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# Nickel-Catalyzed Allylic C(sp$^3$)−F Bond Activation of Trifluoromethyl Groups via $\beta$-Fluorine Elimination: Synthesis of Difluoro-1,4-dienes

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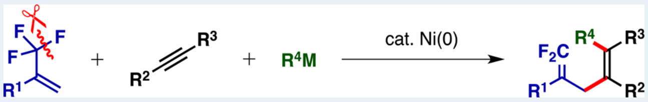
Supporting Information

**ABSTRACT:** The nickel-catalyzed defluorinative coupling of 2-trifluoromethyl-1-alkenes and alkynes with the aid of Et$_3$SiH provides 1,1-difluoro-1,4-dienes under mild reaction conditions. This reaction involves selective allylic C(sp$^3$)−F bond activation via $\beta$-fluorine elimination from nickelacyclopentenes.



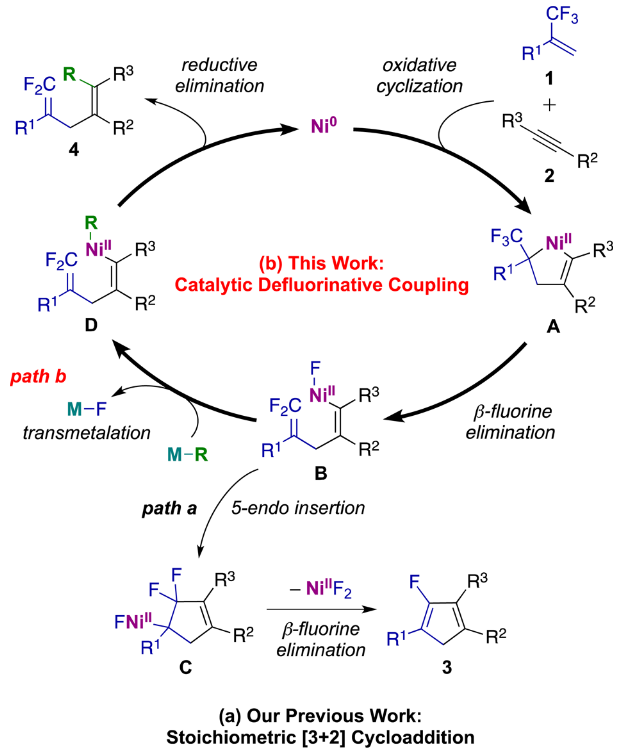
**KEYWORDS:** *C−F bond activation, nickel catalysis, trifluoromethylalkenes, alkynes, 1,4-dienes, β-fluorine elimination*

Carbon−fluorine (C−F) bond activation of the trifluoromethyl group is rarely achieved not only because of the high bond energy but also presumably because of the shielding effect of the lone-pair electrons of the three fluorine atoms.[1] Although defluorinative functionalization of trifluoromethyl-bearing compounds would realize one of the most straightforward approaches to fluorine-containing compounds, harsh reaction conditions have typically been required to cleave C(sp$^3$)−F bonds of trifluoromethyl groups.[1,2]

Recently, we reported the nickel-mediated [3 + 2] cycloaddition of 2-trifluoromethyl-1-alkenes **1** and alkynes **2** via double C−F bond cleavage of a trifluoromethyl group under mild reaction conditions (Scheme 1a).[3] In this reaction, ring-opening of nickelacycle **A**, formed via oxidative cyclization of trifluoromethylalkenes **1** and alkynes **2** with Ni(0), readily proceeded via $\beta$-fluorine elimination[4] to generate alkenylnickel(II) species **B**. Subsequent 5-*endo* insertion and a second $\beta$-fluorine elimination afforded 2-fluoro-1,3-cyclopentadienes **3** (Scheme 1, path a). The potential advantage of $\beta$-fluorine elimination prompted us to develop a nickel-catalyzed three-component coupling reaction of 2-trifluoromethyl-1-alkenes **1**, alkynes **2**, and metal species, which would proceed via the selective cleavage of one of the C(sp$^3$)−F bonds.[5,6] We assumed that alkenylnickel(II) fluorides **B**, intermediates toward 2-fluoro-1,3-cyclopentadienes **3**, might be transmetalated, for example, by an appropriate metal hydride (R = H) to afford the corresponding 1,1-difluoro-1,4-dienes **4** along with regeneration of Ni(0) (Scheme 1b, path b).[7]

