

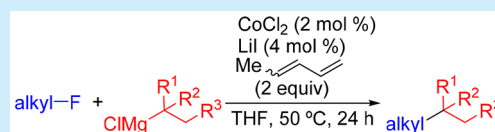
Co-Catalyzed Cross-Coupling Reaction of Alkyl Fluorides with Alkyl Grignard Reagents

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Supporting Information

ABSTRACT: The cross-coupling reaction of unactivated alkyl fluorides with alkyl Grignard reagents by a CoCl₂/LiI/1,3-pentadiene catalytic system is described. The present reaction smoothly cleaved C–F bonds under mild conditions and achieved alkyl–alkyl cross-coupling even when sterically hindered tertiary alkyl Grignard reagents were employed. Since alkyl fluorides are inert toward many reagents and catalytic intermediates, the use of the present reaction enables a new multistep synthetic route to construct carbon frameworks by combining conventional transformations.

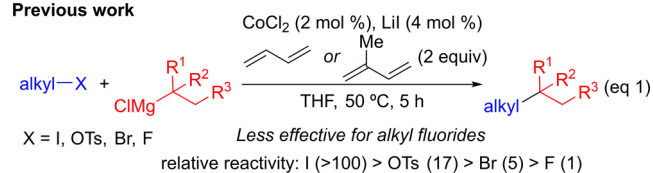


The activation of unreactive chemical bonds in organic compounds is one of the most challenging issues in modern organic chemistry.¹ In this context, transition-metal-catalyzed C–C bond forming reaction through C–F bond cleavage has been developed,² however, most studies are directed to cross-coupling reaction of aromatic C–F bonds and that of aliphatic C–F bonds is still relatively rare due to the inertness of aliphatic C–F bonds toward transition-metal catalysts.³ Our studies on the catalytic C–C bond formation through aliphatic C–F bond cleavage include Ni- and Cu-catalyzed cross-coupling reaction of unactivated alkyl fluorides with Grignard reagents⁴ and catalytic multicomponent coupling reactions of alkyl fluorides.⁵ Since our report on cross-coupling reaction utilizing alkyl fluorides,⁶ Oshima⁷ and Liang⁸ reported Cu- and Fe-catalyzed cross-coupling reaction of alkyl fluorides with Grignard reagents, respectively. Recently, Jarvo reported Ni-catalyzed intramolecular reductive cross-coupling through C–F and C–O bonds cleavage.⁹ Without transition-metal catalyst, metal enolates and enamides¹⁰ as well as organometallic reagents¹¹ coupled with alkyl fluorides through C–F bond cleavage; however, it still remain much room to improve reaction efficiency or scope of the coupling partners.

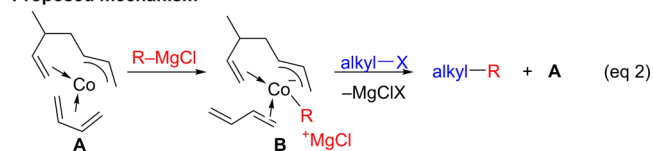
We recently reported Co-catalyzed cross-coupling reaction of alkyl halides with alkyl Grignard reagents by the aid of 1,3-diene (1,3-butadiene or isoprene) and LiI as the additives, where various tertiary alkyl Grignard reagents underwent the coupling reaction to construct a quaternary carbon center (Scheme 1, eq 1).^{12,13} The catalysis involves a unique anionic Co complex B,¹⁴ generated by the reaction of complex A with Grignard reagents, as the key intermediate in C–C bond forming step (Scheme 1, eq 2). However, the reaction using alkyl fluorides as a coupling partner was slow and inefficient leading to only moderate yields of the coupling products. Indeed, the relative reactivity of alkyl halides in the reaction was estimated to be I/OTs/Br/F = > 100:17:5:1,¹⁵ which implied difficulty of the use of alkyl fluorides as a coupling partner. Herein, we report that Co-catalyzed cross-coupling reaction of unactivated alkyl fluorides with alkyl Grignard reagents was drastically improved by the

