

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

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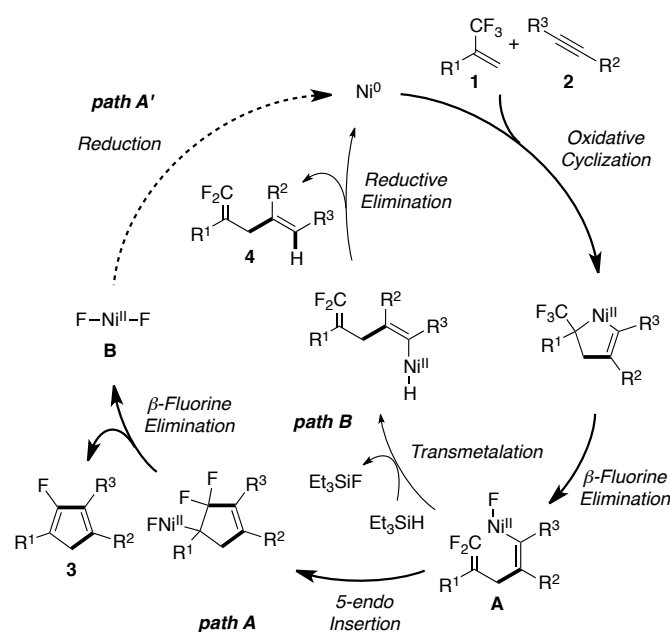
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Nickel-catalyzed [3+2] cycloaddition of 2-trifluoromethyl-1-alkenes with alkynes via domino C–F bond activation was achieved by sequential β -fluorine elimination. The nickel(II) fluoride species formed in this reaction was reduced by a diboron compound, 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.¹ 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 β -fluorine elimination as the key elementary step.^{2,3} 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^{4,5} and β -fluorine elimination.⁶ When stoichiometric amounts of $\text{Ni}(\text{cod})_2$ (cod = 1,5-cyclooctadiene) and PCy_3 are used, cleavage of two C–F bonds of the CF_3 group proceeds via β -fluorine elimination to afford the corresponding 2-fluoro-1,3-cyclopentadienes **3** (Scheme 1, path A).^{3a} In contrast, the addition of Et_3SiH enables the catalytic synthesis of 1,1-difluoro-1,4-dienes **4** via cleavage of a C–F bond of the CF_3 group (Scheme 1, path B).^{3b} In this reaction, the Ni–F bond of the nickel(II) fluorides **A** would be formed from the intermediary nickelacyclopentenes via β -fluorine elimination and transformed into a Ni–H bond by Et_3SiH . The key to this successful catalysis is the regeneration of the active $\text{Ni}(0)$ 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 $\text{Ni}(0)$ species from the NiF_2 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.⁷ We thus attempted to individually remove the fluorine atoms on the nickel using a transmetalation/reductive elimination sequence employing bimetallic species (Scheme 2).⁸ As a result of screening for bimetallic reagents with good affinity for fluorine atoms, we consequently found that the use of bis(neopentylglycolato)diboron ($\text{B}_2(\text{nep})_2$) in the presence of $t\text{-BuOK}$ and MgF_2 successfully induced the nickel-catalyzed synthesis of 2-fluoro-1,3-cyclopentadienes **3** via [3+2] cycloaddition of **1** and **2**.

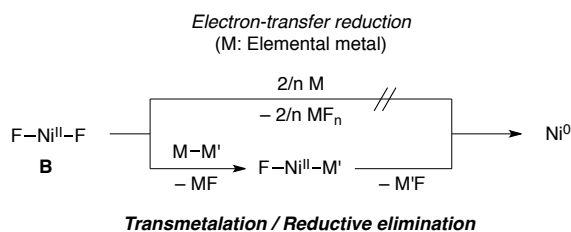


Scheme 1 Nickel-mediated and -catalyzed defluorinative coupling of 2-trifluoromethyl-1-alkenes **1** with alkynes **2**.

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

^a Yield was determined by ¹⁹F NMR measurement using PhCF₃ as an internal standard. ^b N.D. = Not detected. ^c pin = pinacolato. ^d cat = catecholato. ^e nep = neopentylglycolato.

