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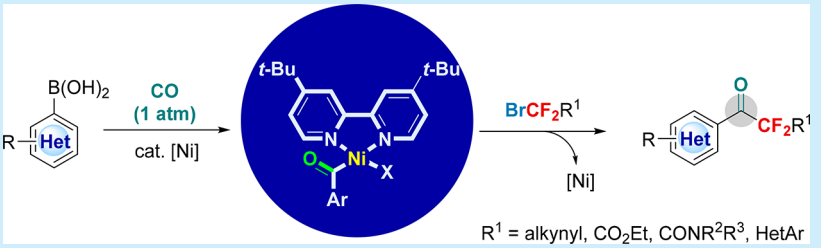
Nickel-Catalyzed Carbonylation of Difluoroalkyl Bromides with Arylboronic Acids

Hai-Yang Zhao,[†] Xing Gao,[†] Shu Zhang,[‡] and Xingang Zhang*[,†]

[†]Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China

[‡]School of Materials and Energy, University of Electronic Science and Technology of China, 2006 Xiyuan Avenue, West High-Tech Zone, Chengdu, Sichuan 611731, China

Supporting Information

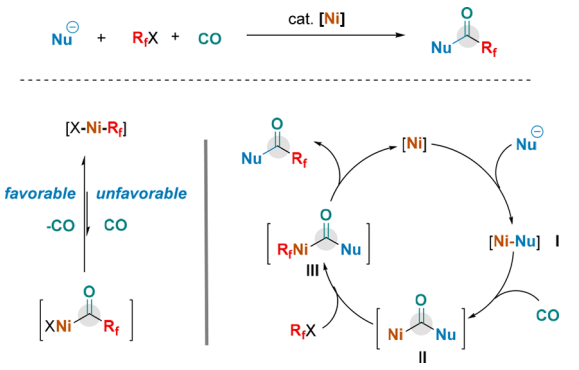


ABSTRACT: A nickel-catalyzed carbonylative difluoroalkylation reaction with arylboronic acids under 1 atm of CO has been developed. The reaction proceeds under mild reaction conditions with high efficiency and high functional group tolerance. Preliminary mechanistic studies reveal that the arylacyl nickel complex is the key intermediate to circumvent the formation of labile fluoroacyl nickel, and bimetallic oxidative addition is likely the key step to facilitate the catalytic cycle.

Transition-metal-catalyzed carbonylation reactions are efficient strategies to access carbonyl compounds. Over the past several decades, numerous carbonylation reactions have been developed and impressive achievements have been made in this area via palladium catalysis.[1] For practical applications, the development of cost-efficient Earth-abundant metals, especially catalysts that are based on first-row transition metals (such as nickel) for carbonylative cross-couplings remains highly desirable. In contrast to palladium-catalyzed carbonylation reactions, similar carbonylation reactions using nickel catalysts have not been well-developed, because of the diminished reactivity of nickel toward carbonylation.[2] Recently, a few examples of nickel-catalyzed carbonylation reactions with CO surrogates have been reported.[3] For nickel-catalyzed carbonylative fluoroalkylation reactions, however, formidable challenges still remain because, compared to their none fluorinated counter parts, the fluoroacyl nickel complexes [Ni(CO)R_f, R_f = fluoroalkyl] are even more susceptible to decarbonylation to generate fluoroalkyl nickel complexes [(CO)Ni-R_f], because of the strong electron-withdrawing effect of fluoroalkyl group (Scheme 1).[4] In addition, the strong σ-type binding between fluoroalkyl groups and nickel (Ni-R_f) is less prone to undergo carbonyl insertion.[5] As a consequence, no example of nickel-catalyzed carbonylative fluoroalkylation reaction has been reported thus far.

