

Site-Selective Magnesiumation of Multi-Fluorinated Arenes Catalyzed by Rhodium–Aluminum Bimetallic Complexes

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KEYWORDS: aryl fluoride, magnesiation, Grignard reagent, cooperative catalysis, C–F activation

ABSTRACT: We report the site-selective C–F magnesiation of multi-fluorinated arenes catalyzed by Rh–Al bimetallic complexes to prepare synthetically important fluorine-containing organomagnesium reagents. We clarified that the catalyst-control site-selectivity stems from the steric and electronic environments of the substrates. The protocol can be applied to the efficient synthesis of fluorine-containing pharmaceuticals and liquid crystal molecules.

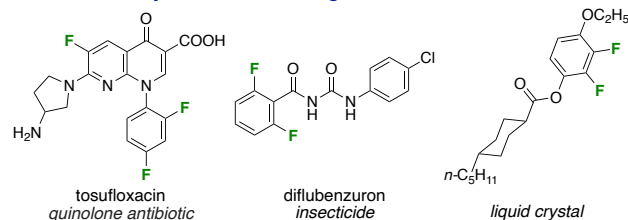
INTRODUCTION

Fluorine is the most electronegative atom and can form the strongest single bond with carbon.¹ These special features provide fluorine-containing compounds with unique properties. Fluoroarenes are often found as key structural motifs in pharmaceuticals,² agrochemicals,³ and organic materials⁴ (Scheme 1A). 22% of small-molecule drugs registered globally in the past three decades contain at least one fluorine atom,^{2a} and the percentages are getting higher in recent years (2015: 34%, 2019: 43%).^{2a} Hence, efficient methods to prepare substituted fluoroarenes are highly desired in modern organic synthesis.⁵

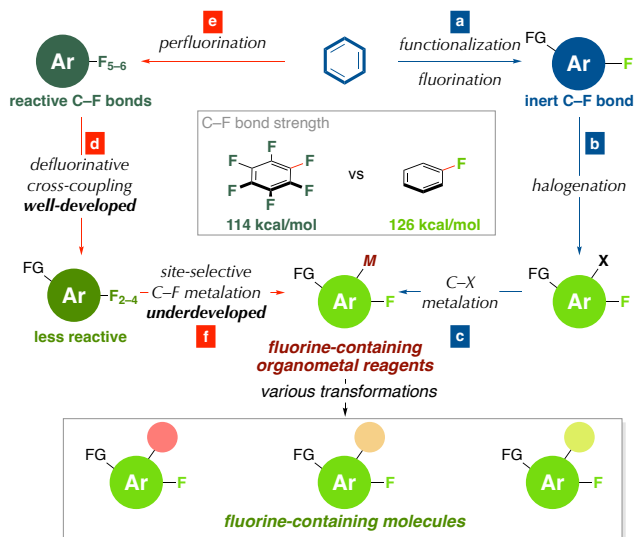
Fluorine-containing organometallic reagents are useful tools for the synthesis of fluorine-containing compounds thanks to the available diverse transformations with their carbon–metal bonds.⁶ Two complementary routes are potentially available to access these reagents (Scheme 1B). Conventionally, fluorine-containing organometallics are prepared by the Balz–Schiemann reaction (step a)⁷ followed by halogenation⁸ (step b) and subsequent oxidative insertion,⁹ halogen/metal exchange reaction (step c),¹⁰ or C–H bond metalation reactions.¹¹ However, harsh reaction conditions for the Balz–Schiemann reaction and an issue of site-selectivity in the C–H bond metalation reaction have hampered their practical use.

