Fluorination **Hot Paper**

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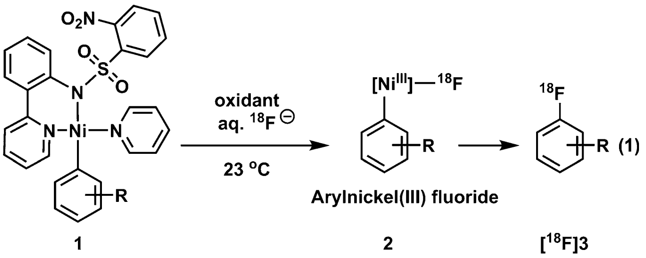
Carbon–Fluorine Reductive Elimination from Nickel(III) Complexes

*Heejun Lee, Jonas Börgel, and Tobias Ritter**

Abstract: *We report a C–F reductive elimination from a characterized first-row aryl metal fluoride complex. Reductive elimination from the presented nickel(III) complexes is faster than C–F bond formation from any other characterized aryl metal fluoride complex.*

Rational catalyst design and mechanistic investigations have enabled recent advances in nickel catalysis.[1] Beginning with Kochi's pioneering work,[2a,b] there have been detailed mechanistic studies for carbon–carbon and carbon–heteroatom (Cl, Br, N, O) bond-forming reactions from high-valent nickel species.[2,3] However, high-valent aryl metal fluoride complexes of the first-row transition metals that undergo reductive elimination to form a C–F bond have never been observed. Previously, we have shown a functional-group-tolerant synthesis of aryl fluorides from arylnickel(II) complexes.[4,5] Herein, we report that the C–F bond formation proceeds through reductive elimination from arylnickel(III) fluorides [Eq. (1)]. Our results substantiate that C–F reductive elimination from nickel(III) proceeds faster than from previously studied high-valent metal fluorides, such as Pd^{IV}–F complexes,[6–8] and provide the first direct evidence of a C–F reductive elimination from a first-row transition-metal fluoride complex.



In several previously reported transition-metal-mediated or -catalyzed C–F bond-forming reactions, reductive elimination from high-valent metal fluoride species has been proposed or established.[6–14] In 2008, we reported the first C–F reductive elimination to form an aryl fluoride from a Pd^{IV} fluoride.[6,7] Sanford and co-workers have reported a catalytic C–H fluorination reaction in which reductive elimination from a Pd^{IV}–F species was proposed to take place,[8a] and the same group subsequently published C(sp^3)–F reductive elimination from an alkyl-substituted Pd^{IV}–F complex.[8b] In comparison, C–F bond formation by reductive elimination from a first-row transition metal is less established, yet a promising strategy for facile fluorination owing to a potentially lower barrier for reductive elimination. The Ribas,[9] Hartwig,[10,11] and Sanford[12] groups have independently established efficient syntheses of aryl fluorides from aryl halides, stannanes, or boronates that are catalyzed or mediated by copper. Regarding the mechanism, Ribas and co-workers observed aryl fluoride formation from arylcopper(III) halide complexes upon addition of fluoride.[9] The Hartwig group has identified a copper(III) fluoride complex that can afford aryl fluorides upon rate-limiting transmetalation from aryl boronates.[10] In both examples, C–F reductive elimination from an arylcopper(III) fluoride has been proposed, but rate-determining ligand exchange and transmetalation to form the aryl metal fluoride complexes, respectively, prevented a detailed study of the subsequent C–F reductive elimination step. In comparison, here we report direct evidence for C–F reductive elimination from an arylnickel(III) fluoride complex.

In 2012, we reported an oxidative fluorination reaction with aqueous [^{18}F]fluoride of arylnickel(II) substrates,[4] and subsequently highlighted the utility of the reaction with the development of a fully automated synthesis of the PET tracer [^{18}F]-5-fluorouracil for cancer imaging in humans.[5] We sought to identify the relevant stereoelectronic requirements for the facile C–F bond formation shown in Equation (1), which proceeds within seconds at 23 °C, and were able to observe C–F reductive elimination from a characterized arylnickel(III) fluoride.