As part of our ongoing study on transition-metal-catalyzed fluoroalkylation reaction via cross-coupling,[6] herein, we demonstrate the feasibility of nickel-catalyzed carbonylative difluoroalkylation. The resulting difluoroalkyl ketones are a prominent structural motif in the synthesis of various useful fluorinated compounds for life and materials sciences, but currently there have been limited approaches to synthesize the valuable motif in a cost-efficient and straightforward manner.[7] To circumvent the formation of labile fluoroacyl nickel complex [Ni(CO)R_f], we envisioned an alternative pathway (Scheme 1) to access difluoroalkyl ketones: the transmetalation of a nucleophile with nickel-catalyst generates a nickel complex [Ni-Nu] **I**, which subsequently undergoes carbonyl insertion to produce acyl nickel complex [Ni(CO)-Nu] **II**. Complex **II** reacts with difluoroalkyl halides via

Scheme 1. Hypothesis for Ni-Catalyzed Carbonylation of Fluoroalkyl Halides



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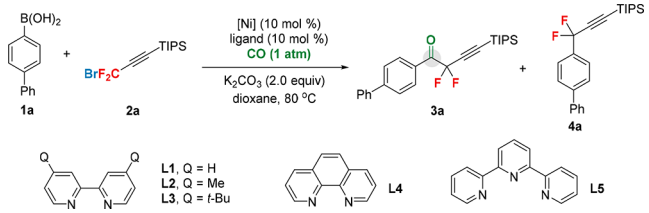
oxidative addition to produce the key intermediate [R_fNi-(CO)Nu] **III**. Finally, reductive elimination of **III** delivers the final product and regenerates the nickel catalyst.

As a result, we disclose the first example of nickel-catalyzed carbonylation of difluoroalkyl halides with arylboronic acids under 1 atm of carbon monoxide (CO). The direct use of CO in nickel-catalyzed carbonylation reactions are not usual;[3] because of the high affinity of CO to nickel, the ready formation of toxic and unreactive nickel complexes $Ni(CO)_3L$ under atmosphere of CO[8] will hamper the nickel species to catalyze the reaction. The current catalytic system is not affected by the use of CO, and can efficiently catalyze carbonylation of a variety of arylboronic acids and difluoroalkyl bromides ($BrCF_2R$, where R = alkynyl, CO_2Et, $CONR^1R^2$, HetAr) under mild reaction conditions with high functional group tolerance, providing a cost-efficient access to difluoroalkyl ketones.

Considering the synthetic versatility of the carbon−carbon triple bond (C≡C) that can provide a good platform for downstream transformations, we focused our initial study on the Ni-catalyzed carbonylation reaction of *gem*-difluoropropargyl bromide **2a** with arylboronic acid **1a** under 1 atm of CO (Table 1). To our delight, a 38% yield of carbonylated product

Table 1. Representative Results for Optimization of Ni-Catalyzed Carbonylation of 1a with 2a[a]



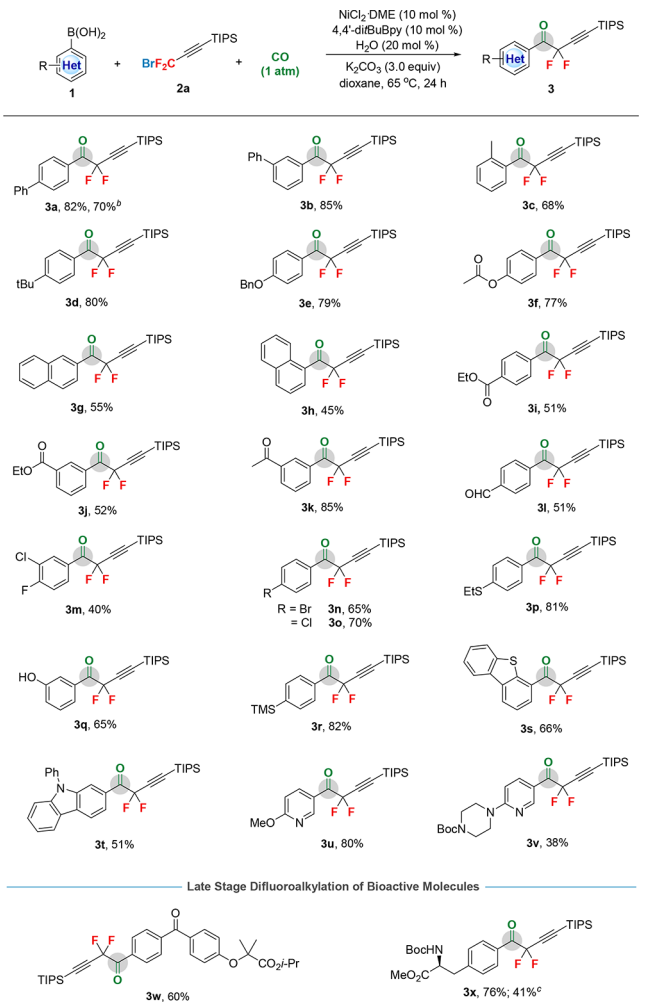
entry	[Ni]	ligand	yield of **3a**/**4a**[b] (%)
1	$NiCl_2$·DME	**L1**	38/ND
2	$NiCl_2$·DME	**L2**	31/ND
3	$NiCl_2$·DME	**L3**	52/ND
4	$NiCl_2$·DME	**L4**	41/ND
5	$NiCl_2$·DME	**L5**	3/41
6	$NiCl_2$	**L3**	11/ND
7	$NiCl_2$(dppe)	**L3**	35/ND
8[c]	$NiCl_2$·DME	**L3**	70/<1
9[c,d]	$NiCl_2$·DME	**L3**	88 (82)/<1

