

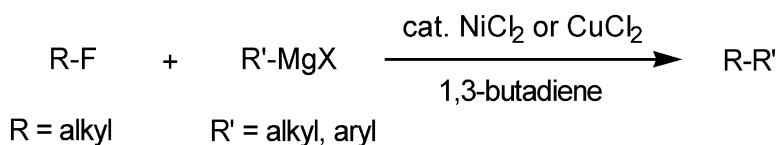
Communication

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Ni- or Cu-Catalyzed Cross-Coupling Reaction of Alkyl Fluorides with Grignard Reagents

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Carbon–fluorine bonds are the strongest single bonds in organic compounds and have been thought to be inert toward many reagents.¹ Therefore, developing reactions that replace fluorine atoms in organic molecules with other atoms or functional groups is a challenging theme in organic chemistry. As for metal-mediated transformations involving cleavage of sp^3C-F bonds, several reactions using fluoroarenes have already been developed, employing catalytic² or stoichiometric³ amounts of transition metal complexes. On the other hand, examples of aliphatic sp^3C-F bond fission by use of transition metal complexes are very rare. They are limited to the following two types of reactions: (i) catalytic defluorination of saturated perfluoroalkanes leading to the corresponding olefins or arenes,⁴ and (ii) hydrodefluorination (i.e., reduction) of fluoroalkanes with $Cp_2^*ZrH_2$, which proceeds only in a stoichiometric manner.⁵

During our study on the synthetic application of alkyl halides in transition metal chemistry,⁶ we have recently revealed that Ni catalyzes cross-coupling reactions of alkyl chlorides, bromides, and tosylates with Grignard reagents in the presence of a 1,3-butadiene derivative under mild conditions.⁷ As an extension of this study, we disclose herein the first example of a catalytic C–C bond-forming reaction using nonactivated alkyl fluorides⁸ (eq 1).

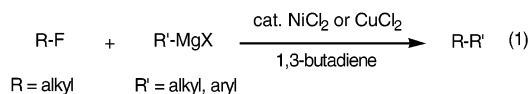


Table 1 summarizes the results of cross-coupling reactions of *n*-octyl fluoride (2 mmol) with *n*-propylmagnesium bromide (0.93 M, 4.3 mL, 2.0 equiv), performed at 25 °C for 6 h using various catalysts (3 mol %) and additives. As shown in entries 1–3, ${}^n\text{C}_8\text{H}_{17}\text{-F}$ did not react at all when no additive is employed, even in the presence of Ni catalyst. However, addition of 10 mol % 1,3-butadiene based on ${}^n\text{C}_8\text{H}_{17}\text{-F}$ enabled alkyl–alkyl cross-coupling to proceed in the presence of NiCl_2 as a catalyst, giving rise to a 9% yield of undecane accompanied by a small amount of octane (entry 4). On increasing the amount of 1,3-butadiene up to 100 mol %, the yield of undecane improved to 64% (entry 7). However, further increase of 1,3-butadiene did not lead to significant improvement of the yield (entry 8).

When 100 mol % isoprene was employed instead of 1,3-butadiene, undecane was obtained in 47% yield (entry 9). However, 2,3-dimethyl-1,3-butadiene, 1,5-cyclooctadiene, and diphenylacetylene did not promote this coupling reaction (entries 10–12). As proposed in our previous paper,⁷ bisallyl Ni complexes would play an important role as active catalytic species. The ineffectiveness of 2,3-dimethyl-1,3-butadiene may be ascribed to lower stability and/or reactivity of its complex due to steric reasons. Under the same conditions as in entry 7, reactions of ${}^n\text{C}_8\text{H}_{17}\text{F}$ with ${}^i\text{Pr-MgBr}$, ${}^t\text{Bu-MgCl}$, and Ph-MgBr afforded coupling products in 3%, 6%, and 31% yield, respectively.

