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Nickel-Catalyzed Reductive Coupling for Transforming Unactivated Aryl Electrophiles into β-Fluoroethylarenes

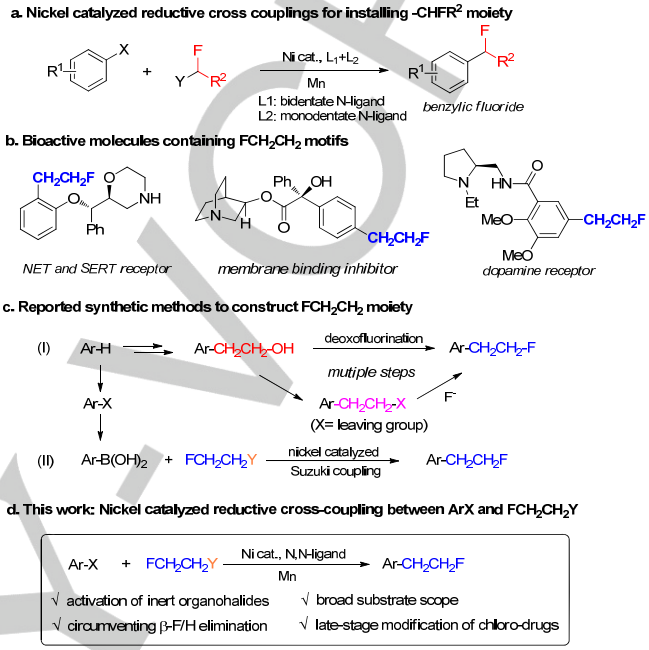
Yi Yang,*[a] Gen Luo,[a] Youlin Li,[a] Xia Tong,[a] Mengmeng He,[a] Hongyao Zeng,[b] Yan Jiang,[a] Yingle Liu,*[a] and Yubin Zheng[a]

Abstract: We report herein a facile synthetic method for converting unactivated (hetero)aryl electrophiles into β-fluoroethylated (hetero)arenes via nickel-catalyzed reductive cross-couplings. This coupling reaction features the involvement of FCH_2CH_2 radical intermediate rather than β-fluoroethyl manganese species which provides effective solutions to the problematic β-fluoride side eliminations. The practical value of this protocol is further demonstrated by the late-stage modification of several complex ArCl or ArOH-derived bioactive molecules.

Introduction

The selective introduction of fluorine atoms or fluorine-containing groups into organic molecules has represented as popular tactics for drug discovery and received substantial attentions within the pharmaceutical and agrochemical communities.[1] Numerous practices of drug modification demonstrated that the precisely-controlled introduction of fluorine atoms could be highly beneficial for improving the pharmacological properties of candidate compounds such as lipophilicity, metabolic stability and binding affinity.[2] It is therefore of great interest to develop novel methods to achieve efficient and site-specific fluorine incorporations. Versus the difficulties of controlling chemo- and regio-selectivity in the methods of direct fluorination on the unbiased and inactive C-H bonds of aliphatic chains,[3] transition metal catalyzed fluoroalkylations become an alternative but effective approach to install the fluorine(s) pre-decorated alkyl moieties.[4] These methods are highlighted by the mildness of reaction conditions and the synthetic convergences from widely available fluorine-containing building blocks such as fluoroolefin[5] and fluoroalkyl halides.[6] Although important progress has been achieved on the theme of polyfluoroalkylations,[7] the direct introduction of partially fluorinated alkyl motifs especially monofluoroalkyl into organic products remains underdeveloped[8] owing to the situation of limited availability of fluoroalkyl metallic reagents[9-10] for coupling with other electrophiles.

On the other hand, the transition-metal-catalyzed reductive cross-coupling reactions between two electrophiles have emerged as powerful tools for the construction of carbon-carbon bonds over the recent few years.[11-12] Unlike the conventional couplings which relied on the union of nucleophilic carbon ($C^{\delta-}$ or "R-[M]") and electrophilic carbon ($C^{\delta+}$ or "R-[X]"), the reductive cross-coupling reactions provide the linkages of two electrophilic carbon based on the turnover of transiton metal catalysts in the presence of sacrificial reductant. Given the mentioned paucity of fluoroalkylmetallics and the ubiquity of fluoroalkyl halides, we envisage that the reductive coupling strategy could provide an elegant approach for the monofluoroalkylation reaction development with omitting the preparation step of problematic fluoroalkylmetallics.[13]



Scheme 1. Strategy toward nickel-catalyzed reductive coupling between 1,2-fluorohaloethane and aryl halide.

