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## Catalytic Defluorinative [3+2] Cycloaddition of Trifluoromethylalkenes with Alkynes via Reduction of Nickel(II) Fluoride Species

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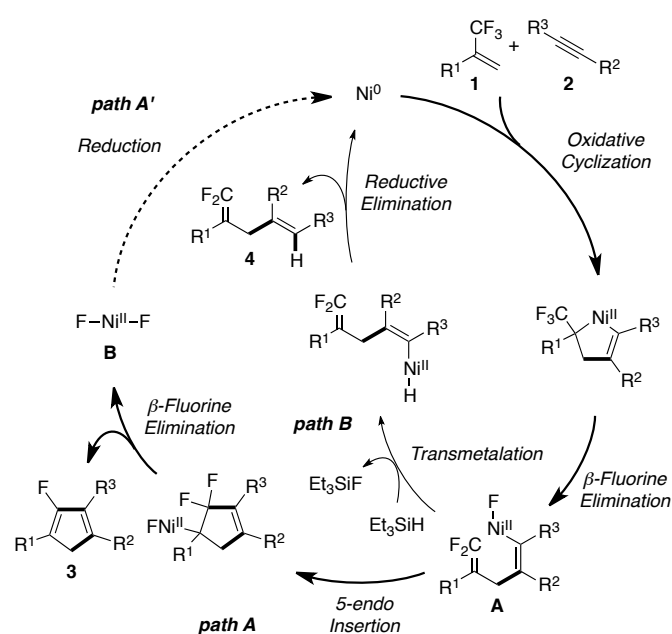
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**Nickel-catalyzed [3+2] cycloaddition of 2-trifluoromethyl-1-alkenes with alkynes via domino C–F bond activation was achieved by sequential  $\beta$ -fluorine elimination. The nickel(II) fluoride species formed in this reaction was reduced by a diboron compound, regenerating the catalytically active nickel(0) species.**

Transition metal-catalyzed carbon–fluorine bond activation has recently been established as one of the most significant areas of research in synthetic, organometallic, and fluorine chemistries.<sup>1</sup> The activation not only is effective for cleaving strong chemical bonds but also provides synthetic methods toward partially fluorinated compounds from multi-fluorinated substrates. Although metal-mediated oxidative addition of C–F bonds has mostly been used for C–F bond activation, we have developed alternative approaches by employing  $\beta$ -fluorine elimination as the key elementary step.<sup>2,3</sup> Quite recently, we reported two types of nickel-mediated defluorinative coupling reactions between 2-trifluoromethyl-1-alkenes **1** and alkynes **2** via a combination of oxidative cyclization<sup>4,5</sup> and  $\beta$ -fluorine elimination.<sup>6</sup> When stoichiometric amounts of Ni(cod)<sub>2</sub> (cod = 1,5-cyclooctadiene) and PCy<sub>3</sub> are used, cleavage of two C–F bonds of the CF<sub>3</sub> group proceeds via  $\beta$ -fluorine elimination to afford the corresponding 2-fluoro-1,3-cyclopentadienes **3** (Scheme 1, path A).<sup>3a</sup> In contrast, the addition of Et<sub>3</sub>SiH enables the catalytic synthesis of 1,1-difluoro-1,4-dienes **4** via cleavage of a C–F bond of the CF<sub>3</sub> group (Scheme 1, path B).<sup>3b</sup> In this reaction, the Ni–F bond of the nickel(II) fluorides **A** would be formed from the intermediary nickelacyclopentenes via  $\beta$ -fluorine elimination and transformed into a Ni–H bond by Et<sub>3</sub>SiH. The key to this successful catalysis is the regeneration of the active Ni(0) catalyst by employing a fluorophilic silicon reagent.

