For Ni-mediated [3+2] cycloaddition of enals, α,β-unsaturated esters, or cyclopropyl ketones with alkynes, see: (a) Chowdhury, S. K.; Amarasinghe, K. K. D.; Heeg, M. J.; Montgomery, J. *J. Am. Chem. Soc.* **2000**, *122*, 6775–6776. (b) Herath, A.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128*, 14030–14031. (c) Ohashi, M.; Yaniguchi, T.; Ogoshi, S. *J. Am. Chem. Soc.* **2011**, *133*, 14900–14903. (d) Tamaki, T.; Ohashi, M.; Ogoshi, S. *Angew. Chem. Int. Ed.* **2011**, *50*, 12067–12070.

[11] For the study on regioselectivity in oxidative cyclization between alkynes and aldehydes on Ni(0) complex, see: (a) Liu, P.; McCarren, P.; Cheong, P. H.-Y.; Jamison, T. M.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 2050–2057. (b) Liu, P.; Montgomery, J.; Houk, K. N. *J. Am. Chem. Soc.* **2011**, *133*, 6956–6959.

[12] Ogoshi recently reported that the oxidative addition of tetrafluoroethylene and hexafluoropropene on nickel(0) complexes proceeds through nickelacyclopropane 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.

[13] For protonolysis of a nickelacyclopentene by treatment with acetic acid, see: Eisch, J. J.; Ma. X.; Han, K. I.; Gitua, J. N.; Kruger, C. *Eur. J. Inorg. Chem.* **2001**, 77–88.

[14] For a recent report on the direct synthesis of multi-substituted cyclopentadienes, see: Geng, W.; Wang, C.; Guang, J.; Hao, W.; Zhang, W.-X.; Xi, Z. *Chem. Eur. J.* **2013**, *19*, 8657–8664.

[15] For selected paper on synthesis and application of metallocene complexes, see: (a) Halterman, R. L. *Chem. Rev.* **1992**, *92*, 965–994. (b) Pool, J. A.; Lobkovsky, E.; Chirik, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 2241–2251.

[16] For selected reports on [4+2] cycloaddition of multi-substituted cyclopentadienes with electron-deficient alkenes or singlet oxygen, see: (a) Lee, J. S.; Fuchs, P. L. *J. Am. Chem. Soc*. **2005**, *127*, 13122–13123. (b) Zhang, W.; Luo, S.; Fang, F.; Chen, Q.; Hu, H.; Jia, X.; Zhai, H. *J. Am. Chem. Soc.* **2005**, *127*, 18–19. (c) Potowski, M.; Bauer, J. O.; Strohmann, C.; Antonchick, A. P.; Waldmann, H. *Angew. Chem. Int. Ed.* **2012**, *51*, 9512–9516.

3.7. Experomantal Section

3.7.1. 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_4Si (for ^{1}H NMR: $\delta = 0.00$), $CDCl_3$ (for ^{13}C NMR: $\delta = 77.0$), C_6F_6 (for ^{19}F NMR: $\delta = 0.0$), and H_3PO_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.

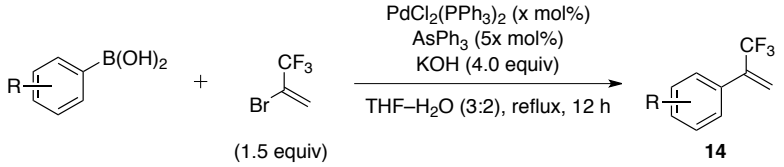
Column chromatography and preparative thin-layer chromatography (PTLC) were conducted on silica gel (Silica Gel 60 N, Kanto Chemical Co., Inc. for column chromatography and Wakogel B-5F, Wako Pure Chemical Industries for PTLC, respectively). All the reactions were conducted under argon. Tetrahydrofuran (THF) and diethylether (Et_2O) 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_6D_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

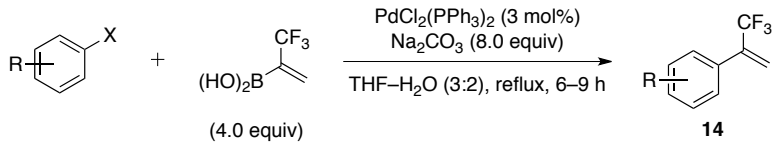
General Procedure A[1)]



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 an 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_4Cl. Organic materials were extracted two times with Et_2O. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography to give the correspomding α-(triflurormethyl)styrenes **14**.

[1] J. Walkowiak, T. M. del Campo, B. Ameduri, V. Gouverneur, *Synthesis* **2010**, *11*, 1883–1890.

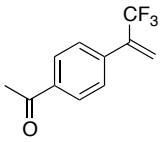
General Procedure B[2)]



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_2CO_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_4Cl. Organic materials were extracted two times with Et_2O. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography to give the correspomding α-(triflurormethyl)styrenes **14**.

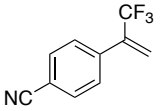
[2] B. Jiang, Q.-F. Wang, C.-G. Yang, M. Xu, *Tetrahedron Lett.* **2001**, *42*, 4083–4085.

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



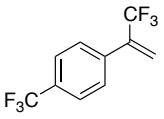
Compound **14a** was prepared according to General Procedure **A** using 4-ethanoylphenylboronic acid (796 mg, 4.85 mmol), 2-bromo-3,3,3-trifluoropropene (1.32 g, 7.52 mmol), $PdCl_2(PPh_3)_2$ (105 mg, 0.15 mmol), $AsPh_3$ (230 mg, 0.751 mmol), aqueous KOH (2.0 M, 10 mL, 20 mmol) and THF (15.0 mL) under 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)



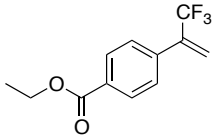
Compound **14b** was prepared according to General Procedure **B** using 4-bromobenzonitrile (910 mg, 5.00 mmol), α-(trifluoromethyl)ethenyl boronic acid (2.90 g, 20.7 mmol), $PdCl_2(PPh_3)_2$ (105 mg, 0.15 mmol), aqueous Na_2CO_3 (2.0 M, 20 mL, 40 mmol), and THF (30 mL) under reflux conditions for 4.5 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): $\tilde{\nu}$ = 2231, 1352, 1194, 1173, 1022, 1978, 845 cm^{-1}. ^1H 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 $C_{10}H_6F_3N$ $[M]^+$ 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_2CO_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)]

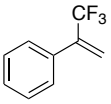
Ethyl 4-(3,3,3-trifluoroprop-1-en-2-yl)benzoate (14d)



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), $PdCl_2(PPh_3)_2$ (46 mg, 66 μmol), aqueous Na_2CO_3 (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): $\tilde{\nu}$ = 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, J_{HF} = 1.6 Hz, 1H), 6.04 (q, J_{HF} = 1.3 Hz, 1H), 7.53 (d, J = 8.2 Hz, 2H), 8.03–8.09 (m, 2H). ^{13}C NMR: δ 14.3, 61.1, 121.8 (q, J_{CF} = 6 Hz), 123.0 (q, J_{CF} = 275 Hz), 127.3, 129.7, 130.9, 137.7, 138.3 (q, J_{CF} = 31 Hz), 166.0. ^{19}F NMR: δ 98.4 (s, 3F). Elemental analysis: Calcd for $C_{12}H_{11}F_3O_2$: C, 59.02; H, 4.54. Found: C, 59.25; H, 4.84.

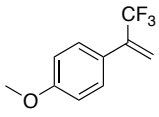
α-(Trifluoromethyl)styrene (14e)



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), $PdCl_2(PPh_3)_2$ (0.211 g, 0.301 mmol), $AsPh_3$ (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), $PdCl_2(PPh_3)_2$ (147 mg, 0.21 mmol), aqueous Na_2CO_3 (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)]

[3] B. Jiang, Y. Xu, *J. Org. Chem.* **1991**, *56*, 7336–7340.

[4] B. S. Nader, J. A. Cordova, K. E. Reese, C. L. Powell, *J. Org. Chem.* **1994**, *59*, 2898–2901.

[5] O. Kobatashi, D. Uraguchi, T. Yamakawa, *J. Fluorine Chem.* **2009**, *130*, 591–594.

II. Synthesis of Alkynes

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

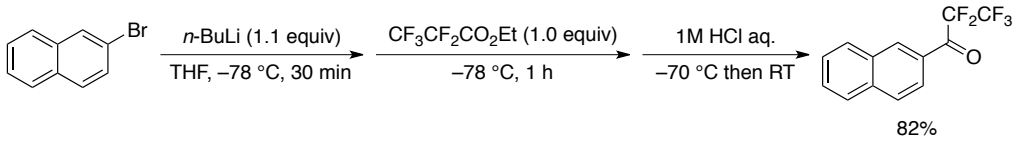
[6] D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 16474–16475.

[7] C. He, J. Ke, H. Xu, A. Lei, *Angew. Chem. Int. Ed.* **2013**, *52*, 1527–1530.

[8] S. R. Chidipudi, I. Khan, H. W. Kam, *Angew. Chem Int. Ed.* **2012**, *51*, 12115–12119.

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

2,2,3,3,3-Pentafluoro-1-(naphthalene-2-yl)propan-1-one[9)]



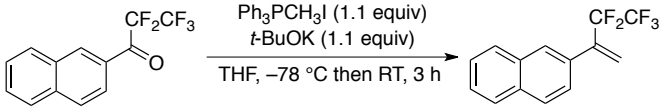
82%

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_2O. The combined extracts were washed with brine and dried over anhydrous Na_2SO_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): $\tilde{\nu}$ = 1701, 1211, 1157, 1126, 1066, 914, 735 cm^{-1}. ^1H NMR: δ 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: δ 108.9 (tq, $^1J_{CF}$ = 269 Hz, $^2J_{CF}$ = 37 Hz), 118.1 (qt,

$^1J_{CF}$ = 288 Hz, $^2J_{CF}$ = 34 Hz), 124.2, 127.4, 127.9, 128.2, 129.0, 130.1, 130.3, 132.1, 133.2 (t, J_{CF} = 5 Hz), 136.4, 183.0 (t, J_{CF} = 27 Hz). ^{19}F NMR: δ 48.0 (s, 2F), 81.4 (s, 3F). HRMS (EI+): Calcd for $C_{13}H_7F_5O$ $[M]^+$ 274.0417, Found 274.0420.

2-(3,3,4,4,4-Pentafluorobut-1-en-2-yl)naphthalene (19a)[10)]



19a 86%

To a THF solution (30 mL) of Ph_3PCH_3I (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_4Cl at that temperature. The mixture was filtered through a pad of Celite (Et_2O), and then filtrate was extracted three times with Et_2O. The combined extracts were washed with brine and dried over anhydrous Na_2SO_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, 820, 748 cm^{-1}. ^{1}H NMR: δ 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: δ 113.1 (tq, $^1J_{CF}$ = 255 Hz, $^2J_{CF}$ = 38 Hz), 119.1 (qt, $^1J_{CF}$ = 287 Hz, $^2J_{CF}$ = 38 Hz), 125.0 (t, J_{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_{CF} = 21 Hz). ^{19}F NMR: δ 49.9 (s, 2F), 80.1 (s, 3F). Elemental analysis: Calcd for $C_{14}H_9F_5$: C, 61.77; H, 3.33. Found: C, 62.07; H, 3.48.

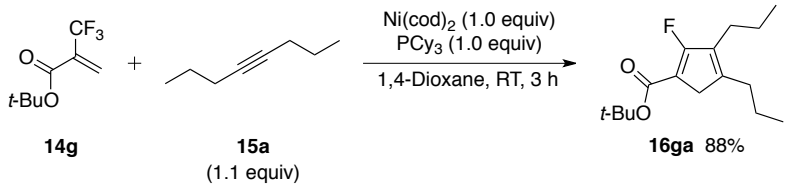
[9] X. Creary, *J. Org. Chem.* 1987, *52*, 5026–5030.

[10] K. van Alem, G. Belder, G. Lodder, H. Zuilhof, *J. Org. Chem.* 2005, *70*, 179–190.

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)**



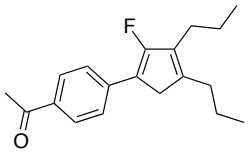
14g **15a** (1.1 equiv) **16ga** 88%

To a 1,4-dioxane solution (3.2 mL) of $Ni(cod)_2$ (86 mg, 0.31 mmol) and PCy_3 (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): $\tilde{\nu}$ = 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). ^{13}C 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). ^{19}F NMR: δ 56.5 (t, J_{FH} = 7.4 Hz, 1F). HRMS (EI+): Calcd for $C_{16}H_{25}FO_2$ $[M]^+$ 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)

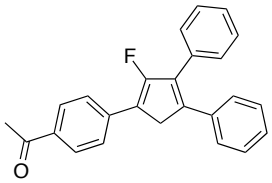


Compound **16aa** was synthesized according to the typical procedure using 1-(4-(3,3,3-Trifluoroprop-1-en-2-yl)phenyl)ethanone (**14a**, 50 mg, 0.23 mmol), 4-octyne (**15a**, 31 mg, 0.28 mmol), $Ni(cod)_2$ (72 mg, 0.26 mmol), PCy_3 (77 mg, 0.27 mmol), and 1,4-dioxane (2.0 mL) at room temperature for 3 h. Purification by preparative thin-layer chromatography (hexane/EtOAc = 50:1) gave **16aa** (50 mg, 74%) as a yellow solid.

16aa: IR (neat): $\tilde{\nu}$ = 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). ^{13}C 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 Hz), 128.8, 133.8, 134.6 (d, J_{CF} = 25 Hz), 138.6 (d, J_{CF} = 5 Hz), 143.2 (d, J_{CF} = 6 Hz), 161.2 (d, J_{CF} = 285 Hz), 197.4. ^{19}F NMR: δ 43.9 (t, J_{FH} = 6.5 Hz, 1F). HRMS (EI+): Calcd for $C_{19}H_{23}FO$ $[M]^+$ 286.1733, Found 286.1730.

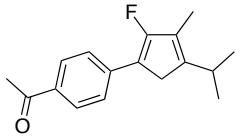
1-(4-(2-Fluoro-3,4-diphenylcyclopenta-1,3-dienyl)phenyl)ethanone (16ab)



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): $\tilde{\nu}$ = 1678, 1601, 1362, 1269, 758, 696 cm^{-1}. ^{1}H NMR: δ 2.61 (s, 3H), 3.81 (d, J_{HF} = 6.3 Hz, 2H), 7.12–7.30 (m, 5H), 7.31–7.50 (m, 5H), 7.71 (d, J = 8.4 Hz, 2H), 7.97 (d, J = 8.4 Hz, 2H). ^{13}C NMR: δ 26.5, 38.4 (d, J_{CF} = 7 Hz), 115.3, 125.7 (d, J_{CF} = 7 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 (d, J_{CF} = 4 Hz), 159.4 (d, J_{CF} = 283 Hz), 197.4. ^{19}F NMR: δ 45.5 (t, J_{FH} = 6.3 Hz, 1F). Elemental analysis: Calcd for $C_{25}H_{19}FO$: 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)

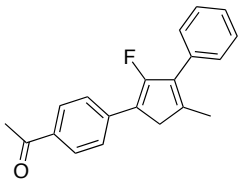


Compound **16ac** was synthesized according to the typical procedure using 1-(4-(3,3,3-Trifluoroprop-1-en-2-yl)phenyl)ethanone (**14a**, 65 mg, 0.31 mmol), 4-methyl-1-pentyne (**15c**, 30 mg, 0.37 mmol), $Ni(cod)_2$ (87 mg, 0.32 mmol), PCy_3 (89 mg, 0.32 mmol), and 1,4-dioxane (3.2 mL) at room temperature 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): $\tilde{\nu}$ = 2962, 2870, 1670, 1601, 1585, 1362, 1272, 1109, 825, 592 cm^{-1}. ^{1}H NMR: δ 1.14 (d, J = 6.9 Hz, 6H), 1.89 (s, 3H), 2.58 (s, 3H), 2.94 (septet, J = 6.9 Hz, 1H), 3.18 (d, J_{HF} = 6.5 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 8.4 Hz, 2H). ^{13}C NMR: δ 8.6, 22.5, 26.4, 27.6 (d, J_{CF} = 2 Hz), 34.1 (d, J_{CF} = 8 Hz), 112.3 (d, J_{CF} = 3 Hz), 125.1 (d. J_{CF} = 7 Hz), 128.3 (d, J_{CF} = 26 Hz),

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: δ 42.1 (t, J_{FH} = 6.5 Hz, 1F). HRMS (EI+): Calcd for $C_{17}H_{19}FO$ $[M]^+$ 258.1420, Found 258.1409.

