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Letter

Ni-Catalyzed Defluorination for the Synthesis of *gem*-Difluoro-1,3dienes and Their [4 + 2] Cycloaddition Reaction

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Supporting Information



ABSTRACT: A nickel-catalyzed defluorination of α -trifluoromethylated allyl/propargyl carbonates using bis(pinacolato)diboron (B₂pin₂) as a reactant is described. The reaction proceeds under relatively mild reaction conditions, providing conjugated *gem*-difluoroalkenes in moderate to good yields. Applications of the resulting 1,1-difluoro-1,3-dienes by [4 + 2] cycloaddition reactions with maleimide led to cyclic fluorinated products efficiently.

he synthesis and applications of fluorinated compounds have attracted extensive attention, because of their importance in agrochemicals, pharmaceuticals, and functional materials.¹ Over the past decades, impressive progress has been made in the synthesis of fluorinated compounds and transitionmetal catalyzed fluorination and fluoroalkylations have emerged as a powerful strategy to introduce fluorinated groups into the organic molecules.² We have also pursued the development of catalytic fluoroalkylation reactions by using transition metals as catalysts,^{2c} especially sustainable and Earth-abundant transition-metals, such as nickel.³ Inspired by our recent nickel-catalyzed cross-coupling reactions,³ we postulate that the α -trifluoromethyl nickel intermediate could undergo a β -defluorination process to produce gem-difluoroalkenes, rather than traditional reductive elimination by employing B₂pin₂ as a promoter, in which the formation of strong B–F bond (ca. 150 kcal/mol)⁴ would be a driving force to facilitate the C-F bond cleavage⁵ (Scheme 1b). gem-Difluoroalkenes are versatile building blocks in organic synthesis⁶ and have wide applications in pharmaceuticals, because the difluorovinylidene moiety has been considered to be a carbonyl mimic.⁷ Therefore, the synthesis of gemdifluoroalkenes has attracted significant interest.⁸ Previously, Kitazume⁹ reported a synthesis of conjugated gem-difluoroalkenes via copper-catalyzed β -fluoride elimination of CF₃substituted allylic acetate with Grignard reagents (Scheme 1a). Herein, we report a nickel-catalyzed defluorination of readily available α -trifluoromethylated allyl/propargyl carbonates with $B_2 pin_2^{10}$ (Scheme 1b).

We began our study by using α -trifluoromethylated allyl carbonate *E*-1a as a model substrate, and the results are summarized in Table 1. Initially, *E*-1a was treated with 1.5

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Scheme 1. Synthesis of Conjugated *gem*-Difluoroalkenes from Trifluoromethyl-Substituted Allylic Substrates



equiv of B_2pin_2 2, 10 mol % NiCl₂·DME, 10 mol % 2,2'bipyridine (bpy) and 1.5 equiv of *t*-BuOK in DME at 30 °C for 12 h and provided the desired product 3a in 12% yield (Table 1, entry 1). Encouraged by this result, a survey of a series of reaction parameters, such as base, reaction temperature, and solvent, was conducted (Table 1, entries 2–12). Among the tested bases (Table 1, entries 2–4), NaOMe was the best choice, providing 3a in 40% yield (Table 1, entry 3); while no 3a was obtained in the absence of base (Table 1, entry 5).

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Table 1. Optimization of the Reaction Conditions^a

C	OCO ₂ Me CF ₃ + E E-1a	NiCl ₂ liga bas 2 2	DME (10 mol % and (10 mol %) se (1.5 equiv) ent, temp., 12 h		F F 3a
entry	ligand	base	solvent	temperature (°C)	yield ^b (%)
1	bpy	t-BuOK	DME	30	12
2	bpy	t-BuONa	DME	30	33
3	bpy	NaOMe	DME	30	40
4	bpy	Cs_2CO_3	DME	30	nr
5	bpy	none	DME	30	nr
6	bpy	NaOMe	DME	60	50
7	bpy	NaOMe	DME	70	54
8	bpy	NaOMe	DME	80	49
9	bpy	NaOMe	THF	70	48
10	bpy	NaOMe	dioxane	70	44
11	bpy	NaOMe	CH ₃ CN	70	nr
12	bpy	NaOMe	DMF	70	nr
13	4,4′-diMe-bpy	NaOMe	DME	70	55
14	4,4'-di <i>t</i> -Bu- bpy	NaOMe	DME	70	34
15	6,6′-diMe-bpy	NaOMe	DME	70	30
16	4,4′-diOMe- bpy	NaOMe	DME	70	65
17 ^c	4,4'-diOMe- bpy	NaOMe	DME	70	82
18 ^c	none	NaOMe	DME	70	nr
19 ^{c,d}	4,4′-diOMe- bpy	NaOMe	DME	70	nr