The other route starting from perfluoroarenes can be more attractive according to the following reasons: 1) Perfluoroarenes such as hexafluorobenzene (C₆F₆) and pentafluoropyridine (C₅F₅N) can be transformed by aromatic nucleophilic substitution (S_NAr) reactions¹² and transition-metal catalyzed cross-coupling reactions¹³ in a site-selective manner thanks to the relatively weakened C–F bonds in perfluoroarenes¹⁴ (step d). 2) Perfluoroarenes can be prepared from upstream fluorine feedstocks such as F₂/CoF₂ or KF through direct perfluorination of arenes using CoF₃ (Fowler process)¹⁵ or perchlorination with Cl₂ followed by S_NAr reaction with metal fluorides (Halex process)¹⁶ (step e). However, this route has been hampered by a lack of site-selective C–F bond metalation (step f) of multi-fluoroarenes (C₆F_nX_{6-n}; n = 2–4).

A. Fluorine in Key Pharmaceutical, Agrochemical, and Material



B. Synthesis of Functionalized Organofluorine Compounds

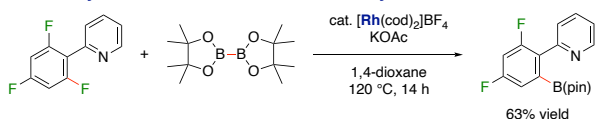


Scheme 1. Importance and synthetic strategies of functionalized aryl fluorides.

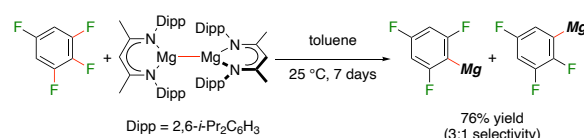
Although site-selective C–F bond metalation reactions of multi-fluoroarenes have been achieved with coordinating directing groups (Scheme 2A)¹⁷ or the *ortho*-fluorine effect,^{13g} the site-selectivity in their absence has been difficult to be controlled. Recently, Crimmin and coworkers developed the site-selective magnesiation of fluoroarenes using a dimeric Mg(I)–Mg(I) reagent (Scheme 2B)¹⁸ and the aluminations of multi-

fluoroarenes using an Al(I) reagent by Pd catalysis (Scheme 2C).¹⁹ However, these systems require stoichiometric amounts of reactive Mg(I) or Al(I) reagents, which are prepared from alkaline metals. Marder and Radius group reported the site-selective C–F bond borylation of multi-fluoroarenes by Rh/Ni dual catalysis (Scheme 2D).²⁰ They have achieved high site-selectivity by promoting the rate-determining transmetalation step with the Rh photocatalyst at room temperature to afford fluorine-containing organoboron compounds.⁶ Nevertheless, modest catalyst efficiency, especially for di- or tri-fluoroarenes, has been noted.

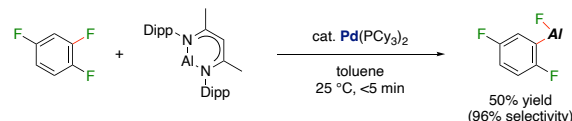
A. Rh-Catalyzed *ortho*-Selective C–F Bond Borylation¹⁷



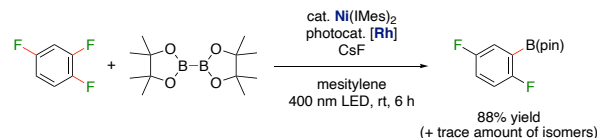
B. Magnesium(I) Complex-Mediated Site-Selective C–F Bond Magnesiumation¹⁸



C. Pd-Catalyzed Site-Selective C–F Bond Alumination¹⁹



D. Ni/Rh-Catalyzed Site-Selective C–F Bond Borylation²⁰

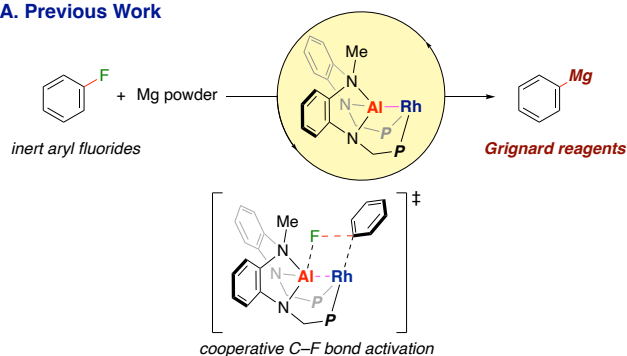


Scheme 2. Selected reports of site-selective C–F bond metalation of multi-fluorinated arenes.