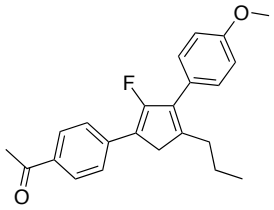
1-(4-(2-Fluoro-4-methyl-3-phenylcyclopenta-1,3-dienyl)phenyl)ethanone (16ad)



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): $\tilde{\nu}$ = 1676, 1601, 1583, 1362, 1271, 1188, 700 cm^{-1}. ^{1}H NMR: δ 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). ^{13}C NMR: δ 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, 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: δ 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)

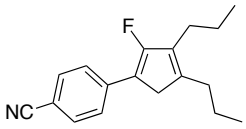


Compound **16ae** was synthesized according to the typical procedure using 1-(4-(3,3,3-Trifluoroprop-1-en-2-yl)phenyl)ethanone (**14a**, 32 mg, 0.15 mmol), 1-methoxy-4-(pent-1-ynyl)benzene (**15e**, 30 mg, 0.17 mmol), Ni(cod)$_2$ (44 mg, 0.16 mmol), PCy$_3$ (45 mg, 0.16 mmol), and toluene (1.6 mL) at 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): $\tilde{\nu}$ = 2958, 1678, 1601, 1510, 1360, 1271, 1250, 1178, 771 cm^{-1}. ^{1}H NMR: δ 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). ^{13}C NMR: δ 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. ^{19}F 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.

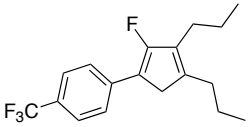
4-(2-Fluoro-3,4-dipropylcyclopenta-1,3-dienyl)benzonitrile (16ba)



Compound **16ba** was synthesized according to the typical procedure using 4-(3,3,3-trifluoroprop-1-en-2-yl)benzonitrile (**14b**, 43 mg, 0.22 mmol), 4-octyne (**15a**, 25 mg, 0.23 mmol), Ni(cod)$_2$ (57 mg, 0.21 mmol), PCy_3 (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): $\tilde{\nu}$ = 2960, 2873, 2224, 1585, 912, 742 cm^{-1}. ^{1}H 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). ^{13}C NMR: δ 13.9, 14.0, 22.3, 23.1, 26.0, 30.8, 37.7 (d, J_{CF} = 7 Hz), 108.0, 112.2, 119.4, 125.5 (d, J_{CF} = 7 Hz), 132.3, 134.6 (d, J_{CF} = 25Hz), 138.2 (d, J_{CF} = 5 Hz), 143.9 (d, J_{CF} = 6 Hz), 161.7 (d, J_{CF} = 285 Hz). ^{19}F 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)

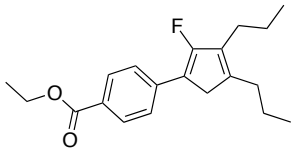


Compound **16ca** was synthesized according to the typical procedure using 1-(trifluoromethyl)-4-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**14c**, 98 mg, 0.41 mmol), 4-octyne (**15a**, 50 mg, 0.45 mmol), Ni(cod)$_2$ (115 mg, 0.42 mmol), PCy_3 (116 mg, 0.41 mmol), and toluene (4.1 mL) at room temperature for 9 h. Purification by silica gel column chromatography (hexane) gave **16ca** (109 mg, 86%) as a colorless liquid.

16ca: IR (neat): $\tilde{\nu}$ = 2960, 2873, 1591, 1321, 1163, 1111, 1066, 835 cm^{-1}. ^{1}H 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). ^{13}C 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). ^{19}F NMR: δ 42.6 (t, J_{FH} = 6.6 Hz, 1F),

100.7 (s, 3F). HRMS (EI+): Calcd for $C_{18}H_{20}F_4$ $[M]^+$ 312.1501, Found 312.1491.

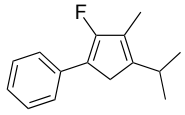
Ethyl 4-(2-fluoro-3,4-dipropylcyclopenta-1,3-dienyl)benzoate (16da)



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), PCy_3 (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): $\tilde{\nu}$ = 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, J_{HF} = 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). ^{13}C NMR: δ 13.9, 14.1, 14.4, 22.3, 23.1, 26.0, 30.8 (d, J_{CF} = 1 Hz), 37.8 (d, J_{CF} = 8 Hz), 60.7, 112.8 (d, J_{CF} = 2 Hz), 124.9 (d, J_{CF} = 7 Hz), 126.9, 129.8, 134.5 (d, J_{CF} = 25 Hz), 138.2 (d, J_{CF} = 5 Hz) 142.8 (d, J_{CF} = 6 Hz), 160.9 (d, J_{CF} = 284 Hz), 166.6. ^{19}F NMR: δ 42.3 (t, J_{FH} = 6.5 Hz, 1F). Elemental analysis: Calcd for $C_{20}H_{25}FO_2$: C, 75.92; H, 7.96. Found: C, 75.74; H, 8.10.

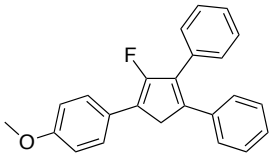
(2-Fluoro-4-isopropyl-3-methylcyclopenta-1,3-dienyl)benzene (16ec)



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), PCy_3 (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): $\tilde{\nu}$ = 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, J_{HF} = 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). ^{13}C NMR: δ 8.7, 22.6, 27.4 (d, J_{CF} = 2 Hz), 34.1 (d, J_{CF} = 8 Hz), 112.7, 125.5 (d, J_{CF} = 4 Hz), 125.5, 128.0 (d, J_{CF} = 27 Hz), 128.5, 134.0 (d, J_{CF} = 6 Hz), 146.2 (d, J_{CF} = 4 Hz), 158.8 (d, J_{CF} = 280 Hz). ^{19}F NMR: δ 36.8 (t, J_{FH} = 6.4 Hz, 1F). HRMS (EI+): Calcd for $C_{15}H_{17}F$ $[M]^+$ 216.1314, Found: 216.1306.

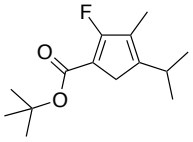
(3-Fluoro-4-(4-methoxyphenyl)cyclopenta-1,3-diene-1,2-diyl)dibenzene (16fb)



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), PCy_3 (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): $\tilde{\nu}$ = 3055, 1606, 1508, 1290, 1248, 1180, 1034, 906, 827, 735, 696 cm^{-1}. ^1H NMR: δ 3.73 (d, J_{HF} = 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). ^{13}C NMR: δ 38.6 (d, J_{CF} = 7 Hz), 55.3, 114.1, 115.9 (d, J_{CF} = 3 Hz), 126.2 (d, J_{CF} = 6 Hz), 127.0, 127.2 (d, J_{CF} = 6 Hz), 127.4, 127.8, 128.3, 128.5, 129.3, 132.9 (d, J_{CF} = 3 Hz), 135.6 (d, J_{CF} = 26 Hz), 135.9 (d, J_{CF} = 3 Hz), 137.6 (d, J_{CF} = 4 Hz), 156.2 (d, J_{CF} = 277 Hz), 158.2 (d, J_{CF} = 3 Hz). ^{19}F NMR: δ 38.2 (t, J_{FH} = 6.4 Hz, 1F). HRMS (EI+): Calcd for $C_{24}H_{19}FO$ $[M]^+$ 342.1420, Found 342.1415.

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

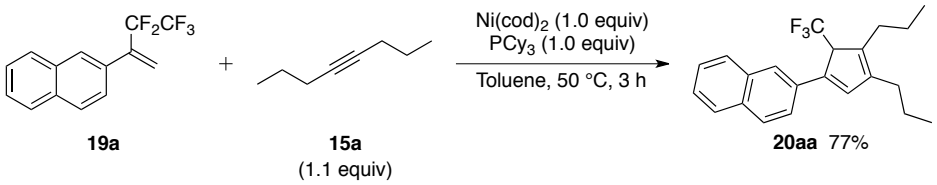


Compound **16gc** was synthesized according to the typical procedure using *t*-butyl 2-(trifluoromethyl)acrylate (**14g**, 55 mg, 0.28 mmol), 4-methyl-2-pentyne (**15c**, 25 mg, 0.31 mmol), $Ni(cod)_2$ (79 mg, 0.29 mmol), PCy_3 (81 mg, 0.29 mmol), and toluene (2.9 mL) at room temperature for 2 h. Purification by silica gel column chromatography (pentane/Et_2O = 5:1) gave compound **16gc** (62 mg, 93%) as a colorless liquid.

16gc: IR (neat): $\tilde{\nu}$ = 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, J_{HF} = 7.5 Hz, J = 1.5 Hz, 2H). ^{13}C NMR: δ 8.3, 22.2, 27.8 (d, J_{CF} = 2 Hz), 28.3, 34.2 (d, J_{CF} = 5 Hz), 79.8, 107.6, 127.4 (d, J_{CF} = 25 Hz), 154.5 (d, J_{CF} = 5 Hz) 162.4 (d, J_{CF} = 4 Hz), 166.7 (d, J_{CF} = 294 Hz). ^{19}F NMR: δ 54.9 (t, J_{FH} = 7.5 Hz, 1F). HRMS (EI+): Calcd for $C_{14}H_{21}FO_2$ $[M]^+$ 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)

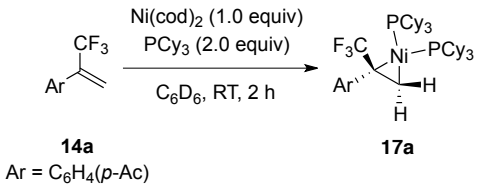


To a toluene solution (2.9 mL) of $Ni(cod)_2$ (80 mg, 0.29 mmol) and PCy_3 (82 mg, 0.29 mmol) were added 2-(3,3,4,4-pentafluorobut-1-en-2-yl)naphthalene (**19a**, 75 mg, 0.28 mmol) and 4-octyne (**15a**, 35 mg, 0.32 mmol) at 50 °C. After stirring for 3 hours at the same temperature, the reaction mixture 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): $\tilde{\nu}$ = 3057, 2960, 2871, 1248, 1165, 1138, 1093, 746 cm^{-1}. ^1H NMR: δ 0.95 (t, J = 7.4 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H), 1.43–1.75 (m, 4H), 2.33 (t, J = 7.5 Hz, 2H), 2.35–2.52 (m, 2H), 4.35 (q, J_{HF} = 9.1 Hz, 1H), 6.75 (s, 1H), 7.40–7.50 (m, 2H), 7.56 (dd, J = 8.5, 1.6 Hz, 1H), 7.74–7.89 (m, 4H). ^{13}C NMR: δ 13.8, 14.1, 22.2, 23.6, 29.1, 29.1, 54.9 (q, J_{CF} = 27 Hz), 125.3, 125.3, 125.5 (q, J_{CF} = 282 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: δ 96.6 (d, J_{FH} = 9.1 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 Nickelacyclopropane Complex

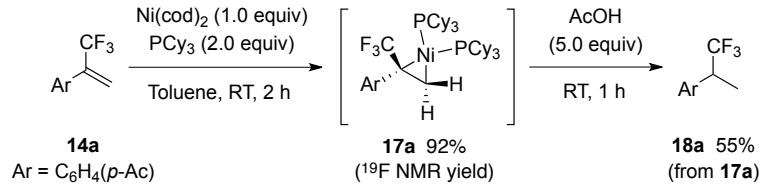
(A) Stoichiometric Reaction of 2-Trifluoromethyl-1-alkene with Ni(0) Complex



To a C_6D_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_6D_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.

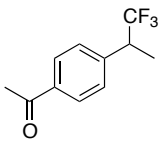
17a: ^{19}F NMR (470 MHz, C_6D_6): δ 108.6 (d, J_{FP} = 8.1 Hz, 3F). ^{31}P NMR (202 Hz, C_6D_6): δ 30.4 (d, J_{PP} = 27 Hz, 1P), 34.2 (dq, J_{PP} = 27 Hz, J_{PF} = 8 Hz, 1P).

(B) Protonation of Nickelacyclopropane Complex 17a



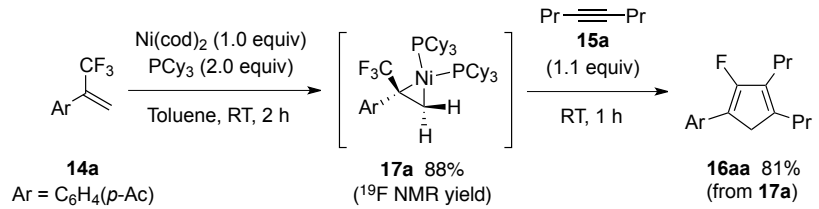
To a toluene solution (2.1 mL) of $Ni(cod)_2$ (59 mg, 0.21 mmol) and PCy_3 (60 mg, 0.21 mmol) was added 2-trifluoromethyl-1-alkene **14a** (43 mg, 0.20 mmol) at room temperature. After stirring for 2 h at room temperature, a toluene solution of **17a** was obtained as a dark red solution (0.18 mmol, 92%; The yield was determined by ^{19}F NMR using $PhCF_3$ 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): $\tilde{\nu}$ = 1687, 1269, 1167, 1132, 912, 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). ^{13}C 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. ^{19}F NMR: δ 91.8 (d, J_{FH} = 9.1 Hz, 3F). HRMS (EI+): Calcd for $C_{11}H_{11}F_3O$ $[M]^+$ 216.0762, Found 216.0755.

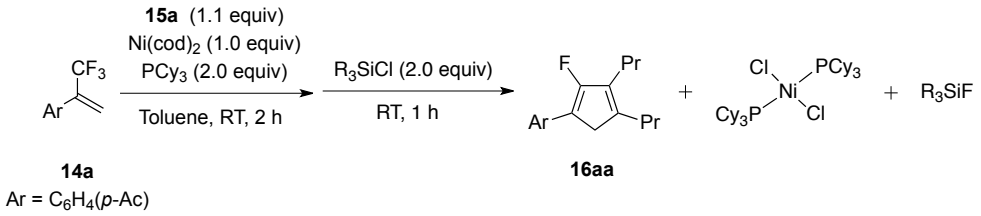
(C) Reaction of Nickelacyclopropane Complex 17a with 4-Octyne (15a)



To a toluene solution (2.1 mL) of $Ni(cod)_2$ (58 mg, 0.21 mmol) and PCy_3 (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 ^{19}F 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 ^{19}F NMR. Then, Et_3SiCl (12 mg, 0.11 mmol) or Ph_3SiCl (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_3SiF were obtained (The generation R_3SiF was confirmed by ^{19}F NMR (**16aa**/R_3SiF = 1:2)). The obtained violet crystallines was washed with cold Et_2O to give *trans*-$NiCl_2(PCy_3)_2$ (The structure of *trans*-$NiCl_2(PCy_3)_2$ was confirmed by X-ray diffraction analysis.)