In the current study, we have used electrophilic fluorination reagents such as Selectfluor and *N*-fluoropyridinium salts for the oxidative fluorination of arylnickel(II) complexes, as opposed to a combination of oxidant and aqueous [^{18}F]fluoride in the original radiofluorination work; the use of fluoride and oxidant allowed for the synthesis of ^{18}F-labeled molecules with high specific activity,[4,5] but to study the mechanism of the reaction, they were replaced by an electrophilic fluorination source for convenience. Upon treatment with Selectfluor in acetonitrile, arylnickel(II) complexes **1** give aryl fluorides **3** (Scheme 1). When acetonitrile is added to a solid mixture of arylnickel(II) complex **1a** and Selectfluor at 23 °C, a red solution is observed immediately upon mixing, followed by the disappearance of the color within a few seconds. We hypothesized that the reaction

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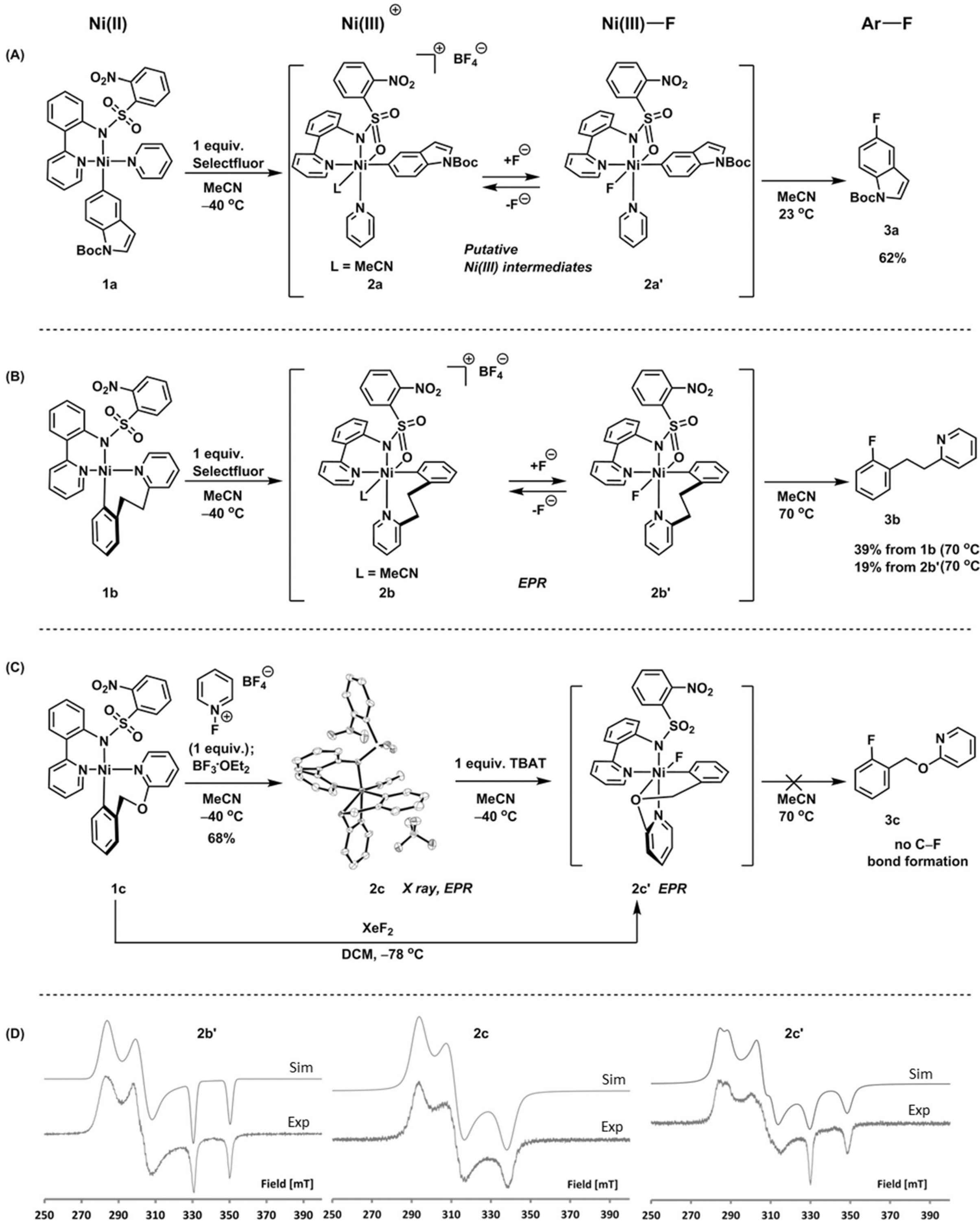


Scheme 1. Oxidative fluorination of related arylnickel(II) complexes. The X-band EPR spectra were measured at 77 K in glassy frozen solutions of MeCN. EPR parameters for **2b′**: $g_x = 2.43$, $g_y = 2.27$, $g_z = 2.03$, $A_z(\mathrm{F}) = 200$ G; **2c**: $g_x = 2.35$, $g_y = 2.21$, $g_z = 2.04$; **2c′**: $g_x = 2.39$, $g_y = 2.22$, $g_z = 2.03$, $A_z(\mathrm{F}) = 200$ G.

