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To be cited as: *Chem. Asian J.* 10.1002/asia.202100348

Link to VoR: https://doi.org/10.1002/asia.202100348

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10.1002/asia.202100348

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Nickel-Catalyzed Cross-coupling of Ethyl Chlorofluoroacetate with Aryl Bromides

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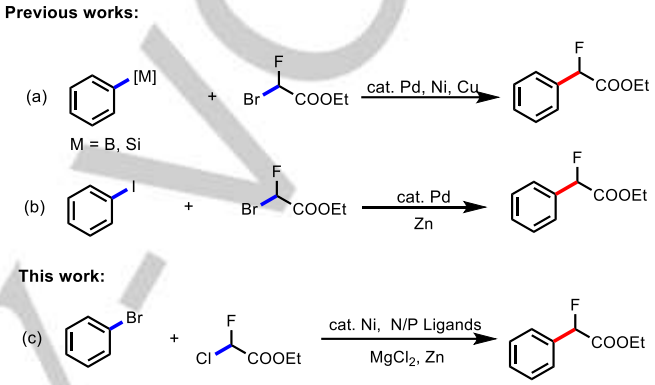
Abstract: A combinatorial nickel-catalyzed monofluoroalkylation of aryl bromides with the industrial raw regent ethyl chlorofluoroacetate has been developed. The two key factors to successful conversion are the combination of nickel with readily available nitrogen and phosphine ligands and the using of a mixture of different solvents. Mechanistic investigations indicated a new zinc regent might generated in situ and be involved in the reaction process.

Fluorine-containing organic compounds have been widely used in pharmaceuticals and agrochemicals due to their unique physical, chemical and biological properties[1]. Accordingly, the development of simple and efficient methods for incorporation of fluorine atom(s) or fluorinated moieties into parent molecules has long been realized as a powerful strategy to discover new biologically active compounds[2]. Among all the fluoriantes motifs, α-aryl-α-fluorocarboxylic acid derivatives have played a key role in synthetic organofluorine chemistry and be found in many active bioactive compounds[3]. The traditional methods to construct such moieties normally underwent C-F bond formation, including electrophilic fluorination[4] of enolates, electrochemical routes[5] and deoxyfluorination[6] of α-hydroxyl esters, which typically required high reactivity fluorinating agents and/or harsh reaction conditions.

To address such issues caused by C-F bond construction, transition-metal-catalyzed fluoroalkylation has been developed as a complementary method to synthesize fluorinated molecules by enabling mild conditions and general synthetic routes. Compared with well-known palladium[7]- and copper[8]-catalysis, nickel-catalyzed fluoroalkylation has recently been established rapidly due to the low cost, ready availability and low toxicity of nickel source. Not only normal cross-coupling, but also reductive coupling with two electrophiles, which avoid the preparation of metal species, have recently been developed for nickel-catalyzed fluoroalkylation of diverse organic molecules. With ethyl bromofluoroacetate used as fluoroalkylating agent, this ''building block'' strategy has been used to synthesize α-aryl-α-fluoroacetates via nickel-catalysis with aryl boronic acids firstly in 2015[9]. However, this method still suffered from poor functional group tolerance, narrow broad substrate scope, and the requirement of pre-prepared reagents. As continuous efforts to develop novel and efficient methods for fluoroalkylation[10], we conceive the direct cross-coupling of fluoroacetate halides and aryl halides could offer a step- and atom-economic path for facile construction of this motif.

Herein, we describe a combinatorial nickel-catalyzed monofluoroacetation of aryl bromides with low-cost industrial regent ethyl chlorofluoroacetate (Scheme 1c). The key factors to realize this reaction are the combination of nickel with readily available nitrogen and phosphine ligands and the using of a mixture of



Scheme 1. Previous arts and current work.

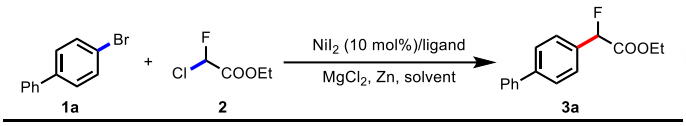
different solvents. Mechanistic studies indicated an in-situ-formed fluoroalkyl zinc reagent was involved in the catalytic cycle, and magnesium dichloride played a key role to activate chlorofluoroacetate to generate the zinc species.