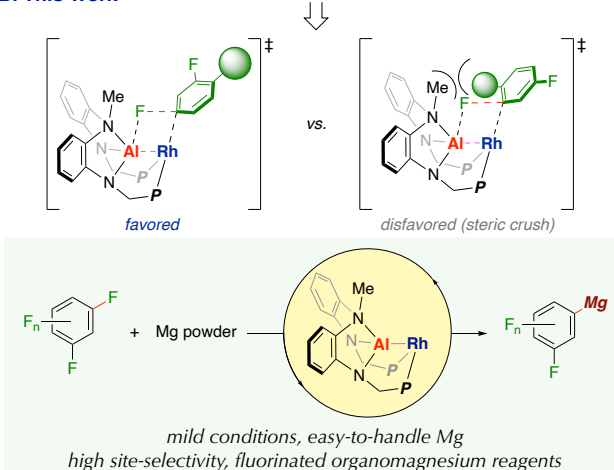
Previously, we have developed the magnesiumation of aryl fluorides catalyzed by Rh–Al bimetallic complexes through C–F bond activation cooperatively by the Rh–Al bond (Scheme 3A).²¹ The cooperative activation of C–F bond by the Rh–Al bond proceeds under very mild conditions, which can be beneficial for controlling the site-selectivity with multi-fluoroarenes. Taking advantage of steric repulsion between arene substituents and the ligand backbone of the Rh–Al complex,²² we report here the undirected site-selective magnesiumation of less hindered C–F bonds of multi-fluoroarenes catalyzed by the Rh–Al bimetallic complexes (Scheme 3B).

The resulting organomagnesium compounds afforded a diverse array of compounds, making them highly promising for applications in organic synthesis. While the oxidative insertion of metallic magnesium into organic halides is a well-established method,⁹ recent years have witnessed numerous reports of magnesiumation reactions catalyzed by transition metals.²³ However, there remains a strong demand for methodologies that enable the selective generation of fluorine-containing organomagnesium reagents from readily accessible precursors.

A. Previous Work



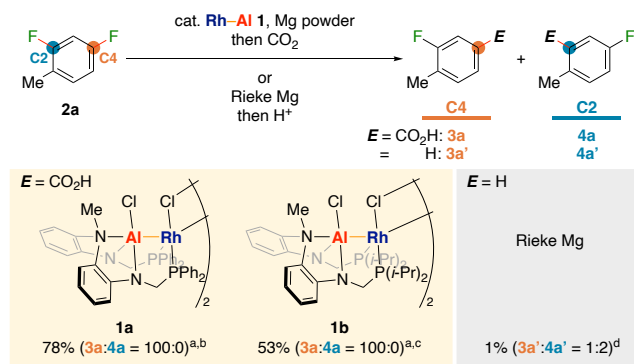
B. This Work



Scheme 3. Previous work and this work.