The more difficult challenge was the catalytic synthesis of 2-fluoro-1,3-cyclopentadienes **3** with the regeneration of catalytically active Ni(0) species from the NiF<sub>2</sub> species **B** formed with **3** (Scheme 1, path A'). Elemental metals were found to be ineffective for the

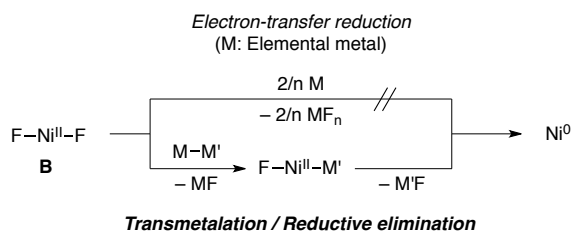
electron-transfer reduction of the nickel(II) fluoride species.<sup>7</sup> We thus attempted to individually remove the fluorine atoms on the nickel using a transmetalation/reductive elimination sequence employing bimetallic species (Scheme 2).<sup>8</sup> As a result of screening for bimetallic reagents with good affinity for fluorine atoms, we consequently found that the use of bis(neopentylglycolato)diboron (B<sub>2</sub>(nep)<sub>2</sub>) in the presence of *t*-BuOK and MgF<sub>2</sub> successfully induced the nickel-catalyzed synthesis of 2-fluoro-1,3-cyclopentadienes **3** via [3+2] cycloaddition of **1** and **2**.



**Scheme 1** Nickel-mediated and -catalyzed defluorinative coupling of 2-trifluoromethyl-1-alkenes **1** with alkynes **2**.

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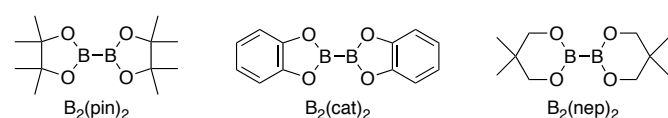


**Scheme 2** Regeneration of Ni(0) species via the reduction of Ni(II) fluoride.

**Table 1** Screening of reagents for the catalytic synthesis of 2-fluoro-1,3-cyclopentadiene **3aa**

Entry	Reagent (equiv)	Yield (%) <sup>a</sup>
1	None	18
2	Na (3.0)	12
3	K (3.0)	N.D. <sup>b</sup>
4	Mn (2.0)	18
5	Zn (2.0)	18
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6	Me <sub>3</sub> SiSiMe <sub>3</sub> (1.1)	16
7	PhMe <sub>2</sub> SiB(pin) (1.1) <sup>c</sup>	18
8	B <sub>2</sub> (pin) <sub>2</sub> (1.1) <sup>c</sup>	17
9	B <sub>2</sub> (cat) <sub>2</sub> (1.1) <sup>d</sup>	4
10	B <sub>2</sub> (nep) <sub>2</sub> (1.1) <sup>e</sup>	19
11	B <sub>2</sub> (pin) <sub>2</sub> (1.1), <sup>c</sup> <i>t</i> -BuOK (1.1)	2
12	B <sub>2</sub> (cat) <sub>2</sub> (1.1), <sup>d</sup> <i>t</i> -BuOK (1.1)	29
13	B <sub>2</sub> (nep) <sub>2</sub> (1.1), <sup>e</sup> <i>t</i> -BuOK (1.1)	45
14	B <sub>2</sub> (nep) <sub>2</sub> (1.1), <sup>e</sup> <i>t</i> -BuOK (1.1), MgF <sub>2</sub> (1.0)	60

<sup>a</sup> Yield was determined by <sup>19</sup>F NMR measurement using PhCF<sub>3</sub> as an internal standard. <sup>b</sup> N.D. = Not detected. <sup>c</sup> pin = pinacolato. <sup>d</sup> cat = catecholato. <sup>e</sup> nep = neopentylglycolato.



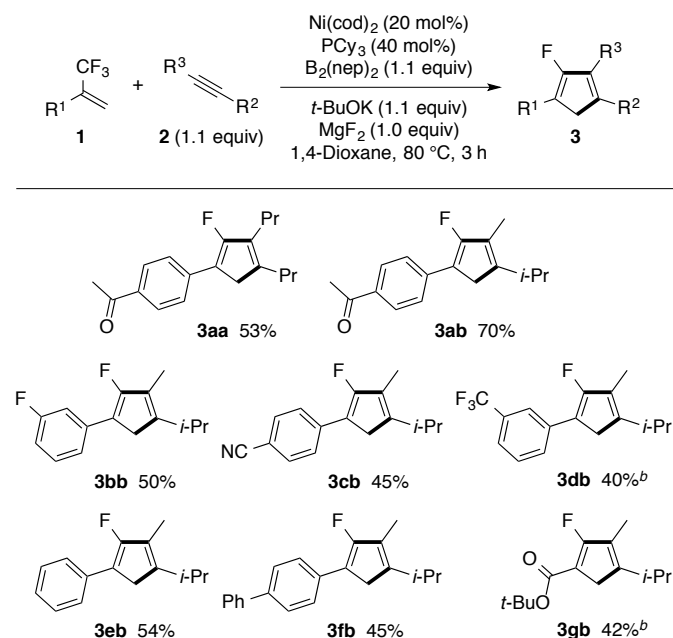
**Fig. 1** List of diboron compounds.

