

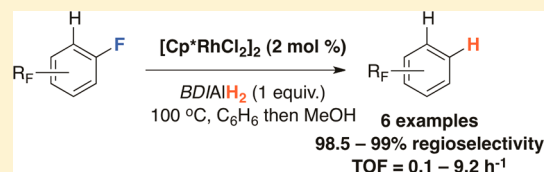
Rhodium Catalyzed, Carbon–Hydrogen Bond Directed Hydrodefluorination of Fluoroarenes

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Supporting Information

ABSTRACT: $[\text{Cp}^*\text{RhCl}(\mu\text{-Cl})]_2$ is reported as a highly efficient and selective precatalyst for the hydrodefluorination of perfluoroarenes using a hydrocarbon-soluble aluminum dihydride as the terminal reductant. Reactions are directed to cleave a C–F bond adjacent to an existing C–H bond with high regioselectivity (98.5–99%). A heterobimetallic complex containing an extremely rare Al–H–Rh functional group has been isolated and shown to be catalytically competent.



The year-on-year expansion of the fluorochemicals market has led to increasingly sophisticated methods to manipulate the fluorine content of organic molecules. Partially fluorinated scaffolds are privileged within this industry, and a survey of contemporary pharmaceuticals and agrochemicals reveals that at least 20% contain one fluorine atom or more.¹ Many groups have promoted the idea of the selective replacement of strong C–F bonds in polyfluorinated building blocks with C–H bonds as a means to reach partially fluorinated intermediates.² This reaction is known as hydrodefluorination (HDF), and catalytic protocols have been reported for the HDF of sp^2 and sp^3 C–F bonds.^{3,4}

Using transition metal catalysis, the HDF of fluoroarenes typically proceeds with not only predictable regioselectivities but also decreasing rates of reaction for each sequential HDF step. For example, the HDF of $\text{C}_6\text{F}_5\text{H}$ catalyzed by $[\text{Rh}(\text{C}_6\text{F}_5)(\text{PMe}_3)_3]$ using a silane as a terminal reductant yields exclusively 1,4- $\text{C}_6\text{F}_4\text{H}_2$ (Figure 1).^{5,6} The same selectivity is observed with a variety of nickel,⁷ iron,⁸ and zirconium-based⁹ catalysts. In 2009, Whittlesey and co-workers documented the selective formation of 1,2- $\text{C}_6\text{F}_4\text{H}_2$ during the HDF of $\text{C}_6\text{F}_5\text{H}$

catalyzed by $[\text{Ru}(\text{IPr})(\text{PPh}_3)_2(\text{CO})\text{H}_2]$ (Figure 1).^{10,11} While the unusual selectivity was later rationalized through DFT studies, this reaction represents an exceptionally rare example in which C–F bond cleavage is directed to the position ortho to the existing C–H bond.¹¹ Although additional examples of *stoichiometric* HDF with the same unusual regiochemistry have been reported by Braun and co-workers,¹² without the use of a suitable directing group the *catalytic* reaction scope has not been extended past a single substrate.^{3e,11}

Herein we show that $[\text{Cp}^*\text{RhCl}(\mu\text{-Cl})]_2$ is a convenient and selective precatalyst for the hydrodefluorination of a series of partially fluorinated arenes. The reactions are highly selective for the cleavage of the C–F bond adjacent to an existing C–H bond and proceed using the hydrocarbon-soluble aluminum dihydride BDIAIH_2 as the terminal reductant (Figure 1).

Hydrodefluorination of $\text{C}_6\text{F}_5\text{H}$. The reaction of 2 equiv of $\text{C}_6\text{F}_5\text{H}$ with BDIAIH_2 catalyzed by 1 mol % of $[\text{Cp}^*\text{RhCl}(\mu\text{-Cl})]_2$ (1) in benzene proceeded readily at 80 °C and yielded 1,2- $\text{C}_6\text{F}_4\text{H}_2$ as the major product, as evidenced by ^1H , ^{19}F , and ^{19}F – ^{19}F NMR spectroscopy. The reaction was highly regioselective, and while only trace amounts of 1,4- $\text{C}_6\text{F}_4\text{H}_2$ were observed, 1,2,3- $\text{C}_6\text{F}_3\text{H}_3$ and $[\text{BDIAI}(\text{2-}\text{C}_6\text{F}_4\text{H})\text{F}]$ were formed in significant quantities (Scheme 1). We have previously described aluminum aryls as side products in the zirconium-catalyzed HDF of fluoroarenes.⁹ This represents a formal C–F to C–Al bond transformation, and the aluminum