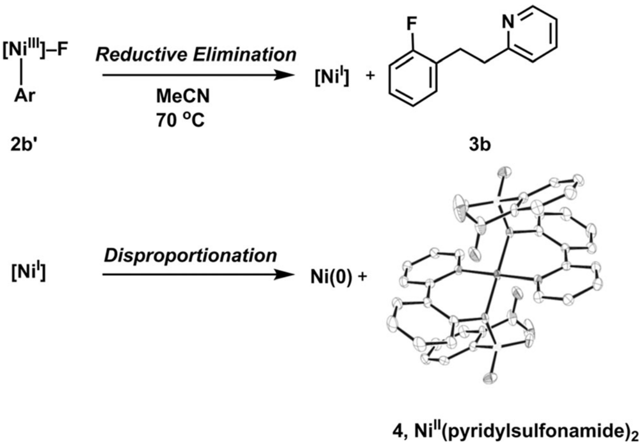
progresses via a reactive high-valent arylnickel fluoride species that undergoes fast reductive elimination to form the C−F bond. When arylnickel(II) complex **1a** is oxidized by Selectfluor at −40 °C, an EPR-active species indicates the formation of a nickel(III) species, which forms 5-fluoro-*N*-Boc-indole in 62 % yield upon warming to 23 °C (Scheme 1 A). Structural characterization of the observed EPR-active species, proposed as **2a** and **2a′** in equilibrium, by X-ray crystallography was not successful owing to their propensity to form the C−F bond.

Rigid ligands have been reported to stabilize high-valent metal complexes, including those of palladium and nickel.[3a,7,15] To better characterize the relevant nickel(III) intermediates, we synthesized the rigid arylnickel(II) complex **1b** (Scheme 1B) in which the arene and pyridine moieties of **1** are linked by an ethylene group, which we expected to increase the barrier towards productive C–F reductive elimination. When **1b** is oxidized with Selectfluor (1 equiv) at −40 °C, two high-valent arylnickel(III) complexes are observed, which we assigned as cationic arylnickel(III) complex **2b** and arylnickel(III) fluoride **2b′** based on EPR studies. Treatment of **1b** with 1 equiv of Selectfluor in acetonitrile at 70 °C results in the formation of the corresponding aryl fluoride **3b** in 39 % yield. The lower yield compared to C–F bond formation from parent compound **1a** is consistent with a more challenging reductive elimination from complex **1b** featuring a more rigid ligand than complex **1a**.[7,15]

To gain stronger evidence for the structural assignments, we designed complex **1c**, which would induce even more structural rigidity upon oxidation of the corresponding nickel(II) because of the incorporation of an oxygen atom capable of coordinating to the high-valent nickel(III) center. We expected the corresponding oxidized complex **2c′** to be unable to undergo reductive elimination owing to the constrained geometry, which should enable the isolation and further characterization of the complex. Indeed, after oxidation of complex **1c** with *N*-fluoropyridinium tetrafluoroborate followed by treatment with BF_3 etherate at −40 °C, the cationic arylnickel(III) complex **2c** was isolated and structurally characterized by single-crystal X-ray crystallography. X-ray characterization of **2c** shows the distorted octahedral geometry of the nickel(III) center, which is in agreement with the expected Jahn–Teller distortion of a d^7 complex. The bond lengths are consistent with reported nickel(III) complexes. The EPR spectrum of **2c** shows a rhombic signal with $g_{av} =$ 2.20 close to those of other known arylnickel(III) complexes of octahedral geometry.[2i,17] Most importantly, Ni^{III} complex **2c** displays an EPR spectrum that is very similar to that of **2b** ($g_{av} = 2.20$), which further supports our assignments of complexes **2a** and **2b**.