We sought appropriate reagents for the nickel-catalyzed [3+2] cycloaddition of **1** and **2**.  $\alpha$ -Trifluoromethylstyrene **1a** bearing an acetyl group and 4-octyne (**2a**) were used as model substrates along with 20 mol% of Ni(cod)<sub>2</sub> and 40 mol% of PCy<sub>3</sub> (Table 1). First, to perform the electron-transfer reduction of the intermediary nickel(II) fluoride species, several elemental metals were examined as additives (Entries 2–5). Alkali metals, i.e., sodium and potassium, possessing strongly negative formal potentials<sup>9</sup> afforded lower yields of cyclopentadiene **3aa**, compared with the case when no additive was added (Entries 2 and 3 vs. Entry 1). Although manganese and zinc are often used as reductants for nickel(II) halides, no positive effect was observed for the present reaction (Entries 4 and 5). We expected fluorophilic bimetallic species to promote stepwise abstraction of fluoride from the nickel species, which might allow for the catalytic [3+2] cycloaddition (vide supra).

Although the treatment of 1.1 equiv of disilane, silylboron, or diboron compounds afforded cyclopentadiene **3aa**, its catalytic synthesis was not achieved (Entries 6–10). Among the diboron compounds examined (Fig. 1), the combination of B<sub>2</sub>(nep)<sub>2</sub> and *t*-BuOK for borate formation improved the yield of **3aa** up to 45% (Entry 13 vs. Entries 11 and 12). Finally, the ternary additive system of B<sub>2</sub>(nep)<sub>2</sub> and *t*-BuOK with MgF<sub>2</sub> for fluoride abstraction was adopted, affording **3aa** in 60% yield (Entry 14).

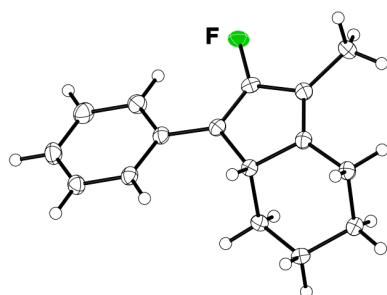
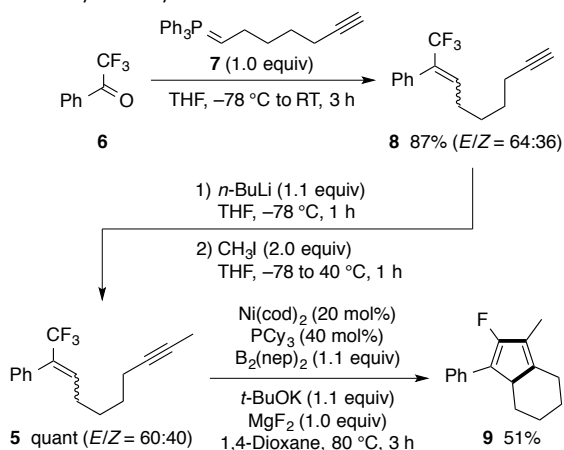
The substrate scope was then investigated using the optimized conditions (Table 2).<sup>‡</sup> Unsymmetrical 4-methylpent-2-yne (**2b**) also participated in the catalytic [3+2] cycloaddition to afford 2-fluoro-1,3-cyclopentadienes **3ab–gb** with complete regioselectivity, which is consistent with those obtained in other nickel-catalyzed coupling reactions via oxidative cyclization.<sup>10</sup>  $\alpha$ -Trifluoromethylstyrenes **1a–d** bearing electron-withdrawing acetyl, fluoro, cyano, and further trifluoromethyl groups as well as unsubstituted and phenyl-substituted  $\alpha$ -trifluoromethylstyrenes **1e–f** provided the corresponding cyclopentadienes **3bb–fb**. The cycloaddition of *tert*-butyl 2-(trifluoromethyl)acrylate (**1g**) with **2b** also proceeded smoothly to afford cyclopentadiene **3gb** in 42% yield.