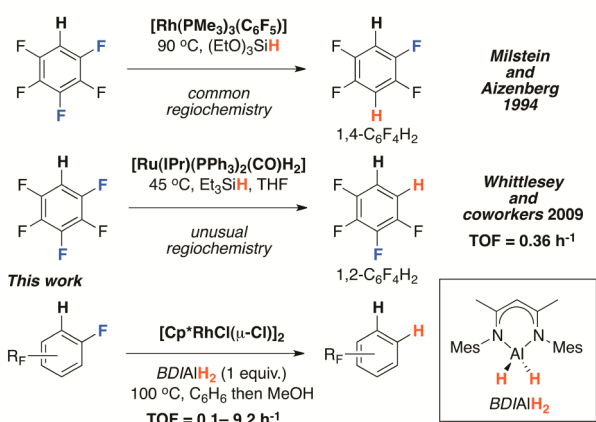
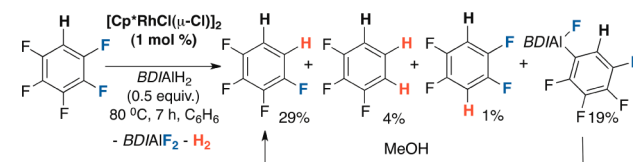


Figure 1. Selectivity in the hydrodefluorination of fluoroarenes.

Scheme 1. HDF of $\text{C}_6\text{F}_5\text{H}$ Catalyzed by 1

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aryl liberates 1,2- $C_6F_4H_2$ upon protonolysis with methanol. 1,2,3- $C_6F_3H_2$ derives from a regioselective HDF of 1,2- $C_6F_4H_2$.

In order to probe the importance of the terminal reductant, we investigated a number of main-group hydrides. Preparations substituting Et_3SiH or $PhSiH_3$ for $BDIAIH_2$ did not yield HDF products. Furthermore, regardless of the order of addition, the reaction of C_6F_5H with Et_3SiH catalyzed by 1 mol % of **1** and 2 mol % of $BDIAIH_2$ failed to give significant quantities of C–F bond cleavage products. This latter experiment suggests that $BDIAIH_2$ is needed for more than just initiation of the rhodium chloride precatalyst. Reactions conducted without catalyst or with $[Cp^*IrCl(\mu-Cl)]_2$ in place of **1** gave only trace conversion of C_6F_5H after 8 h at 80 °C in C_6D_6 .

Reaction Scope. The conditions were optimized to a reaction temperature of 100 °C, a catalyst loading of 2 mol % of **1**, 1 equiv of $BDIAIH_2$, use of C_6H_6 as a solvent to obfuscate a problem of H/D exchange (vide infra), and addition of a methanol quench at the end of the reaction to protonate the C–Al bond containing side products. The catalytic reaction was extended to a number of substrates, and high regioselectivities were observed. In Figure 2, the data are presented such that the first fluorine atom to be replaced by a hydrogen atom is labeled F^1 , the second F^2 , and the third F^3 .