Scheme 1. Co-Catalyzed Cross-Coupling Reaction of Alkyl Halides with Alkyl Grignard Reagents

Previous work



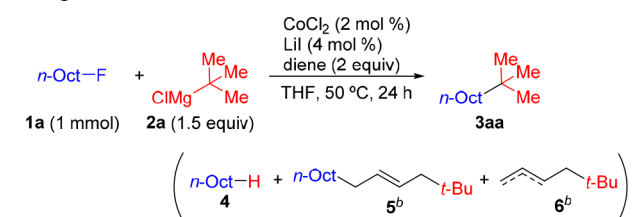
Proposed mechanism



use of 1,3-pentadiene as the ligand precursor, and bulky tertiary alkyl groups could be efficiently introduced into a terminal sp³-carbon of alkyl fluorides with C–F bond cleavage.

We initiated our continuing study on the coupling reaction employing *n*-Oct-F **1a** and *t*-BuMgCl, **2a**, in the presence of 2 mol % of CoCl₂, 4 mol % of LiI, and 2 equiv of isoprene. Scrutinizing the reaction products by GC analysis indicated that not only a reduction product, octane **4**, but also byproducts **5** and **6** arising from carbomagnesiation¹⁶ of isoprene with *t*-BuMgCl followed by the coupling with *n*-Oct-F and protonation, respectively, were formed (Table 1, entry 1). The reaction using isoprene as an additive showed low reproducibility, and the yields of the coupling product varied from 8% to 82% probably due to the competing formation of these byproducts leading to the functionalization of 1,3-dienes.^{5b,6,17} This result prompted us to screen 1,3-diene additives, and the results are summarized in Table 1. Surprisingly, 1,3-pentadiene, which showed a similar additive effect on the Co-catalyzed cross-coupling,¹² suppressed

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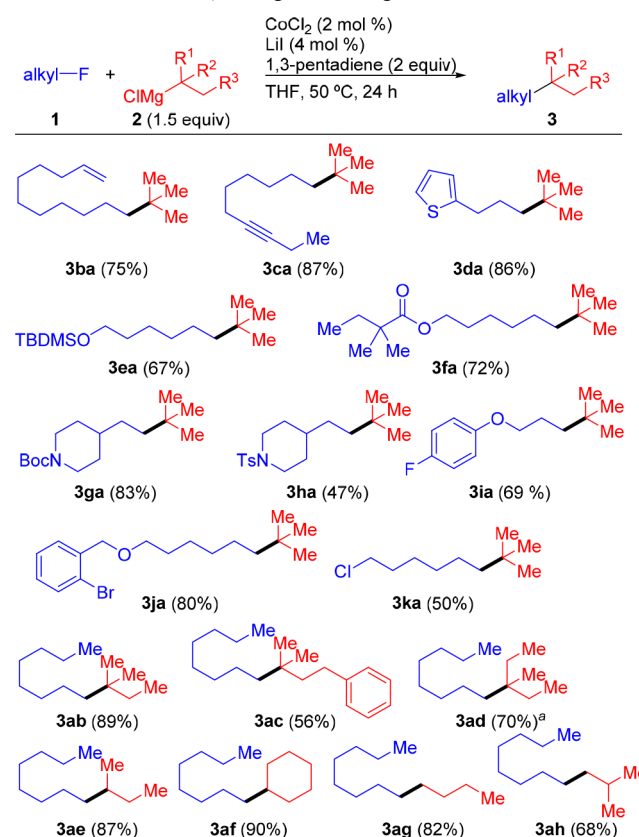
Table 1. Cross-Coupling Reaction of *n*-Oct-F with *t*-BuMgCl^a

entry	diene	1a, conv (%) ^c	3aa (%) ^c	4/5/6 (mmol) ^c
1		84-99	8-82	0.01-0.22:0.13-0.56:0.03-0.50
2		94	91(89) ^d	<0.02:<0.02;n.d.
3		88	30	0.08:0.25:n.d.
4		78	35	<0.02:0.30:0.92
5	none	94	4	0.47:-:-
6 ^e		17	5	n.d.:n.d.:n.d.