Recently, Wang group disclosed a nickel-catalyzed reductive monofluoroalkylation reaction for access to benzylic fluorides (ArCHFR, R = H or alkyl) from Ar-X (X= Br or I) and YCHFR (Y = Br or I) electrophiles (Scheme 1a).[14] Their reaction was highlighted by utilizing *gem*-dihaloalkane as starting material and bypassing the generation of elusive Y-M-CHFR metallic nucleophiles. Inspired by these seminal results, it is anticipated that the isomeric 1,2-fluorohaloethanes (FCH_2CH_2Y, a vicinal dihalide) could be coupled with the widely available aryl electrophiles to furnish the value-added $ArCH_2CH_2F$ structural motifs[15] through this flourishing nickel-catalyzed reductive coupling stragegy (Scheme 1b-d). Although the construction of homobenzylic fluoride ($ArCH_2CH_2F$) has been concisely achieved by nickel catalyzed Suzuki-type coupling between $ArB(OH)_2$ and FCH_2CH_2I in our group (Scheme 1c-II),[16] this method still pertains to the following restrictions: limited patterns of arylborons especially those bearing complex bioactive structural units which requires lengthy preliminary synthetic steps, unfavored group tolerance and competitive

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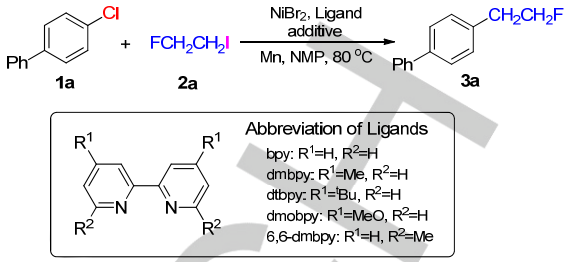
protodeboronation caused by basic activators.[17] Undoubtedly, the nickel-catalyzed reductive coupling between ArX and FCH_2CH_2Y electrophiles could address these limitations and constitute a superior and complementary method with high step-efficiency. To be specific, the current reductive coupling reaction system needs to meet these following requirements: (i) The NiL_n catalytic system should be adequately active to ensure the carbon-halogen bond clevage of unactivated aryl electrophiles and 1,2-fluorohaloethanes, then fulfill the subsequent reductive elimination of aryl and fluoroethyl groups; (ii) The competitive hydrodehalogenation[18] and β-fluoride elimination[19] of 1,2-fluorohaloethanes should be suppressed by proper choice of metallic catalytic species and reductant; (iii) The further conversion of aliphatic homobenzylic C-F bond[20] of $ArCH_2CH_2F$ product should be precluded in the reaction system. Based on the above considerations, we explore the feasibility of reductive fluoroethylation reaction development in the step-efficient manner and report its use for the structural modifications of Ar-Cl or Ar-OH derived scaffolds in the present paper.

Results and Discussion

We commenced the study with examining the effectiveness of the designed transformation by utilizing 4-chlorobiphenyl and FCH_2CH_2I as coupling partners in the presence of a catalytic loading of $NiBr_2$/4,4'-dimethyl-2,2'-bipyridine (dmbpy, a privileged ligand in Wang's monofluoroalkylation[13]) and stoichiometric reductant Mn (Table 1). Through a systematic examination of reaction parameters (See SI), we found that the addition of additive was crucial for the effective conversion of 4-chlorobiphenyl in this nickel-catalyzed reductive coupling chemistry. Similar to some reported examples of Gong[12j,21] and Zhang's[13b] reductive couplings, $MgCl_2$ was proved to be the most effective which improved the yield from 14% to 61%. Other additives like TMSCl[12f-12g], NaI, KI, $ZnCl_2$ and LiCl showed inferior or deleterious effects in promoting this coupling (Table 1, entries 2-7). Attempts to improve the reaction outcome via employing combinatorial ligand system[14] were unsuccessful by screening within a series of pyridinyl monodentate ligands which are decorated by either electron-donating or electron-withdrawing groups (Table 1, entries 8-13). Further interrogation on the structural motifs of bidentate nitrogen ligands indicated that the electron-rich 4,4'-dimethoxy-2,2'-bipyridine (dmobpy) with steric-unhindered coordination site was optimal and improved the coupling yield to 77% (Table 1, entries 14-18). Finally, control experiment indicated that both the nickel salts and supporting ligands were indispensable for the success of this coupling (Table 1, entry 19).