To prove our hypothesis, we sought a metal hydride reagent suitable for the coupling reaction of $\alpha$-trifluoromethylstyrene (**1a**) and 4-octyne (**2a**) in the presence of a catalytic amount of Ni(cod)$_2$ and PCy$_3$ in toluene at 50 °C (Table 1). In the absence of any hydride sources, fluorocyclopentadiene **3aa** was obtained in 3% yield, as we reported previously (Table 1, entry 1). The use of *i*-PrONa as a hydride source afforded 1,1-difluoro-1,4-diene **4aa** with the *E* configuration as the sole product in 74% yield via cleavage of the C−F bond in the trifluoromethyl group and formation of the C−C and C−H bonds (entry 2).[7a] When 9-BBN or DIBAL-H was employed, **1a** was decomposed to give a complex mixture because of their electrophilic reactivity (entries 3 and 4). Consequently, Et$_3$SiH was found to be highly effective for improving the product yield to 92% (entry 5).[7b] Even 5 mol % of the Ni catalyst successfully promoted the coupling reaction to give **4aa** in 93% isolated yield (entry 6).

**Scheme 1. Ni-Catalyzed Defluorinative Coupling of 2-Trifluoromethyl-1-alkenes 1 with Alkynes 2**



The scope of suitable trifluoromethylalkene substrates **1** and alkynes **2** was then examined under the reaction conditions

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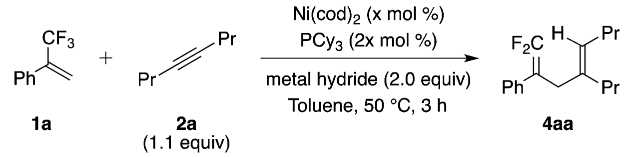
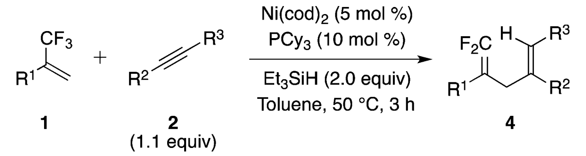
**Table 1. Optimization of the Reaction Conditions for Ni-Catalyzed Defluorinative Coupling of 1a with 2a**



| entry | $x$/mol % | metal hydride | 4aa/%[a] | 3aa/%[a] |
|---|---|---|---|---|
| 1 | 10 | none | 0 | 3 |
| 2 | 10 | *i*-PrONa | 74 | 0 |
| 3 | 10 | 9-BBN | 15 | 0 |
| 4 | 10 | DIBAL-H | 0 | 0 |
| 5 | 10 | $Et_3SiH$ | 92 | 0 |
| 6 | 5 | $Et_3SiH$ | 93[b] | 0 |

[a] Yield was determined by $^{19}F$ NMR measurement using $PhCF_3$ as an internal standard. [b] Isolated yield.

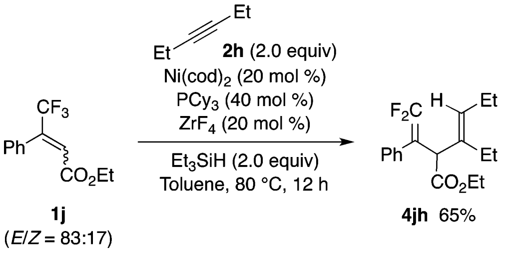
**Table 2. Synthesis of 1,1-Difluoro-1,4-dienes 3 via Ni-Catalyzed Defluorinative Coupling of 1 with 2[a]**



| entry | $R^1$ (1) | $R^2$, $R^3$ (2) | yield/% |
|---|---|---|---|
| 1 | Ph (**1a**) | Pr, Pr (**2a**) | **4aa** 93 |
| 2 | $C_6H_4$(*o*-OMe) (**1b**) | Pr, Pr (**2a**) | **4ba** 84 |
| 3 | $C_6H_4$(*p*-OMe) (**1c**) | Pr, Pr (**2a**) | **4ca** 80 |
| 4 | $C_6H_4$(*p*-Ac) (**1d**) | Pr, Pr (**2a**) | **4da** 94 |
| 5[b] | $C_6H_4$(*p*-$CO_2Et$) (**1e**) | Pr, Pr (**2a**) | **4ea** 88 |
| 6[c] | $C_6H_4$(*p*-Cl) (**1f**) | Pr, Pr (**2a**) | **4fa** 91 |
| 7[d,e] | $CH_2CH_2Ph$ (**1g**) | Pr, Pr (**2a**) | **4ga** 86 |
| 8[d,f] | $SiMe_2Ph$ (**1h**) | Pr, Pr (**2a**) | **4ha** 79 |
| 9[g,h] | Ph (**1a**) | Ph, Ph (**2b**) | **4ab** 72 |
| 10[i] | H(**1i**) | Ph, Ph (**2b**) | **4ib** 77 |
| 11[g,j] | Ph (**1a**) | Pr, Ph (**2c**) | **4ac** 99 |
| 12[g,j] | Ph (**1a**) | Pr, $C_6H_4$(*p*-OMe) (**2d**) | **4ad** 99 |
| 13[g,j] | Ph (**1a**) | Pr, $C_6H_4$(*p*-$CO_2Et$) (**2e**) | **4ae** 65 |
| 14[j] | Ph (**1a**) | Me, Ph (**2f**) | **4af** 91 |
| 15[k] | Ph (**1a**) | *i*-Pr, Me (**2g**) | **4ag** 88 (95:5)[l] |