^aReaction conditions: *n*-Oct-F (1.0 mmol), *t*-BuMgCl (1.5 mmol), CoCl₂ (2 mol %), LiI (4 mol %), and diene additive (2 mmol) in THF (2.8 mL) at 50 °C for 24 h. ^bMethyl substituent(s) was omitted for clarity. The formation of isomers was confirmed by GC-MS. ^cDetermined by GC using decane as an internal standard. ^dIsolated yield is in parentheses. ^eWithout LiI.

alkylation of 1,3-dienes,^{5b,c} which gave rise to the corresponding coupling product **3aa** in 91% yield along with small amounts of octane **4** and **5** (Table 1, entry 2). In contrast, the use of 1,3-butadiene and 2,3-dimethyl-1,3-butadiene resulted in lower yields of **3aa** along with the formation of considerable amounts of byproducts **5** or **6** (Table 1, entries 3 and 4). These results could be explained by the reactivities of these dienes toward carbomagnesiation. Indeed, when these dienes were treated with *t*-BuMgCl, **2a**, in the presence of CoCl₂ and LiI, isoprene afforded 0.035 mmol of carbomagnesiation products **6**, whereas the corresponding products **6** were not detected in the case of 1,3-pentadiene. The addition of a 1,3-diene was essential for the cross-coupling reaction. The reaction without 1,3-diene resulted in reduction of *n*-Oct-F to give **4** in 47% yield (Table 1, entry 5). Only 5% yield of the coupling product **3aa** was obtained in the absence of LiI (Table 1, entry 6). Systematic screening of metal salts revealed that LiI showed the best additive effect, and the reaction using NaI, KI, and MgI₂ afforded the coupling product **3aa** in 22%, 32%, and 31% yields, respectively. Chloride and bromide salts of Li, Na, K, and Mg were found to be ineffective additives, and more than 80% of *n*-Oct-F was recovered in all cases.¹⁸

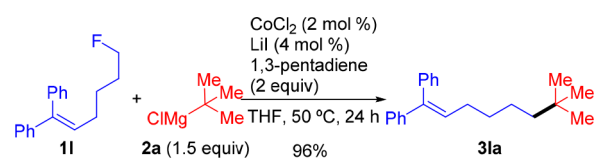
With optimized conditions for alkyl fluorides in hand, we investigated the scope of the present coupling reaction, and the results are summarized in Scheme 2. Alkyl fluorides carrying a terminal alkene (**1b**) or an internal alkyne (**1c**) coupled with *t*-BuMgCl in good yields without affecting these unsaturated bonds. An alkyl fluoride bearing thiophene (**1d**) underwent the coupling reaction to give **3da** in 86% yield. Functional groups such as silyl ether (**1e**), ester (**1f**), *N*-Boc and *N*-tosyl amides (**1g** and **1h**), and aromatic and benzylic ethers (**1i** and **1j**) were all tolerated. It should be noted that the present Co catalyst selectively cleaved the sp³C–F bond even in the presence of

Scheme 2. Co-Catalyzed Cross-Coupling Reaction of Alkyl Fluorides with Alkyl Grignard Reagents

^aCoCl₂ (5 mol %), LiI (10 mol %), and 1,3-pentadiene (5 equiv) were used.

