

Catalytic Carbon-Fluorine Bond Activation with Monocoordinated Nickel-Carbene Complexes: Reduction of Fluoroarenes

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Abstract: Monocoordinate nickel/*N*-heterocyclic carbene complexes reveal unexpected reactivity towards aryl fluorides. Defluorination reactions were efficiently performed with a β -hydrogen-containing alkoxide (3 equiv.) in the presence of 3 mol % of [1:1] Ni(0)/IMes·HCl catalyst (IMes = 1,3-dimesitylimidazol-2-ylidene).

Keywords: catalysis; fluoroarenes; nickel(0)/*N*-heterocyclic carbene complex; reduction

The activation of C–F bonds of fluoroaromatic compounds by reaction at transition metal centres is an exciting challenge in organometallic chemistry and catalyst development due to the remarkable thermal and chemical stability of organofluorine compounds. Although the stoichiometric activation and functionalisation of C–F bonds by transition metal complexes has been shown to proceed under mild conditions,^[1] catalytic transformations of C–F bonds are still poorly developed.

Murai studied Si–F exchange reactions between fluorobenzenes and Me₃SiSiMe₃ catalysed by [Rh(cod)₂]BF₄.^[2] Kumada^[3] and Herrmann^[4] have demonstrated the catalytic cross-coupling of aryl fluorides with Grignard reagents mediated respectively by Ni(dmpe)Cl₂ [dmpe = 1,2-bis(dimethylphosphanyl)ethane] and Ni(cod)₂ associated to an *N*-heterocyclic carbene (NHC), 1,3-di(2,6-di-isopropylphenyl)imidazolin-2-ylidene. The nickel-catalysed activation of the C–F bond of 2-fluoropyridines and pyrimidines has also been reported.^[5–8]

Dehalogenation of fluorocarbons is also an important process since the chemical inertness of the C–F bond translates into environmental persistence and such compounds are quite difficult to degrade. Fluorine-hydrogen exchange is also of interest in multistep syntheses in which the fluorine atom is used as a directing group.^[9] Despite recent advances in activation

of C–F bonds by reaction at transition metal centres, only few defluorination methods are currently available. Heterogeneous rhodium-catalysed hydrogenolyses require high temperatures and/or pressure.^[10] An improved process was recently described using rhodium complexes tethered on a silica-supported palladium heterogeneous catalyst.^[11] Homogeneous rhodium^[12] or zirconium^[13] catalysts are also efficient as is also the decamethylferrocene-photoinduced defluorination of perfluoroalkanes.^[14] Catalytic reductions of fluorocarbons can finally be achieved using YbCp₂(dme)^[15] and Group 4 metallocenes such as Cp₂TiF₂ or CpZrCl₂ associated to terminal reductants such as magnesium or aluminium metals.^[16] However, these methods often yielded partial defluorination and new protocols are still of interest.

From our part, we have embarked upon a program of work which has been directed toward the preparation of a range of Ni(0)/*N*-heterocyclic carbene (NHC) complexes and examination of their reactivity. We have recently demonstrated that Ni(0) clusters, *in situ* generated by reduction of Ni(acac)₂ with alkoxide-activated sodium hydride, associated to strong electron-donating ligands such as NHCs^[17] can be used to mediate aminations of aryl chlorides.^[18] We have also prepared complex **1** *via* a solution-phase method and we demonstrated that **1**, combined with *i*-PrONa was an efficient catalyst for the dehalogenation of functionalised aryl chlorides, bromides, iodides and polyhalogenated hydrocarbons.^[19] With aryl fluorides, the procedure was, however, less efficient and only partial defluorination, not exceeding 40%, was observed.

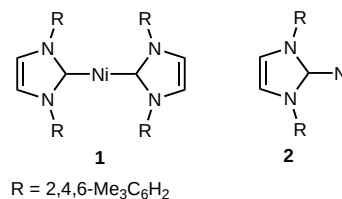


Figure 1. Di- and monocoordinated nickel complexes **1** and **2**.

Recent reports of Hartwig,^[20] Nolan^[21] and Caddick^[22] on cross-coupling reactions of amines with aryl halides catalysed by Pd/NHC complexes suggested that initially formed dicoordinated Pd/NHC species dissociate to form mono(carbene) palladium complexes which undergo oxidative addition of the aryl halide. Since activation of C–F bonds requires highly reactive and electron-rich metal centres, we wondered if complex **2**, *in situ* generated using Ni(0) and the imidazolium salt **3** in a 1:1 ratio, could yield a catalyst with enhanced performances in defluorination reactions. In this communication, we wish to report the first example of a reduction of the C–F bond in monofluoroarenes using a catalytic 1:1 combination of Ni(0)/NHC associated to a β -hydrogen-containing alkoxide.

