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C−O/C−H Coupling of Polyfluoroarenes with Aryl Carbamates by Cooperative Ni/Cu Catalysis

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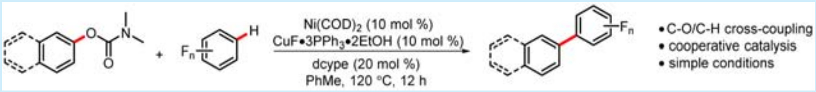
S *Supporting Information*



ABSTRACT: Cross-coupling of polyfluoroarenes with aryl carbamates through the cleavage of both sp^2 C−O and C−H bonds is reported. The reaction conditions are simple, and only transition-metal catalysts and ligands are essential. Mechanistic studies indicated that Ni catalyst played an important role in activating C−O bond, while the Cu one in activating C−H Bond. The developed system proved to be effective for cross-coupling of terminal alkynes with aryl carbamates.

Transition-metal catalysis has been found to be the most powerful method for both C−H[1] and C−O[2] activation reactions. Taking advantage of both C−H and C−O activation, challenges remain to carry out direct cross-coupling of hydrocarbon and "inert" O-based electrophiles. Although the relatively active C−O (allylic and benzylic position)/C−H coupling has been achieved,[3] the "inert" C−O/C−H coupling was not achieved until 2012. Itami and co-workers pioneered direct arylation of azoles with aryl pivalates by using Ni(COD)$_2$/dcype [COD = 1,5-cyclooctadiene, dcype = 1,2-bis(dicyclohexylphosphino)ethane] catalyst.[4] Direct α-arylation of ketones with aryl pivalates was also achieved.[5] Later on, enantioselective version of such an α-arylation was developed by Martin's group.[6]

Indeed, the combination of both C−H and C−O activation to carry out new organic transformations is still highly appealing. We envisioned that the key point of the coupling between "inert" C−O and C−H bonds might be to make two different activation processes thermodynamically and kinetically compatible. Compared to single catalysis, cooperative catalysis with different transition-metal catalysts showed unique features.[7] We set out to search for a cooperative catalytic system to activate both C−O and C−H bonds, respectively, to carry out the desirable cross-couplings.

Fluorine-containing compounds have drawn much attention due to their unique physicochemical and biological properties.[8] In previous reports, coupling reactions of aryl halides/sulfonates with polyfluoroarene have been developed to synthesize fluorine-containing biaryl compounds by using Pd[9] or Cu[10] catalysts in the presence of strong bases. These methods showed their reliability and were broadly used, but efforts to search for other easily available coupling partners were never halted. Cheap and easily available O-based electrophiles appeared to be good choices, and many groups made important contributions to use them in cross-couplings.[4−6,11] We considered that the coupling of easily available phenol derivatives, such as carbamates, with polyfluoroarenes might be reachable by using rational cooperative catalysis.

Based on previous developments on C−O activation, nickel complexes with electron-rich ligands are essential.[2] Thus, a proper nickel catalyst should be a good choice to activate the "inert" C−O bonds of aryl carbamates. Activation of the C−H bonds of polyfluoroarenes might be achieved by other transition metals. On the basis of the reported literature,[12] pentafluorophenyl copper complex was synthesized, characterized, and directly used as a reagent in organometallic synthesis.[13] The properties of this organocopper species indeed met our needs. Therefore, the proper copper salt might be the second metal catalyst to activate the C−H bonds in our design (Scheme 1).

We initiated our experiment by using naphthalen-2-yl *N*,*N*-dimethylcarbamate (**1a**) as a model substrate and pentafluorobenzene (**2a**) as a coupling partner. Since Ni-catalyzed C−H functionalization of pentafluorobenzene was also well-documented,[14] we first conducted the experiments using Ni(COD)$_2$ as catalyst under different conditions in the absence of copper catalyst. Indeed, the desired product **3aa** was obtained, but the yield was very low (see Table S1). These results indicated that the bases might have a bad influence, which was different from previous reports.[9,10] We also detected the reductive coupling byproduct between the C−O and C−F bonds. This process required consumption of the low-valent nickel catalyst and, thus, terminated the catalytic cycle. Therefore, as predicted, increasing the rate of transmetalation of pentafluorophenyl