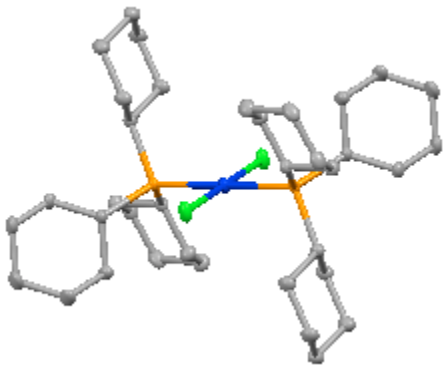


Figure S1. X-Ray Crystal Structure of *trans*-$NiCl_2(PCy_3)_2$

Table S1. Crystal Data Collection Parameters for *trans*-$NiCl_2(PCy_3)_2$

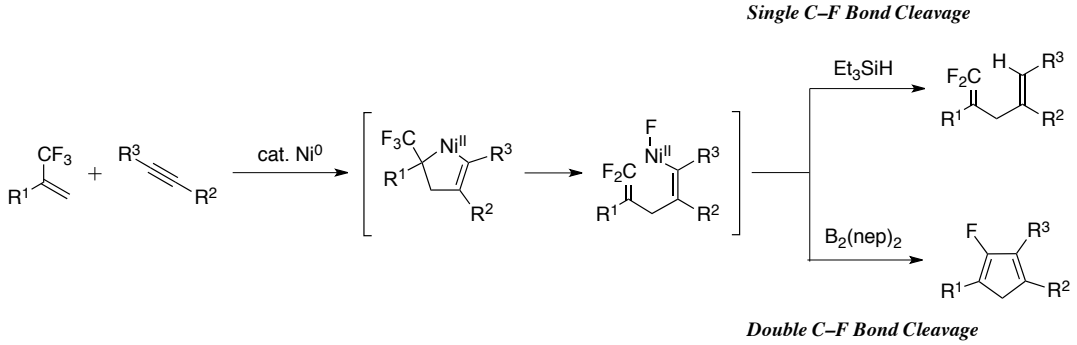
complex	*trans*-$NiCl_2(PCy_3)_2$
formula	$C_{18}H_{22}Cl_2NiP_2$
crystal system	brock
space group	*P*-1
R, R_w ($I > 2\sigma(I)$)	0.0279, 0.1080
$R1, wR2$ (all data)	0.0306, 0.1121
GOF on F^2	0.954
a (Å)	9.891(2)
b (Å)	10.173(2)
c (Å)	10.510(2)
α (deg)	112.255(2)
β (deg)	109.417(2)
γ (deg)	91.778(3)
V (Å^3)	908.041
Z	2
T (K)	120(2)
crystal size (mm)	0.30, 0.20, 0.20
D_{calcd} (g/cm^3)	1.613
$2\theta_{min}, 2\theta_{max}$ (deg)	4.40, 55.12
no. refln measured (unique)	5139
no. refln measured ($I > 2\sigma(I)$)	3892
no. parameters	3592

CHAPTER 4

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

Abstract

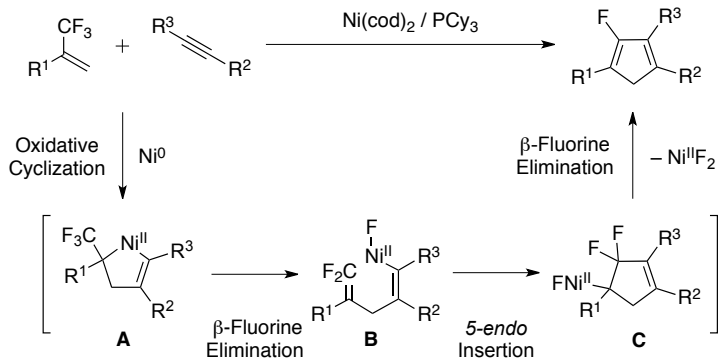
The nickel-catalyzed defluorinative coupling reactions of trifluoromethylated alkenes with alkynes have been developed. These reactions involve the allylic C–F bond activation via β-fluorine elimination from the intermediary nickelacyclopentenes. The product selectivity was controlled by the choice of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



4.1. Introduction

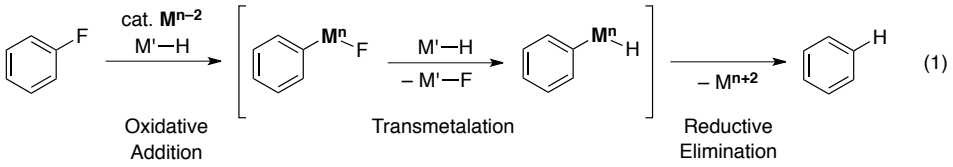
Difluorovinylidene compounds have attracted considerable attention in the realms of medicinal and materials sciences, because of their unique properties derived from fluorine atoms. Therefore, the development of synthetic methodologies for difluorovinylidene compounds is a significant research area. 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



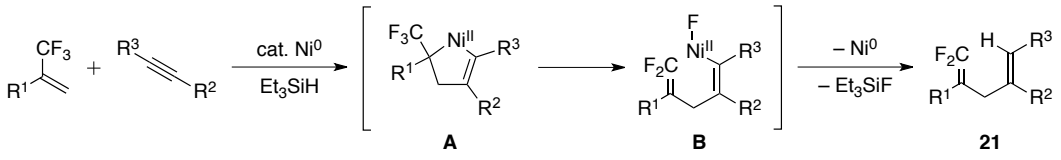
As shown in Chapter 3, I achieved the nickel-mediated [3+2] cycloaddition of 2-trifluoromethyl-1-alkenes and alkynes via double C–F bond cleavage of a trifluoromethyl group under mild reaction conditions (Scheme 1). In this reaction, ring-opening of nickelacycle **A**, formed by oxidative cyclization of a 2-trifluoromethyl-1-alkene and an alkyne with Ni^0, readily proceeded by β-fluorine elimination to generate alkenylnickel 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(sp^3)–F bond activation.



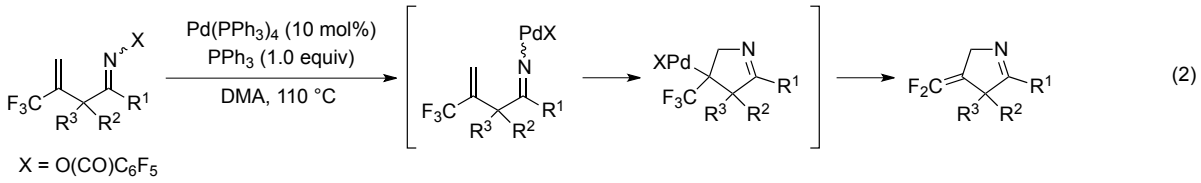
To establish the catalytic synthesis of difluorovinylidene compounds, I hypothesized that the intermediary alkenylnickel fluoride **B** could be reduced with the appropriate metal hydride to afford the corresponding product, 1,1-difluoro-1,4-dienes **21**, along with the regenerated Ni(0) (Scheme 2). 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).[4] After screening metal hydride reagents, I found that the combination of the nickel catalyst and Et_3SiH 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

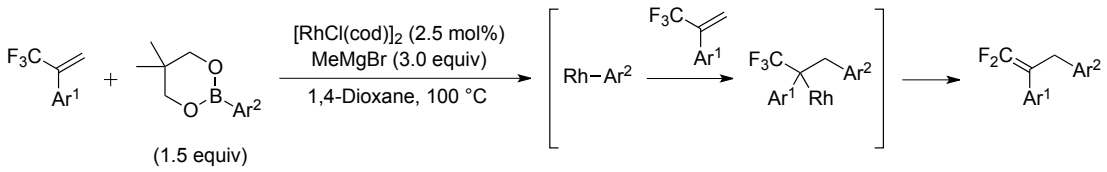


Although the transition metal-catalyzed C–F bond activation has been considered to be the most effective approach to cleave the strong C–F bond, there are only a few reports on a C(sp^3)–F bond activation of the trifluoromethyl group (eqs 2–4).[3] The present method is the first example of

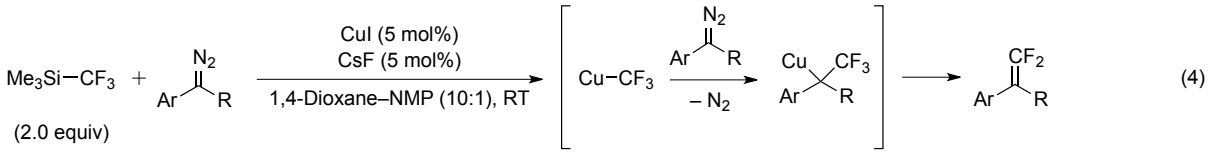
allylic C(sp^3)–F bond activation by using a nickel catalyst, which is a much more inexpensive than palladium and rhodium ones.



(2)



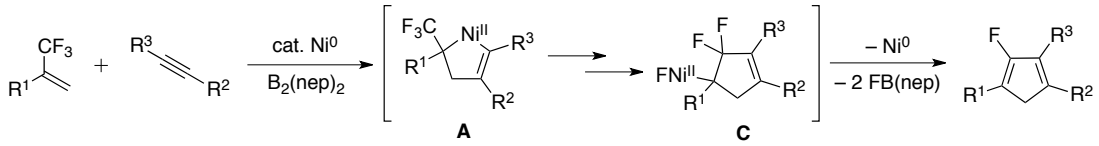
(3)



(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 NiF_2 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)F_2 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 NiF_2 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.

Scheme 3. Ni-Catalyzed Synthesis of Fluorocyclopentadienes

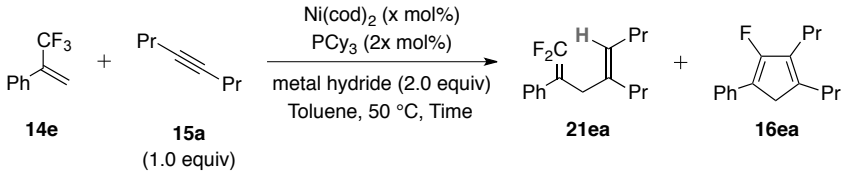


4.2. Defluorinative Coupling of Trifluoromethylated Alkenes with Alkynes

4.2.1. Optimization of Reaction Conditions

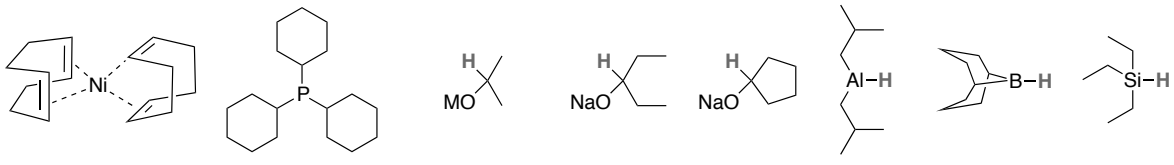
As mentioned in Section 4.1, the intermediary alkenylnickel fluoride **B**, generated via an oxidative cyclization–β-fluorine elimination sequence, could be reduced by an appropriate metal hydride reagent, which leads to the catalytic synthesis of 1,1-difluoro-1,4-dienes **21** (Scheme 2).[5] To prove 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 PCy_3 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). Et_3SiH, 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**



Entry	x (mol%)	metal hydride	Time (h)	**21ea** (%)[a]	**16ea** (%)[a]	Recovery of **14e** (%)[a]
1	10	none	3	0	3	95
2	10	*i*-PrONa	12	74	0	0
3	10	$(Et_2CH)ONa$	36	17	0	37
4	10	CyONa	36	66	0	11
5	10	*i*-PrOLi	12	44	0	00
6	10	*i*-PrOK	12	trace	0	00
7	10	9-BBN	48	15	0	13
8	10	DIBAL-H	12	0	0	0
9	10	Et_3SiH	4	92	0	6
10[b]	5	Et_3SiH	3	96	0	0
11[b,c]	5	Et_3SiH	3	95	0	0
12[b,d]	5	Et_3SiH	3	84	0	0

[a] ^{19}F NMR yield using $PhCF_3$ as the internal standard. [b] **15a** (1.1 equiv) was used.
[c] Room temperature. [d] 80 °C.



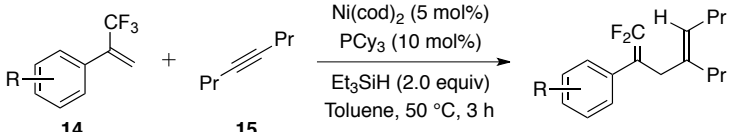
$Ni(cod)_2$ PCy_3 *i*-PrOM (M = Li, Na, K) $(Et_2CH)OH$ CyONa DIBAL-H 9-BBN Et_3SiH

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

14d 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**



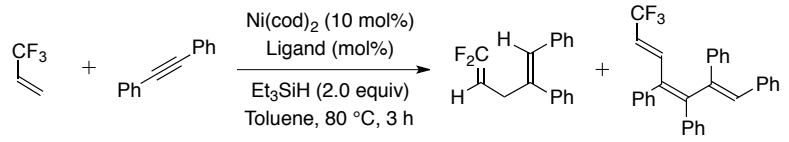
Entry	**14**	R	**21**	Yield (%)[a]	Entry	**14**	R	**21**	Yield (%)[a]
1	**14e**	H	**21ea**	93	4	**14a**	*p*-Ac	**21aa**	94
2	**14h**	*o*-OMe	**21ha**	84	5	**14d**	*p*-CO_2Et	**21da**	88
3	**14f**	*p*-OMe	**21fa**	80	6	**14i**	*p*-Cl	**21ia**	91

[a] 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 PCy_3 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).[9] 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**.[7b]

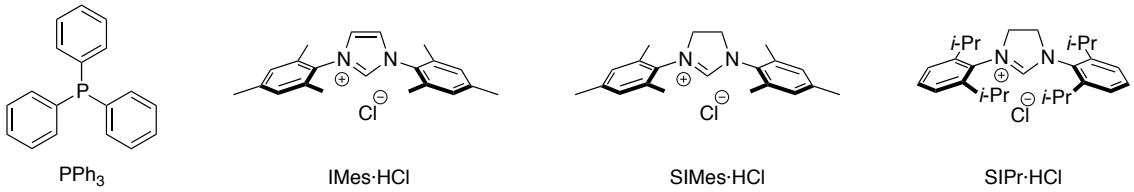
Table 3. Defluorinative Coupling of Trifluoropropene **14j** with **15b**



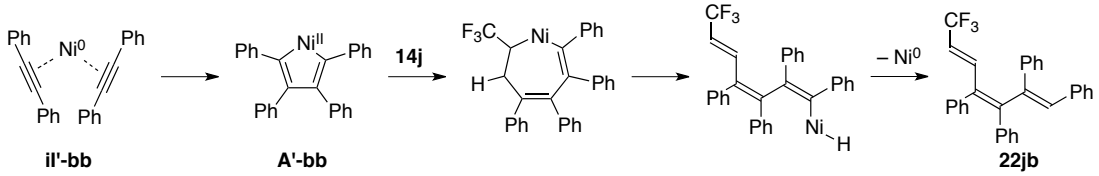
14j (1 atm) **15b** (1.0 equiv) **21jb** **22jb**

Entry	Ligand (mol%)	Time (h)	**21jb** (%)[a]	**22jb** (%)[a]
1	PPh_3 (20)	17	0	23
2	PCy_3 (20)	10	56	20
3	IMes·HCl (10) + *t*-BuOk (10)	17	54	0
4	SIMes·HCl (10), *t*-BuOk (10)	10	77[b]	0
5	SIPr·HCl (10), *t*-BuOk (10)	17	30	0

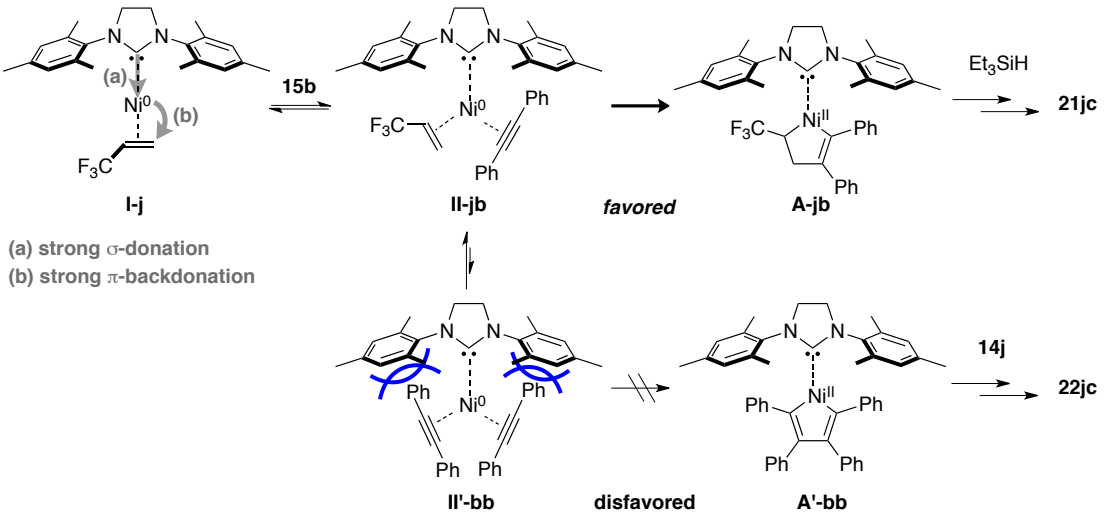
[a] ^{19}F NMR yield using $PhCF_3$ as the internal standard. [b] Isolated yield.