[a] Reaction conditions: $Ni(cod)_2$ (5 mol %), $PCy_3$ (10 mol %), **1** (0.50 mmol), **2** (0.55 mmol), $Et_3SiH$ (1.0 mmol), toluene (2.5 mL), 50 °C, 3 h. [b] 4 h. [c] 2 h. [d] $Ni(cod)_2$ (10 mol %), $PCy_3$ (20 mol %) and $ZrF_4$ (10 mol %) were used as catalysts. [e] 80 °C, 15 h. [f] RT, 2 h. [g] SIMes-HCl (5 mol %) and *t*-BuOK (5 mol %) were used instead of $PCy_3$. [h] RT, 8 h. [i] Reaction was performed using $Ni(cod)_2$ (10 mol %), SIMesHCl (10 mol %), *t*-BuOK (10 mol %), **1i** (1.0 atm), **2b** (0.37 mmol), $Et_3SiH$ (0.74 mmol), toluene (1.9 mL), 80 °C, 10 h. [j] RT, 3 h. [k] $Ni(cod)_2$ (10 mol %), $PCy_3$ (20 mol %), 4 h. [l] Regioisomer ratio was determined by $^{19}F$ NMR.

obtained above (Table 2). The $\alpha$-trifluoromethylstyrenes **1b** and **1c** bearing electron-donating methoxy groups provided 1,1-difluoro-1,4-dienes **4ba** and **4ca**, in good yields (entries 2 and 3, respectively), as did the $\alpha$-trifluoromethylstyrenes **1d** and **1e** bearing electron-withdrawing acetyl and ethoxycarbonyl groups (**4da** and **4ea**, entries 4 and 5, respectively). Intriguingly, $\alpha$-trifluoromethylstyrene **1f** with a chlorine substituent, which could undergo oxidative addition to Ni(0), also participated in the reaction without the loss of the C−Cl bond (entry 6). Alkyl- and silyl-substituted trifluoropropenes **1g** and **1h** successfully underwent the coupling reaction with **2a** in the presence of 10 mol % $ZrF_4$ as a cocatalyst, leading to high yields of **4ga** and **4ha** (entries 7 and 8), respectively.[8] The use of diphenylacetylene (**2b**) with **1a** resulted in the formation of the corresponding coupling product **4ab** in 72% yield (entry 9). In the case of coupling between **2b** and 3,3,3-trifluoropropene (**1i**), use of SIMes instead of $PCy_3$ promoted the reaction to afford **4ib** in 77% yield (entry 10). Unsymmetrical 1-phenylpent-1-yne (**2c**), 1-(4′-methoxyphenyl)pent-1-yne (**2d**), 1-(4′-ethoxycarbonylphenyl)pent-1-yne (**2e**), 1-phenylprop-1-yne (**2f**), and 4-methylpent-2-yne (**2g**) also participated in this reaction with **1a** to afford the corresponding 1,1-difluoro-1,4-dienes **4ac**−**4ag** in good to excellent yields with good to complete regioselectivities (entries 11−15). The obtained regioselectivities were in agreement with literature reports of nickel-catalyzed coupling reactions of alkynes via oxidative cyclization.[9] Furthermore, the reaction of $\beta$-trifluoromethylcinnamate **1j** ($E/Z$ = 83:17) successfully proceeded with 3-hexyne (**2h**) to afford the corresponding 1,1-difluoro-1,4-diene **4jh** in 65% yield eq 1.