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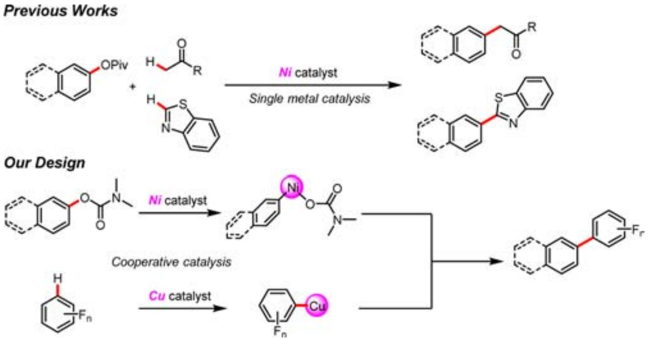
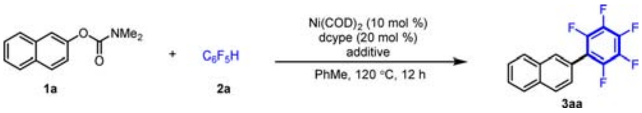
Scheme 1. Inert C−O/C−H Coupling



group to the nickel center via a copper catalyst might restrain this side reaction and be beneficial for our desired transformation.

Subsequently, based on the results of using Zn powder as additive (Table 1, entry 1), we tested different copper catalysts.

Table 1. Optimization of Reaction Conditions[a]



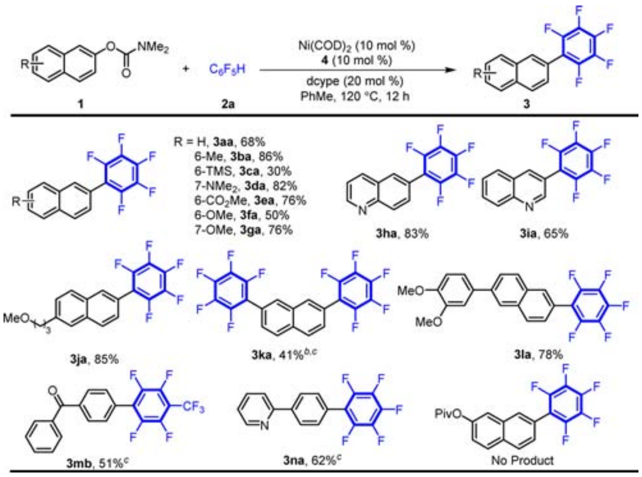
entry	additive (equiv)	yield[b] (%)
1	Zn (2)	8
2	Zn (2) + $CuCl_2$ (1)	trace
3	Zn (2) + CuF_2 (1)	28
4	Zn (2) + CuF_2 (0.2)	42
5	Zn (2) + CuI (0.1)	trace
6	Zn (2) + $CuBr(PPh_3)$ (Phen) (0.2)	12
7	Zn (2) + Cu_2O (0.1)	trace
8	$CuF\cdot 2H_2O$ (0.05)	33
9	**4** (0.1)	65[c]
10[d]	**4** (0.1)	0
11[e]	**4** (0.1)	0
12		<10

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), $Ni(COD)_2$ (0.01 mmol), dcype (0.02 mmol), PhMe (1 mL), 120 °C, 12 h. [b] The yield was determined on the basis of ^{19}F NMR with benzotrifluoride as internal standard. [c] Isolated yield. [d] Without $Ni(COD)_2$. [e] NiF_2 instead of $Ni(COD)_2$. Phen = 1,10-phenanthroline.