METHODS

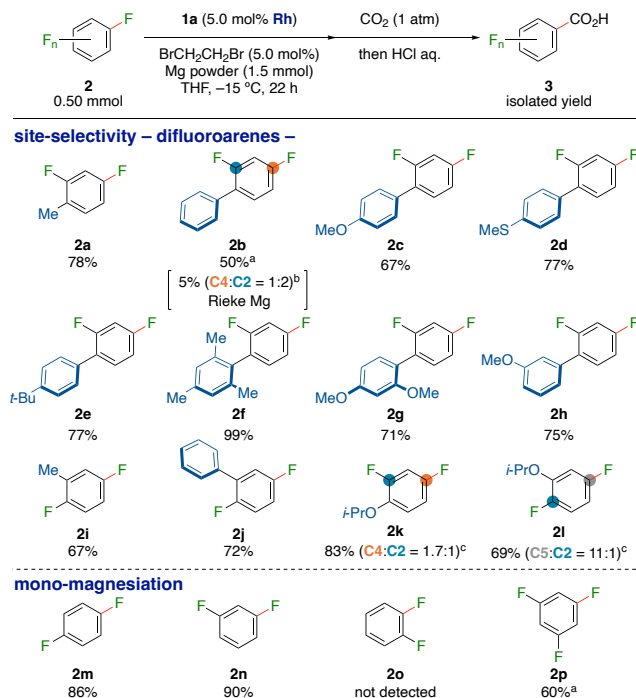
We examined the reaction of 2,4-difluorotoluene (**2a**, 0.50 mmol, 1.0 equiv.) with Mg powder (1.5 mmol, 3.0 equiv.), which was preactivated upon treatment with 1,2-dibromoethane (5.0 mol%), in the presence of Rh–Al complex **1a** (5.0 mol% Rh) in THF (1.5 mL, 0.33 M) at –15 °C (Scheme 4). 3-Fluoro-4-toluic acid (**3a**) was selectively obtained in 78% yield through C(4)–F functionalization without formation of C2-carboxylated product **4a** after quenching the reaction with CO₂ followed by 3 M HCl aq. This result indicated that the less sterically hindered C4-position underwent the magnesiumation exclusively over the C2-position to give the corresponding diarylmagnesium Ar₂Mg.²¹ Rh–Al complex **1b**, which bears *i*-Pr groups on the phosphorus atoms instead of phenyl groups, also gave **3a** in a site-selective manner, albeit in a moderate yield. When the reaction was carried out with Rieke Mg²⁴ in the absence of the catalyst, a mixture of 2-fluorotoluene (**3a'**) and 4-fluorotoluene (**4a'**) was obtained in low yield in a ratio of **3a'**:**4a'** = 1:2 after protonation with NH₄Cl aq. The observed site-selectivities were thus governed by the Rh–Al complexes. These results demonstrate the potential of the present catalytic method for the selective preparation of fluorine-containing building blocks from readily available multi-fluoroarenes.



^a **2a** (1.0 equiv.), Mg powder (1.5 or 3.0 equiv.), 1,2-dibromoethane (5.0 mol%), and **1** (5.0 mol% Rh) in THF at –15 °C for 22 h. 3-Fluoro-4-toluic acid was obtained after carboxylation with CO₂. ^b Isolated yield. ^c The yield and site-selectivity were confirmed by ¹H NMR spectroscopy. ^d **2a** (1.0 equiv.) and Rieke Mg (1.0 equiv.) in THF at 80 °C for 3 h. The yield and site-selectivity were confirmed by ¹⁹F NMR spectroscopy after protonation with NH₄Cl aq.

Scheme 4. Magnesiumation of 2a with 1 or Rieke Mg.