**Table 2** Nickel-catalyzed synthesis of 2-fluoro-1,3-cyclopentadienes **3<sup>o</sup>**



<sup>a</sup> Isolated yield. <sup>b</sup> Toluene was used as the solvent instead of 1,4-dioxane.

**Scheme 3** Preparation and nickel-catalyzed intramolecular [3+2] cycloaddition of 1-trifluoromethyl-1-en-7-yne **5**.



**Fig. 2** ORTEP drawing of **9** with 50% ellipsoid probability.

The catalytic [3+2] cycloaddition was applied to an intramolecular reaction of CF<sub>3</sub>-bearing enyne **5**, which was readily prepared via the Wittig reaction of commercially available 2,2,2-trifluoroacetophenone (**6**) with ylide **7**,<sup>11</sup> followed by methylation of the terminal alkyne carbon of **8** (Scheme 3). The reaction of enyne **5** (*E/Z* = 60:40) proceeded under the aforementioned conditions to afford bicyclic cycloaddition product **9** in 51% yield as a racemic mixture. Single-crystal X-ray structural analysis revealed that compound **9** had a 5,6,7,7a-tetrahydro-4H-indene skeleton<sup>12</sup> and a fluorine substituent at the 2-position (Fig. 2).<sup>§</sup>

In summary, we have developed a catalytic synthesis of 2-fluoro-1,3-cyclopentadienes via [3+2] cycloaddition of 2-trifluoromethyl-1-alkenes and alkynes using a nickel catalyst and a diboron-based ternary additive system. In contrast, as we previously reported, treatment using Et<sub>3</sub>SiH instead of the diboron system in the presence of the same catalyst, 1,1-difluoro-1,4-dienes were obtained from the same two kinds of substrates. Thus, we achieved high product selectivity in the defluorinative coupling reaction through the choice of additives.

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## Notes and references

† Typical procedure for the synthesis of 2-fluoro-1,3-cyclopentadiene **3** via nickel-catalyzed [3+2] cycloaddition: In a 30-mL Schlenk tube were placed Ni(cod)<sub>2</sub> (14 mg, 0.051 mmol), PCy<sub>3</sub> (29 mg, 0.10 mmol), B<sub>2</sub>(nep)<sub>2</sub> (62 mg, 0.27 mmol), *t*-BuOK (30 mg, 0.27 mmol), MgF<sub>2</sub> (16 mg, 0.26 mmol), and 1,4-dioxane (3 mL). After stirring for 10 min at room temperature, 2-trifluoromethyl-1-alkene **1a** (53 mg, 0.25 mmol) and 4-octyne (**2a**, 30 mg, 0.28 mmol) were added to the mixture. After stirring for 3 h at 80 °C, the reaction was quenched with aqueous HCl (1 M). Organic materials were extracted with Et<sub>2</sub>O two times. The combined extracts were washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (hexane:EtOAc = 50:1) to give 2-fluoro-1,3-cyclopentadiene **3aa** (38 mg, 53%) as a yellow solid.

§ Crystal data for **9**: CCDC 1402817, C<sub>16</sub>H<sub>17</sub>F, *M* = 228.30, monoclinic, space group *P*2<sub>1</sub>/*n*, crystal size = 0.20 × 0.10 × 0.10 mm<sup>3</sup>, *a* = 10.246(4) Å, *b* = 10.131(4) Å, *c* = 11.645(4) Å, α = 90°, β = 91.857(4)°, γ = 90°, *V* = 1208.2(8) Å<sup>3</sup>, *Z* = 4, *T* = 120(2) K, *D*<sub>calcd</sub> = 1.255 g/cm<sup>3</sup>, 2θ<sub>min</sub> = 5.22°, 2θ<sub>max</sub> = 55.02°, 6664 reflections measured, of which 2745 are unique (*R*<sub>int</sub> = 0.034), *R*<sub>1</sub> [*I* > 2σ(*I*)] = 0.0449, *wR*<sub>2</sub> (all data) = 0.1065, goodness of fit on *F*<sup>2</sup> = 1.049.

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