$CuCl_2$ (entry 2) totally shut down the reaction, but CuF_2 improved the reaction to 28% yield (entry 3). A better yield was obtained with a catalytic amount of CuF_2 (42%, entry 4). In addition, some Cu(I) salts were also tested, but the yield was no more than 10% (entries 5−7). We also tested $CuF_2\cdot 2H_2O$ without Zn powder (entry 8), and the yield was slightly promoted to 33%. Many previous reports showed that phosphine ligands could reduce Cu(II) species to a Cu(I) phosphine complex in wet solvent.[15] In order to identify whether CuF complex was generated in situ to accelerate the reaction, we synthesized the $CuF\cdot 3PPh_3\cdot 2EtOH$ (**4**) complex according to a previous report[16] and used it as the cocatalyst. To our delight, the yield was dramatically improved to 65% (entry 9), which indicated that the active cocatalyst was the CuF species. Changing the temperature and prolonging reaction time did not give better results. Without $Ni(COD)_2$ (entry 10) or using Ni(II) catalyst instead (entry 11), the reaction did not occur at all. The absence of copper catalyst gave a low yield (entry 12), indicating that CuF cocatalyst was very important and essential.

The reactivity of different aryl carbamates was subsequently investigated (Scheme 2). Alkyl-substituted naphthyl carbamates gave better results (**3ba**), probably because of the better solubility of both starting material and product. Arising from the existence of fluoride anion, the trimethylsilyl group was partially desilylated and the yield was decreased to 30% (**3ca**). An *N*,*N*-dimethylamino substituent on the naphthyl ring was well tolerated (**3da**). The electronic nature of the naphthyl ring slightly affected the reaction. The electron-deficient substrate (**3ea**) gave a better result than the electron-rich one (**3fa**). Consistent with this point, 7-OMe substrate (**3ga**) showed higher reactivity than 6-OMe one (**3fa**). Quinolinyl *N*,*N*-dimethylcarbamates were also used, and good yields were obtained (**3ha** and **3ia**). When there were 2 equiv reaction sites on the naphthyl ring, diarylation product (**3ka**) was the major one. It was understandable because when one pentafluorophenyl group was attached to naphthyl ring, it would be more electron deficient to enhance the reactivity. Both aryl ether and alkyl ether groups (**3fa**, **3ga**, **3ja**, **3la**) were tolerated, although they showed the credible reactivity in Ni-catalyzed transformations.[11a,b,17] This catalytic system could also be used in the transformation of benzoylphenyl and biaryl carbamate, but a higher catalyst loading was needed (**3mb** and **3na**). When there was a pivalic group at the symmetric position of the carbamate moiety, no product was obtained, but compounds **1a** and **3aa** could be detected by GC−MS (for details, see the SI). This result indicated that the C−OPiv bond is slightly easier to cleave than $C−CONMe_2$. At this stage, phenyl or naphthalen-1-yl carbamates only gave low yields (see the SI).

Scheme 2. Substrate Scope of Aryl Carbamates[a]



[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.2 mmol), $Ni(COD)_2$ (0.02 mmol), **4** (0.02 mmol), dcype (0.04 mmol), PhMe (1 mL), 120 °C, 12 h. [b] The yield was determined on the basis of ^{19}F NMR with benzotrifluoride as internal standard. [c] Catalyst (Ni and Cu) loading (20 mol %) and ligand (40 mol %).

Different polyfluoroarenes were further tested (Scheme 3). Electronic features had a great influence on the reactivity. The trifluoromethyl-substituted tetrafluorobenzene gave a good yield (**3gb**), while the methyl-substituted tetrafluorobenzene gave full conversion in quantitative yield (**3gc**). Because of the relatively weaker acidity of the C−H bond in 2,3,5,6-tetrafluoroanisole, a moderate yield was obtained (**3gd**) with