Next, we investigated the scope of substrates on a 0.50 mmol scale under the optimized conditions using **1a** (Scheme 5). 2,4-Difluorobiphenyl (**2b**) afforded the C4-carboxylated product **3b** as a sole product in 50% yield. Again, the Rieke conditions gave a mixture of isomers (C4:C2 = 1:2) in 5% yield. Electron-rich or sterically demanding 2,4-difluorobiphenyls **2c–2h** participated in the reaction to afford corresponding products **3c–3h** through the C–F functionalization at the less hindered C4-position in good to high yield. It was worth noting that the electron-rich arenes and hetero-atoms did not affect the site-selectivity. This protocol could also be applied to the C5-selective magnesiumation of 2,5-difluoroarenes **2i** and **2j**. Although 2,5-difluoro-1-*iso*-propoxybenzene (**2l**) was preferentially magnesiumated at the C5-position (C5:C2 = 11:1), 2,4-difluoro-1-*iso*-propoxybenzene (**2k**) showed markedly decreased selectivity to give a mixture of isomers (C4:C2 = 1.7:1). In the case of **2k**, the reaction proceeded at the sterically demanding C2-position probably due to coordination of the *iso*-propoxy group to the Lewis acidic Al center. However, in the case of **2l**, the C5-position was magnesiumated predominantly. This was probably because the C–F bond at the C5-position of **2l** was electronically activated by the negative inductive effect of the *Oi*-Pr group (Hammett parameter; $\sigma_m = 0.10$, $\sigma_p = -0.45$),²⁵ whereas the C–F bond at the C4-position of **2k** was electronically deactivated by a positive resonance effect of *Oi*-Pr. The reactions of di- and tri-fluorobenzenes **2m–2p** proceeded in a mono-selective manner. For example, 4-fluorobenzoic acid (**3m**) was selectively formed in 87% yield without forming products derived from further magnesiumation. 1,3-Difluorobenzene (**2n**) and 1,3,5-trifluorobenzene (**2p**) afforded 3-fluorobenzoic acid (**3n**) in 99% yield and methyl 3,5-difluorobenzoate (**3p**) in 60% yield, respectively. On the other hand, 1,2-difluorobenzene (**2o**) gave a complex mixture and did not form the desired product.

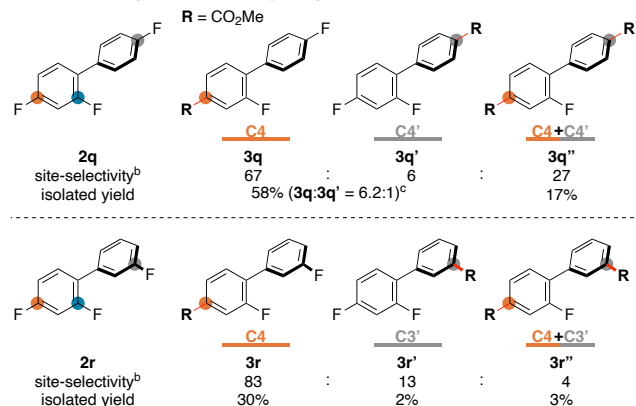


^a The methyl esters were isolated after reacting with TMSCHN₂. ^b Aryl fluoride (1.0 mmol) and Rieke Mg (1.0 mmol) without **1a** in THF (30 mL) at 80 °C for 3 h. Yield and site-selectivity were confirmed by gas chromatography after protonation with NH₄Cl aq. ^c The reactions are carried out at –20 °C. The site-selectivity was estimated based on ¹H NMR analysis of the crude products.

Scheme 5. Substrate scope.

We then studied the reactions of trifluorobiphenyls **2q** and **2r** (Scheme 6). 2,4,4'-Trifluorobiphenyl (**2q**) was preferentially reacted at the C4-position to give **3q**, accompanied by isomer **3q'** and double magnesiumation product **3q''** in a ratio of 67:6:27, as determined by ¹⁹F NMR spectroscopies of the crude mixture. The subsequent purification gave a mixture of **3q** and **3q'** in 58% yield (**3q**:**3q'** = 6.2:1), and **3q''** in 17% yield. A slightly better site-selectivity was observed (**3r**:**3r'**:**3r''** = 83:13:4) when 2,3',4-trifluorobiphenyl (**2r**) was reacted. In both cases, the less sterically demanding and electron-deficient C–F bonds were activated.

Site-Selectivity of Trifluorobiphenyl^a



^a Aryl fluoride **2** (0.50 mmol), Mg powder (1.5 mmol), which was activated using 1,2-dibromoethane (5.0 mol%) beforehand,

and **1a** (5.0 mol% Rh) in THF (1.5 mL) at $-30\text{ }^{\circ}\text{C}$ for 22 h. The resulting mixture treated with CO_2 (1 atm). The methyl esters were isolated after reacting with TMSCHN_2 .^b The site-selectivity was estimated from ^{19}F NMR spectroscopy of the crude mixture.^c The ratio was estimated from ^1H NMR spectroscopy of the purified mixture of **3q** and **3q'**.