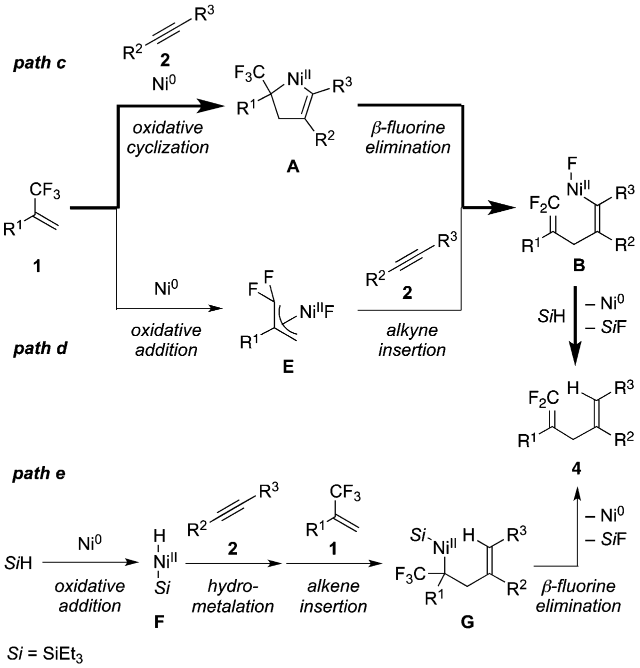
(1)

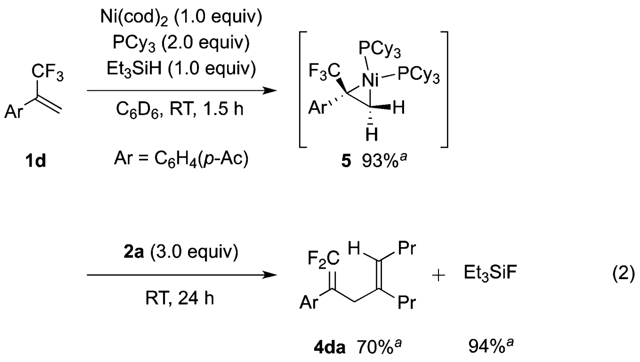
For this reaction, there are three plausible mechanisms that can be induced by different initial steps: (i) oxidative cyclization of 2-trifluoromethyl-1-alkenes **1** and alkynes **2** with Ni(0) (Scheme 2, path c), (ii) oxidative addition of a C−F bond of **1** to Ni(0) (path d),[10] and (iii) oxidative addition of an Si−H bond to Ni(0) (path e).[11,12] In paths c and d, the common intermediates **B** are formed via an oxidative cyclization/$\beta$-fluorine elimination or an oxidative addition/insertion sequence. Transmetalation of **B** with $Et_3SiH$ and subsequent reductive elimination afford 1,1-difluoro-1,4-dienes **4**. Conversely, in path e, oxidative addition of $Et_3SiH$ to Ni(0) initially occurs to provide silylnickel hydride **F**. Subsequent hydrometalation of alkyne and alkene insertion followed by $\beta$-fluorine elimination from the alkylnickel complexes **G** gives **4**.

To elucidate the mechanism, the stoichiometric reaction of 2-trifluoromethyl-1-alkene **1d** and $Et_3SiH$ with a Ni(0) complex in $C_6D_6$ at room temperature was performed and monitored by $^1H$, $^{19}F$, and $^{31}P$ NMR eq 2. Nickelacyclopropane **5** was obtained as the sole product in 93% yield, and neither allylnickel(II) complex **E** nor silylnickel hydride **F** generated by oxidative addition of **1d** or $Et_3SiH$ to Ni(0) was observed. Thus, the possibility of path e was lessened. Moreover, treatment of the obtained reaction mixture with alkyne **2a** afforded the coupling product **4da** in 70% yield from **1d** along with 94% yield of $Et_3SiF$. These results suggest that the C−F bond activation may proceed via an oxidative cyclization/$\beta$-fluorine elimination sequence in this reaction (Scheme 2, path c). Note that the oxidative cyclization process determined the stereochemistry of alkyne-derived alkene moieties of **4** (*syn* addition).

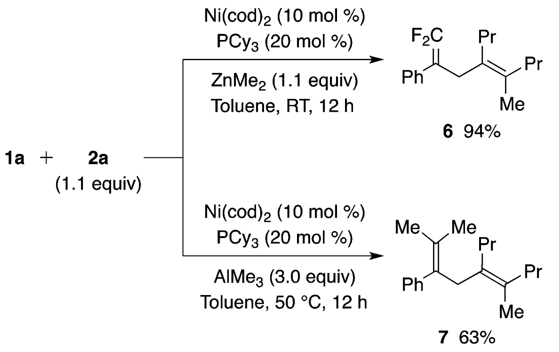
Organozinc and organoaluminum reagents were also employed as a third component in the catalytic coupling reactions eqs 3 and 4.