Scheme 4. Plausible Reaction Mechanism for Subgeneration of **22jb**

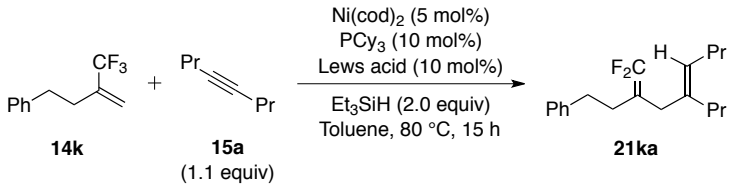


Scheme 5. Ligand-Controlled Chemoselective Coupling Reaction



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 nickelacyclopentene **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**

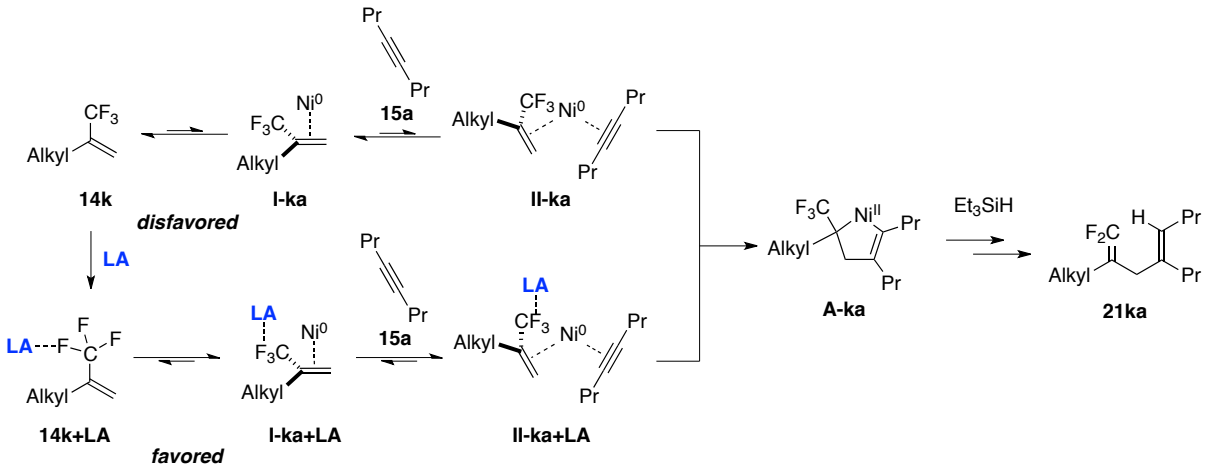


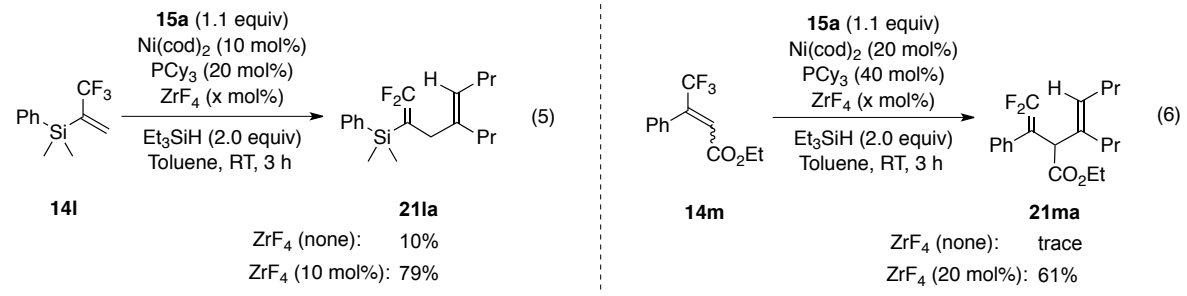
14k **15a** (1.1 equiv) **21ka**

Entry	Lews acid	Yield **21ka** (%)[a]	Recover of **14k** (%)[a]	Entry	Lews acid	Yield **21ka** (%)[a]	Recover of **14k** (%)[a]
1[b]	none	15	74	5	TiF_4	44	52
2	MgF_2	0	96	6	ZrF_4	77	15
3	$BF_3{\cdot}OEt_2$	0	98	7[c]	ZrF_4	85[d]	6
4	AlF_3	70	23	8	$ZrCl_4$	0	93

[a] ^{19}F NMR yield using $PhCF_3$ as the internal standard. [b] 5 h. [c] $Ni(cod)_2$ (10 mol%), PCy_3 (20 mol%). [d]Isolated yield.

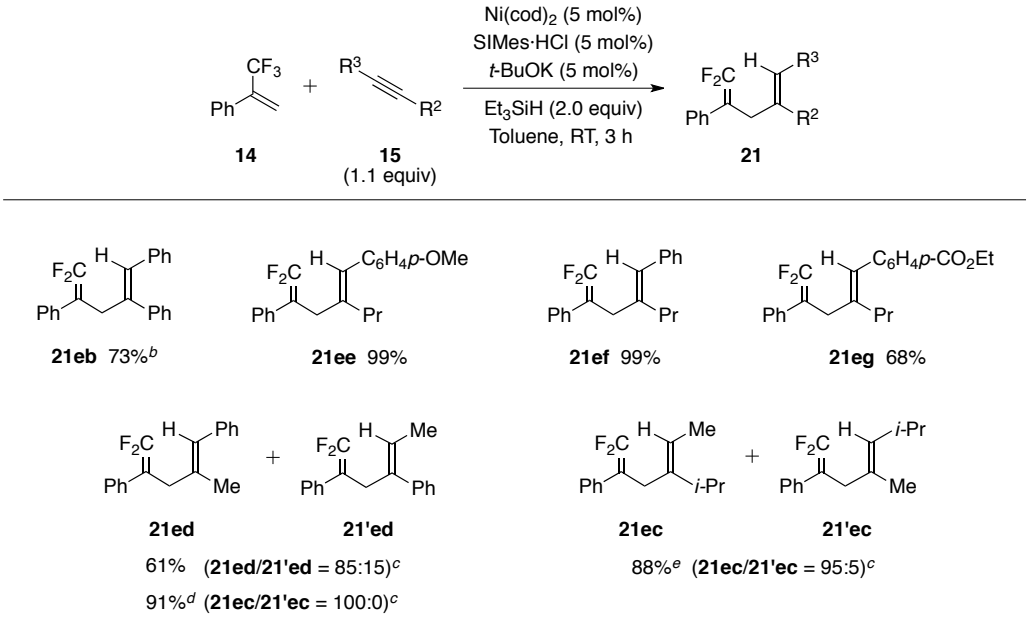
Scheme 6. Lewis Acid-Promoted Defluorinative Coupling





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.[12]

Table 5. Nickel-Catalyzed Synthesis of 1,1-difluoro-1,4-dienes **21**: Scope of Alkynes **15**[a]



[a] Isolated yield. [b] 8 h. [c] Regio isomer ratio was determined by ^{19}F NMR mesurement. [d] PCy_3 (10 mol%) was used instead of SIMes. $Ni(cod)_2$ (10 mol%), 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).[5] β-Fluorine elimination from nickelacycle **A** proceeds to generate the corresponding alkenylnickel fluoride **B**.[3] Subsequent transmetalation of the intermediate **B** with Et_3SiH gives alkenylnickel 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.

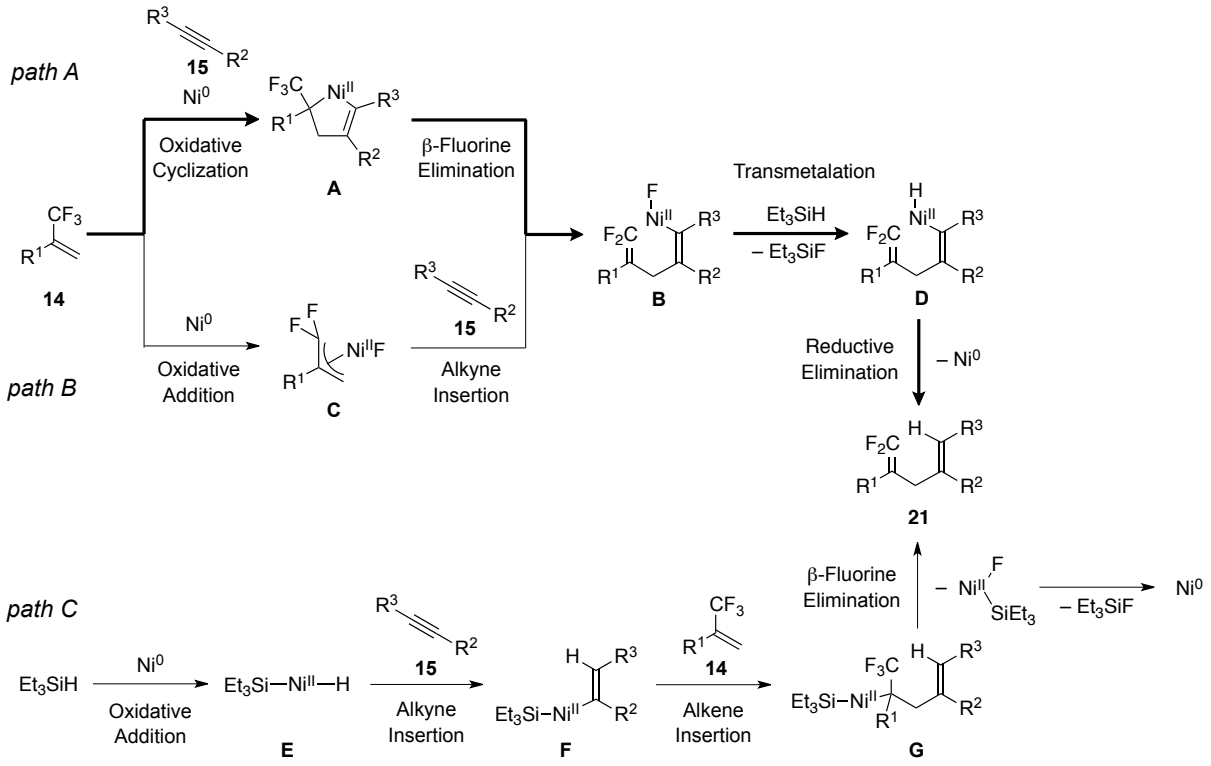
Path B: Oxidative Addition–Alkyne Insertion

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).[13] Alkyne insertion into the C–Ni bond of **C** leads to the formation of intermediate **B**, followed by transmetalation of **B** with Et_3SiH to afford the same coupling product **21**.

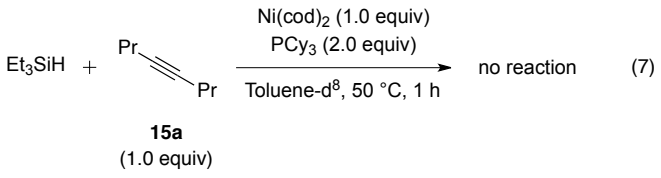
Path C: Alkyne Insertion–β-Fluorine Elimination

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 alkenylnickel complex **F** (Scheme 7, path C).[14,15] Subsequent insertion of **14** into the C–Ni bond gave the alkylnickel complex **G** having a CF_3 group on the carbon α to the nickel center.[3a–c] 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.

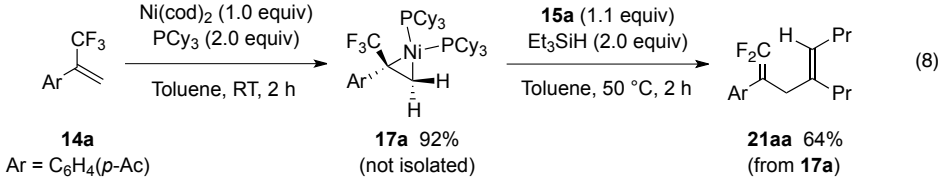
Scheme 7. Plausible Reaction Mechanism



To clarify the mechanism, several experiments were performed. First, to examine the possibility of path C, the stoichiometric reaction of Ni(0) complex with Et_3SiH 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 Et_3SiH and **15a** with a stoichiometric amount of $Ni(cod)_2$ and PCy_3 in toluene-d^8 at 50 °C, no consumption of Et_3SiH and no generation of the corresponding organonickel species were observed by ^1H and ^{31}P NMR measurements. Thus, the possibility of path C was ruled out.



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 Et_3SiH 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).



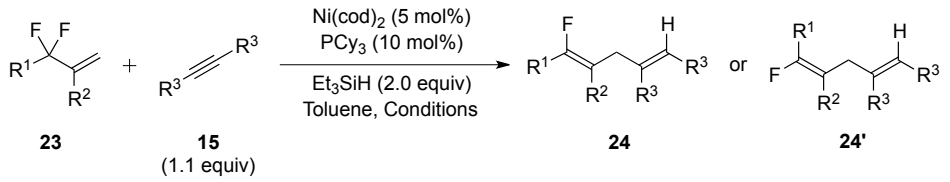
(8)

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

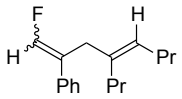
Monofluoroalkenes have been widely recognized to be important such as the peptide bond isosteres, enzymatic inhibitors, liquid crystalline materials, and so on. One of the most straightforward approaches to monofluoroalkenes is defluorinative functionalization of 3,3-difluoropropene derivatives, which 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 Et_3SiH via allylic C–F bond cleavage to afford the corresponding 1-fluoro-1,4-diene **24aa** in 82% yield (Table 6).

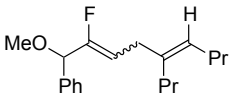
Table 6. Nickel-Catalyzed Defluorinative Coupling of Acyclic 3,3-Difluoropropenes **23** with Alkynes **15**



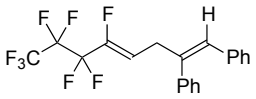
23 **15** (1.1 equiv) **24** **24'**



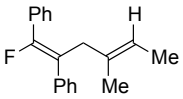
24aa 82% (*E*/*Z* = 50:50)[b] (50 °C, 2 h)



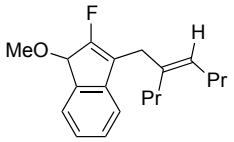
24ba 63%[c,d] (*E*/*Z* = 11:89)[b] (70 °C, 24 h)



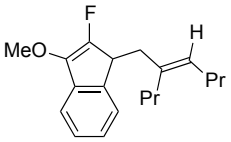
24cb 86%[c,d] (80 °C, 7 h)



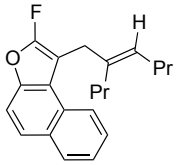
24'dh 99%[c,e] (50 °C, 5 h)



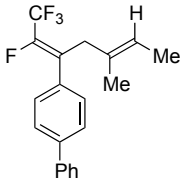
24fa 88% (RT, 2 h)



24''fa 9%[f]

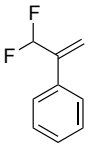


24ga 75%[b] (50 °C, 3 h)

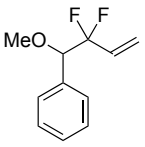


24'eh 95% (*E*/*Z* = 2:98)[b,e] (50 °C, 3 h)

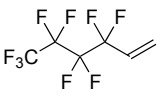
[a] Isolated yield. [b] Isomer ration was determined by ^{19}F NMR. [c] $Ni(cod)_2$ (10 mol%), PCy_3 (20 mol%), [d] Et_3SiH (1.0 equiv).
[e] **15h** (2.0 equiv). [f] ^{19}F NMR yield using $PhCF_3$ as the internal standard.



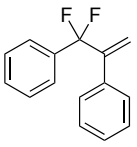
23a



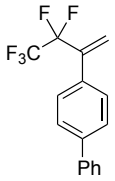
23b



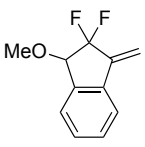
23c



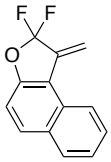
23d



23e



23f



23g

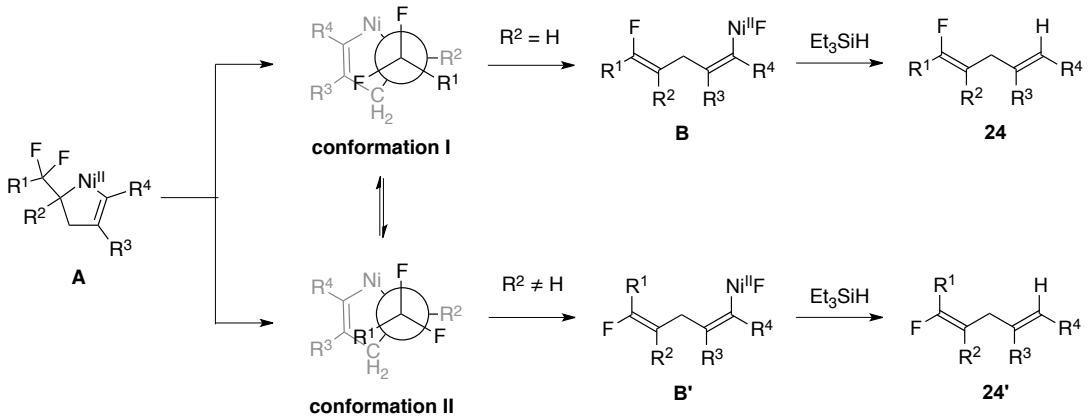
Figure 1. List of Substrates

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-difluoropeopenes **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 R^1 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 R^1 substituent and the R^2 substituent to afford **24'**.