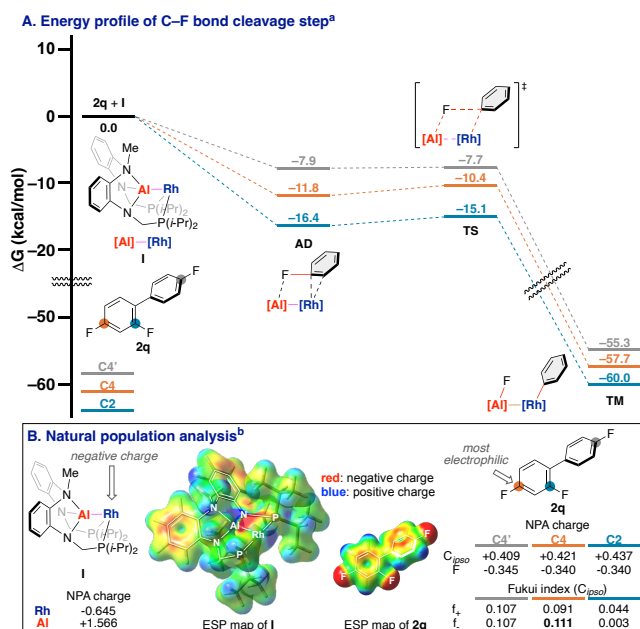
Scheme 6. Site-selectivity of trifluorobiphenyl.

To elucidate the key factors governing site-selectivity, we conducted theoretical study of the C–F bond cleavage processes using **2q** and the Rh–Al complex **I** (Scheme 7). Our findings are summarized as follows: 1) The binding energies of **2q** and **I** follow the order: $\text{AD}_{\text{C}2}$ ($\Delta G_{\text{AD-C}2}^{\circ} = -16.4\text{ kcal mol}^{-1}$) > $\text{AD}_{\text{C}4}$ ($\Delta G_{\text{AD-C}4}^{\circ} = -11.8\text{ kcal mol}^{-1}$) > $\text{AD}_{\text{C}4'}$ ($\Delta G_{\text{AD-C}4'}^{\circ} = -7.9\text{ kcal mol}^{-1}$). 2) The C–F bond cleavage steps are nearly barrierless and are similar across different sites ($\Delta G_{\text{C}4'}^{\circ} = 0.2\text{ kcal mol}^{-1}$, $\Delta G_{\text{C}4}^{\circ} = 1.4\text{ kcal mol}^{-1}$, $\Delta G_{\text{C}2}^{\circ} = 1.3\text{ kcal mol}^{-1}$). 3) The C–F bond cleavage steps are highly exergonic ($\Delta G_{\text{TM-C}4'}^{\circ} = -55.3\text{ kcal mol}^{-1}$, $\Delta G_{\text{TM-C}4}^{\circ} = -57.7\text{ kcal mol}^{-1}$, $\Delta G_{\text{TM-C}2}^{\circ} = -60.0\text{ kcal mol}^{-1}$), indicating that these processes are likely irreversible. These results suggest that the coordination step is crucial in determining the site-selectivity. Although the C2-coordination is thermodynamically feasible, the corresponding product was not observed. This suggests that C2-coordination is kinetically unfavorable, likely due to the steric hindrance at the C2-position preventing effective interaction with the hindered Rh–Al bond.²²