Ni complexes bearing phosphine ligands, such as $(\text{PPh}_3)_2\text{NiCl}_2$ and $(\text{dppp})\text{NiCl}_2$, afforded undecane in 8% and 57% yield, respec-

Table 1. Cross-Coupling Reaction of ${}^n\text{C}_8\text{H}_{17}\text{-F}$ with ${}^n\text{C}_3\text{H}_7\text{-MgBr}^a$

entry	catalyst	additive (mol %)	product yield (%) ^b		
			undecane	octane	octenes ^c
1	NiCl_2	none	0	0	0
2	$(\text{PPh}_3)_2\text{NiCl}_2$	none	0	0	0
3	$(\text{dppp})\text{NiCl}_2$	none	0	0	0
4	NiCl_2	1,3-butadiene (10)	9	1	0
5	NiCl_2	1,3-butadiene (50)	44	2	1
6	NiCl_2	1,3-butadiene (70)	50	2	2
7	NiCl_2	1,3-butadiene (100)	64	4	2
8	NiCl_2	1,3-butadiene (200)	67	3	1
9	NiCl_2	isoprene (100)	47	0	0
10	NiCl_2	2,3-methyl-1,3-butadiene (100)	0	0	0
11	NiCl_2	1,5-cyclooctadiene (100)	0	0	0
12	NiCl_2	diphenylacetylene (100)	0	0	0
13	$(\text{PPh}_3)_2\text{NiCl}_2$	1,3-butadiene (100)	8	3	2
14	$(\text{dppp})\text{NiCl}_2$	1,3-butadiene (100)	57	3	2
15	FeCl_2	1,3-butadiene (100)	0	0	0
16	CoCl_2	1,3-butadiene (100)	0	0	0
17	PdCl_2	1,3-butadiene (100)	23	1	4
18	CuCl_2	1,3-butadiene (100)	97	0	0
19	CuCl	1,3-butadiene (100)	94	0	0
20	Li_2CuCl_4	1,3-butadiene (100)	30	0	0

^a Conditions: ${}^n\text{Oct-F}$ (2 mmol), 3 mol % catalyst, additive (mol % based on the substrate), and ${}^n\text{Pr-MgBr}$ (2 equiv, 1 M), in THF, 25 °C, 3 h. ^b Determined by GC. ^c A mixture of 1-octene and 2-octenes.

tively, in the presence of 1,3-butadiene (entries 13 and 14). FeCl_2 and CoCl_2 did not give any products (entries 15 and 16), whereas PdCl_2 afforded undecane in 23% yield (entry 17). Surprisingly, copper salts, such as CuCl_2 and CuCl , showed the highest activities for this cross-coupling reaction with complete suppression of formation of octane and octenes (entries 18 and 19). When Li_2CuCl_4 was used, only a moderate yield of undecane was obtained (entry 20).

Representative results of the CuCl_2 -catalyzed cross-coupling reaction of ${}^n\text{C}_8\text{H}_{17}\text{-F}$ with some Grignard reagents are shown in Table 2. It was found that 1.3 equiv of R-MgX and 10 mol % 1,3-butadiene (based on the halide, 0.07 M in THF) are sufficient to promote the primary alkyl–alkyl coupling reaction efficiently (Table 2, entry 1). Isoprene (entry 2), diphenylacetylene, and $m\text{-CF}_3\text{C}_6\text{H}_4\text{CH=CH}_2$ were less effective under these conditions. 1-Octene and 1,5-cyclooctadiene were ineffective.

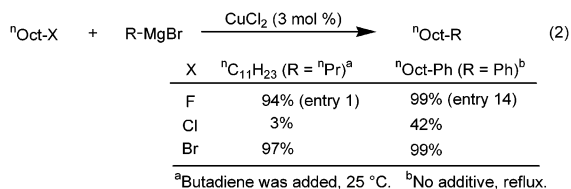
It should be noted that the coupling product, undecane, was obtained in 20% yield in the presence of CuCl_2 in the absence of 1,3-butadiene at 25 °C for 6 h (entry 3). Prolonged reaction time did not improve the yield (25% for 20 h). Interestingly, when the reaction was performed at –20 °C, the coupling reaction proceeded slowly without significant loss of catalytic activity (entries 4 and 5) even in the absence of 1,3-butadiene, resulting in the formation of undecane in 68% yield after 48 h (entry 6). This reaction did not proceed at –40 °C (entry 7). The coupling reaction of ${}^i\text{Pr-MgBr}$ was also facilitated by 1,3-butadiene at ambient temperature (entries 8 and 9). These results may imply that 1,3-butadiene plays an important role in stabilizing an active species in the Cu-catalyzed cross-coupling reaction.