We commenced our study by utilizing ethyl chlorofluoroacetate (**2**) as fluorinating agent, 4-bormo-biphenyl (**1a**) as coupling partner, zinc as reductant, and $MgCl_2$ as the additive, in the presence of a catalytic amount of NiI_2 (10 mol%) in DMA at 80 °C. Based on the experience of previous research, a systematic investigation of ligands was firstly performed, which clearly indicated that ligand combinations played a key role to improve the yield in this catalytic system. Nitrogen ligand 5,5'-dmbpy could afford **3a** in 52% yield and phosphine ligand BINAP displayed no reactivity (entries 1-2). The combination of 5,5'-dmbpy with other ligands could improve the yield while the mixtures of 5,5'-dmbpy and BINAP as ligands with the optimal yield of 72% (entries 6-8, for details, see the SI). Further attempts to improve the efficiency of the reaction via screening of solvents were unsuccessful (entries 9-10), however, simply mixing two different solvents could achieve this goal (entries 11-12) and DMA/THF was demonstrated as the best choice with a 96% isolated yield (entry 13). Finally, several control experiments indicated that the nickel catalyst, ligands, $MgCl_2$ and reductant were indispensable for the success of this catalytic system (entries 14-17).

With the viable reaction conditions established, we then investigated the scope of this monofluoroalkylation protocol and the results were showed in Scheme 2. First, a series of *para*-substituted derivatives were tested, and they were arranged according to their Hammett substituent constants[11]. Substrates containing strongly electron-withdrawing functional groups, such as sulfone (**1b**), cyano (**1c**), trifluoromethyl (**1d**), acetyl (**1e**),

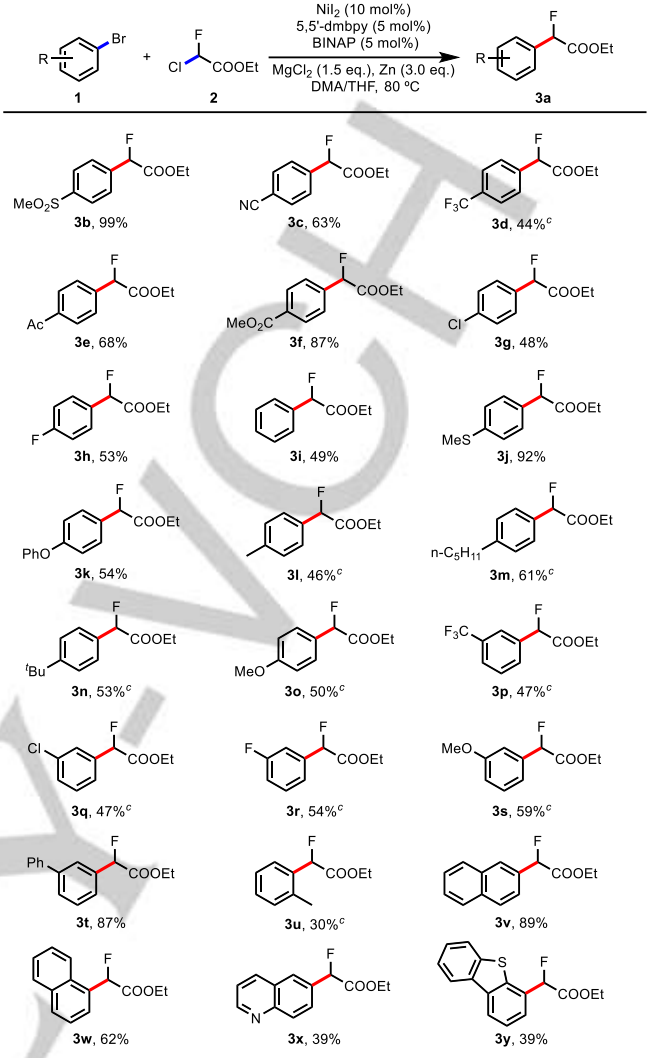
ester (**1f**) were found transformed smoothly to give the desired arenes in good to excellent yields. Aryl bromides installed with the F and Cl (**1g**-**1h**) were well-tolerated with the corresponding products in satisfactory yields. Likewise, substrates installed with neutral and electron-donating groups on the aryl rings (**1i**-**1o**) were also well tolerated in this reaction, affording the monofluoroalkylation arenes in moderate to excellent yields. Meanwhile, aryl bromides bearing *meta*-substituents (trifluoromethyl **1p**, halogen **1q**-**1r**, methoxy **1s** and phenyl **1t**) were also compatible well, furnishing the products in moderate to good yields in this catalytic system. Additionally, aryl bromides(**1u**) bearing *ortho*-substituent could serve as the suitable coupling partner, however, the yield of monofluoroalkylation product was relatively low affected by the steric properties of its substituent. Although substrates bearing active proton were found to be incompatible, aryl bromides derived from naphthalene (**1v**-**1w**) and heterocyclic arenes, such as quinolone (**1x**) and dibenzothiophene (**1y**) were monofluoroalkylated successfully, in satisfactory yields under the standard reaction conditions.