We further investigated why the C4-position preferentially coordinates to the Rh center, despite a similar steric environment to the C4'-position. Calculations of the electrostatic potential (ESP) map and the natural population analysis (NPA) of **2q** revealed that C4-position is relatively more electropositive (NPA of **2q**: +0.421 for C4 vs +0.409 for C4'). Moreover, Fukui indices of C_{ipso} -positions indicated the C4-position is the most electrophilic site (f. of **2q**: 0.111 for C4 vs 0.107 for C4').²⁶ In contrast, the Rh center in **I** exhibited a negative character due to strong σ -donation from the X-type Al ligand,^{27a} while the Al center showed a positive character (NPA of **I**: -0.645 for Rh, +1.566 for Al). Consequently, the coordination of **2q** to the Rh center is driven by electrostatic interactions favoring the more electrophilic position. The Fukui function analysis of **2r** also indicated that the C4-position is the most electrophilic site (f. of **2r**: 0.109 for C4 vs -0.019 for C3'), which is where the reaction predominantly proceeded.

Despite the tendency of typical Rh(I)^{28a} and Rh(III)^{28b} complexes to strongly coordinate with less-fluorinated arenes rather than multi-fluorinated (electron-deficient) arenes, the Rh–Al complex **I** preferentially coordinates to electron-deficient arenes due to strong π -back-donation from the electron-rich Rh center.^{27b} Indeed, our group previously reported that the ethylene-coordinating Rh–Al complex exhibits greater π -back-donation from Rh to the ethylene π^* orbital than σ -donation from the ethylene π orbital to Rh.^{27b}

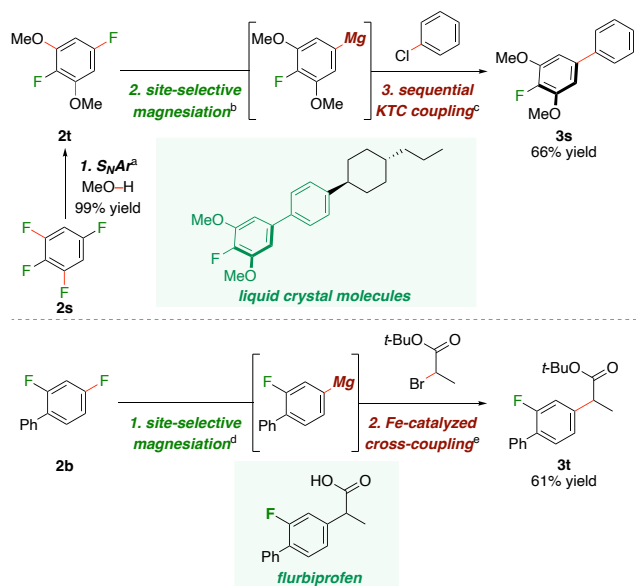
Hence, the site-selective η^2 -coordination of multi-fluoroarenes to the electron-rich Rh center facilitated by electrostatic interaction, promoting site-selective C–F bond magnesiation.



^a Energy profiles of the C–F bond cleavage step were calculated at B3PW91-D3/SDD for Rh, 6-311+G(d2) for Al, 6-311G for others with PCM(THF) level of theory. ^b The natural populations and ESP maps were calculated at B3PW91/SDD for Rh, 6-311+G(d) for others. **I** (−0.020000 au (red) to 0.150000 au (blue)). Isovalue is 0.020000 au. **2q** (−0.005000 au (red) to 0.100000 au (blue)). Isovalue is 0.010000 au.

Scheme 7. Theoretical study of the site-selectivity with **2q**.