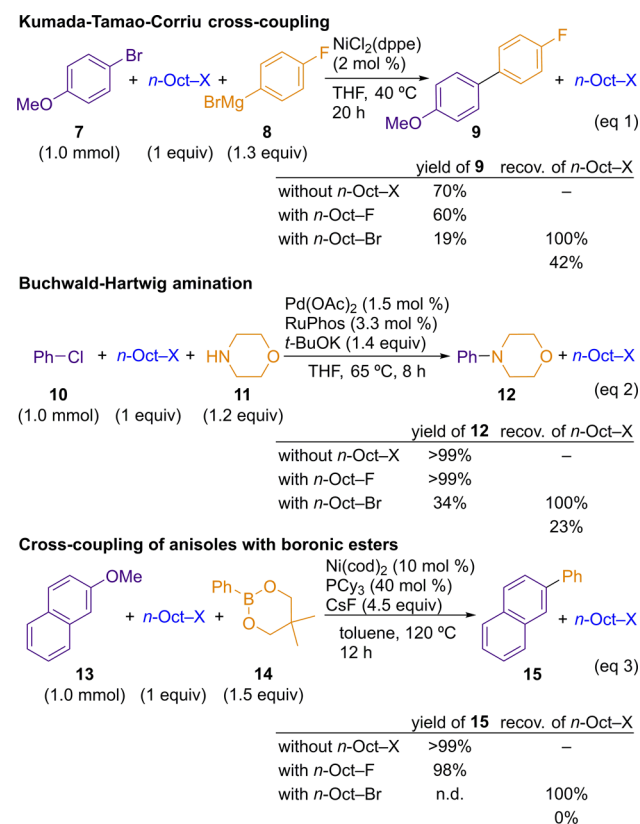
Ar–F or Ar–Br bond as well as sp³C–Cl bond. Next, we turned our attention to the scope of alkyl Grignard reagents. Tertiary alkyl Grignard reagents having one Et (**2b**) or phenethyl (**2c**) group smoothly coupled with *n*-Oct-F **1a** giving **3ab** and **3ac** in good yields. A more sterically hindered tertiary alkyl Grignard reagent **2d** coupled with *n*-Oct-F to give **3ad** in 70% yield by increasing the catalyst loading. The present catalytic system could be applicable to acyclic and cyclic secondary alkyl Grignard reagents as well as primary ones. In all cases, no isomerization of the branched alkyl groups, through β-hydrogen elimination and insertion sequence, was observed. This is an advantage of the present Co-catalyzed reaction over Ni and Pd catalytic systems.¹⁹

To shed some light on reaction mechanism, we conducted the reaction of 1,1-diphenyl-6-fluorohex-1-ene **1l** with *t*-BuMgCl, **2a**, and obtained the corresponding coupling product **3la** in 96% yield without any evidence of 5-*exo* radical cyclization (Scheme 3).²⁰ This result may rule out radical intermediates in the C–F bond cleavage event (see Supporting Information for details).

Scheme 3. Radical Clock Experiment

Recently, a number of cross-coupling reactions through inactive bond cleavage have been developed. Such C–C bond forming reactions allow us to construct complex carbon frameworks by a combination with conventional cross-coupling reactions through iterative coupling reactions to serve as a new synthetic strategy. To demonstrate the synthetic advantage of the present reaction, we examined the tolerance of alkyl fluorides in various cross-coupling reactions (Scheme 4).

Scheme 4. Tolerance of Alkyl Fluorides under Transition-Metal-Catalyzed Cross-Coupling Reactions