Scheme 8. Stereoselectivity of Monofluoroalkenes **24**

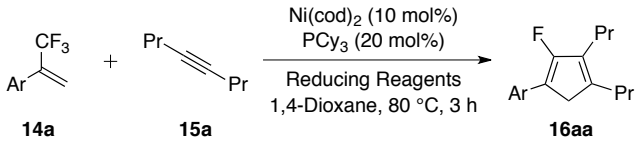


4.4. Catalytic [3+2] Cycloaddition of Trifluoromethylated Alkenes with Alkynes

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 NiF_2. The most challenging point in developing the desired catalytic reaction is the selective reduction of the $Ni(II)F_2$ 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 PCy_3 in 1,4-dioxane at 80 °C (Table 7). First, I attempted the direct reduction of the NiF_2 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 NiX_2 (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 NiF_2 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 $B_2(nep)_2$ and *t*-BuOK was found to be effective for the reduction of the NiF_2 (Entry 10). Furthermore, the addition of MgF_2 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).

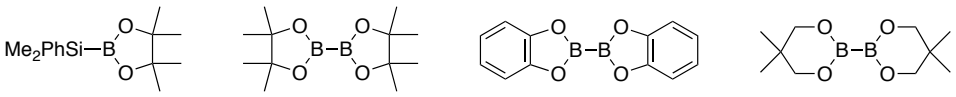
Table 7. Optimization of Reaction Conditions in Nickel-Catalyzed [3+2] Cycloaddition



14a Ar = C_6H_4*p*-Ac | **15a** (1.1 equiv) | **16aa**

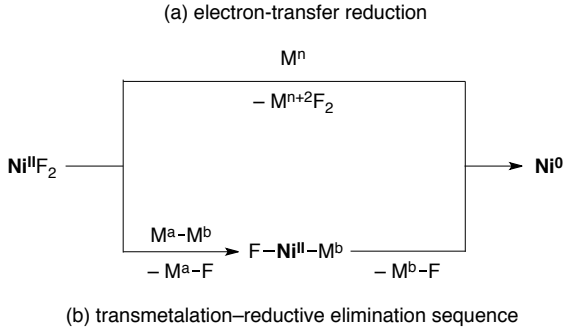
Entry	Reducing Reagent (equiv)	Yield (%)[a]	Entry	Reducing Reagent (equiv)	Yield (%)[a]
1	none	1	7	$B_2(pin)_2$ (1.1)	5
2	Na (3.0)	6	8	$B_2(cat)_2$ (1.1)	6
3	Mn (2.0)	5	9	$B_2(nep)_2$ (1.1)	8
4	Zn (2.0)	5	10	$B_2(nep)_2$ (1.1), *t*-BuOK (1.1)	21
5	$Me_3SiSiMe_3$ (1.1)	5	11	$B_2(nep)_2$ (1.1), *t*-BuOK (1.1), MgF_2 (1.0)	33
6	$Me_2PhSiB(pin)$ (1.1)	7	12[b]	$B_2(nep)_2$ (1.1), *t*-BuOK (1.1), MgF_2 (1.0)	60

[a] ^{19}F NMR yield using $PhCF_3$ as the internal standard. [b] $Ni(cod)_2$ (20 mol%), PCy_3 (40 mol%).



$Me_2PhSiB(pin)$ $B_2(pin)_2$ $B_2(cat)_2$ $B_2(nep)_2$

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

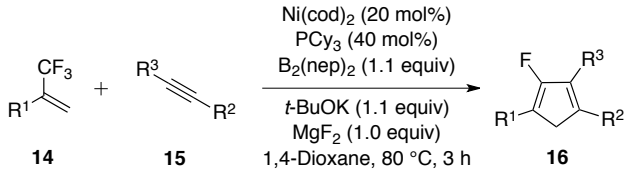


With the optimized reaction conditions in hand, I carried out the synthesis of various 2-fluoro-1,3-cyclopentadienes **16** via the nickel-catalyzed [3+2] cycloaddition (Figure 2, Table 8). Unsymmetrical 4-methyl-2-pentyne (**15c**) also participated in this catalytic reaction to afford the corresponding 2-fluoro-1,3-cyclopentadienes **16ac** in 70% yield with a complete regioselectivity.

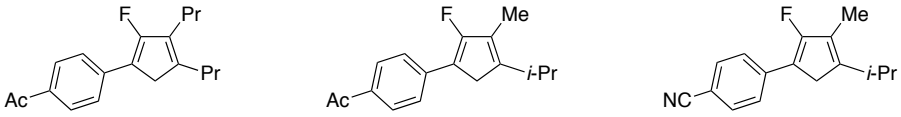
α-Trifluoromethylstyrenes **14b** and **14n** bearing electron-withdrawing cyano and fluorine groups also provided cyclopentadienes **16bc** and **16nc** in 48% and 50% yields, respectively. Non-substituted α-trifluoromethylstyrenes **14e** successfully underwent cycloaddition with **15c**. Furthermore, 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

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



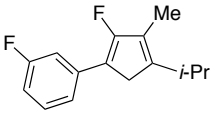
14 **15** **16**



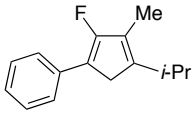
16aa 53% (60%)[b]

16ac 70%

16bc 48% (60%)[b]

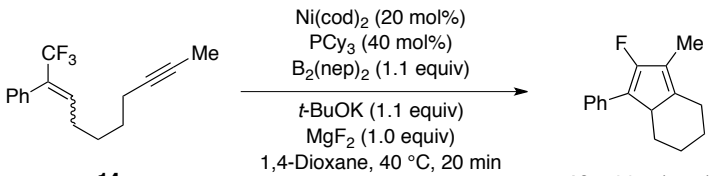


16nc 50%



16ec 48%

[a] Isolated yield. [b] ^{19}F NMR yield using $PhCF_3$ as the internal standard.



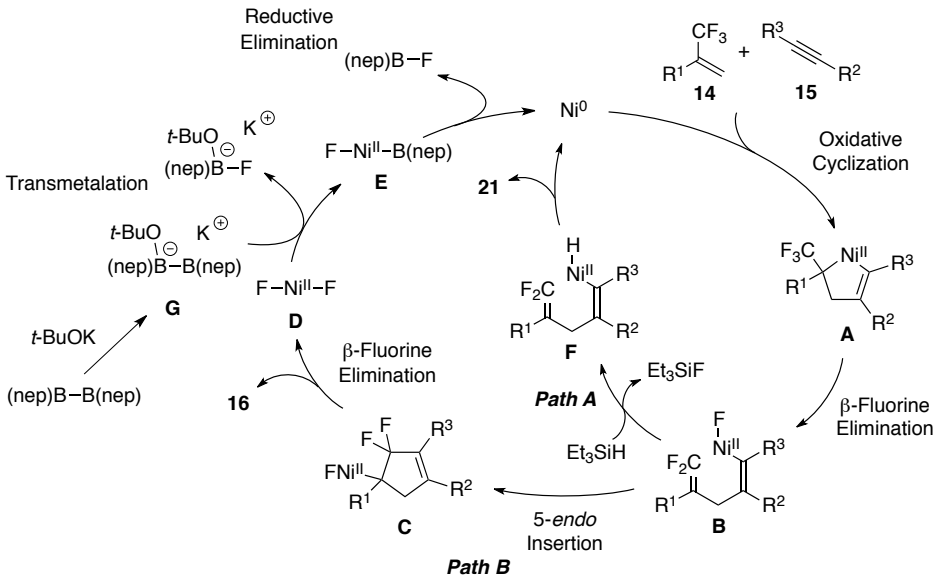
14o
(*E*/*Z* = 60:40)

16o 36% (47%)[a]

[a] ^{19}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 Et_3SiH is used as the reducing regent, transmetalation of intermediate **B** with Et_3SiH 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 $B_2(nep)_2$ and base would be slower than 5-*endo* insertion from intermediate **B**, probably due to the lower reactivity of **G** compared to Et_3SiH (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 NiF_2 complex **D**. Finally, the NiF_2 is reduced to Ni(0) with the boron–ate complex **G** through subsequent transmetalation and reductive elimination, which completes the catalytic cycle.

Scheme 10. Plausible Reaction Mechanism



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

[1] For selected reviews on C–F bond activation, see: (a) Amii, H.; Uneyama, K.; *Chem. Rev.* **2009**, *109*, 2119–2183. (b) Stahl, T.; Klare, H. F. T.; Oestreich, M. *ACS Catal.* **2013**, *3*, 1578–1587. (c) Ahrens, T.; Kohlmann, J.; Ahrens, M.; Braun, T. *Chem. Rev.* DOI: 10.1021/cr500257c.

[2] For selected reports on C–F bond activations of trifluoromethyl groups, see: (a) Fuchibe, K.; Kaneko, T.; Mori, K.; Akiyama, T. *Angew. Chem. Int. Ed.* **2009**, *48*, 8070–8073. (b) Terao, J.; Nakamura, M.; Kambe, N. *Chem. Commun.* **2009**, 6011–6033. (c) Iida, T.; Hashimoto, R.; Aikawa, K.; Ito, S.; Mikami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 9535–9538. (d) Stahl, T.; Klare, H. F. T.; Oestreich, M. *J. Am. Chem. Soc.* **2013**, *135*, 1248–1251. (e) Ahrens, M.; Scholz, G.; Braun, T.; Kemnitz, E. *Angew. Chem. Int. Ed.* **2013**, *52*, 3528–3532. (f) Caputo, C. B.; Hounjet, L. J.; Dobrovetsky, R.; Stephan, D. W. *Science* 2013, 341, 1374–1377.

[3] For transition metal-catalyzed C–F bond activations of trifluoromethyl groups using β-fluorine elimination, see: (a) Ichikawa, J.; Nadano, R.; Ito, N. *Chem. Commun.* **2006**, 4425–4427. (b) Miura, T.; Ito, Y.; Murakami, M. *Chem. Lett.* **2008**, *37*, 1006–1007. (c) Corberan, R.; Mszar, N. W.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2011**, *50*, 7079–7082. (d) Hu, M.; He, Z.; Gao, B.; Li, L.; Ni, C.; Hu J. *J. Am. Chem. Soc.* **2013**, *135*, 17302–17305.

[4] For selected papers on transition metal-catalyzed hydrodefluorinations, see: [hydrodefluorinations of aryl fluorides] (a) Kuhl, S.; Schneider, R.; Fort, Y. *Adv. Synth. Catal.* **2003**, *345*, 341–344. (b) Fischer, P.; Götz, K.; Eichhorn, A.; Radius, U. *Organometallics* **2012**, *31*, 1374–1383. (c) Chen, Z.; He, C.-Y.; Yin, Z.; Chen, L.; He, Y.; Zhang, X. *Angew. Chem. Int. Ed.* **2013**, *52*, 5813–5817. [hydrodefluorinations of vinyl fluorides] (d) Peterson, A. A.; McNeill, K. *Organometallics* **2006**, *25*, 4938–4940. (e) Braun, T.; Wehmeier, F.; Altenhöner, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 5321–5324. (f) Kühnel, M. F.; Lentz, D. *Angew. Chem. Int.*

Ed. **2010**, *49*, 2933–2936.

[5] For review on nickel-catalyzed multicomponent coupling reactions of electron-deficient alkenes and alkynes with organometallic reagents, see: [Reviews] (a) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467–473. (b) Ikeda, S.; *Acc. Chem. Res.* **2000**, *33*, 511–519. (c) Montgomery, J. *Angew. Chem. Int. Ed.* **2004**, *43*, 3890–3908. (d) Moslin, R. M.; Miller-Moslin, K.; Jamison, T. F. *Chem. Commun.* **2007**, 4441–4449. [initial studies] (e) Ikeda, S.; Sato, Y. *J. Am. Chem. Soc.* **1994**, 116, 5975–5976. (f) Montgomery, J.; Savchenko, A. V. *J. Am. Chem. Soc.* **1996**, *118*, 2099–2100.

[6] For selected papers on nickel-catalyzed reaction via oxidative addition of aryl chlorides, see: (a) Yoshikai, N.; Matsuda, H.; Nakamura, E. *J. Am. Chem. Soc.* **2009**, *131*, 9590–9599. (b) Everson, D. A.; Jones, B. A.; Weix, D. J. *J. Am. Chem. Soc.* **2012**, *134*, 6146–6159. (c) Ge, S.; Green, R. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *134*, 1617–1627. (d) Tasker, S. Z.; Gutierrez, A. C.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2014**, *53*, 1858–1861.

[7] For nickel-catalyzed cotrimerization of electron-deficient alkenes and alkynes, see: (a) Sambaiah, T.; Li, L.-P.; Huang, D.-J.; Lin, C.-H. Rayabarapu D. K.; Cheng, C.-H. *J. Org. Chem.* **1999**, *64*, 3663–3670. (b) Horie, H.; Kurahashi, T.; Matsubara, S. *Chem. Commun.* **2010**, *46*, 7229–7231.

[8] For selected reviews on NHC ligands, see: (a) Cavallo, L.; Correa, A.; Costabile, C.; Jacobsen, H. *J. Organomet. Chem.* **2005**, *690*, 5407–5413. (b) Würtz, S.; Glorius, F. *Acc. Chem. Res*. **2008**, *41*, 1523–1533.

[9] (a) Tolman, C. A. *J. Am. Chem. Soc.* **1974**, *96*, 2780–2789. (b) Ohashi, M.; Shibata, M.; Saijo, H.; Kambara, T.; Ogoshi, S. *Organometallics* **2013**, *32*, 3631–3639.

[10] For Lewis acid-mediated allylic C–F bond activation, see: (a) Kobayashi, Y.; Nagai, T.; Kumadaki, I.; Takahashi, M.; Yamaguchi, T. *Chem. Pharm. Bull.* **1984**, *32*, 4382–4387. (b) Ooi, T.; Uraguchi, D.; Kagoshima, N.; Maruoka, K. *Tetrahedron Lett.* **1997**, *38*, 5679–5682.

[11] (a) Tobisu, M.; Xu, T.; Shimasaki, T.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 19505–19511. (b) Ohashi, M.; Doi, R.; Ogoshi, S. *Chem. Eur. J.* **2014**, *20*, 2040–2048.

[12] For the study on regioselectivity in oxidative cyclization between alkynes and aldehydes on Ni(0) complex, see: (a) Liu, P.; McCarren, P.; Cheong, P. H.-Y.; Jamison, T. M.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 2050–2057. (b) Liu, P.; Montgomery, J.; Houk, K. N. *J. Am. Chem. Soc.* **2011**, *133*, 6956–6959. (c) Jackson, E. P.; Montgomery, J. *J. Am. Chem. Soc.* **2015**, *137*, 958–963.

[13] For oxidative addition of allylic C–F bond to Pd(0), see: (a) Narumi, T.; Tomita, K.; Inokuchi, E.; Kobayashi, K.; Oishi, S.; Ohno, H.; Fijii, N. *Org. Lett.* **2007**, *9*, 3465–3468. (b) Hazari, A.; Gouverneur, V.; Brown, J. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 1296–1299. (c) Pigeon, X.; Bergeon, M.; Barabé, F.; Dubé, P.; Frost, H. N.; Paquin, J.-F. *Angew. Chem. Int. Ed.* **2010**, *49*, 1123–1127. (d) Ohashi, M.; Shibara, M.; Ogoshi, S. *Angew. Chem. Int. Ed.* **2014**, *53*, 13578–13582.

[14] For oxidative addition of Si–H bond to Ni(0), see: (a) Lappert, M. F.; Speier, G. *J. Organomet. Chem.* **1974**, *80*, 329–339. (b) Iluc, V. M.; Hillhouse, G. L. *Tetrahedron* **2006**, *62*, 7577–7582. (c) Zell, T.; Schaub, T.; Radacki, K.; Radius, U. *Dalton Trans.* **2011**, *40*, 1852–1854.

[15] For nickel-catalyzed hydrosolylations of alkynes, see: (a) Tillack, A.; Pulst, S.; Baumann, W.; Baudisch, H.; Kortus, K.; Rosenthal U. *J. Organomet. Chem.* **1997**, *532*, 117–123. (b) Chaulagain, M. R.; Mahandru G. M.; Montgomery, J. *Tetrahedron* **2006**, *62*, 7560–7566.

[16] For allylic C–F bond activation of 3,3-difluoropropenes, see: (a) Okada, M.; Nakamura, Y.; Saito, A.; Sato, A.; Horikawa, H.; Taguchi, T. *Tetrahedron Lett.* **2002**, *43*, 5845–5847. (b)

Yanai, H.; Okada, H.; Sato, A.; Okada, M.; Taguchi, T. *Tetrahedron Lett.* **2011**, *52*, 2997–3000. (c) Bergeron, M.; Johnson, T.; Paquin, J.-F. *Angew. Chem., Int. Ed.* **2011**, *50*, 11112–1116.