The synthetic utility of the site-selective magnesiation reaction can be demonstrated through the synthesis of a fluorine-containing liquid crystal molecule and a drug molecule (Scheme 8). 2,5-Difluoro-1,3-dimethoxybenzene (**2t**) was prepared through an aromatic nucleophilic substitution reaction ($\text{S}_{\text{N}}\text{Ar}$) of 1,2,3,5-tetrafluorobenzene (**2s**) with MeOH ,^{12b} and then was subjected to the present magnesiation reaction. The less hindered C–F bond was reacted in a site-selective manner to give a fluoroarylmagnesium species. It was successfully transformed to **3s**, which can be found as a part of a liquid crystal molecule,²⁹ in 66% yield through the Kumada–Tamao–Corriu (KTC) cross-coupling reaction catalyzed by **1a**.³⁰ The magnesiation of **2b** was followed by the Fe-catalyzed cross-coupling reaction³¹ with *tert*-butyl 2-bromopropionate to give a synthetic precursor **3t** for a non-steroidal anti-inflammatory drug, flurbiprofen,^{11g,32} in 61% yield (44% in the absence of the Fe catalyst).



^a **2s** (12 mmol), MeOH (2.2 equiv.), KHMDS (2.2 equiv.), DMF (30 mL), 0 °C to rt, 48 h. ^b **2t** (0.42 mmol), Mg powder (3.0 equiv.), **1a** (5.0 mol% Rh), BrCH₂CH₂Br (5.0 mol%), THF (1.5 mL), rt, 22 h, then filtration with THF (1.0 mL). ^c PhCl (5.0 equiv.), 60 °C, 36 h. ^d **2b** (0.50 mmol), Mg powder (3.0 equiv.), **1a** (5.0 mol% Rh), BrCH₂CH₂Br (5.0 mol%), THF (1.5 mL), rt, 22 h, then filtration with THF (1.0 mL). ^e Fe(acac)₃ (3.0 mol%), (*R,R*)-BenzP* (6.0 mol%), *tert*-butyl 2-bromopropionate (1.5 equiv.), 0 °C, 1 h.

Scheme 8. Synthetic application of the present method toward preparation of useful molecules.

CONCLUSION

We have developed the site-selective magnesiation of multi-fluorinated arenes catalyzed by Rh–Al bimetallic complexes to prepare fluorinated arylmagnesium reagents, that allow rapid access to various fluoroarenes through diverse transformations of the Grignard reagents. It is worth mentioning that the catalyst could precisely recognize the steric and electronic environments of fluoroarene substrates to control the site-selectivity.

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Funding Sources

This work was financially supported by JSPS KAKENHI Grant Numbers JP20H00376 (Y.N.), JP22K19026 (K.S.), JP21J14457 (I.F.), Toray Science Foundation (Y.N.), The Mitsubishi Foundation (K.S.), Grant for Basic Science Research Projects from The Sumitomo Foundation (K.S.), and Mizuho Foundation (K.S.) for the Promotion of Sciences.

Notes

Any additional relevant notes should be placed here.

ASSOCIATED CONTENT

Supporting Information

The authors have cited additional references within the Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

ACKNOWLEDGMENT

I.F. is grateful for the Research Fellowship of the Japan Society for the Promotion of Science (JSPS) for Young Scientists, the G-7 Scholarship Foundation, and the Iwadare Scholarship Foundation.

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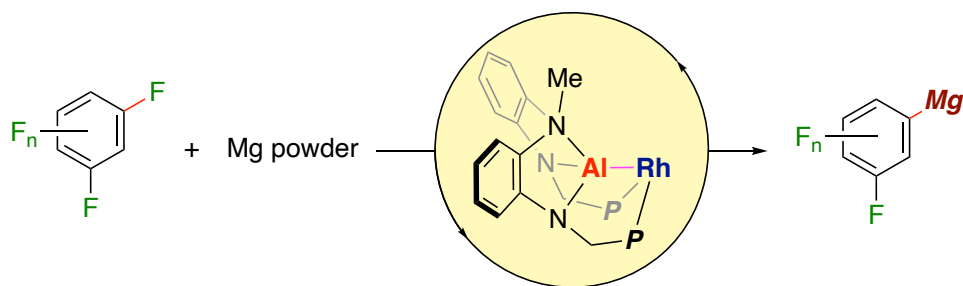
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Table 1. Example of a Double-Column Table

Column 1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7	Column 8

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