With the optimized reaction conditions established, the scope of the aryl eletrophiles was subsequently investigated (Scheme 2). A variety of *para*- and *meta*-substituted aryl halides (Ar-X) were found to couple smoothly with FCH_2CH_2Y to give the desired β-fluoroethylated arenes. For example, the electron-rich or -neutral aryl halides (**1a**-**1d**) could provide the corresponding fluoroethylation products (**3a**-**3d**) in moderate to good yield. Likewise, the electron-withdrawing functional groups including (aldehyde **1e**, ketone **1f-1g**, **1l**-**1m**, ester **1h**, sulfone **1i**, and

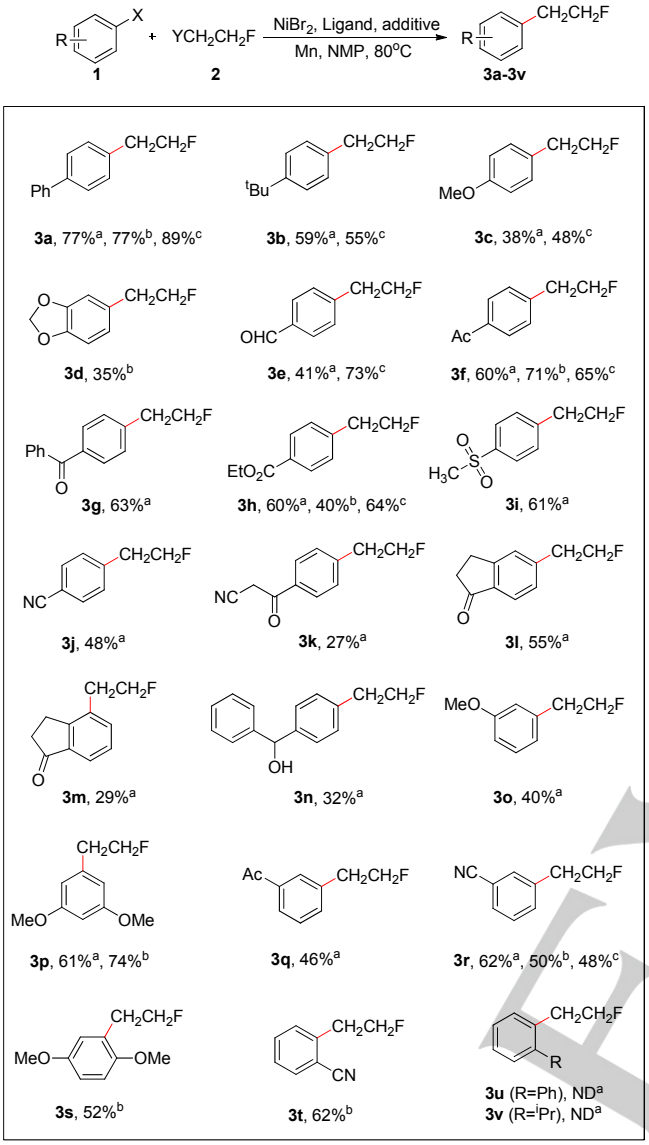
Table 1. Optimization of the reductive coupling reaction conditions[a]



Entry	Ligand/(x mol%)	Additive/(y eq.)	Yield/%[b]
1	dmbpy (x = 10)	None	14
2	dmbpy (x = 10)	TMSCl (y = 1.5)	8
3	dmbpy (x = 10)	NaI (y = 1.5)	29
4	dmbpy (x = 10)	KI (y = 1.5)	22
5	dmbpy (x = 10)	$ZnCl_2$ (y = 1.5)	8
6	dmbpy (x = 10)	LiCl (y = 1.5)	56
7	dmbpy (x = 10)	$MgCl_2$ (y = 1.5)	61
8	dmbpy (x = 10)/Py (x'= 10)	$MgCl_2$ (y = 1.5)	45
9	dmbpy (x = 10)/4-CN-Py (x' = 10)	$MgCl_2$ (y = 1.5)	45
10	dmbpy (x = 10)/4-CF_3-Py (x' = 10)	$MgCl_2$ (y = 1.5)	38
11	dmbpy (x = 10)/2-CN-Py (x' = 10)	$MgCl_2$ (y = 1.5)	56
12	dmbpy (x = 10)/DMAP (x' = 10)	$MgCl_2$ (y = 1.5)	51
13	dmbpy (x = 10)/4-MeO-Py (x' = 10)	$MgCl_2$ (y = 1.5)	30
14	bpy (x = 10)	$MgCl_2$ (y = 1.5)	67
15	phen (x = 10)	$MgCl_2$ (y = 1.5)	65
16	dtbpy (x = 10)	$MgCl_2$ (y = 1.5)	68
17	dmobpy (x = 10)	$MgCl_2$ (y = 1.5)	77/73[c]
18	6,6-dmbpy (x = 10)	$MgCl_2$ (y = 1.5)	29
19[d]	-	$MgCl_2$ (y = 1.5)	0