[17] The reduction of NiX_2 with organometallic reagents, see: (a) Henningsen, M. C.; Jeropoulos, S.; Smith, E. H. *J. Org. Chem.* **1989**, *54*, 3015–3018. (b) Krysan, D. J.; Mackenzie, P. B. *J. Org. Chem.* **1990**, *55,* 4229–4230.

[18] For the reduction of NiX_2 with Mn or Zn metal, see: (a) Everson, D. A.; Shrestha, R.; Weix, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 920–921. (b) Fujihara, T.; Nogi, K.; Xu, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* **2012**, *134*, 9106–9109. (c) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 7442–7445.

[19] Ishii, Y.; Chatani, N.; Yorimitsu, S.; Murai, S. *Chem. Lett.* **1998**, 157–158.

[20] (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508–7510. (b) Mannathan, S.; Jeganmohan, M.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2009**, *48*, 2192–2195. (c) Gao, M.; Thorpe, S. B.; Santos, W. L. *Org. Lett.* **2009**, *11*, 3478–3481.

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_4Si (for ^{1}H NMR: $\delta = 0.00$), $CDCl_3$ (for ^{13}C NMR: $\delta = 77.0$), C_6F_6 (for ^{19}F NMR: $\delta = 0.0$), and H_3PO_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.

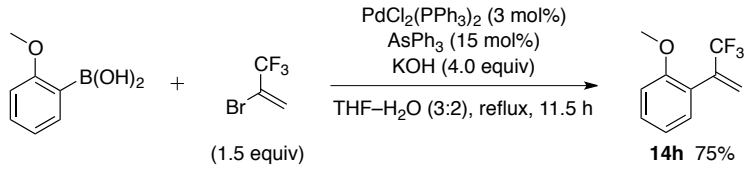
Column chromatography and preparative thin-layer chromatography (PTLC) were conducted on silica gel (Silica Gel 60 N, Kanto Chemical Co., Inc. for column chromatography and Wakogel B-5F, Wako Pure Chemical Industries for PTLC, respectively). All the reactions were conducted under argon. Tetrahydrofuran (THF) and diethylether (Et_2O) 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_6D_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_3SiH, $B_2(nep)_2$, *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

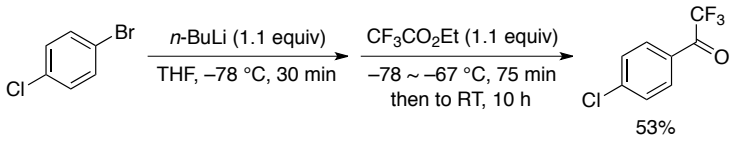
1-Methoxy-2-(3,3,3-trifluoroprop-1-en-2-yl)benzene (14h)[1]



To a THF solution (16 mL, 0.3 M) of $PdCl_2(PPh_3)_2$ (108 mg, 0.154 mmol) and $AsPh_3$ (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 NH_4Cl. Organic materials were extracted two times with Et_2O. The combined extracts were washed with brine and dried over Na_2SO_4. 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 gave **14h** (778 g, 75%) as a colorless liquid.

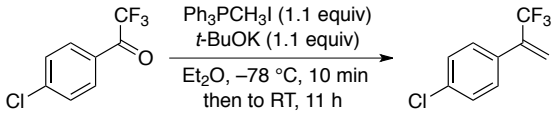
Spectral data for this compound showed good agreement with the literature data.[2]

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 NH_4Cl was added. Organic materials were extracted three times with Et_2O. The combined extracts were washed with brine and dried over anhydrous Na_2SO_4. 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)

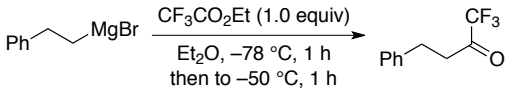


14i 33%

To a Et_2O solution (50 mL) of Ph_3PCH_3I (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 Et_2O 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 NH_4Cl at that temperature. Organic materials were extracted three times with Et_2O. The combined extracts were washed with brine and dried over anhydrous Na_2SO_4. 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

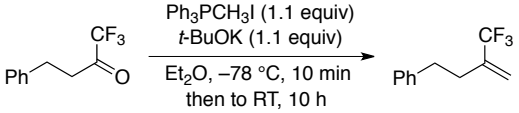


74%

To a Et_2O solution (100 mL) of ethyl trifluoroacetate (7.16 g, 50.0 mmol) was added phenetylmagnesium bromide (1.0 M in Et_2O, 50.0 mL, 50.0 mmol) prepared from phenetylbromide (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 NH_4Cl was added at that temperature. Organic materials were extracted three times with Et_2O. The combined extracts were washed with brine and dried over anhydrous Na_2SO_4. 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]

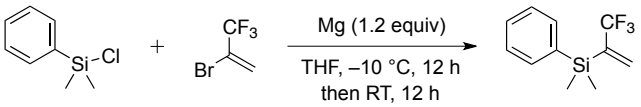
[3-(Trifluoromethyl)-3-butenyl]benzene (14k)



14k 77%

To a Et_2O solution (64 mL) of Ph_3PCH_3I (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 Et_2O 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 Et_2O. The combined extracts were washed with brine and dried over anhydrous Na_2SO_4. 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)



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 Et_2O. The combined extracts were washed with brine and then dried over Na_2SO_4. After removal of the solvent, the residue was purified by silicagel 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.).

[1] J. Walkowiak, T. M. del Campo, B. Ameduri, V. Gouverneur, *Synthesis* **2010**, *11*, 1883–1890.

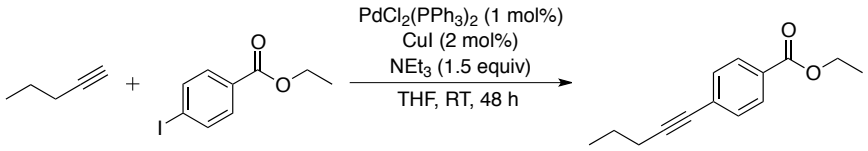
[2] O. Kobatashi, D. Uraguchi, T. Yamakawa, *J. Fluorine Chem.* **2009**, *130*, 591–594.

[3] Fuchibe, K.; Jyono, H.; Fujiwara, M.; Kudo, T.; Yokota, M.; Ichikawa, J. *Chem. Eur. J.* **2011**, *17*, 12175–12185.

[4] Ichikawa, J.; Ishibashi, Y.; Fukui, H. *Tetrahedron Lett.* **2003**, *44*, 707–710.

[2] Synthesis of Alkynes

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



To a THF solution (20 mL) of $PdCl_2(PPh_3)_2$ (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 NEt_3 (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 Et_2O. The combined extracts were washed with brine and dried over anhydrous Na_2SO_4. 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): $\tilde{\nu}$ = 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). ^{13}C 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 $C_{14}H_{16}O_2$ $[M]^+$ 216.1150, Found 216.1141.

Diphenylacetylene (**15b**)[6], and 1-phenyl-1-propyne (**15d**)[5], 1-methoxy-4-(pent-1-ynyl)benzene (**15e**)[7], 1-phenyl-1-pentyne (**15f**)[7] were prepared by the literature procedures. Spectral data for these compounds showed good agreement with the literature data.

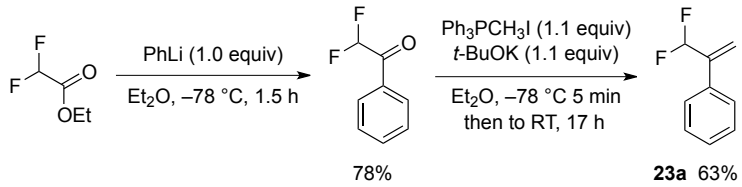
[5] D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 16474–16475.

[6] C. He, J. Ke, H. Xu, A. Lei, *Angew. Chem. Int. Ed.* **2013**, *52*, 1527–1530.

[7] S. R. Chidipudi, I. Khan, H. W. Kam, *Angew. Chem Int. Ed.* **2012**, *51*, 12115–12119.

[3] Synthesis of 3,3-Difluoropropene Derivatives 23

α-Difluoromethylstyrene (23a)

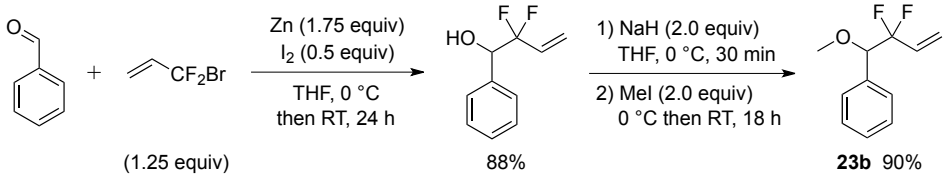


Synthesis of ketone: To a Et_2O solution (70 mL) of ethyl 2,2-difluoroacetate (2.33 g, 10.0 mmol) was added slowly a Bu_2O–Et_2O solution of PhLi (12.5 mL, 1.60 M in Bu_2O, 10.5 mmol and Et_2O 7.5 mL) at –78 °C over 50 min. After stirring for 1.5 h at that temperature, the reaction mixture was quenched with aqueous HCl (1.0 M). Organic materials were extracted two times with Et_2O. The combined extracts were washed with brine and dried over anhydrous Na_2SO_4. 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 Et_2O solution (70 mL) of Ph_3PCH_3I (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 Et_2O 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 NH_4Cl at that temperature. The mixture was filtered through a pad of Celite (Et_2O), and then filtrate was extracted three times with Et_2O. The combined extracts were washed with brine and dried over anhydrous Na_2SO_4. 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)

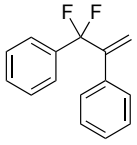


Zinc-mediated difluoroallylation: To a suspension of zinc power (2.29 g, 35 mmol) in THF (25 mL) was added I_2 (2.54 g, 10.0 mmol) in several portions at 0 °C. After stirring for 30 min at room temperature, benzaldehyde (2.1 g, 20.0 mmol) was added to the mixture and then cooled to 0 °C. To

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 Na_2SO_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-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]

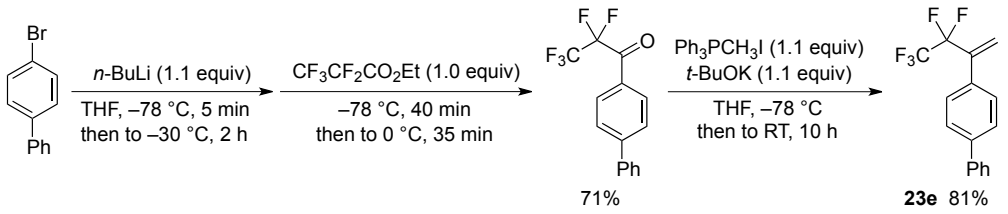
Methylation of the alcohol: To a suspension of sodium hydride (55 wt%, 436 mg, 10.0 mmol) in THF (8 mL) was added slowly a THF solution (2.0 mL) of 2,2-difluoro-1-phenylbut-3-en-1-ol (921 mg, 5.00 mmol) at 0 °C. After stirring for 30 min at 0 °C, iodomethane (0.623 mL, 10.0 mmol) was added to the reaction 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 Et_2O. The combined extracts were washed with brine and then dried over Na_2SO_4. 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: ^{1}H NMR: δ 3.28 (s, 3H), 4.31 (dd, J_{HF} = 9.6, 9.6 Hz, 1H), 5.37 (d, J = 11.1 Hz, 1H), 5.48 (ddd, J = 17.4, 2.5, 2.5 Hz, 1H), 5.78–5.93 (m, 1H), 7.24–7.33 (m, 5H). ^{13}C NMR: δ 57.9, 85.0 (dd, J_{CF} = 30, 30 Hz), 118.8 (dd, J_{CF} = 245, 245 Hz), 120.9 (dd, J_{CF} = 9, 9 Hz), 128.1, 128.4, 128.7, 129.9 (dd, J_{CF} = 26, 26 Hz), 134.4 (d, J_{CF} = 4 Hz). ^{19}F NMR: δ 53.9 (ddd, J_{FF} = 249 Hz, J_{FH} = 10, 10 Hz, 1F), 58.1 (ddd, J_{FF} = 249 Hz, J_{FH} = 10, 10 Hz, 1F). Elemental analysis: Calcd for $C_{11}H_{12}F_2O$: 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-(3,3,4,4,4-Pentafluorobut-1-en-2-yl)biphenyl (23e)[10,11]

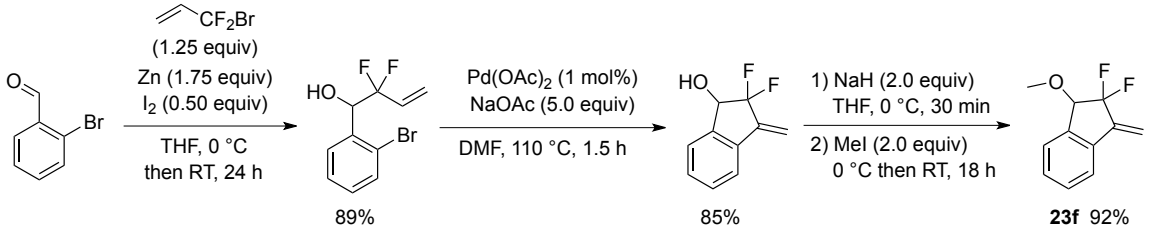


Synthesis of ketone: To a THF solution (30 mL) of 4-bromobiphenyl (2.33 g, 10.0 mmol) was added *n*-BuLi (6.60 mL, 1.59 M in hexane, 10.5 mmol) at –78 °C over 5 min. The mixture was warmed to –30 °C over 2 h, and then transferred by using a double-ended needle to a THF solution (30 mL) of ethyl 2,2,3,3,3-pentafluoropropionate (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_2O. The combined extracts were washed with brine and dried over anhydrous Na_2SO_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): $\tilde{\nu}$ = 1705, 1605, 1228, 1171, 912, 870 cm^{-1}. ^1H NMR: δ 7.45 (t, J = 7.4 Hz, 1H), 7.50 (dd, J = 7.4, 7.1 Hz, 2H), 7.65 (d, J = 7.1 Hz, 2H), 7.77 (d, J = 8.3 Hz, 2H), 8.17 (d, J = 8.3 Hz, 2H). ^{13}C NMR: δ 108.8 (tq, J_{CF} = 270, 37 Hz), 118.0 (qt, J_{CF} = 287, 34 Hz), 127.4, 127.6, 128.9, 129.1, 129.6, 130.7, 139.1, 148.2, 182.7 (t, J_{CF} = 27 Hz). ^{19}F NMR: δ 47.4 (s, 2F), 81.3 (s, 3F). HRMS (EI+): Calcd for $C_{15}H_9F_5O$ $[M]^+$ 300.0574, Found 300.0574.

Wittig Reaction: To a THF solution (33 mL) of Ph_3PCH_3I (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_4Cl at that temperature. The mixture was filtered through a pad of Celite (Et_2O), and then filtrate was extracted three times with Et_2O. The combined extracts were washed with brine and dried over anhydrous Na_2SO_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): $\tilde{\nu}$ = 1333, 1205, 1165, 1140, 1086, 1018, 908, 739 cm^{-1}. ^1H NMR: δ 5.84 (t, J = 1.3 Hz, 1H), 6.03 (t, J = 1.6, 1H), 7.37 (tt, J = 7.3, 1.2 Hz, 1H), 7.41–7.49 (m, 4H), 7.55–7.63 (m, 4H). ^{13}C NMR: δ 113.0 (tq, J_{CF} = 255, 38 Hz), 119.1 (qt, J_{CF} = 288, 38 Hz), 124.6 (t, J_{CF} = 8 Hz), 127.0,

127.1, 127.7, 128.85, 128.90, 133.7, 138.2 (t, J_{CF} = 22 Hz), 140.3, 141.7. ^{19}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-1*H*-indene (23f)



Zinc-mediated difluoroallylation: 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_2SO_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.

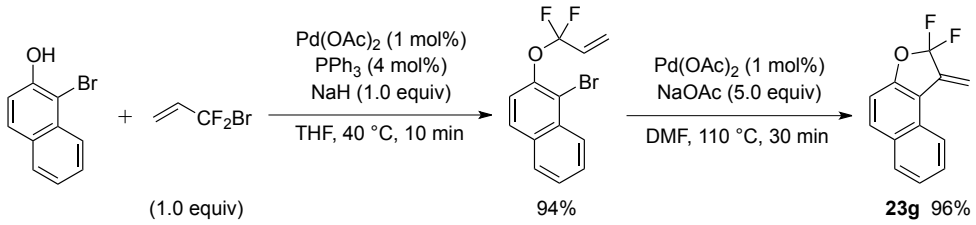
Palladium-catalyzed Heck cyclization: To a DMF solution (2.0 mL) of 2,2-difluoro-1-(4-bromophenyl)but-3-en-1-ol (132 mg, 0.50 mmol) and palladium acetate (1.1 mg, 0.005 mmol) was added sodium acetate (205 mg, 2.5 mmol), and the mixture was heated to 110 °C. After stirring for 90 min at the same temperature, 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_2SO_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-1*H*-inden-1-ol (77 mg, 85%) as a white solid.

