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Nickel-Catalyzed Alkenylation and Alkylation of Fluoroarenes via Activation of C−H Bond over C−F Bond

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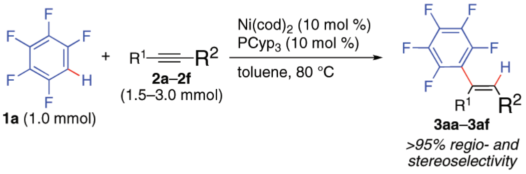
There has been an increasing demand for methods to introduce F-containing groups into organic molecules because of the unique effects of F-substituents in pharmaceutical, agrochemical, and materials science.[1] Polyfluoroarenes are a representative class of such fluoroorganic molecules, and thus, the development of efficient methods for their introduction has been an important issue for synthetic chemists. Although polyfluoroarenes can be functionalized via deprotonation of their acidic hydrogens with a stoichiometric amount of organometalic bases followed by the reactions with electrophiles,[2] the use of a catalytic amount of metal to effect direct functionalization of C−H bonds of polyfluoroarenes is highly desired. While recent work by Fagnou[3] and Daugulis[4] allows the direct coupling reactions of C−H bonds of polyfluoroarenes with aryl and alkenyl halides with Pd and Cu catalysts, respectively, a repertoire for catalytic direct transformations of such highly electron-deficient arenes remains unexplored in spite of the recent extensive studies on the catalytic C−H activation of arenes.[5] Herein, we report that Ni/P(c-C_5H_9)$_3$ (PCyp$_3$) catalyst is highly effective for direct alkenylation and alkylation of polyfluoroarenes via C−H activation followed by the insertion of alkynes, 1,3-dienes, and vinylarenes.[6]

Whereas many late transition metal complexes undergo the oxidative addition of C−H bonds of polyfluoroarenes over C−F bonds,[7] experimental[8] and theoretical[9] studies have shown that Ni(0) complexes favor oxidative insertion into C−F bonds of polyfluoroarenes exclusively rather than C−H bonds.[10] Nevertheless, the reaction of pentafluorobenzene (**1a**, 1.0 mmol) with 4-octyne (**2a**, 1.5 mmol) in the presence of Ni(cod)$_2$ (3 mol %) and PCyp$_3$ (3 mol %) in toluene at 80 °C for 3 h gave (*E*)-pentafluoro(octen-4-yl)benzene (**3aa**) quantitatively (entry 1 of Table 1). Other tri(*sec*-alkyl)phosphines including P(*i*-Pr)$_3$ and PCy$_3$ were also comparatively effective to give **3aa** in >85% yields as estimated by ^{1}H NMR, whereas use of PMe$_3$, PBu$_3$, and P(*t*-Bu)$_3$ as a ligand afforded only a trace amount of the adduct. A catalyst prepared in situ from bench-stable Ni(acac)$_2$, [HPCyp$_3$]BF$_4$, and AlMe$_3$[6e] with a standard Schlenck technique effectively gave **3aa** in 87% yield.[11] Bis(silylmethyl)acetylene **2b** underwent the reaction with **1a** to give pentafluorophenyl-substituted allylsilane **3ab** (entry 2). Diphenylacetylene (**2c**) also gave the corresponding *cis*-adduct, although slow addition of the alkyne was essential to diminish the competitive tri- and oligomerization of the alkyne (entry 3). Sterically biased unsymmetrical alkynes underwent the addition reaction with excellent regioselectivities to give *cis*-adducts having a bulkier substituent *trans* to the pentafluorophenyl group exclusively (entries 4−6).

Other polyfluorobenzenes also underwent the addition reaction across **2a** (Table 2). Substrates with a lower number of F gave the corresponding adducts in lower yields possibly due to the lower acidity of the C−H bond to be activated (entries 1−9).[12] Using excess **2a** generally gave good yields of dialkenylated products, which were also observed competitively even in the presence of polyfluorobenzenes in excess to give monoalkenylated products in modest yields (entries 2−5). Among possible reaction sites, the C−H bonds *ortho* to a F substituent are exclusively activated (entries 6−9). The selective alkenylation at the *ortho*-position of fluoro groups was also achieved in the presence of an electron-withdrawing ester group (entry 10). These data clearly suggest that the activation of C−H bonds *ortho* to F is preferred kinetically and/or thermodynamically.[7,13] The electron-donating methoxy group of **1j** did not affect the reaction (entry 11). Similar trends were also seen in the alkenylation of polyfluoropyridines to give the corresponding adducts in good yields (entries 12 and 13).

Table 1. Alkenylation of Pentafluorobenzene Catalyzed by Nickel

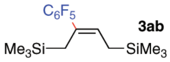
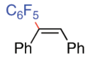
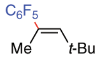
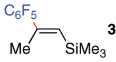
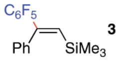


1a (1.0 mmol)

2a–2f (1.5–3.0 mmol)

3aa–3af

>95% regio- and stereoselectivity

entry	R^1, R^2 in **2**	mmol	time (h)	product		yield (%)[a]
1[b]	Pr (**2a**)	1.5	3		**3aa**	99
2	CH$_2$SiMe$_3$ (**2b**)	3.0	6		**3ab**	75
3[c]	Ph (**2c**)	3.0	3.5		**3ac**	68
4[b]	Me, *t*-Bu (**2d**)	1.5	3		**3ad**	89
5[d]	Me, SiMe$_3$ (**2e**)	1.5	13		**3ae**	47
6[d]	Ph, SiMe$_3$ (**2f**)	1.5	15		**3af**	63

[a] Isolated yields. [b] Reaction run with a 3 mol % catalyst. [c] Slow addition of **2c** over 2.5 h. [d] Reaction run at 100 °C.