^{*a*}Reaction conditions (unless otherwise specified): *E*-1a (0.3 mmol, 1.0 equiv), 2 (1.5 equiv), DME (2 mL). ^{*b*}Determined by ¹⁹F NMR, using fluorobenzene as an internal standard. nr = no reaction. ^{*c*}Reaction runs for 6 h. ^{*d*}Reaction runs in the absence of NiCl₂·DME.

Increasing the reaction temperature to 70 °C benefited the reaction efficiency and 54% yield of **3a** was obtained (Table 1, entry 7). But higher reaction temperature diminished the yield (Table 1, entry 8). Ethereal solvents proved to be critical for the reaction (Table 1, entries 8–10) and DME remains the optimal reaction medium; other solvents, such as CH₃CN and DMF, showed no activity (Table 1, entries 11 and 12). A screening of the ligands (Table 1, entries 13–16) showed that an electron-rich bipyridyl-based ligand (4,4'-diOMe-bpy) could provide **3a** in 82% yield by shortening the reaction time to 6 h (Table 1, entry 17). The absence of Ni or ligand led to no product (Table 1, entries 18 and 19), demonstrating that Ni and ligand play an essential role in promotion of the reaction.

With the optimized reaction conditions in hand, the scope of substrates E-1 was then examined with B_2pin_2 (Scheme 2). Substrates bearing electron-donating or electron-withdrawing substituents all underwent the current defluorination process smoothly (3e, 3h, and 3i). In addition, both *meta-* and *ortho*-substitutions on the aromatic ring were compatible with the reaction conditions, providing the corresponding products 3c and 3d in moderate yields. The low isolated yield of 3a is because of its volatility. Important functional groups, such as chloride, bromide, and ester, exhibits good tolerance to the reaction (3f, 3g, 3h). However, pyridyl-containing substrates were not applicable to the reaction. In the cases of preparation of 3g and 3h, *t*-butyl carbonates instead of methyl carbonates were used, because of their ready availability. The branched allyl carbonates with substituents on the C=C double bond





^{*a*}Reaction conditions (unless otherwise specified): *E*-1 (0.6 mmol, 1.0 equiv), **2** (1.5 equiv), DME (4 mL). Number in the parentheses is the yield determined by ¹⁹F NMR, using fluorobenzene as an internal standard. ^{*b*}Reaction runs for 7 h. ^{*c*}t-Butyl carbonate was used as a substrate. ^{*d*}E-1 (1.2 mmol, 1.0 equiv), **2** (1.5 equiv), DME (8 mL).

did not interfere with the reaction efficiency, but a Z/E mixture (Z/E = 1.3:1) of 3i was obtained when trisubstituted *E*-alkene *E*-1j was examined, indicating that a π -allyl nickel complex is involved in the reaction, as a result a Z/E mixture of 3i was obtained. The Z/E isomers of the products was characterized by ¹H NMR and ¹⁹F NMR. However, a diphenyl-substituted 1,3-diene 3k with 71% yield was obtained when the substituent R^2 was a phenyl group. Moreover, allyl carbonates bearing alkyl groups were also applicable to the reaction, providing the corresponding products in good yields with a Z/E mixture. For examples, substrates bearing active functional groups, such as heterocyclic furyl group and remote C=C double bond, afforded gem-difluoro-1,3-dienes 3m and 3n in 52% and 60% yields, respectively. Notably, α -trifluoromethylated propargylic carbonates were also suitable substrates and furnished envnes 30 and 3p smoothly.