Methylation of the alcohol: 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-1*H*-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_2O. The combined extracts were washed with brine and then dried over Na_2SO_4. After removal of the solvent, the

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-1*H*-indene (**23f**, 689 mg, 92%) as a colorless liquid.

23f: IR (neat): $\tilde{\nu}$ = 2935, 2835, 1223, 1093, 1059, 980, 912, 733 cm^{-1}. ^1H NMR: δ 3.68 (s, 3H), 4.76 (dd, J_{HF} = 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). ^{13}C NMR: δ 58.8 (d, J_{CF} = 2 Hz), 83.0 (dd, J_{CF} = 31, 19 Hz), 109.7, 121.0, 123.8 (dd, J_{CF} = 258, 252 Hz), 125.8, 129.8, 130.1, 135.9 (dd, J_{CF} = 8, 8 Hz), 138.4 (d, J_{CF} = 8 Hz), 142.4 (dd, J_{CF} = 23, 23 Hz). ^{19}F NMR: δ 49.7 (d, J_{FF} = 251 Hz, 1F), 62.2 (dd, J_{FF} = 251 Hz, J_{FH} = 12 Hz, 1F). HRMS (EI+): Calcd for $C_{11}H_{10}F_2O$ $[M]^+$ 196.0700, Found 196.0697.

2,2-Difluoro-1-methylene-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-naphtholl (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_2SO_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): $\tilde{\nu}$ = 3057, 1630, 1527, 1460, 1392, 1296, 1267, 1174, 1097, 978, 808, 742 cm^{-1}. ^1H NMR: δ 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: δ 111.6, 113.3, 113.6 (t, J_{CF} = 2 Hz), 122.3, 124.8, 127.8 (t, J_{CF} = 261Hz), 128.6, 128.9, 129.7, 130.6, 133.2, 138.5 (t, J_{CF} = 25 Hz), 156.3. ^{19}F NMR: δ 94.0 (s, 2F). HRMS (EI+) Calcd for $C_{13}H_8F_2O$ $[M]^+$: 218.0543, Found 218.0534.

[8] Yang, Z-.Y.; Burton, D. J. *J. Org. Chem.* **1991**, *56*, 1037–1041.

[9] Min, Q.-Q.; Yin, Z.; Feng, Z.; Guo, W.-H.; Zhang, X. *J. Am. Chem. Soc.* **2014**, *136*, 1230–1233.

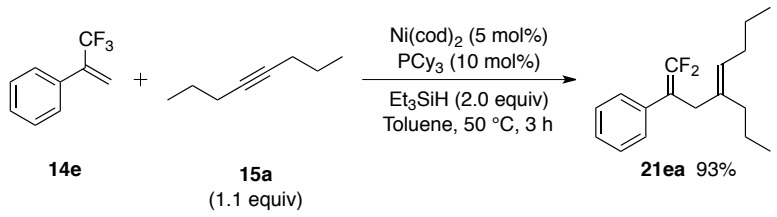
[10] X. Creary, *J. Org. Chem.* **1987**, *52*, 5026–5030.

[11] K. van Alem, G. Belder, G. Lodder, H. Zuilhof, *J. Org. Chem.* **2005**, *70*, 179–190.

[12] Pravst, I.; Zupan, M.; Stavber, S. *Synthesis* **2005**, *18*, 3140–3146.

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

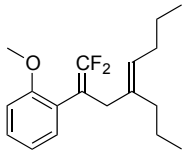
(*E*)-(1,1-Difluoro-4-propylocta-1,4-dien-2-yl)benzene (21ea): Typical Procedure A



To a toluene solution (3.2 mL) of $Ni(cod)_2$ (8.9 mg, 0.032 mmol) and PCy_3 (15 mg, 0.055 mmol) were added α-trifluoromethylstyrene (**14e**, 110 mg, 0.64 mmol) and Et_3SiH (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.

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

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

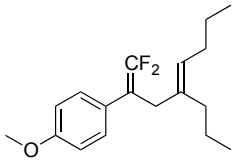


Compound **21ha** was synthesized according to the typical procedure A using 1-Methoxy-2-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**14h**, 99 mg, 0.49 mmol), 4-octyne (**15a**, 59 mg, 0.54 mmol), Et_3SiH (113 mg, 0.97 mmol), $Ni(cod)_2$ (6.7 mg, 0.024 mmol), PCy_3 (14 mg, 0.051 mmol), and Toluene (2.4 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.

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

= 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). ^{13}C NMR: δ 13.5, 14.0, 21.2, 22.9, 29.7, 31.6, 35.2, 55.3, 88.0 (dd, J_{CF} = 23, 16 Hz), 110.8, 120.2, 122.7 (dd, J_{CF} = 4, 2 Hz), 127.4, 128.8, 131.1, 135.2 (dd, J_{CF} = 2, 2 Hz), 153.4 (dd, J_{CF} = 288, 288 Hz), 157.1. ^{19}F NMR: δ 69.0 (d, J_{FF} = 42 Hz, 1F), 73.4 (d, J_{FF} = 42 Hz, 1F). Elemental analysis: Calcd for $C_{18}H_{24}F_2O$: C, 73.44; H, 8.22. Found: C, 73.41; H, 8.12.

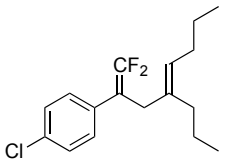
(*E*)-1-(1,1-Difluoro-4-propylocta-1,4-dien-2-yl)-4-methoxybenzene (21fa)



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), Et_3SiH (118 mg, 1.0 mmol), $Ni(cod)_2$ (7.0 mg, 0.025 mmol), PCy_3 (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): $\tilde{\nu}$ = 2960, 2935, 2873, 1614, 1591, 1321, 1163, 1111, 1066, 835 cm^{-1}. ^{1}H 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). ^{13}C NMR: δ 13.6, 14.1, 21.3, 22.9, 29.8, 32.0, 35.2, 55.2, 90.1 (dd, J_{CF} = 20, 13 Hz), 113.6, 126.3 (dd, J_{CF} = 6, 6 Hz), 127.3, 129.3 (dd, J_{CF} = 4, 4 Hz), 135.1 (dd, J_{CF} = 2, 2 Hz), 154.0 (dd, J_{CF} = 291, 287 Hz), 158.5. ^{19}F NMR: δ 71.0 (d, J_{FF} = 44 Hz, 1F), 71.1 (d, J_{FF} = 44 Hz, 1F). Elemental analysis: Calcd for $C_{18}H_{24}F_2O$: C, 73.44; H, 8.22. Found: C, 73.55; H, 8.24.

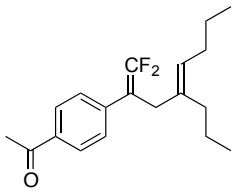
(*E*)-1-Chloro-4-(1,1-difluoro-4-propylocta-1,4-dien-2-yl)benzene (21ia)



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), Et_3SiH (113 mg, 0.97 mmol), $Ni(cod)_2$ (6.7 mg, 0.024 mmol), PCy_3 (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): $\tilde{\nu}$ = 2958, 2931, 2871, 1722, 1493, 1238, 1092, 999, 827, 771 cm^{-1}. ^1H NMR: δ 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: δ 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: δ 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.

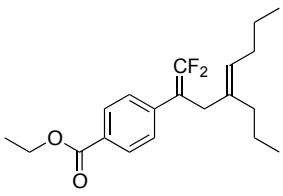
(*E*)-1-(4-(1,1-Difluoro-4-propylocta-1,4-dien-2-yl)phenyl)ethanone (21aa)



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_3SiH (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): $\tilde{\nu}$ = 2958, 2931, 2871, 1716, 1684, 1606, 1267, 1238, 1217, 771 cm^{-1}. ^1H NMR: δ 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: δ 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: δ 74.6 (d, J_{FF} = 35 Hz, 1F), 74.7 (d, J_{FF} = 35 Hz, 1F). Elemental analysis: Calcd for $C_{19}H_{24}F_2O$: C, 74.48; H, 7.90. Found: C, 74.47; H, 7.86.

(*E*)-Ethyl 4-(1,1-difluoro-4-propylocta-1,4-dien-2-yl)benzoate (21da)

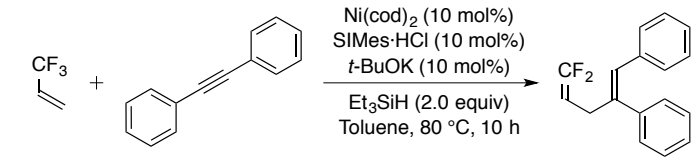


Compound **21da** was synthesized according to the typical procedure A using ethyl 4-(3,3,3-trifluoroprop-1-en-2-yl)benzoate (**1d**, 143 mg, 0.58 mmol), 4-octyne (**15a**, 71 mg, 0.64 mmol), Et_3SiH (135 mg, 1.2 mmol), $Ni(cod)_2$ (8.0 mg, 0.029 mmol), PCy_3 (16 mg, 0.058 mmol), and Toluene (2.9 mL) 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): $\tilde{\nu}$ = 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). ^{13}C 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. ^{19}F NMR: δ 74.4 (s, 2F). HRMS (EI+): Calcd for $C_{20}H_{26}F_2O_2$ $[M]^+$ 336.1901, Found 336.1898.

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

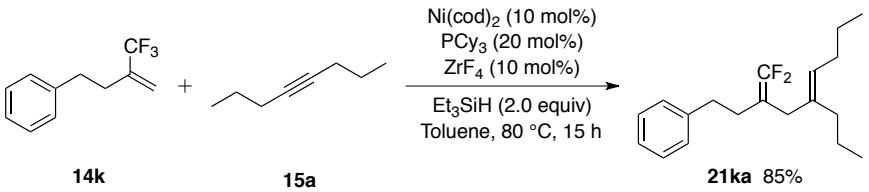


14j (1.0 atm) **15b** (1.0 equiv) **21jb** 77%

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 Et_3SiH (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): $\tilde{\nu}$ = 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 (dtd, 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). ^{13}C 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). ^{19}F NMR: 71.0 (dd, J_{FF} = 44 Hz, J_{FH} = 25 Hz, 1F), 74.0 (d, J_{FF} = 44 Hz, 1F). HRMS (EI+): Calcd for $C_{17}H_{14}F_2$ $[M]^+$ 256.1064, Found 256.1058.

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

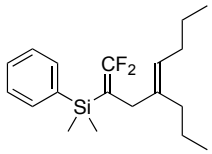


14k **15a** (1.1 equiv) **21ka** 85%

To a toluene solution (2.5 mL) of $Ni(cod)_2$ (14 mg, 0.051 mmol) and PCy_3 (28 mg, 0.10 mmol), ZrF_4 (8.6 mg, 0.051 mmol) were added [3-(trifluoromethyl)-3-buten-1-yl]benzene (**14k**, 103 mg, 0.51 mmol) and Et_3SiH (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): $\tilde{\nu}$ = 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). ^{13}C 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). ^{19}F NMR: δ 66.8 (d, J_{FF} = 54 Hz, 1F), 68.1 (d, J_{FF} = 54 Hz, 1F). HRMS (EI+): Calcd for $C_{19}H_{26}F_2$ $[M]^+$ 292.2003, Found 292.2007.

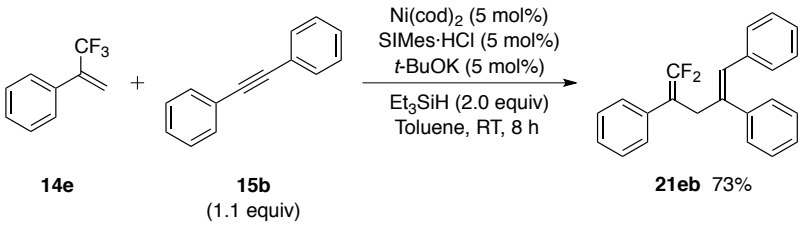
(*E*)-(1,1-Difluoro-4-propylocta-1,4-dien-2-yl)dimethyl(phenyl)silane (21la)



To a toluene solution (2.7 mL) of $Ni(cod)_2$ (15 mg, 0.054 mmol) and PCy_3 (30 mg, 0.11 mmol), ZrF_4 (9.0 mg, 0.054 mmol) were added dimethylphenyl[1-(trifluoromethyl)ethenyl]silane (**14l**, 125 mg, 0.54 mmol) and Et_3SiH (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 $NaHCO_3$. Organic materials were extracted three times with Et_2O. The combined extracts were washed with brine and dried over anhydrous Na_2SO_4. 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): $\tilde{\nu}$ = 2958, 2931, 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). ^{13}C 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). ^{19}F NMR: δ 87.5 (d, J_{FF} = 34 Hz, 1F), 89.5 (d, J_{FF} = 34 Hz, 1F). HRMS (EI+): Calcd for $C_{19}H_{28}F_2Si$ ($[M]^+$–PhH) 244.1459, Found 244.1453.

(*Z*)-(5,5-Difluoropenta-1,4-diene-1,2,4-triyl)tribenzene (21eb): Typical Procedure B

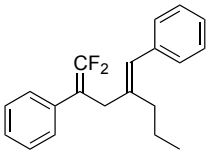


14e **15b** (1.1 equiv) **21eb** 73%

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_3SiH (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): $\tilde{\nu}$ = 3060, 3024, 1732, 1240, 912, 742, 696 cm^{-1}. ^1H NMR: δ 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: δ 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: δ 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.

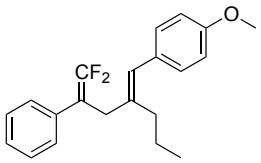
(*E*)-(5,5-Difluoro-2-propylpenta-1,4-diene-1,4-diyl)dibenzene (21ef)



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_3SiH (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): $\tilde{\nu}$ = 2960, 2871, 1724, 1495, 1446, 1236, 993, 771, 696 cm^{-1}. ^1H NMR: δ 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: δ 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: δ 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.

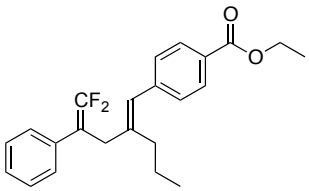
(*E*)-1-(5,5-Difluoro-4-phenyl-2-propylpenta-1,4-dien-1-yl)-4-methoxybenzene (21ee)



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), Et_3SiH (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): $\tilde{\nu}$ = 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). ^{13}C 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. ^{19}F NMR: δ 72.6 (s, 2F). HRMS (EI+): Calcd for $C_{21}H_{22}F_2O$ $[M]^+$ 328.1639, Found 328.1627.

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

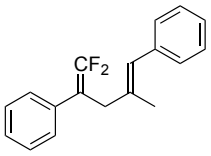


Compound **21eg** was synthesized according to the typical procedure **B** using α-trifluoromethylstyrene (**14e**, 92 mg, 0.53 mmol), ethyl 4-(pent-1-ynyl)benzoate (**15g**, 126 mg, 0.58 mmol), Et_3SiH (124 mg, 1.1 mmol), $Ni(cod)_2$ (7.3 mg, 0.027 mmol), SIMes·HCl (11 mg, 0.027 mmol), *t*-BuOK (3.0 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): $\tilde{\nu}$ = 2960, 2871, 1714, 1606, 1271, 1236, 1101, 766, 696 cm^{-1}. ^1H NMR: δ 0.89 (t, *J* = 7.4 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). ^{13}C 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. ^{19}F NMR: δ 73.0 (d, J_{FF} = 39 Hz, 1F), 73.1 (d, J_{FF} = 39 Hz,

1F). HRMS (EI+): Calcd for $C_{23}H_{24}F_2O_2$ $[M]^+$ 370.1744, Found 370.1752.

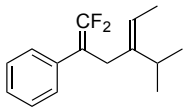
(*E*)-(5,5-Difluoro-2-methylpenta-1,4-diene-1,4-diyl)dibenzene (21ed)



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), Et_3SiH (149 mg, 1.3 mmol), $Ni(cod)_2$ (8.8 mg, 0.032 mmol), PCy_3 (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): $\tilde{\nu}$ = 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). ^{13}C NMR: δ 17.5, 38.5, 90.4 (dd, J_{CF} = 20, 14 Hz), 126.1, 126.9, 127.2, 128.0, 128.2 (dd, J_{CF} = 3, 3 Hz), 128.3, 128.8, 133.7, 134.9 (dd, J_{CF} = 2, 2 Hz), 138.0, 154.3 (dd, J_{CF} = 292, 289 Hz). ^{19}F NMR: δ 72.6 (d, J_{FF} = 40 Hz, 1F), 72.7 (d, J_{FF} = 40 Hz, 1F). HRMS (EI+): Calcd for $C_{18}H_{16}F_2$ $[M]^+$ 270.1220, Found: 270.1210.