To extend the present alkenylation catalysis to catalytic direct alkylation of polyfluorobenzenes, we examined the addition of **1a** across other unsaturated compounds. The reaction of **1a** (1.0 mmol) with 1-phenyl-1,3-butadiene under identical conditions proceeded at its terminal double bond to give **5** in 67% yield (Scheme 1). Likewise, 2-vinylnaphthalene also inserted into the C−H bond of **1a** under Ni catalysis to give 1,1-diarylethane **6** in 83% yield.

The catalytic reactions should be initiated by the formation of η^2-arene complex **A** followed by the oxidative addition of the C−H bond of the polyfluoroarene to give **B** (Scheme 2).[6,9] The insertion of an alkyne into the Ni−H bond occurs after the preceding coordination in the direction avoiding steric repulsion between the bulkier R^2 and the polyfluorophenyl group on the Ni center.

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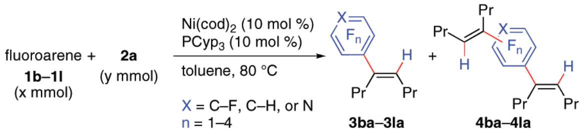
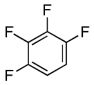
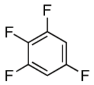
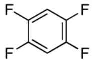
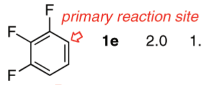
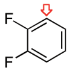
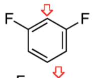
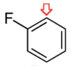
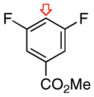
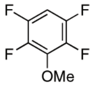
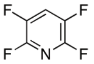
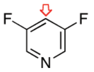
Table 2. Nickel-Catalyzed Alkenylation of Fluoroarenes



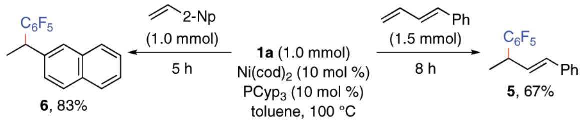
entry	fluoroarene		x	y	temp (°C)	time (h)	yield of **3** (%)[a]	yield of **4** (%)[a]
1		**1b**	1.0	1.5	80	12	71 (**3ba**)	<5 (**4ba**)
2		**1c**	1.0	4.0	80	14	<5 (**3ca**)	87 (**4ca**)
3[b]			2.0	1.0	80	5	48 (**3ca**)	7 (**4ca**)
4[b]		**1d**	1.0	4.0	80	10	<5 (**3da**)	99 (**4da**)
5			2.0	1.0	80	1	53 (**3da**)	7 (**4da**)
6		**1e**	2.0	1.0	100	3	35 (**3ea**)	2 (**4ea**)
7		**1f**	1.0	1.5	100	10	9 (**3fa**)	<5 (**4fa**)
8		**1g**	1.0	1.5	100	10	54 (**3ga**)	7 (**4ga**)
9		**1h**	1.0	1.5	100	20	8 (**3ha**)	<5 (**4ha**)
10		**1i**	1.0	1.5	80	2	71 (**3ia**)	<5 (**4ia**)
11		**1j**	1.0	1.5	80	2	87 (**3ja**)	—
12[b]		**1k**	1.0	1.0	80	18	85 (**3ka**)	—
13[b]		**1l**	2.0	1.0	80	2	99 (**3la**)	<5 (**4la**)

[a] Isolated yields. [b] Reaction run with a 3 mol % catalyst.

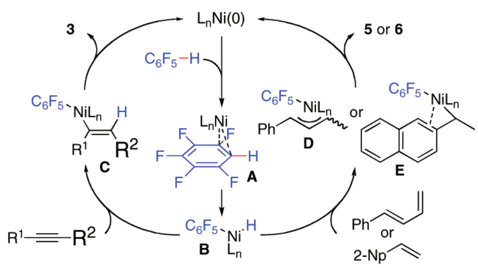
Reductive elimination gives alkenylated polyfluoroarene **3** and regenerates the Ni(0) species. The insertion of 1,3-dienes and vinylarenes into the Ni−H bond takes place at the olefin terminus to give π-allyl- and benzylnickel intermediates **D** and **E**,[6i] respectively. Reductive elimination at the methyl-substituted carbon results in the formation of the alkylation products and regenerates Ni(0). The reaction of **1a**, **1j**-d_1, and **2a** gave only a small amount (<10%) of crossover products, supporting the proposed catalytic cycle.[11]

Here, we have uncovered a Ni catalyst for the activation of C−H over C−F bonds of polyfluoroarenes and demonstrated their direct alkenyl- and alkylation to allow efficient synthesis of a variety of polyfluoroarenes having alkenyl and alkyl groups in regio- and stereoselective manners. Experimental and theoretical mechanistic studies determining the origin of the dramatic ligand effect on the Ni catalysis for C−H activation of polyfluoroarenes and further development of other C−H functionalizations of F-containing substrates via Ni catalysis are being pursued in our laboratories.

Scheme 1. Alkylation of **1a** Catalyzed by Nickel



Scheme 2. Plausible Mechanism



L = PCyp$_3$ and/or unsaturated compounds

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Supporting Information Available: Detailed experimental procedures including spectroscopic and analytical data. This material is available free of charge via the Internet at http:/pubs.acs.org.

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