[a]Reaction conditions (unless otherwise specified): **1a** (0.3 mmol, 1.0 equiv), **2a** (2.0 equiv), dioxane (2 mL), 80 °C, 24 h. [b]Determined by ^{19}F NMR using fluorobenzene as an internal standard; the number given in parentheses is the isolated yield. [c]**1a** (1.5 equiv), **2a** (0.3 mmol, 1.0 equiv). 65 °C. [d]20 mol % H_2O was used.

3a was obtained without observation of cross-coupling side product **4a** when the reaction was performed with **1a** (1.0 equiv), **2a** (2.0 equiv), and 1 atm of CO in the presence of $NiCl_2$·DME (10 mol %), bipyridyl (**L1**) (10 mol %), and K_2CO_3 (2.0 equiv) in dioxane at 80 °C (Table 1, entry 1). A survey of the ligand reveals that bipyridyl-based ligand 4,4′-di-^{t}BuBpy (**L3**) is the optimal choice, providing **3a** in 52% yield (Table 1, entry 3; for details, see the Supporting Information (SI)). 1,10-Phenanthroline (**L4**) is also a suitable ligand, but a slightly lower yield was obtained (Table 1, entry 4). In contrast, when terpyridine (**L5**) was examined, **4a** instead of **3a** was provided as a major product (Table 1, entry 5). The choice of nickel source is also critical to the reaction efficiency (see Table 1, entries 6 and 7, as well as the SI). Among the tested nickel sources, $NiCl_2$·DME remained the best one. Finally, the optimal reaction conditions were identified by increasing the ratio of **1a**/**2a** from 1:2 to 1.5:1 with 3.0 equiv of K_2CO_3 as a base and 20 mol % H_2O as an additive at 65 °C, providing **3a** in 82% yield upon isolation (Table 1, entry 9). However, the use of 1.0 equiv of **1a** led to only a 56% yield of **3a** (see the SI). The role of water is probably to facilitate the transmetalation step by activating the arylboronic acid.[9] No product was observed without nickel catalyst or ligand, thus demonstrating the essential of role of Ni/**L3** in the promotion of the reaction (see the SI).

With the optimized reaction conditions in hand, a wide range of arylboronic acids were examined to react with **2a** (Scheme 2). Overall, this transformation allows a wide range of aryl boronic acids with moderate to high yields and exhibits high functional group tolerance (**3f**−**3r**), even toward aryl bromide (**3n**) and phenol moiety (**3q**). Heteroaromatic rings, such as dibenzo[*b*,*d*]thiophene, carbazole, and pyridine-containing boronic acids are also suitable substrates (**3s**−**3v**).

Scheme 2. Ni-Catalyzed Carbonylation of Arylboronic Acids 1 with Difluoroalkyl Bromides 2[a]



[a]Reaction conditions (unless otherwise specified): **1** (0.45 mmol, 1.5 equiv), **2a** (0.3 mmol, 1.0 equiv), dioxane (2 mL). [b]Gram-scale synthesis. [c]1.0 equiv of arylboronic acid was used, the yield was determined by ^{19}F NMR.