[a] General Reaction conditions: 4-chlorobiphenyl (0.2 mmol, 1.0 equiv), FCH_2CH_2I (0.3 mmol, 1.5 equiv), $NiBr_2$ (0.02 mmol, 10 mol%), ligand (10-20 mol%), Mn (0.8 mmol, 4.0 equiv). [b] Isolated yield. [c] Gram-scale synthesis (6.0 mmol scale). [d] Reaction without $NiBr_2$ or supporting ligand.

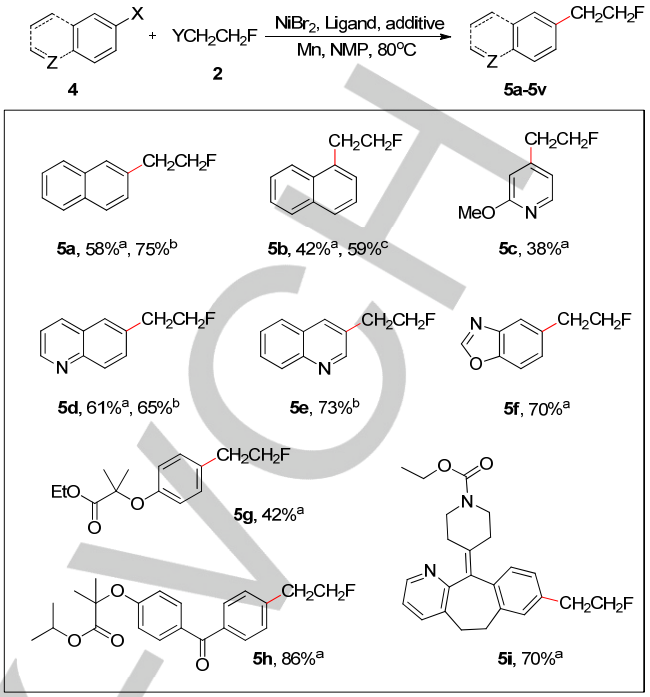
nitrile **1j**-**1k**) on the *para*-position on the phenyl ring were also all compatible well and they were not reduced under the current reductive coupling conditions. Interestingly, the active and acidic hydrogen in alcohol **1n** did not disrupt the reaction efficiency, furnishing the product **3n** in moderate yield. Furthermore, the *meta*-substituted substrates (**1o**-**1r**) were proved to be viable under the current reaction systems regardless of the substituents' electron-rich or electron-poor properties. However, this reductive fluoroethylation displayed high steric sensitivity and failed to realize the coupling when utilizing the *ortho*-substituted substrates (**1u**-**1v**), and only the linear and uncongested *ortho*-cyano substrate **1t** delivered the corresponding product **3t** in 62% yield. Collectively, the coupling condition **A** was generally amenable to the aryl chlorides.[13b] While using the more active aryl bromides and aryl iodides as electrophiles, we found that the addition of $MgCl_2$ as promoter was not necessary and only required few adjustments of reaction conditions (condition **B** and **C**) which featured the