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



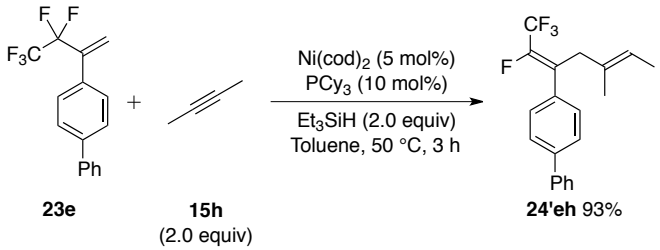
Compound **21ec** was synthesized according to the typical procedure A using α-trifluoromethylstyrene (**14e**, 91 mg, 0.53 mmol), 4-methyl-2-pentyne (**15c**, 54 mg, 0.66 mmol), Et_3SiH (140 mg, 1.2 mmol), $Ni(cod)_2$ (16.6 mg, 0.060 mmol), PCy_3 (34 mg, 0.12 mmol), and Toluene (3.0 mL) at room temperature for 4 h. Purification by silica gel column chromatography (hexane) gave **21ec** (110 mg, 88%) as a colorless liquid.

21ec: IR (neat): $\tilde{\nu}$ = 2962, 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). ^{13}C NMR: δ 12.7, 20.5, 28.3, 29.3, 90.3 (dd, J_{CF} = 21, 12 Hz), 118.1, 126.9, 127.9 (dd, J_{CF} = 3, 3 Hz), 128.2, 134.4 (dd, J_{CF} = 3, 3 Hz), 140.2, 154.1 (dd, J_{CF} = 293, 288 Hz). ^{19}F NMR: δ 72.7 (d, J_{FF} = 40 Hz, 1F), 72.9 (d, J_{FF} = 40 Hz, 1F). HRMS (EI+): Calcd for $C_{15}H_{18}F_2$ $[M]^+$ 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-((2*Z*,5*E*)-1,1,1,2-Tetrafluoro-5-methylhepta-2,5-dien-3-yl)-1,1'-biphenyl (24'eh)



23e **15h** (2.0 equiv) **24'eh** 93%

To a toluene solution (3.1 mL) of $Ni(cod)_2$ (8.7 mg, 0.032 mmol) and PCy_3 (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), Et_3SiH (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): $\tilde{\nu}$ = 2922, 1333, 1306, 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). ^{13}C 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). ^{19}F NMR: δ 35.0 (q, J_{FF} = 8 Hz, 1F), 98.2 (d, J_{FF} = 8 Hz, 3F). Elemental analysis: Calcd for $C_{20}H_{18}F_4$: 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.

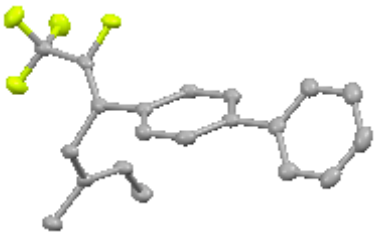
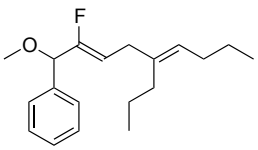


Figure S1. X-Ray Crystal Structure of **24'eh**

Table S1. Crystal Data Collection Parameters for **24'eh**

complex	**24'eh**
formula	$C_{20}H_{18}F_4$
crystal system	rod
space group	$P2_1/a$
R, R_w ($I > 2\sigma(I)$)	0.0546, 0.1409
$R1$, $wR2$ (all data)	0.1032, 0.1726
GOF on F^2	0.915
a (Å)	6.1162(19)
b (Å)	15.020(5)
c (Å)	17.666(6)
α (deg)	90.00
β (deg)	96.537(5)
γ (deg)	90.00
V (Å^3)	1612.34
Z	4
T (K)	120(2)
crystal size (mm)	0.60, 0.04, 0.01
D_{calcd} (g/cm^3)	1.377
$2\theta_{min}$, $2\theta_{max}$ (deg)	2.32, 55.06
no. refln measured (unique)	9182
no. refln measured ($I > 2\sigma(I)$)	3672
no. parameters	2259

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

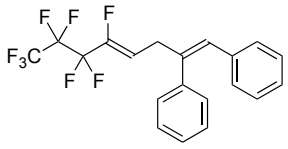


Compound **24ba** was synthesized according to the typical procedure using (2,2-difluoro-1-methoxybut-3-en-1-yl)benzene (**23b**, 100 mg, 0.51 mmol), 4-octyne (**15a**, 62 mg,

0.56 mmol), Et_3SiH (60 mg, 0.51 mmol), $Ni(cod)_2$ (14 mg, 0.052 mmol), PCy_3 (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: ^{1}H 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). ^{19}F NMR: δ 40.9 (dd, J_{FH} = 36 Hz, 16 Hz, 1F).

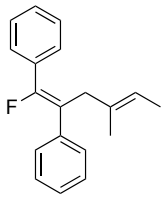
((1*Z*,4*Z*)-5,6,6,7,7,8,8,8-Octafluoroocta-1,4-diene-1,2-diyl)dibenzene (24cb)



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), Et_3SiH (149 mg, 0.55 mmol), $Ni(cod)_2$ (15 mg, 0.055 mmol), PCy_3 (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): $\tilde{\nu}$ = 1230, 1186, 1120, 912, 742 cm^{-1}. ^{1}H 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). ^{13}C 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). ^{19}F 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+): Calcd for $C_{20}H_{14}F_8$ $[M]^+$ 406.0968, Found: 406.0975.

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



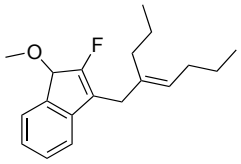
Compound **24'dh** was synthesized according to the typical procedure using (1,1-difluoroprop-2-ene-1,2-diyl)dibenzene (**23d**, 82 mg, 0.36 mmol), 2-butyne (**15h**, 38 mg, 0.70 mmol), Et_3SiH (82 mg, 0.70 mmol), $Ni(cod)_2$ (10 mg, 0.035 mmol), PCy_3 (19 mg, 0.069 mmol), and Toluene (1.8 mL) at 50 °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): $\tilde{\nu}$ = 3059, 2916, 2860, 1496, 1444, 1261, 1061, 767, 696 cm^{-1}. ^{1}H 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.

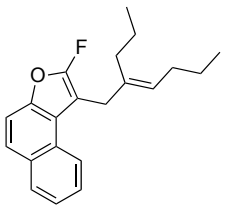
(*E*)-2-Fluoro-1-methoxy-3-(2-propylhex-2-en-1-yl)-1*H*-indene (24fa)



Compound **24fa** was synthesized according to the typical procedure using 2,2-difluoro-1-methoxy-3-methylene-2,3-dihydro-1*H*-indene (**23f**, 105 mg, 0.534 mmol), 4-octyne (**15a**, 65 mg, 0.59 mmol), Et_3SiH (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): $\tilde{\nu}$ = 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), 5.30 (t, J = 7.2 Hz, 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-1-(2-propylhex-2-en-1-yl)naphtho[2,1-*b*]furan (24ga)



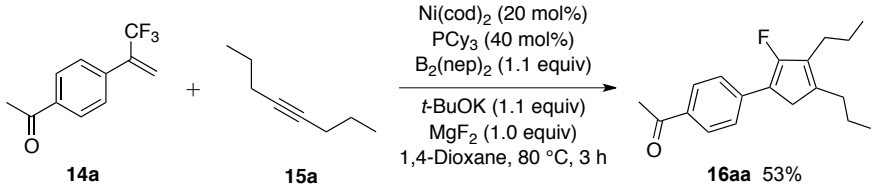
Compound **24ga** was synthesized according to the typical procedure using 2,2-difluoro-1-methylene-1,2-dihydronaphtho[2,1-*b*]furan (**23g**, 27 mg, 0.12 mmol), 4-octyne (**15a**, 15 mg, 0.14 mmol), Et_3SiH (29 mg, 0.25 mmol), $Ni(cod)_2$ (3 mg, 0.012 mmol), PCy_3 (7 mg, 0.025 mmol), and Toluene (0.7 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): $\tilde{\nu}$ = 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). ^{13}C 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). ^{19}F NMR: δ 42.6 (s, 1F).

4.7.5. Nickel-Catalyzed [3+2] Cycloaddition of 2-Trifluoromethyl-1-alkenes with Alkynes: Synthesis of 2-Fluoro-1,3-cyclopentadienes

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

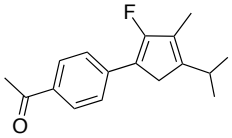
1-(4-(2-Fluoro-3,4-dipropylcyclopenta-1,3-dienyl)phenyl)ethanone (16aa)



$Ni(cod)_2$ (14 mg, 0.051 mmol), 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, 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 ºC, the reaction mixture was quenched by addition of 1 M HCl. Organic materials were extracted two times with Et_2O. The combined extracts were washed with brine and dried over Na_2SO_4. 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)

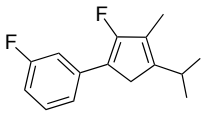


Fluorocyclopentadiene **16ac** was synthesized according to the typical procedure. Purification by silica gel column chromatography (hexane/EtOAc = 50:1) gave **16ac** (45 mg, 70%) as a yellow

solid.

The spectral data of **16ac** is shown in Chapter 3 (page 73).

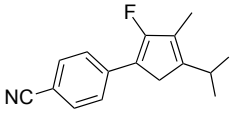
3-(2-Fluoro-4-isopropyl-3-methylcyclopenta-1,3-dienyl)fluorobenzene (16nc)



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): $\tilde{\nu}$ = 2962, 2868, 1651, 1610, 1595, 1365, 1269, 1176, 781, 686 cm^{-1}. ^{1}H NMR: δ 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). ^{13}C NMR: δ 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), ^{19}F NMR: δ 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.

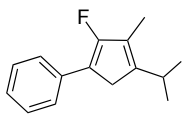
4-(2-Fluoro-4-isopropyl-3-methylcyclopenta-1,3-dienyl)benzonitrile (16bc)



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): $\tilde{\nu}$ = 2958, 2868, 2222, 1585, 912, 742 cm^{-1}. ^{1}H NMR: δ 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). ^{13}C NMR: δ 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). ^{19}F NMR: δ 43.4 (t, J_{FH} = 7.0 Hz, 1F). HRMS (EI+): Calcd for $C_{16}H_{16}FN$ $[M]^+$ 241.1267, Found 241.1270.

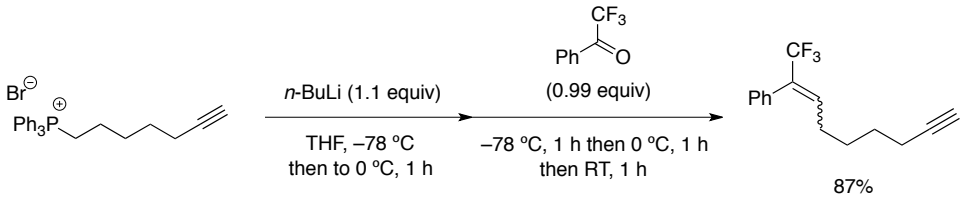
(2-Fluoro-4-isopropyl-3-methylcyclopenta-1,3-dienyl)benzene (16ec)



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): $\tilde{\nu}$ = 2960, 1653, 1597, 1367, 1192, 912, 742, 692 cm^{-1}. ^{1}H 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, J_{HF} = 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). ^{13}C NMR: δ 8.7, 22.6, 27.4 (d, J_{CF} = 2 Hz), 34.1 (d, J_{CF} = 8 Hz), 112.7, 125.5 (d, J_{CF} = 4 Hz), 125.5, 128.0 (d, J_{CF} = 27 Hz), 128.5, 134.0 (d, J_{CF} = 6 Hz), 146.2 (d, J_{CF} = 4 Hz), 158.8 (d, J_{CF} = 280 Hz). ^{19}F NMR: δ 36.8 (t, J_{FH} = 6.4 Hz, 1F). HRMS (EI+): Calcd for $C_{15}H_{17}F$ $[M]^+$ 216.1314, Found: 216.1306.

Synthesis of Trifluoromethylated Enyne 14o

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



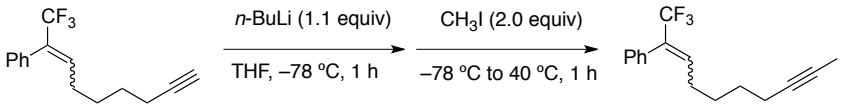
To a solution of phosphonium salt (481 mg, 1.1 mmol) in tetrahydrofuran (5 mL) was added *n*-BuLi (1.60 M in hexane, 0.76 mL, 1.2 mmol) at –78 ºC. After stirring for 5 min at –78 ºC, the reaction solution was warmed to 0 ºC, stirred for 1 h, and then cooled to –78 ºC. A solution of 2,2,2-trifluoroacetophenone (174 mg, 1.0 mmol) in tetrahydrofuran (4 mL) was added via cannula over 3 min. The reaction mixture was maintained at –78 ºC for 1 h. Then, the temperature was raised to 0 ºC. After stirring for 1 h at 0 ºC, the temperature was then raised to room temperature. After stirring for 1 h, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl. Organic materials were extracted two times with Et_2O. The combined extracts were washed with brine and dried over Na_2SO_4. 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-trifluorononon-2-en-8-yn-2-yl)benzene: IR (neat): $\tilde{\nu}$ = 2941, 2864, 1302, 1169, 1113, 758, 700, 632 cm^{-1}. ^{1}H 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 (tq, J = 6.8 Hz, J_{HF} = 1.6 Hz, 1H), 7.14–7.16 (m, 2H), 7.28–7.33 (m, 3H). ^{13}C NMR: δ 18.1, 27.7, 27.9, 28.2, 68.5, 83.9, 123.5 (q, J_{CF} = 273 Hz), 128.2, 128.4, 129.7, 131.5 (q, J_{CF} = 29 Hz), 132.3, 136.2 (q, J_{CF} = 5 Hz). ^{19}F NMR: δ 96.0 (s, 3F). HRMS (EI+): Calcd for $C_{15}H_{15}F_3$ $[M]^+$ 252.1126, Found: 252.1112.

(*Z*)-(1,1,1-trifluorononon-2-en-8-yn-2-yl)benzene: IR (neat): $\tilde{\nu}$ = 2941, 2864, 1302, 1169, 1113, 758, 700, 632 cm^{-1}. ^{1}H 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)



14o

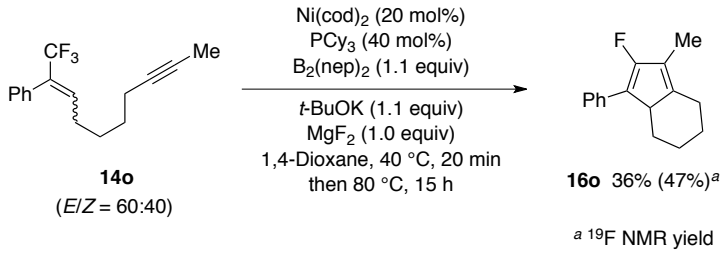
To a solution of (1,1,1-trifluorononon-2-en-8-yn-2-yl)benzene (251 mg, 0.994 mmol) in tetrahydrofuran (10 mL) was added *n*-BuLi (1.60 M in hexane, 0.68 mL, 1.1 mmol) at –78 ºC. After stirring for 1 h at –78 ºC, iodomethane (0.13 mL, 2.0 mmol) was added to the reaction solution. Then the reaction mixture 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_2O. The combined extracts were washed with brine and dried over Na_2SO_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): $\tilde{\nu}$ = 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): $\tilde{\nu}$ = 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)



14o (*E*/*Z* = 60:40)

16o 36% (47%)[a]

[a] ^{19}F NMR yield

$Ni(cod)_2$ (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 filterd 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: δ 0.84 (dddd, *J* = 13.2 Hz, *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: δ 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: δ 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] cycloadditon 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(sp^3)–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

   Chemistry Letters **2011**, *40*, 986–988.

2. "Double C–F Bond Activation through β-Fluorine Elimination: Nickel-Mediated [3+2] Cycloaddition of 2-Trifluoromethyl-1-alkenes with Alkynes"

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

   Angewandte Chemie International Edition **2014**, *53*, 7564–7568.

   Selected as Cover Picture: *Angewandte Chemie International Edition* **2014**, *53*, 7371.

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. Takanohashi, T. Fujita, J. Ichikawa

   Journal of Fluorine Chemistry **2015**, *170*, 29–37.