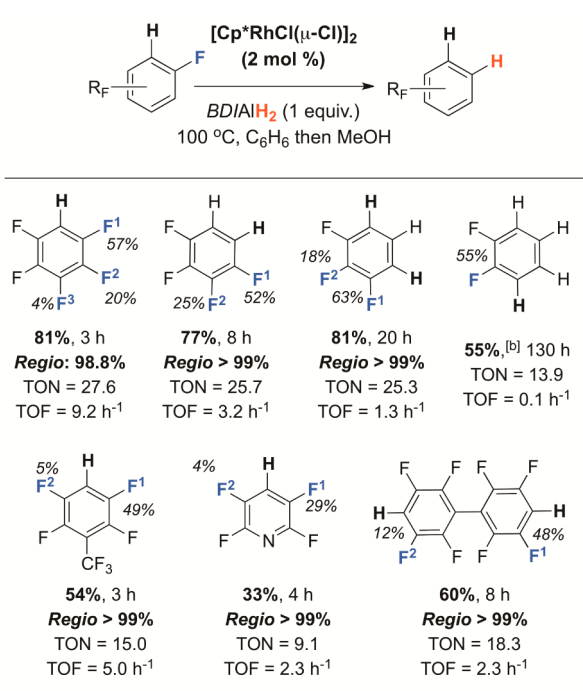


Figure 2. Scope of the HDF of fluoroarenes catalyzed by **1**: (a) 0.16 M in substrate, Regio = regioselectivity = percentage of HDF products derived from cleavage of a C–F bond adjacent to an existing C–H bond, TON = $\sum((\text{mmol of HDF product})(\text{number of new H atoms in each product})) / (\text{mmol of Rh})$, TOF = TON h^{-1} ; (b) control reaction in which C_6F_5H was exposed to the catalytic conditions gave <1% consumption of the starting material.

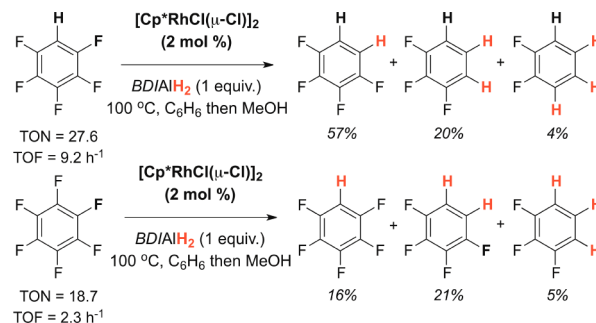
Mixtures of **1** and $BDIAIH_2$ are an extremely active catalyst system for C–F bond cleavage. TOFs range from 0.1 to 9.2 h^{-1} at 100 °C for a series of challenging substrates. The high catalyst activity results in a loss of chemoselectivity as sequential HDF reactions occur in one pot. The catalyst system is capable of working its way around the aromatic ring such that pentafluorobenzene may be sequentially transformed,

$C_6F_5H \rightarrow 1,2-C_6F_4H_2 \rightarrow 1,2,3-C_6F_3H_3 \rightarrow 1,2,3,4-C_6F_2H_4 \rightarrow C_6F_5H$, with each step being regioselective if not chemoselective.

In all cases, reactions are selective for the cleavage of C–F bonds adjacent to existing C–H bonds. For example, under the optimized conditions, the HDF of C_6F_5H gives 57% of 1,2- $C_6F_4H_2$, 20% of 1,2,3- $C_6F_3H_3$ and 4% of 1,2,3,4- $C_6F_2H_4$. Only very small amounts of 1,4- $C_6F_4H_2$ are observed (<1.5%). Control reactions in which 1,4- $C_6F_4H_2$ or 1,3- $C_6F_4H_2$ is exposed to the catalytic conditions formed complex mixtures of regioisomers that rule out these species as unstable intermediates in the HDF of C_6F_5H (see the Supporting Information, Table S1). A partially fluorinated pyridine and toluene also undergo selective HDF. Here the first and second HDF steps both occur adjacent to the existing C–H bond of the substrate (Figure 2).

The HDF of C_6F_6 is less efficient and less chemoselective than that of C_6F_5H . Hence, the reaction of C_6F_6 gives 1,2- $C_6F_4H_2$ as the major product while also yielding C_6F_5H and 1,2,3- $C_6F_3H_3$ (Scheme 2). Both the turnover number and

Scheme 2. Comparison of the HDF of C_6F_6 and C_6F_5H Catalyzed by **1**



turnover frequency for this substrate are lower than those for C_6F_5H . In combination, these data suggest that the rate of HDF of C_6F_5H is faster than that of C_6F_6 and imply that the C–H bond may play an important role in the intimate reaction mechanism (vide infra).