Scheme 2. Scope of aryl halides. [a] General reaction conditions: Ar-Cl (0.2 mmol, 1.0 equiv), FCH_2CH_2I **2a** (0.3 mmol, 1.5 equiv), $NiBr_2$ (0.02 mmol, 10 mol %), dmobpy (0.02 mmol, 10 mol%), Mn (0.8 mmol, 4 equiv), $MgCl_2$ (0.3 mmol, 1.5 equiv), NMP (1.0 mL), 80 °C, N_2, isolated yield. Abbreviated as condition **A**. [b] Ar-Br (0.2 mmol, 1.0 equiv), FCH_2CH_2Br **2b** (0.3 mmol, 1.5 equiv), $NiBr_2$ (0.02 mmol, 10 mol%), dmbpy (0.02 mmol, 10 mol%), Mn (0.8 mmol, 4 equiv), tetrabutylammonium iodide (0.04 mmol, 0.2 equiv), NMP (1.0 mL), 80 °C, N_2. Abbreviated as condition **B**. [c] Ar-I (0.2 mmol, 1.0 equiv), FCH_2CH_2I (0.3 mmol, 1.5 equiv), $NiBr_2$ (0.02 mmol, 10 mol %), dmbpy (0.02 mmol, 10 mol%), Mn (0.8 mmol, 4 equiv), NMP (1.0 mL), 80 °C, N_2. Abbreviated as condition **C**.

utilization of less electron-rich dmbpy as supporting ligands.

The facile access to the fluorinated fused-ring and heterocyclic aromatic compounds was highly relevant with material science and medicinal chemistry. Gratifyingly, the naphthalene (**4a**-**4b**), pyridine (**4c**), quinoline (**4d**-**4e**) and benzooxazole (**4f**) rings-containing substrates were smoothly installed with the β-fluoroethyl motifs under the opitimized conditions. Notably, this protocol can also extended to the late-

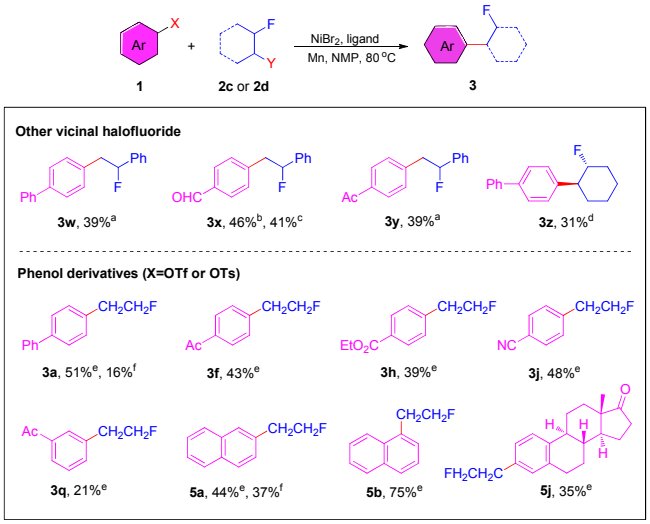


Scheme 3. Substrate scope expansion to the fused-ring aromatic and heteroaromatic electrophiles.[a] Condition **A** for Ar-Cl; isolated yield. [b] Condition **B** for Ar-Br. [c] Condition **C** for Ar-I.

stage modification of several Ar-Cl derived medicinal molecules (clofibrate **4g**, fenofibrate **4h**, and Loratadine **4i**), leading to β-fluoroethylated products in satisfactory yields (**5g**-**5i**) (Scheme 3). Thus, these successes demonstrated the potential application of this methodology in drug discovery and development.

Further extension of this protocol to other vicinal halofluorinated scaffolds (**2c**-**2d**) was also productive which delivered the more complicated homobenzylic fluorides correspondingly (Scheme 4). Interestingly, the phenol derivatives such as aryl triflate and tosylate (*pseudo*-halides)[22] could serve as the suitable coupling partners via C-O bond scission under the coupling conditions. Similar to the previous reports,[22] the aryl triflate displayed better reactivity order than the counterpart tosylate (**3a** and **5a**). Importantly, a series of *para*-electron-neutral or electron-withdrawing groups were well tolerated (**3a**, **3f**, **3h** and **3j**) in these examples whereas the electron-donating groups such as methoxyl and tert-butyl greatly retarded the coupling reactions. This phenomenon might be ascribed to the difficulties in the C-O cleavage (oxidative addition) with the increasing of electron density[23]. Finally, the fluoroethylated cross-coupling product of estrone **5j** was successfully synthesized which further exhibit the utility and practicality of this method in the functionalization of phenol-derived bioactive molecules.