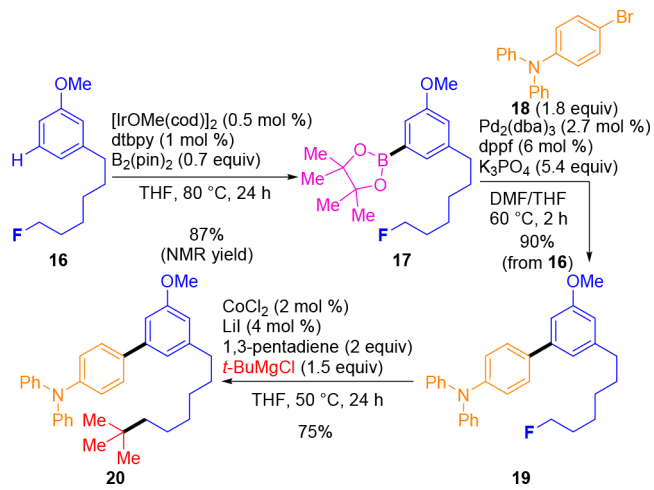


Initially, we conducted Kumada–Tamao–Corriu coupling reaction of *p*-bromoanisole **7** with *p*-fluorophenyl Grignard reagent **8** in the presence of an alkyl fluoride catalyzed by 2 mol % of NiCl₂(dppe) (dppe = bis(diphenylphosphino)ethane) (Scheme 4, eq 1).²¹ The original reaction provided biaryl product **9** in 70% yield. When *n*-Oct-F **1a** (1 equiv) was added to the reaction mixture, *n*-Oct-F did not essentially affect the reaction to give **9** in a comparable yield (60%), and 100% of *n*-Oct-F was recovered unchanged. In contrast, the addition of *n*-Oct-Br largely affected the Kumada–Tamao–Corriu coupling reaction to depress the yield of **9** to 19% along with the formation of byproducts including 1-fluoro-4-octylbenzene (0.19 mmol), 4-octylanisole (0.16 mmol), octane (0.04 mmol), and hexadecane (0.01 mmol). Next, we tested Pd-catalyzed Buchwald–Hartwig coupling of **10** with **11** (Scheme 4, eq 2).²² Similar competitive experiments showed an excellent resistance of alkyl fluorides toward the Pd catalysis, smoothly providing an amination product of PhCl **10** without loss of catalytic performance. In contrast, the addition of *n*-Oct-Br gave a complex mixture including the corresponding amination product (0.39 mmol), octane (0.05 mmol), and octene (0.27 mmol). A more striking result was obtained in the Ni-catalyzed

cross-coupling reaction of anisole derivative **13** with phenyl boronic ester **14** (Scheme 4, eq 3).²³ Although the reaction requires relatively harsh conditions to cleave the C–O bond, *n*-Oct-F was completely recovered, and the expected cross-coupling product **15** was obtained in 98% yield. This is in sharp contrast to the reaction in the presence of *n*-Oct-Br, which completely suppressed the formation of **15**.

Further demonstration of the practicality of the present method is shown in Scheme 5. Miyaura–Hartwig C–H

Scheme 5. Late-Stage Introduction of Quaternary Carbon



borylation²⁴ of an aryl ring in alkyl fluoride **16** and subsequent Suzuki–Miyaura cross-coupling with bromoarene **18** in a one-pot²⁵ forged biaryl skeleton in 90% yield (2 steps) without loss of the C–F bond. The cross-coupling reaction of thus obtained alkyl fluoride **19** with *t*-BuMgCl, **2a**, afforded **20** in 75% yield. These results clearly demonstrate that sp³ C–F bonds survive in many conventional catalytic reactions and allow stepwise manipulation of molecules by the combination of various conventional reactions with the present Co catalytic system that functionalizes sp³C–F bond as a new synthetic strategy to construct carbon frameworks.

In summary, we examined the Co-catalyzed cross-coupling reaction of unactivated alkyl fluorides with bulky alkyl Grignard reagents via C–F bond cleavage. The present reaction smoothly proceeds with tertiary alkyl Grignard reagents to construct a quaternary carbon center efficiently without isomerization of the alkyl group. The C–F bond cleavage takes place in an ionic mechanism via a cobaltate intermediate **B** (Scheme 1, eq 2). It was also demonstrated that alkyl fluorides are inert toward various cross-coupling reactions. This will allow us to design new synthetic routes by the combined use of the present catalytic reaction and conventional cross-coupling reactions as well as C–H functionalizations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01370.

Additional results, procedures, characterization data, NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Marian Mikołajczyk on the occasion of his 80th birthday.

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(14) Although we previously proposed a different structure for the complex **B** in which 5-methylhepta-2,6-dien-1-yl moiety of the complex **B** intramolecularly coordinated to Co in η^1 fashion, see ref 12, ongoing theoretical calculations suggest that the present structure with η^3 coordination of the allyl group is more likely than the previously proposed structure. Mechanistic studies including theoretical calculations are underway, and the results will be published in due course.

(15) Alkyl chlorides are sluggish in the present cross-coupling reaction. Similar tendency was observed in transformations using alkyl halides catalyzed by other anionic transition metal complexes as the key intermediates, see refs 5b and 5c for instances.

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