Preliminary Mechanistic Study. Sequential oxidative addition of a C–H bond to a Rh(I) complex followed by β -fluoride elimination to generate a benzyne intermediate that could be hydrogenated under the reaction conditions would explain the observed regiochemistry.¹³ Jones, Perutz, and co-workers have shown that thermolysis of $[Cp^*Rh(PMe_3)(H)(Ph)]$ in the presence of partially fluorinated arenes gives metalated species in which the new Rh–Ar bond is formed ortho to an existing C–F bond.¹⁴ Although β -fluoride elimination has not been reported for rhodium fluoroaryl complexes, reaction of $[Cp^*Ir(PMe_3)(H)(C_6F_5)]$ with $tBuLi$ yields an Ir-coordinated benzyne adduct.¹⁵

The reaction of C_6F_5H with $BDIAIH_2$ catalyzed by **1** at 80 °C was monitored as a function of time by ^{19}F NMR spectroscopy (Figure 3). Data are consistent with a brief induction period along with the expected consumption of 1,2- $C_6F_4H_2$ at a later stage of the reaction. A radical-trap experiment with 9,10-dihydroanthracene and a heterogeneous catalyst test with $Hg(0)$ reveal no effect of these additives on the reaction kinetics (Figure 3). These experiments suggest a homogeneous catalytic reaction that does not proceed by single-electron transfer. In addition to the C–F bond activation products, a

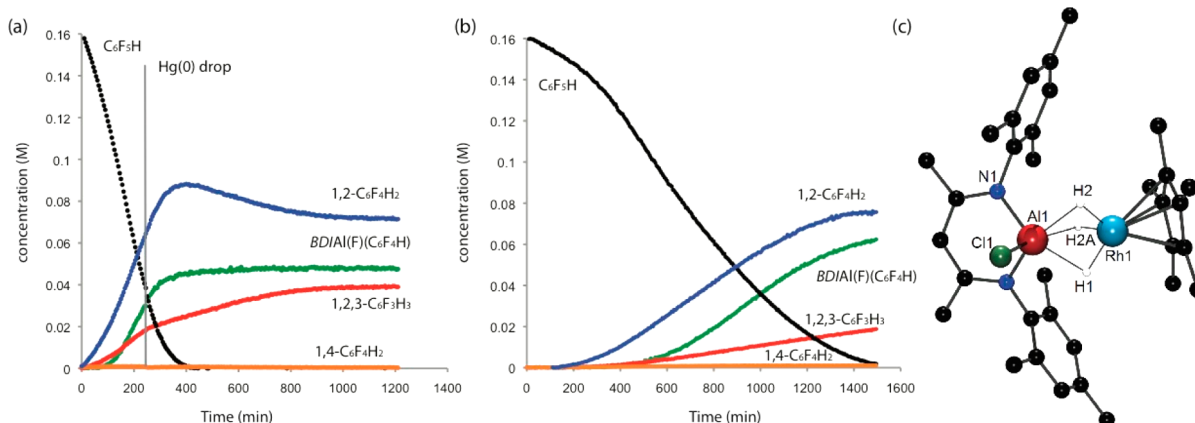
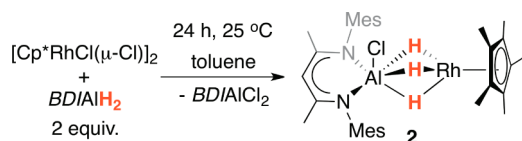


Figure 3. Kinetics of the reaction of C_6F_5H (0.16 M) with $BDIAIH_2$ (0.16 M) in C_6H_6 at $80^\circ C$ catalyzed by (a) **1** (0.003 M) with an $Hg(0)$ drop at 4 h 5 min and (b) **2** (0.006 M). (c) Crystal structure of **2**. Selected bond lengths (\AA) and bond angles (deg): Rh–Al 2.4101(10), Al–N 1.905(2), N–C(1) 1.339(3), N(1)–C(4) 1.451(3); N–Al–Cl 102.22(7), N–Al–Rh 116.78(7), Cl–Al–Rh 119.49(5). Hydrides were located in the Fourier map.

significant amount of H/D exchange was recorded during reactions of C_6F_5H catalyzed by **1** in C_6D_6 or toluene- d_8 . These data are consistent with reversible C–H bond activation being competitive with nonreversible C–F bond activation.¹⁶

Catalyst initiation was probed by monitoring the reaction of $BDIAIH_2$ with **1** in C_6D_6 by 1H NMR spectroscopy. At $25^\circ C$, the slow formation of **2** and $BDIAICl_2$ occurred (Scheme 3).