**Scheme 2. Plausible Reaction Mechanisms for the Ni-Catalyzed Defluorinative Coupling Reaction**





(2)

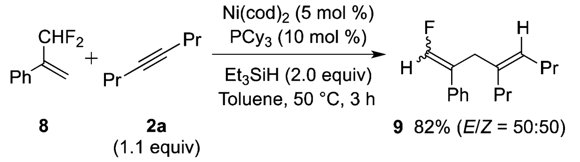


(3)

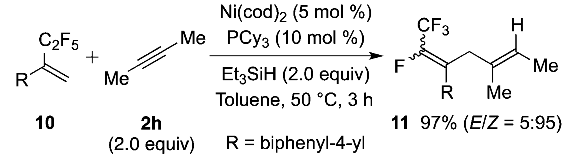
(4)

On treatment with $ZnMe_2$, 2-trifluoromethyl-1-alkene **1a** and alkyne **2a** underwent the nickel-catalyzed defluorinative coupling to afford methylated 1,1-difluoro-1,4-dienes **6** eq 3. Transmetalation of alkenylnickel(II) fluorides **B** with $ZnMe_2$ caused introduction of a methyl group into the product. In contrast, the reaction of 1**a** and 2**a** with $AlMe_3$ afforded triply methylated 1,4-diene **7** via cleavage of the three C−F bonds eq 4.[2b,13]

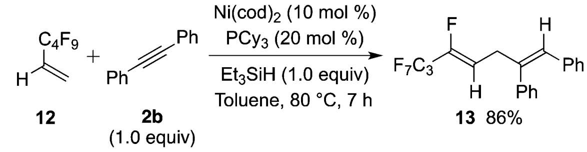
Furthermore, not only trifluoromethylalkenes but also difluoroallylic compounds underwent nickel-catalyzed defluorinative coupling eqs 5−7. The reaction of α-difluoromethylstyrene (**8**)



(5)



(6)



(7)

with alkyne **2a** was promoted by the nickel catalyst in the presence of 2.0 equiv of $Et_3SiH$. Allylic C−F bond cleavage afforded the corresponding 1-fluoro-1,4-diene **9** in 82% yield (*E*/*Z* = 50:50, eq 5). Regioselective C−F bond activation of perfluoroalkyl alkenes was also affected by this method eqs 6 and 7. The 2-pentafluoroethyl-1-alkene **10** readily reacted with 2-butyne (**2h**) and $Et_3SiH$ in the presence of the nickel catalyst. Allylic C−F bond cleavage selectively occurred to afford the corresponding trifluoromethylated fluorodiene **11** in 97% yield with high stereoselectivity for the Z fluoroalkene moiety (*E*/*Z* = 5:95, eq 6).[14] Similarly, the reaction of 2-nonafluorobutyl-1-alkene **12** smoothly proceeded to afford heptafluoropropylated fluorodiene **13** in 86% yield with exclusive *Z*-selectivity in the fluoroalkene moiety eq 7.[14]

In summary, we have developed a methodology for catalytic $C(sp^3)$−F bond activation of the trifluoromethyl group via *β*-fluorine elimination from nickelacyclopentenes generated by the stepwise oxidative cyclization of 2-trifluoromethyl-1-alkenes **1** and alkynes **2** with Ni(0). The metal−fluorine bond in the intermediary alkenylnickel(II) fluoride is effectively transformed into a metal−hydrogen (methyl) bond by a hydrosilane (a dialkylzinc), regenerating Ni(0). This reaction provides a regio- and stereoselective method for the synthesis of multisubstituted difluoroalkenes, which have attracted considerable attention as bioisosteres of carbonyl compounds in pharmaceutical science[15] and as building blocks for further transformation into fluorine-containing compounds.[1,16]

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b01463.

Experimental procedures and characterization data of new compounds (PDF)
Crystallographic data (CIF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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(13) In the presence of 10 mol % of $Ni(cod)_2$ and 20 mol % of $PCy_3$, the reaction of compound **6** with 2.0 equiv of $AlMe_3$ in toluene at 50 °C for 7 h afforded compound **7** in 54% yield, while no reaction occurred without the nickel catalyst. This indicates that the nickel catalyst is required for the substitution of vinylic C−F bonds of the difluoroalkene moiety with $AlMe_3$.

(14) The stereoselectivity of the fluoroalkene moiety was determined in the *β*-fluorine elimination step, which was likely controlled by steric effects. In the reaction of **10**, *syn-β*-fluorine elimination from nickelacycle **A** proceeded to avoid the steric hindrance between the trifluoromethyl group and the biphenyl-4-yl group. Conversely, when **12** was used as the substrate, *syn-β*-fluorine elimination occurred to avoid the steric hindrance between the heptafluoropropyl group and the methylene of nickelacycle **A**.

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