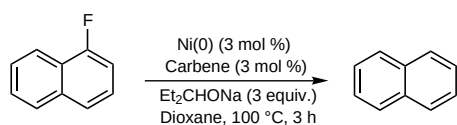
The reduction of 1-fluoronaphthalene performed with complex **2**, *i*-PrONa in refluxing THF was undertaken first. Compared to the modest yield (36%) observed with the two-coordinate nickel catalyst **1**, we were pleased to find out that mono-(carbene)-complex **2** afforded an improved (57%) defluorination yield.

A study aimed at determining the optimum Ni(0)/NHC system and the reaction conditions for the catalytic dehalogenation of aryl fluorides was then undertaken.

Using complex **2** as defluorination catalyst, either dioxane or THF appears to be a suitable solvent whereas toluene led to partial catalyst decomposition. Reaction rates are however lower in dioxane compared to THF. Curiously, the sodium alkoxide Et₂CHONa gave significantly greater rates of reduction than *i*-PrONa. Other alkoxides (e.g., MeONa) were ineffective.

A survey of the catalytic efficiency of various imidazolium salts was finally undertaken. Results are summarised in Table 1.

Table 1. Assessment of carbene precursors in the Ni(0)-catalysed defluorination of 1-fluoronaphthalene.^[a]



Entry	Imidazolium salt	Yield [%] ^[b]
1	–	0
2	IMes · HCl, 3	92
3	IPr · HCl, 4	87
4	5	51
5	SIMes · HCl, 6	68
6	SIPr · HCl, 7	53
7	8 ^[c]	7
8	9 ^[c]	8

^[a] Reaction conditions: 1-fluoronaphthalene (10 mmol), Et₂CHONa (30 mmol), Ni(0) (0.3 mmol), imidazolium salt (0.3 mmol), dioxane, 100 °C.

^[b] Determined by ¹H NMR on the crude reaction product.

^[c] 1.5 mol % imidazolium salt.

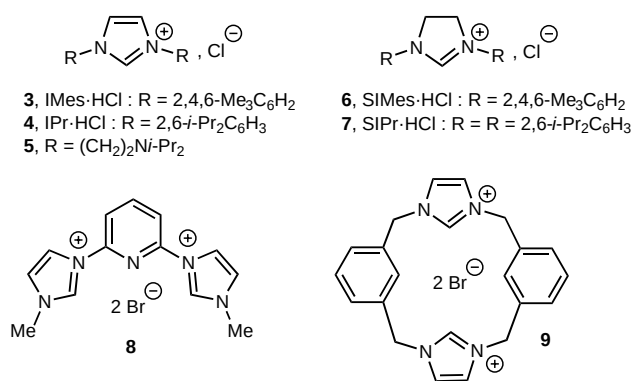


Figure 2. Carbene precursors.

As expected, dehalogenation run without ligand resulted in no detectable reaction product (entry 1). The imidazolium IMes · HCl **3** was found to be the most effective NHC precursor leading to naphthalene in 92% yield (entry 2). The NHC generated from the sterically demanding IPr · HCl **4** can also be used (entry 3). All other imidazolium salts that were investigated led to the formation of moderately active catalysts (entries 4–8).

Table 2 shows the results of the defluorination of various aromatic fluorides using the optimal conditions previously determined. Fluoronaphthalenes were reduced to naphthalene within 3 h (entries 1 and 2). Using 3- or 4-fluorotoluene (entries 3 and 4), the reaction was much slower and afforded the reduction product in a modest 30% yield. In the series of fluoroanisoles (entries 5–7), a considerable dependency of the dehalogenation yield on the position of the methoxy group was observed. 2-Fluoroanisole was quantitatively converted into anisole after 2.5 h. GC analysis of the reaction mixture revealed that the rate of formation of anisole was slower with 3- and, especially, 4-fluoroanisole. Only 53% and 28% yields, respectively, of the reduction product were observed after 2.5 h. This effect has already been observed in carbon-nitrogen couplings mediated by Ni(0)/NHC complexes^[18b] and might result from a coordination of the nickel centre at oxygen atom of 2-fluoroanisole. It is noteworthy that the reduction of 3-fluoro-*N*-methylaniline required an additional equimolar amount of alkoxide due to the partial deprotonation of the amine (entry 8). Dehalogenation was finally not observed with 2-fluoropyridine (entry 9). Only 1-ethylpropyl (2-pyridyl) ether was produced in 97% yield by a classic S_NAr reaction.

At the end of the dehalogenation, pentan-3-one was clearly identified in the reaction products by GC. Moreover, clean formation of 1-deuteronaphthalene was observed when the dehalogenation was conducted with the deuterium-labelled sodium alkoxide Et₂CDONa.