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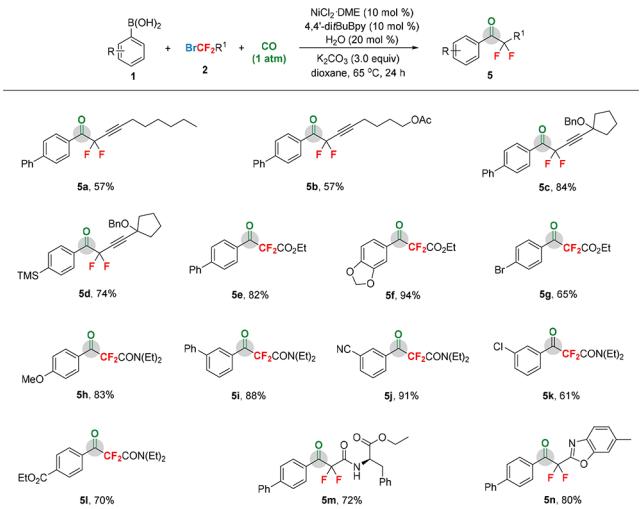
The scalability and reliability of the current process has been demonstrated by the gram-scale synthesis of **3a**. Most importantly, this transformation can also be applied to the late-stage synthesis of difluoroalkylated bioactive molecules. As shown in **3w** and **3x**, the late-stage difluoroalkylation of Fenofibrate[10] and tyrosine-derived arylboronic acids proceeded smoothly, thus providing a potential opportunity to discover some new interesting bioactive molecules.

The reaction is not restricted to **2a**, as aliphatic *gem*-difluoropropargyl bromides are also applicable to the reaction, leading to the corresponding products efficiently (Scheme 3, **5a**–**5d**). However, aromatic *gem*-difluoropropargyl bromide led to poor yield due to significant defluorination side reactions. Other difluoroalkyl bromides, including bromodifluoroacetate, bromodifluoroacetamides, and heteroaryldifluoromethyl bromide, are all competent coupling partners and provided the corresponding difluoroalkyl ketones with high efficiency (**5e**–**5n**). Unfortunately, unactivated difluoroalkyl bromides failed to provide the desired products. Again, excellent functional group tolerance is observed. In particular, the successful carbonylation of amino-acid-derived bromodifluoroacetamide is highly relevant to the medicinal chemistry (**5m**), in light of the important applications of difluoalkyl ketone-based peptides in anti-HIV agents.[11]

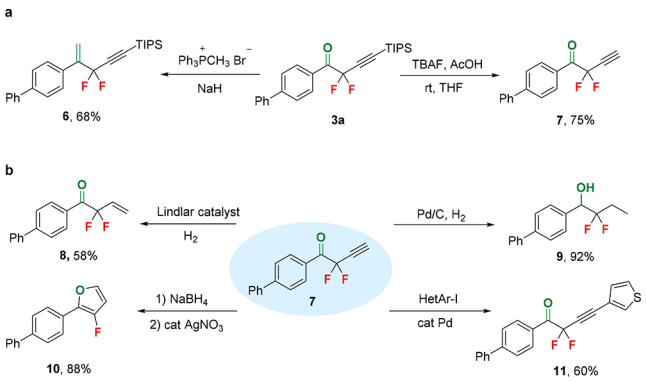
Scheme 3. Ni-Catalyzed Carbonylation of Arylboronic Acids 1 with Difluoroalkyl Bromides 2[a]



[a]Reaction conditions: **1** (1.5 equiv), **2** (0.3 mmol, 1.0 equiv), dioxane (2 mL).