Table 2. Cu-Catalyzed Cross-Coupling Reaction of n Oct-F with Grignard Reagents

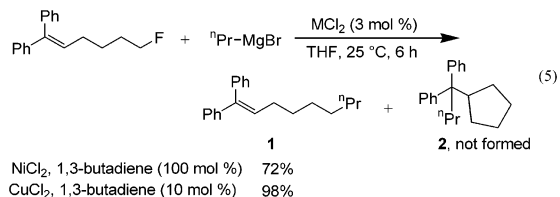
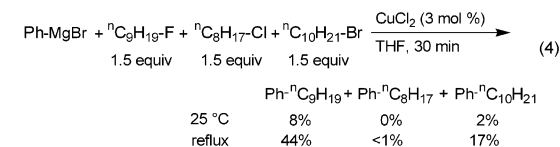
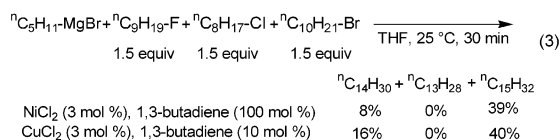
entry	n Oct-F 2 mmol	+ R-MgX 2.6 mmol	$\xrightarrow[\text{THF}]{\text{CuCl}_2 (3 \text{ mol } \%)}$	n Oct-R	GC yield (%)
	R-MgX	additive (0.2 mmol)	temp ($^{\circ}\text{C}$)	time (h)	
1	$n\text{C}_3\text{H}_7\text{-MgBr}$	1,3-butadiene	25	6	94
2		isoprene	25	6	34
3		none	25	6	20
4		1,3-butadiene	-20	6	38
5		none	-20	6	36
6		none	-20	48	68
7		none	-40	6	3
8	$i\text{C}_3\text{H}_7\text{-MgBr}$	1,3-butadiene	25	6	81
9		none	25	6	35
10	$i\text{C}_4\text{H}_9\text{-MgCl}$	1,3-butadiene	25	6	99
11		none	25	6	99
12	Ph-MgBr	1,3-butadiene	25	6	38
13		none	25	6	53
14		none	67 (reflux)	1	99

In contrast to the reactions involving the primary and secondary alkyl Grignard reagents mentioned above, 1,3-butadiene exerted little effect in the reaction using tertiary alkyl and phenyl Grignard reagents. These reactions gave rise to the corresponding coupling products in good to high yields without additives (entries 10–14). Cyclohexyl fluoride and bis(*p*-trifluoromethylphenyl)-methane could not be alkylated under similar conditions.

When *n*-octyl bromide was allowed to react with $n\text{Pr-MgBr}$ or Ph-MgBr under identical conditions (entries 1 and 14 in Table 2, respectively), the corresponding coupling products were obtained in high yields. In contrast, *n*-octyl chloride gave poor to moderate yields of products (eq 2).



We also examined the relative reactivities of alkyl halides (RX; X = F, Cl, Br) by competitive experiments using $n\text{C}_5\text{H}_{11}\text{-MgBr}$. To a mixture of 1,3-butadiene and equimolar amounts of *n*-nonyl fluoride, *n*-octyl chloride, and *n*-decyl bromide were added a THF solution of $n\text{C}_5\text{H}_{11}\text{-MgBr}$ and 3 mol % NiCl_2 or CuCl_2 (eq 3). For both catalysts, the reactivity of alkyl halides was observed to be in the order chloride < fluoride < bromide. Interestingly, similar experiments using Ph-MgBr and CuCl_2 in the absence of 1,3-butadiene revealed that fluoride was the most reactive halide (eq 4).



diene revealed that fluoride was the most reactive halide (eq 4). Such high reactivities of fluorides cannot reasonably be explained yet⁹ because the mechanistic details are not known.¹⁰

When the Ni- and Cu-catalyzed cross-coupling reactions depicted in eq 5 were run employing 6-fluoro-1,1-diphenyl-1-hexene, **1** was obtained as the sole coupling product in 72% and 98% yield, respectively, without formation of **2**, which may arise from intramolecular cyclization of a 6,6-diphenyl-5-hexenyl radical.¹¹ This result would rule out this radical mechanism.

In conclusion, we revealed the first example of a metal-catalyzed cross-coupling reaction of alkyl fluorides with Grignard reagents. These reactions proceed efficiently between primary alkyl fluorides and various Grignard reagents under mild conditions in the presence of nickel or copper salts.

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Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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