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



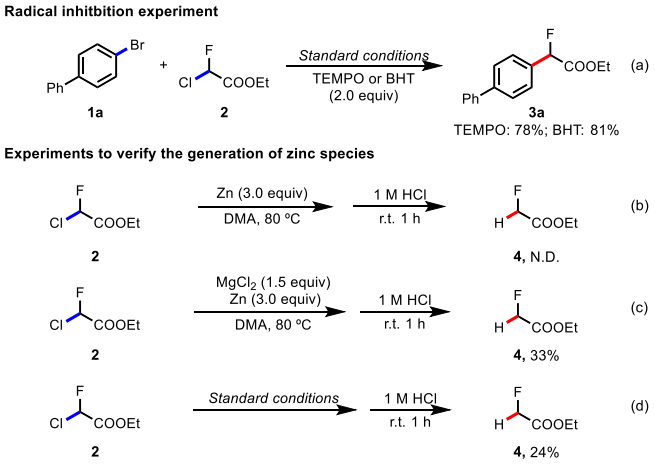
Entry	Ligand (mol%)	Solvent	Yield (%)[b]
1	5,5'-dmbpy (10)	DMA	52
2	BINAP (10)	DMA	0
3	dmbpy (5)/BINAP (5)	DMA	37
4	dombpy (5)/BINAP (5)	DMA	25
5	dtbpy (5)/BINAP (5)	DMA	39
6	5,5'-dmbpy (5)/2,6-lutidine (10)	DMA	44
7	5,5'-dmbpy (5)/PPh_3 (10)	DMA	28
8	5,5'-dmbpy (5)/BINAP (5)	DMA	72
9	5,5'-dmbpy (5)/BINAP (5)	DMF	42
10	5,5'-dmbpy (5)/BINAP (5)	NMP	26
11	5,5'-dmbpy (5)/BINAP (5)	DMA/dme	80
12	5,5'-dmbpy (5)/BINAP (5)	DMA/MeCN	75
13	5,5'-dmbpy (5)/BINAP (5)	DMA/THF	88 (96)
14	-	DMA/THF	0
15[c]	5,5'-dmbpy (5)/BINAP (5)	DMA/THF	0
16[d]	5,5'-dmbpy (5)/BINAP (5)	DMA/THF	0
17[d]	5,5'-dmbpy (5)/BINAP (5)	DMA/THF	0

[a] Unless otherwise noted, the reaction conditions were as follows: **1a** (0.2 mmol, 1.0 equiv), **2** (2.0 equiv), NiI_2 (10 mol%), 5,5'-dmbpy (5 mol%), BINAP (5 mol%), $MgCl_2$ (1.5 equiv), Zn (3.0 equiv), DMA (1.4 mL), THF (0.6 mL), 80 ˚C, 16 h. [b] Yields were determined by ^{19}F NMR with benzotrifluoride as internal standard, numbers in parentheses were yields of isolated products. [c] Lack of NiI_2. [d] Lack of $MgCl_2$. [d] Lack of Zn.



Scheme 2. Scope of aryl bromides. [a] Unless otherwise noted, the reaction conditions were as follows: **1** (0.2 mmol, 1.0 equiv), **2** (2.0 equiv), NiI_2 (10 mol%), 5,5′-dmbpy (5 mol%), BINAP (5 mol%), $MgCl_2$ (1.5 equiv), Zn (3.0 equiv), DMA (1.4 mL), THF (0.6 mL), 80 ˚C, 16 h. [b] isolated yields were reported. [c] 3Å M.S. was added.