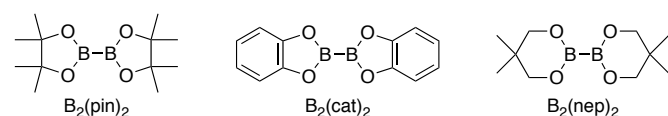


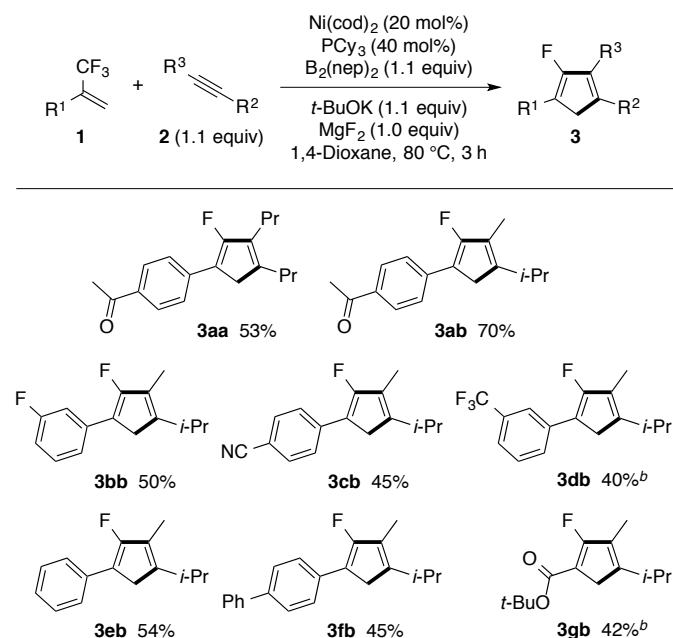
Fig. 1 List of diboron compounds.

We sought appropriate reagents for the nickel-catalyzed [3+2] cycloaddition of **1** and **2**. α -Trifluoromethylstyrene **1a** bearing an acetyl group and 4-octyne (**2a**) were used as model substrates along with 20 mol% of Ni(cod)₂ and 40 mol% of PCy₃ (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 potentials⁹ 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 B₂(nep)₂ 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 B₂(nep)₂ and *t*-BuOK with MgF₂ for fluorine abstraction was adopted, affording **3aa** in 60% yield (Entry 14).

The substrate scope was then investigated using the optimized conditions (Table 2).[‡] 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.¹⁰ α -Trifluoromethylstyrenes **1a–d** bearing electron-withdrawing acetyl, fluoro, cyano, and further trifluoromethyl groups as well as unsubstituted and phenyl-substituted α -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**^a



^a Isolated yield. ^b 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**.

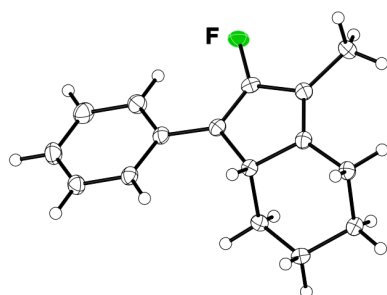
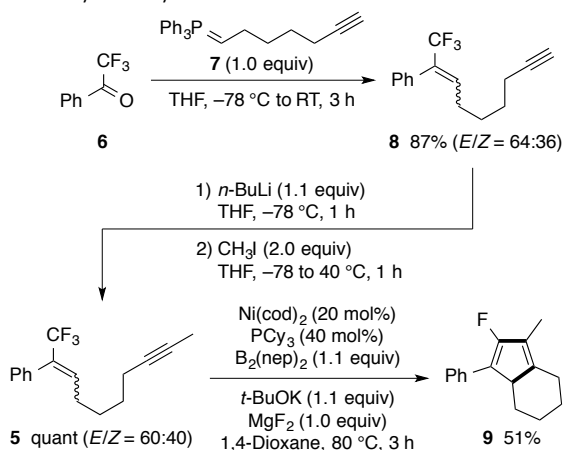


Fig. 2 ORTEP drawing of **9** with 50% ellipsoid probability.

The catalytic [3+2] cycloaddition was applied to an intramolecular reaction of CF₃-bearing enyne **5**, which was readily prepared via the Wittig reaction of commercially available 2,2,2-trifluoroacetophenone (**6**) with ylide **7**,¹¹ 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 skeleton¹² and a fluorine substituent at the 2-position (Fig. 2).§

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 Et₃SiH 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)₂ (14 mg, 0.051 mmol), PCy₃ (29 mg, 0.10 mmol), B₂(nep)₂ (62 mg, 0.27 mmol), *t*-BuOK (30 mg, 0.27 mmol), MgF₂ (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 Et₂O two times. The combined extracts were washed with brine and dried over Na₂SO₄. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (hexane:EtOAc = 50:1) to give 2-fluoro-1,3-cyclopentadiene **3aa** (38 mg, 53%) as a yellow solid.

§ Crystal data for **9**: CCDC 1402817, C₁₆H₁₇F, *M* = 228.30, monoclinic, space group *P*2₁/*n*, crystal size = 0.20 × 0.10 × 0.10 mm³, *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) Å³, *Z* = 4, *T* = 120(2) K, *D*_{calcd} = 1.255 g/cm³, 2θ_{min} = 5.22°, 2θ_{max} = 55.02°, 6664 reflections measured, of which 2745 are unique (*R*_{int} = 0.034), *R*₁ [*I* > 2σ(*I*)] = 0.0449, *wR*₂ (all data) = 0.1065, goodness of fit on *F*² = 1.049.

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