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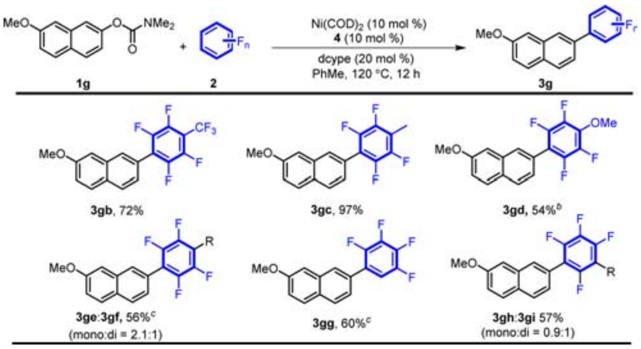
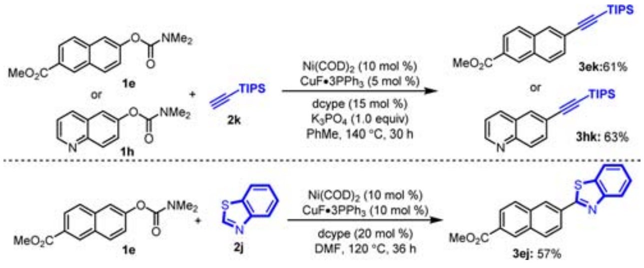
Scheme 3. Substrate Scope of Polyfluorobenzenes[a]



[a]Reaction conditions: **1g** (0.3 mmol), **2** (0.2 mmol), Ni(COD)$_2$ (0.02 mmol), **4** (0.02 mmol), dcype (0.04 mmol), PhMe (1 mL), 120 °C, 12 h. [b]Changes: mesitylene (1 mL), 140 °C. [c]Changes: **1g** (0.2 mmol), **2** (0.3 mmol). R = H or 7-methoxynaphthalenyl.

higher temperature in a high-boiling point solvent. Nonsubstituted tetrafluorobenzene could also act as a coupling partner, and both arylation and diarylation products were isolated in moderate yields (**3ge**, **3gf**, **3gh**, and **3gi**). For **3gg**, a good yield of monoarylation product was obtained since steric hindrance probably inhibited the second coupling. More electron-deficient or electron-rich polyfluorobenzenes were unsuccessful (see the SI).

Scheme 4. Extension of the Cooperative Catalytic System



To date, there has been no successful example of the cross-coupling of terminal alkynes with inert O-based electrophiles, although one successful reaction has been reported to demonstrate the cross-coupling between alkynyl Grignard reagents and anisole derivatives.[17a] By using this cooperative catalytic system, direct alkynylation reaction occurred smoothly (**3ek** and **3hk**) (Scheme 4). However, removing the copper catalyst or using other common Cu(I) salts could not ensure the same high efficiency (for details, see the SI). Using DMF as solvent, benzothiazole could also be used as the coupling partner, and the desired product (**3ej**) was obtained in 57% yield in the absence of any bases, which were considered essential in Itami's work.[4b]

To shed light on the mechanism of this Ni/Cu-cocatalyzed coupling, we tried to identify the key intermediates. The C−O oxidative addition of phenol derivatives to Ni(0) species has been proved by Itami and Lei to be based on the isolation of aryl nickel(II) pivalate complex.[4a] We conducted the reaction of aryl carbamate with stoichiometric Ni(COD)$_2$/dcype. GC−MS results showed that **1a** was completely consumed. Protonation, decarboxylation, and homocoupling products were detected by GC−MS (for details, see the SI). This result proved that the C−O bond cleavage could occur smoothly only in the presence of nickel/dcype complex. Pentafluorophenyl copper complex **5** ((C$_6$F$_5$Cu)$_2$·dioxane) was synthesized according to the reported literature.[13] We examined both stoichiometric and catalytic reactions of **5**, and **3aa** was isolated in 28% and 42% yields, respectively (Figure 1 (1)), indicating that the pentafluorophenyl copper species might act as an active species as well as a possible key intermediate in the catalytic cycle. In the stoichiometric reaction, about 10% of the reductive coupling product between the C−O and C−F bond was observed, implying that high concentration of pentafluorophenyl anion species notably increased the rate of C−F oxidative addition to Ni(0) species and consumed the catalyst, thus leading to the low yield. This inference also accounted for why strong bases were not beneficial for this reaction.