To support the proposed structure of arylnickel(III) fluoride **2b′**, fluoride addition to the cationic arylnickel(III) complex **2c** was studied. When 1 equiv of fluoride source is added to **2c** at −40 °C, the high-valent nickel(III) fluoride species **2c′** is observed by EPR spectroscopy, which displays a rhombic signal ($g_{av} = 2.21$) that shows superhyperfine coupling to the fluorine substituent ($I = \frac{1}{2}$) in the g_z component (Scheme 1D). Furthermore, we oxidized **1c** with 0.5 equiv of XeF_2 in DCM at −78 °C (Scheme 1C), and obtained an identical EPR spectrum to that of the fluoride adduct of **2c′**, which is very similar to the EPR spectrum of **2b′**. Therefore, by comparison, we assigned the structures of cationic nickel(III) complex **2b** and nickel(III) fluoride **2b′** as shown in Scheme 1B, although other structures, including those with two acetonitrile ligands coordinated to the nickel center, cannot be excluded as possible structures of **2b**.[18]

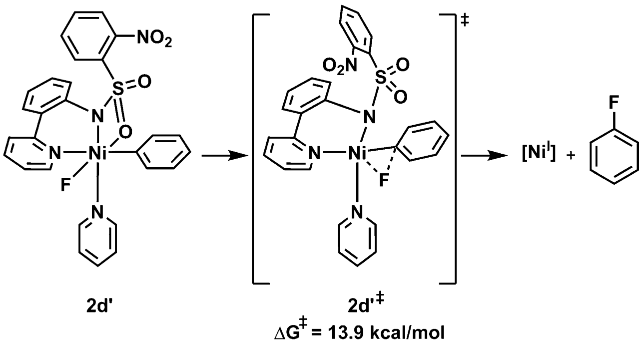
Upon heating an acetonitrile solution of **2b′** to obtain aryl fluoride **3b** (19 %), nickel(II) complex **4** and black nickel(0) are also formed (Scheme 2). We hypothesize that arylnickel(III) fluoride **2b′** undergoes fast C–F reductive elimination to form an unstable nickel(I) species, which then disproportionates to nickel(II) complex **4** and nickel(0) species.[2d,i,k]



Scheme 2. Formation of Ni^{II} and Ni^0 by reductive elimination and disproportionation.

When arylnickel(III) fluoride **2b′**, formed in situ and monitored by EPR spectroscopy, is treated with extra equivalents of external oxidants capable of generating a Ni^{IV} species (e.g., XeF_2), no aryl fluoride formation is observed, which suggests that Ni^{III} is the preferred oxidation state for product formation from nickel sulfonamide complexes. The 1 e^- oxidation ability of Selectfluor has been reported in the literature.[16] We speculate that after 1 e^- oxidation of the arylnickel(II) complexes by Selectfluor to form arylnickel(III) complexes **2**, the Selectfluor radical cation is further reduced by solvent molecules by H atom abstraction.[16b]

The facile C–F bond formation from arylnickel(III) complexes such as **1a** was investigated by DFT calculations on a truncated model system of the phenylnickel(III) fluoride complex **2d′** (Scheme 3). The transition state shows a distorted trigonal-bipyramidal geometry where the sulfonamide oxygen atom is dissociated from the nickel(III) center. The calculated free energy for the reductive elimination from **2d′** is $-29.5\ \text{kcal mol}^{-1}$, and the calculated $\Delta G^{\ddagger}$ for the reductive elimination from **2d′** is $13.9\ \text{kcal mol}^{-1}$, which is about $9\ \text{kcal mol}^{-1}$ less than the barrier calculated for reductive



Scheme 3. Proposed mechanism for C–F reductive elimination from **2**.

elimination of a related benzo[*h*]quinolyl sulfonamide Pd^{IV}–F complex.[7]

In conclusion, we have reported a C–F reductive elimination from a high-valent arylnickel(III) fluoride complex. Crucial features for facile reductive elimination are the nickel(III) oxidation state and a ligand system that can stabilize high-valent nickel as well as undergo a geometry change to induce reductive elimination with productive orbital overlap of the aryl and the fluoride ligands in the transition state. The new insight with respect to the structural and electronic properties is anticipated to aid in the design of improved complexes and catalysts for fast C–F bond formations.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: aryl fluorides · fluorination · nickel · reductive elimination

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[18] DFT results for the ground-state structure of untethered complexes **2** show that the structure with sulfonamide oxygen coordination to the nickel center is more stable than the structure with acetonitrile coordinated to the nickel center.

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Communications

Fluorination

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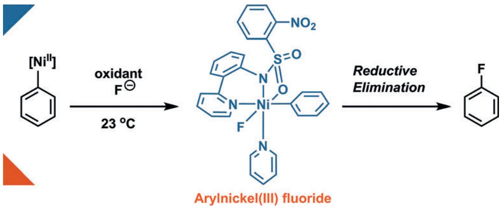
Carbon–Fluorine Reductive Elimination from Nickel(III) Complexes



Fast and facile: Facile C–F reductive elimination from an arylnickel(III) fluoride complex is reported. The C–F bond reductive elimination from nickel(III) complexes presented herein is faster than the C–F bond formation from any other characterized aryl metal fluoride complex.