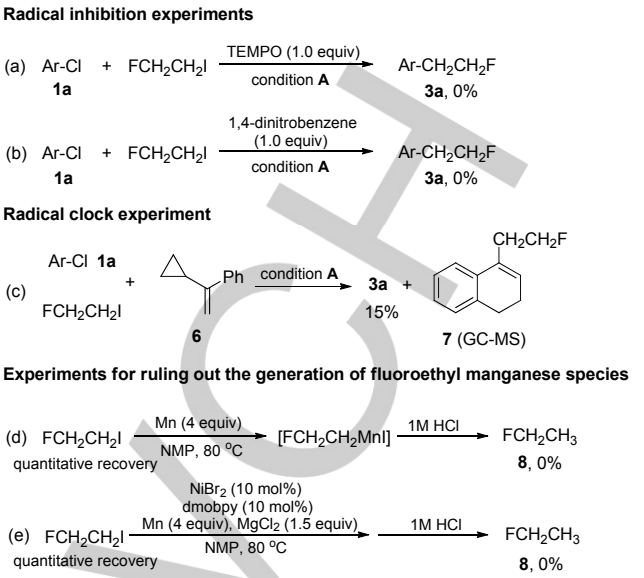
To probe whether the viable fluoroethylation species was free radical or nucleophilic organometallic intermediate, a series of radical inhibition experiments were initially conducted. It was found that the coupling reaction was completely quenched upon the subjection of radical inhibitor TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) under the standard reaction conditions (Scheme 5a).[13a] In addition, this reaction was readily inhibited by the



Scheme 4. Further extension of the scope of vicinal halofluorides and aryl electrophiles. [a] Condition **B**, using Ar-Br and $PhCH(F)CH_2Br$ **2c** instead; isolated yield. [b] Condition **B**, using Ar-I and $PhCH(F)CH_2Br$ **2c** instead. [c] Condition **C**, using Ar-I and $PhCH(F)CH_2Br$ **2c** instead. [d] Condition **A**, using Ar-I and 1-fluoro-2-iodocyclohexane **2d** instead. The trans configuration of the racemic product **3z** was determined by ^1H–^1H COSY spectra. [e] Condition **A**, using Ar-OTf and 1-fluoro-2-iodoethane **2a** instead. [f] Condition **A**, using Ar-OTs and 1-fluoro-2-iodoethane **2a** instead.

addition of electron transfer scavenger 1,4-dinitrobenzene (Scheme 5b). These results were indicative of SET process (single electron transfer) and the involvement of radical intermediates within the catalytic cycle. Further evidence was obtained from the radical clock experiment (Scheme 5c). The interfering effects of radical clock α-cyclopropylstyrene **6** led to the suppression of reductive fluoroethylation reaction and the formation of FCH_2CH_2 radical attaching/cyclopropane ring-openning product **7**.

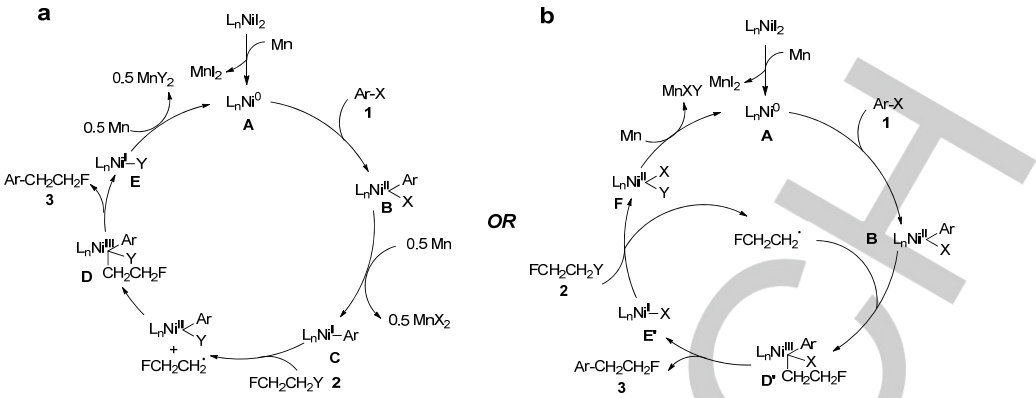
With the above evidence about the intermediacy of FCH_2CH_2 radical identified, several verification experiments were further implemented to rule out the possible generation of fluoroethyl manganese species (a hypothesized intermediate that could result in problematic beta-fluorine elimination).[14] We found that the β-fluoroalkyl electrophile (FCH_2CH_2I) kept untouched under the treatment of manganese powder in NMP at 80 °C (Scheme 5d) or under the standard condition **A** in the absence of aryl chloride (Scheme 5e). These results indicated that the generation of homobenzylic fluoride product from the cross-coupling between β-fluoroethyl manganese species and aryl chloride was less likely. The alternative reaction intermediate in the form of β-fluoroethyl radical rather than β-fluoroethyl