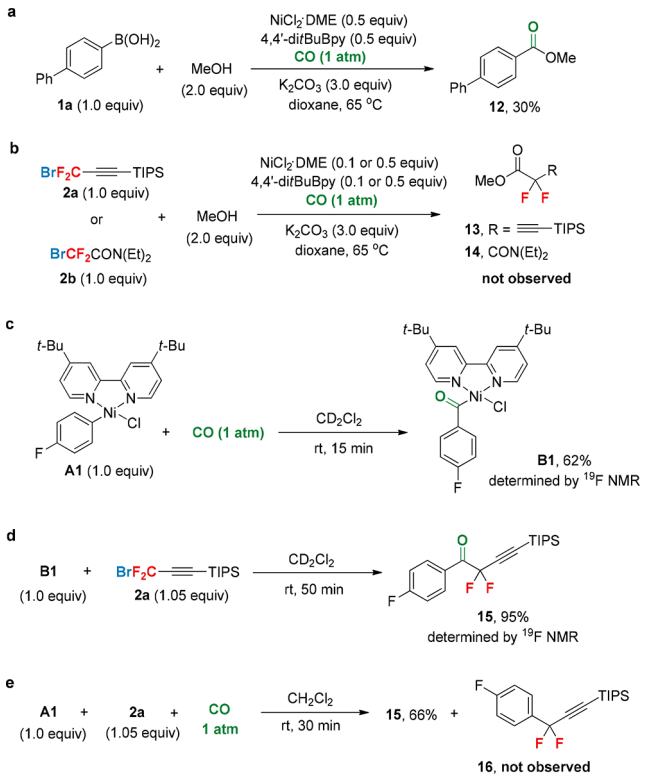
The utility of the current process can also be demonstrated by the synthesis of a variety of fluorinated compounds from **3a** through transformations of the C≡C bond and carbonyl group (Scheme 4). Wittig reaction of **3a** leads to alkene **6** efficiently (Scheme 4a). The silyl group can be readily deprotected by TBAF (Scheme 4a) and the resulting terminal alkyne **7** can function as a good platform for diversity-oriented synthesis (Scheme 4b). Hydrogenation of **7** under different reaction conditions selectively provided alkene **8** and alcohol **9** with high efficiency. A fluorinated furan ring can also be efficiently constructed from **7** by reduction of carbonyl group with $NaBH_4$, followed by cyclization and defluorination. The Sonogashira reaction of **7** with 3-iodothiophene also proceeds smoothly, providing a complementary method to access *gem*-difluoromethlenated heteroaromatic alkyne.

Scheme 4. Transformations of Compound 3



To gain mechanistic insight into the current nickel-catalyzed carbonylative process, we performed specific studies on the key step reactions that are likely occurring in this catalytic cycle (Scheme 5). First, in the reaction with methanol under 1 atm of CO in the presence of $NiCl_2$·DME (0.5 equiv) and K_2CO_3 in dioxane at 65 °C, arylboronic acid **1a** provided methyl arylcarboxylate **12** in 30% yield (Scheme 5a), whereas difluoroalkyl bromides **2a** or **2b** did not afford any methyl esters (Scheme 5b).[12] These results suggest that an arylacyl nickel complex [ClNi(L)(CO)Ar] **B** is likely involved in the current catalytic cycle, consistent with our initial proposal in Scheme 1. Second, the formation pathway of complex **B** is verified by the immediate transformation of an aryl nickel complex **A1**,[13] which is a plausible active species generated from the transmetalation of nickel precursor with aryl boronic acid, into the arylacyl nickel complex **B1** in 62% yield in the presence of CO (1 atm) in CD_2Cl_2 at room temperature

Scheme 5. Mechanistic Studies



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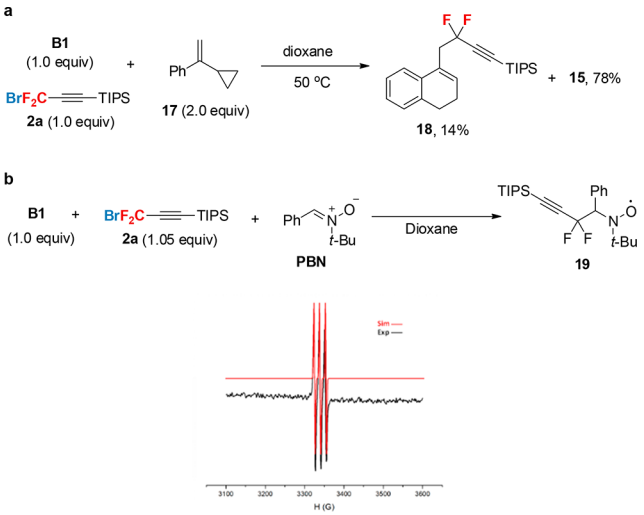
within 15 min (Scheme 5c).[14] The resulting acyl nickel complex **B1** showed high reactivity toward *gem*-difluoropropargyl bromide **2a** and provided the corresponding ketone in 95% yield at room temperature (Scheme 5d). Furthermore, a 66% yield of **15** without observation of cross-coupling side product **16** from the reaction of **A1** with **2a** and CO suggests the fast reaction rate of the current carbonylation reaction over the Ni-catalyzed difluoroalkylation reaction (Scheme 5e).