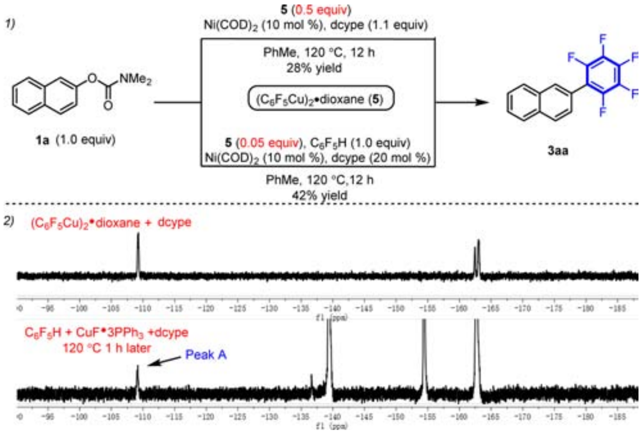


Figure 1. (1) Stoichiometric and catalytic coupling with **5**. (2) Reaction monitoring using ^{19}F NMR spectroscopy. The ^{19}F chemical shift of peak A appears at −109.3 ppm.

In order to gain more information about this reaction, we also monitored the reaction by using ^{19}F NMR spectroscopy (solvent: toluene) to identify the existing state of the pentafluorophenyl group (Figure 1 (2)). Comparison of the spectra of complex **5** and the mixture of **5** with dcype (see the SI) indicated that dcype coordinated to the copper to form a new complex species whose form might be C$_6$F$_5$Cu(dcype). We further heated the mixture of pentafluorobenzene, CuF·3PPh$_3$, and dcype in toluene at 120 °C for 1 h. A new downfield peak (peak A in Figure 1) appeared ($\delta = -109.3$ ppm) whose chemical shift was in accordance with the *o*-F atom ($\delta = -109.3$ ppm) of C$_6$F$_5$Cu(dcype) based on the reference,[13] proving that CuF·3PPh$_3$ could react with **2a** to form pentafluorophenyl copper species in situ with the assistance of dcype.

Based on the mechanistic studies, we proposed catalytic pathways as showed in Scheme 5. C−OCONMe$_2$ went through oxidative addition to Ni(0)/dcype complex **A** to form complex **B**. Decarboxylation of **B** might occur to form complex **C**. At the same time, deprotonation of nucleophile (HNu) by CuF complex formed copper species **D**, which could transfer the nucleophilic group to the complex **B** or **C**, accompanied by the release of Cu(I) species **F**. Complex **F** abstracted proton from HNu to regenerate the copper species **D** to complete the Cu cycle. When dimethylamine anion was attached to the copper center, the deprotonation process seemed easier. Then, reductive elimination of complex **E** gave the desired product **3**, regenerating the Ni(0) catalyst to fulfill the Ni cycle.

In summary, we have developed a cooperative catalytic system with Cu/Ni to achieve the coupling reaction of aryl carbamates with polyfluoroarenes. This catalytic system was

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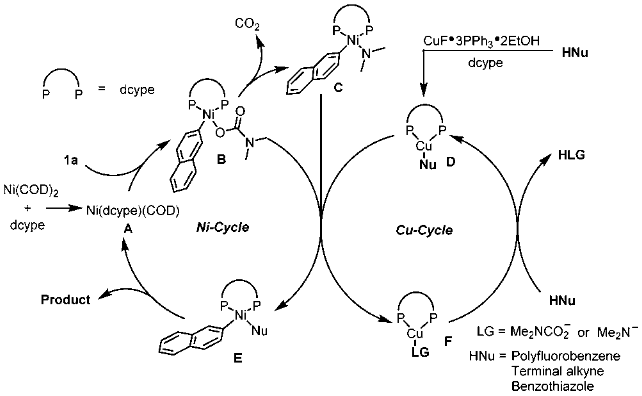
Scheme 5. Proposed Mechanism



extended to the coupling reaction of aryl carbamates with terminal alkynes and benzothiazoles. The reaction conditions are simple, and only catalysts and ligands are essential. Mechanistic studies indicated that the CuF species played a unique role in C−H functionalization and facilitated the transmetalation process. Further developments in C−H/C−O bond cross-coupling are ongoing 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.orglett.6b00819.

Experimental procedures, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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