Scheme 5. Control experiments for verifying the intermediacy of fluoroethyl radicals.

manganese thus provided effective solutions for the frequently-encountered problematic β-fluoride side eliminations.[19]

Based on the above experimental observation of the key $FCH_2CH_2^{\bullet}$ radical intermediate involving in this coupling reaction and the previous similar reports[12c,13-14], the putative reaction mechanisms were accordingly proposed (Scheme 6). The left catalytic cycle started with the oxidative addition between the Ar-X electrophile and L_nNi^0 (**A**) (generated from the reduction of Ni^{II} salt precusors) to deliver the $L_nNi^{II}(Ar)(X)$ intermediate **B**. This divalent nickel complex **B** was reduced by the manganese to produce an arylated univalent nickel species **C** which underwent stepwise oxidative addition with FCH_2CH_2Y (a halogen abstraction/$FCH_2CH_2^{\bullet}$ radical cage-rebound process) to afford $L_nNi^{III}(Ar)(Y)(CH_2CH_2F)$ **D**. Further reductive elimination of **D** gave the target product $ArCH_2CH_2F$ and released the univalent $L_nNi^{I}(Y)$ **E** which proceeded 1e reduction into L_nNi^0 (**A**) to complete the catalytic cycle. Alternatively, the interception of $L_nNi^{II}(Ar)(X)$ intermediate **B** by the diffused $FCH_2CH_2^{\bullet}$ radical (cage-escaped radical) could also be possible. The prodcuced trivalent intermediate $L_nNi^{III}(Ar)(X)(CH_2CH_2F)$ **D′** underwent reductive elimination to deliver the $ArCH_2CH_2F$ product and $L_nNi^{I}(X)$ **E′**. The further grabbing of halogen Y atom from FCH_2CH_2Y provided $L_nNi^{II}(X)(Y)$ **F** and $FCH_2CH_2^{\bullet}$ radical that escaped from the solvent cage to attach with the anterior intermediate **B**. At last, conversion of $L_nNi^{II}(X)(Y)$ **F** into L_nNi^0 (**A**) via 2e reduction regenerated L_nNi^0 (**A**) to fulfill the right catalytic cycle.



Scheme 6. Proposed reaction mechanisms: (a) radical-cage-rebound process or (b) radical chain process.

Conclusions

In conclusion, we have reported a nickel-catalyzed reductive coupling protocol for facile installing β-fluoroethyl into aromatic rings from readily accessible aryl chlorides and 1,2-fluorohaloethane. This novel catalytic method features the mildness of reaction conditions, broad scope with respect to both the aryl and β-monofluoroalkyl electrophiles, and excellent group compatibilities towards free proton or reducible group containing substrates, thus offering an efficient approach for the late-stage functionalization of complex Ar-Cl or Ar-OH derived bioactive molecules. We believe that the success of suppressing β-fluorine side elimination via the fluoroalkyl radical intermediate during the coupling reaction could draw more attention towards the derivatization of fluoroalkyl halides. Further explorations of this reaction strategy to more diversified fluoroalkylated electrophiles for access to the precisely-controlled construction of complicated fluorine-added organoproducts are ongoing in our laboratory, and the results will be reported in due course.

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Keywords: Nickel • Reductive Coupling • Unactivated bond • Homobenzylic Fluoride • Methodology and Reactions

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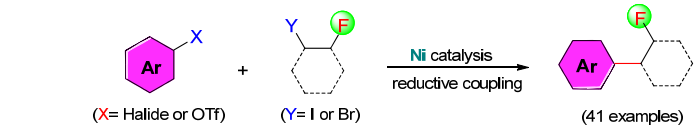

■ Step-simplicity protocol to β-fluoroethylarene ■ Wide scope of unactivated (hetero)aryl electrophiles

■ Circumvent undesirable beta-fluoride elimination ■ Good group-tolerance for late-stage modification

We report herein a facile synthetic method for converting unactivated (hetero)aryl electrophiles into β-fluoroethylated (hetero)arenes via nickel-catalyzed reductive cross-couplings. This method can be applied for the late-stage modification of several complex ArCl or ArOH-derived bioactive molecules with high efficiency.

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Nickel-Catalyzed Reductive Coupling for Transforming Unactivated Aryl Electrophiles into β-Fluoroethylarenes