Scheme 3. Synthesis of the Rh–Al Heterobimetallic Species **2**



Hydride ligand transfer from main-group reagents to **1** is well established.¹⁷ For example, reaction with an excess of $HSiEt_3$ yields the rhodium(V) complex $[Cp^*Rh(H)_2(SiEt_3)_2]$ and $ClSiEt_3$.¹⁸

The 1H NMR spectrum of **2** in C_6D_6 displayed a characteristic hydride resonance at $\delta -13.49$ ppm (d, $^1J_{Rh-H} = 29.2$ Hz). Cooling of a toluene- d_8 solution of **2** to $-80^\circ C$ did not result in decoalescence of the Rh–H–Al signal, and fast exchange of all three hydride positions occurs on the NMR time scale. A selective 1D NOE experiment showed that, upon irradiation of the resonance at $\delta -13.49$ ppm, signal enhancement occurs at the C_5Me_5 position along with the *o*-Me positions of the aromatic flanking groups. This experiment provides support for the integrity of **2** in solution. Infrared spectroscopy revealed the metal hydrides as a series of overlapping absorptions with maxima at 2040, 1957, and 1897 cm^{-1} . The absorptions are shifted to a frequency lower than that of 2099 cm^{-1} found in the terminal hydride $[Cp^*Rh(PMe_3)(H)_2]$.¹⁷ Electrospray mass spectrometry allowed identification of an $[M + H]^+$ peak at m/z 637.2341 (calcd m/z for $C_{33}H_{49}AlClN_2Rh$ 637.2376). Single-crystal X-ray diffraction confirmed the structure and provided unambiguous evidence for the inclusion of a chloride ligand on aluminum (Figure 3). The Rh–Al distance of 2.4101(10) \AA is within the sum of the covalent radii.¹⁹

Although observed under catalytic reaction conditions, isolated and pure samples of **2** do not react with C_6F_5H at

$100^\circ C$ in C_6H_6 to give C–F bond cleavage products. Reaction of **2** with PPh_3 at $80^\circ C$ led to extremely slow formation of small amounts of the ligand-exchange product $[Cp^*Rh(PPh_3)(H)_2]$; in contrast to the case for $[Cp^*Rh(H)_2(SiEt_3)_2]$ and $[Cp^*Rh(H)_2(Bpin)(SiEt_3)]$, the 18-electron complex **2** does not undergo facile ligand dissociation.²⁰ Nevertheless, isolated samples of **2** produce $1,2-C_6F_4H_2$ in a single-turnover experiment and are catalytically competent for the hydrodefluorination of C_6F_5H with $BDIAIH_2$ in C_6H_6 with similar selectivities but a kinetic profile different from that recorded for **1** (Figure 3).

The kinetic experiments suggest that **2** may be off-cycle.²¹ While the current data do not allow a definitive conclusion on the mechanism,²² the stark dependence of the efficiency of the catalytic reaction on an existing C–H bond, the precedent for $[Cp^*Rh(PMe_3)(H)(Ph)]$ to activate sp^2 C–H bonds of fluoroarenes, and the observation of H/D exchange under catalytic conditions suggest that C–H activation may play an important role in directing the catalyst to an adjacent C–F bond.

Conclusions. In summary, we report a rare and highly selective catalyst system capable of the regioselective hydrodefluorination of fluoroarenes. Reactions are directed to cleave a C–F bond adjacent to an existing C–H bond. We are continuing to investigate the mechanism of this reaction and develop new catalysts for C–F bond activation with heavier main-group hydrides.

ASSOCIATED CONTENT

Supporting Information

Text, figures, tables, and a CIF file giving experimental procedures, characterization data, control reactions, and X-ray crystallographic data for **2**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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