On the basis of the previous reports, ^{5b,c,11} and the fact that the use of 10 mol % Ni(cod)₂ as a catalyst could also lead to **3a** in 37% yield, a plausible mechanism via a Ni(0/II) cycle was proposed in Scheme 3 (path I): The reaction is initiated by reduction of $[Ni^{II}L_n]$ with B₂pin₂ to generate Ni⁰L_n species **A**, ^{5b,11c} which subsequently undergoes oxidative addition with allyl carbonate **1** to produce π -allylnickel complex $[allyl(L_n)-Ni^{II}]$ **B**. Transmetalation of complex **B** with B₂pin₂ affords π allylborylnickel species $[allyl(L_n)Ni^{II}Bpin]$ **C**. Finally, β -fluoride elimination with the coordination of B to F atom as a driving force produces the *gem*-difluoroalkene **3**. The resulting nickel



Scheme 3. Proposed Reaction Mechanisms

fluoride $[Bpin(L_n)Ni^{II}-F]$ complex **D** undergoes reductive elimination to regenerate active nickel species Ni⁰L_n, along with Bpin-F. However, a nickel(I/III) catalytic cycle cannot be ruled out. In this pathway (path II), initially, a borylnickel complex $[L_nNi^{I}Bpin]$ **E** is generated by reaction of nickel(II) catalyst with B₂Pin₂.^{11a,b} Subsequently, complex **E** undergoes oxidative addition with allyl carbonate **1** to produce π allylborylnickel intermediate $[allyl(L_n)Ni^{III}Bpin]$ **F**.^{11a} Finally, the product **3** is formed via β -fluoride elimination with the coordination of B to F atom as a driving force.¹² The resulting nickel fluoride $[Bpin(L_n)Ni^{III}-F]$ undergoes reductive elimination to produce nickel(I) species **G** and Bpin-F. Transmetalation of **G** with B₂pin₂ regenerates active nickel complex **E**.

Diels-Alder reactions are widely used for the synthesis of six-membered rings,¹³ while the inactivated gem-1,1-difluoro-1,3-dienes have rarely been utilized as dienes, because of their poor reactivity.¹⁴ We found that Diels-Alder reaction of N-(4bromophenyl)maleimide 4 could provide the corresponding cycloadducts efficiently. But other dienophiles, such as acrylonitrile and methyl isopropenyl ether, failed to provide desired products. As shown in Scheme 4a, subjecting N-(4bromophenyl)maleimide 4 to gem-difluoro-1,3-dienes 3 proceeded smoothly. However, the cycloadducts 5 were unstable upon silica gel chromatography, which underwent the elimination of HF to provide the 1,3-diene products 6 in good yields. It should be mentioned that even the inactive substrate 3f bearing an electron-withdrawing group on the aromatic ring was still applicable to the cycloaddition, providing the corresponding product 6c in 62% yield.





Importantly, the resulting dienes **6** can be readily converted to fluorinated aromatic compounds via oxidation. For instance, compound **6a** was aromatized with DDQ to afford compound 7 in 76% yield (Scheme 4b). This selective sequential C–F bond cleavage strategy is noteworthy, because, from the readily available α -trifluoromethylated allyl carbonates, we can easily access different fluorinated structural motifs that are of interest in life and materials sciences.

In conclusion, we have developed an efficient method for the synthesis of gem-difluoro-1,3-dienes and gem-difluoro-1-en-3-ynes¹⁵ by nickel-catalyzed defluorination of α -trifluoromethy-lated allyl/propargyl carbonates. The resulting conjugated dienes and enynes could serve as versatile building blocks for the organic synthesis. Applications of the resulting conjugated gem-difluoro-1,3-dienes by [4 + 2] cycloadditions with *N*-(4-bromophenyl)maleimide could lead to different fluorinated compounds. The advantages of this protocol are the synthetic simplicity and selective sequential cleavage of C–F bonds from the CF₃ group, thus providing a useful route for applications in organic synthesis and related chemistry. Further studies to uncover the reaction mechanism are now in progress in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b03841.

Detailed experimental procedures, and characterization data for new compounds (PDF)

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All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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