Mercury tests also confirmed that defluorination reactions performed with the Ni(0)/IMes complex are homogeneously catalysed.^[23] Two types of experiments

Table 2. Results of the Ni(0)/IMes · HCl defluorination reactions.^[a]

Entry	Aromatic fluoride	Time [h] ^[b]	Yield [%] ^[c]	Recovered aromatic fluoride [%] ^[b]
1	1-Fluoronaphthalene	3	92	5
2	2-Fluoronaphthalene	3	100	0
3	3-Fluorotoluene	15	30	70
4	4-Fluorotoluene	15	30	70
5	2-Fluoroanisole	2.5	100	0
6	3-Fluoroanisole	3.5	75	19
7	4-Fluoroanisole	12	46	54
8	3-Fluoro- <i>N</i> -methylaniline	23	89 ^[d]	9
9	2-Fluoropyridine	3.5	0 ^[e]	0
10	3-Fluoropyridine	2	100	0

^[a] The typical reactions conditions: aromatic fluoride (10 mmol), Et₂CHONa (30 mmol), Ni(0) (0.3 mmol), IMes · HCl (0.3 mmol), dioxane, 100 °C.

^[b] Determined by GC.

^[c] Yield was determined by GC.

^[d] Et₂CHONa (40 mmol).

^[e] 1-Ethylpropyl (2-pyridyl) ether was produced in quantitative yield by an S_NAr reaction.

were performed to evaluate the effect of Hg on the catalyst. First, the reduction of 3-fluoroanisole was stopped after 1.5 h (45% conversion) and mercury (321 equiv.) was added. No further catalytic activity was observed after 2 hours heating at 100 °C (46% conversion). Second, when Hg was added to a freshly prepared Ni(0)/IMes complex just before 3-fluoroanisole, a complete poisoning of the catalyst is observed (< 4% conversion).

Taking into account these observations, a general catalytic cycle for the defluorination of aryl fluorides in the presence of the Ni(0) complex **2** is presented in Scheme 1. The first step involves the formation of Ni(0) by reduction of Ni(acac)₂ with Et₂CHONa activated sodium hydride followed by coordination of the carbene

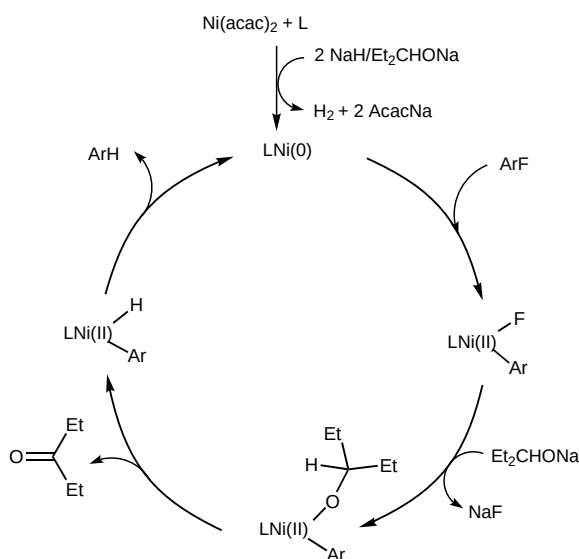
ligand (L = IMes) to the metal centre. Oxidative addition of the aryl fluoride to the Ni(0) complex is followed by Et₂CHONa attack at nickel and displacement of the fluorine atom. Finally, reductive elimination of the arene from an intermediate nickel-hydride complex obtained by β-elimination regenerates the Ni(0)-carbene catalyst.

In conclusion, we have shown that the monocoordinate nickel-carbene complex **2** efficiently promotes the activation of aromatic C–F bonds and demonstrated that this catalyst, associated to Et₂CHONa, can be used in defluorination reactions. These findings may be useful for the design of new nickel-carbene catalysts for organic synthesis.

Experimental Section

General

All manipulations were carried out using standard Schlenk techniques under an atmosphere of nitrogen. Gas chromatographic analyses were performed on a Shimadzu GC-17 capillary gas chromatograph fitted with an “Optima 5” column (22 m × 0.25 mm, ID × 0.25 μm). All quantifications of reaction constituents were achieved by gas chromatography using a known quantity of dodecane as reference standard. The ¹H and ¹³C NMR spectra were recorded on a Bruker AM 400 spectrometer, respectively at 400.13 and 100.40 MHz using CDCl₃ as solvent. Aryl fluorides, arenes and nickel(II) acetylacetonate were purchased from Acros and used as received. Sodium hydride (65% in mineral oil) was purchased from Fluka and used after two washings with THF under nitrogen. Dioxane was distilled over sodium/benzophenone and stored over sodium wires. Pentan-3-ol was purchased from Acros and distilled over sodium before use. All imidazolium salts were synthesised according to the literature procedures.^[24]



Scheme 1. Proposed mechanism for the defluorination reaction.

Typical Procedure for the Catalytic Reduction of Aryl Fluorides

A Schlenk tube was loaded with degreased NaH (30.6 mmol), Ni(acac)₂ (0.3 mmol), IMes·HCl (0.3 mmol) and 8 mL of dioxane and the mixture was heated to 100 °C. A solution of Et₂CHOH (30 mmol) in 2 mL dioxane was then added dropwise and the mixture was further heated for 1 h. A solution of aryl fluoride (10 mmol) in dioxane (3 mL) was then added. The progress of reactions was monitored by GC. All quantifications of reaction constituents were achieved by GC.

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