These results clearly demonstrate that the production of difluoroalkyl ketone via an arylacyl nickel(II) intermediate is a reasonable pathway. To identify whether a difluoroalkyl radical is involved in the catalytic cycle, a radical clock experiment has been performed (Scheme 6a). A ring-expanded product **18** was

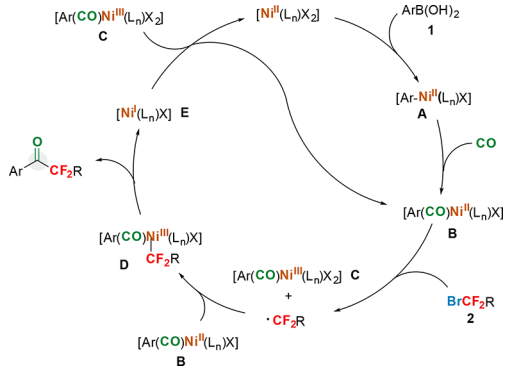
Scheme 6. Trapping Difluoroalkyl Radical



obtained in 14% yield when the reaction mixture of **B1** and **2a** was treated with α-cyclopropyl styrene **17**,[15] implying that a difluoroalkyl radical may be generated between **B1** and **2a**. The formation of a difluoroalkyl radical was further confirmed by the EPR study of reaction of **2a** with spin-trapping agent phenyl *tert*-butyl nitrone (PBN) in the presence of **B1** (see Scheme 6b, as well as the SI).[16] Given the facts that a 95% yield of **15** was obtained from the stoichiometric reaction of acyl nickel complex **B1** with **2a** (Scheme 5d) and a difluoroalkyl radical is involved in the reaction, we propose that a bimetallic oxidative addition[17] is the key step to generate the difluoroalkyl ketone.

On the basis of above results and previous reports,[18,3f] a plausible reaction mechanism is proposed (Scheme 7). The reaction is initiated by a transmetalation of $[Ni^{II}(L_n)X_2]$ with the aryl boronic acid to generate an aryl nickel(II) complex $[ArNi^{II}(L_n)X]$ **A**. Subsequently, insertion of CO into complex **A** produces the arylacyl nickel(II) complex $[Ar(CO)Ni^{II}(L_n)X]$ **B**. Complex **B** reacts with difluoroalkyl bromide **2** to generate a difluoroalkyl radical species and a nickel(III) complex $[Ar(CO)Ni^{III}(L_n)X_2]$ **C**. The difluoroalkyl radical is then trapped by another arylacyl nickel(II) complex **B** to afford the key intermediate $[Ar(CO)Ni^{III}(L_n)CF_2R(X)]$ **D**, which undergoes reductive elimination to produce the difluoroalkyl ketone and nickel(I) complex $[Ni^{I}(L_n)X]$ **E**. Finally, **E** reacts with the newly formed nickel(III) complex **C** via a comproportionation reaction to regenerate nickel(II) catalyst $[Ni^{II}(L_n)X_2]$ and **B**.[19] The formation of nicke(II) species was

Scheme 7. Proposed Reaction Mechanism



supported with cyclic voltammograms of **B1** and **2a** in CH_2Cl_2 (see Figure S6 in the SI).[20]

In conclusion, we have developed the first example of nickel-catalyzed carbonylative fluoroalkylation reaction. In sharp contrast to the previous nickel-catalyzed carbonylation reactions using CO surrogates,[3] the present carbonylation proceeds smoothly under mild reaction conditions using 1 atm of CO. The reaction allows a wide range of arylboronic acids and difluoroalkyl bromides with high functional group tolerance, providing a cost-efficient and straightforward access to difluoroalkyl ketones. Notably, many of the resulting difluoroalkyl ketones bearing a C≡C bond are previously unknown and can function as versatile building blocks for diversified synthesis of various useful fluorinated compounds that are of great interest in life and materials sciences. Preliminary mechanistic studies reveal that an arylacyl nickel complex exists in the current catalytic cycle, which subsequently undergoes a bimetallic oxidative addition with difluoroalkyl bromide, followed by reductive elimination to produce the difluoroalkyl ketones.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b04070.

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

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xgzhang@mail.sioc.ac.cn.

ORCID

Xingang Zhang: 0000-0002-4406-6533

Author Contributions

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

Notes

The authors declare no competing financial interest.

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