In order to gain some insights into the mechanism of this reaction, a series of control experiments were next carried out. First of all, radical inhibition experiments showed the subjection of TEMPO or BHT into the standard conditions could not quench the reaction, and the desired product **3a** were afforded in 78% and 81%, respectively (Scheme 3a). Both results suggested that the monofluoroalkyl radical was not involved in the catalytic cycle, and a fluoroalkyl zinc species might generate in-situ and couple with the aryl bromide by nickel catalysis. To confirme this speculation, several more verification experiments were further performed. While ethyl chlorofluoroacetate **2** was recovered almost entirely under the treatment of zinc powder in DMA at 80 ˚C and no hydrogenated product **4** was detected (Scheme 3b), to our interests, the addition of $MgCl_2$ along with zinc powder under the similar conditions afforded **4** in 33% yield (Scheme 3c). Not surprisingly, 24% yield of hydrogenated product **4** could be detected under the standard conditions in the absence of aryl bromides (Scheme 3d). All these results clearly implied that a monofluoroalkyl zinc species generated in situ in the reaction,

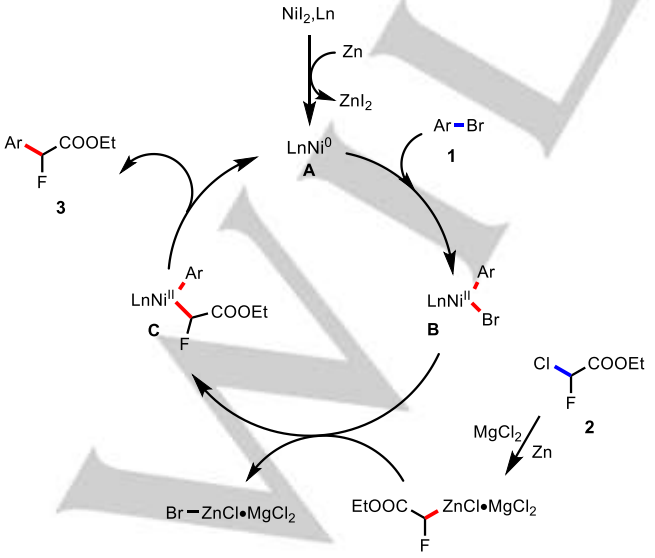


Scheme 3. Control experiments.

and $MgCl_2$ played a key role in promoting zinc power to insert the C-Cl bond of chlorofluoroacetate **2**.

Although the definite mechanism remains unclear, on the basis of above results and previous similar reports[12], a plausible mechanism via Negishi cross-coupling is accordingly proposed as Scheme 4. The catalytic cycle started by the oxidative addition of ArBr (**1**) to Ni(0) species (**A**), which generated by the reduction of NiI_2 with zinc power, affording the [$ArNi^{II}(Ln)Br$] intermediate **B**. Transmetalation of **B** with monofluoroalkyl zinc regent that generated in situ by reduction of ethyl chlorofluoroacetate **2** with zinc powder with the assistance of $MgCl_2$, delivered Ni(II) complex **C**. The final C-C bond forming reductive elimination from **C** furnished the target product **3** and released the $LnNi^0$ (**A**) to complete the catalytic cycle.

In summary, the first monofluoroalkylation of aryl bromides with ethyl chlorofluoroacetate has been successfully developed by combinatorial nickel-catalyzed cross-coupling. This novel method has demonstrated high catalytic reactivity, mild reaction conditions and excellent function-group compatibility. Further exploration of the mechanistic details and studies to expand the substrates scope and their applications in synthesis are currently in progress.



Scheme 4. Plausible Mechanism.

Experimental Section

General procedure

Aryl bromine **1** (1.0 equiv, 0.2 mmol, if solid), NiI_2 (10 mol %, 0.02 mmol, 6.3 mg), 5,5'-dmbpy (5 mol%, 0.01 mmol, 1.8 mg), BINAP (5 mol%, 0.01 mmol, 6.2 mg), $MgCl_2$ (1.5 equiv, 0.3 mmol, 28.5 mg) and Zn (3.0 equiv, 0.6 mmol, 39.2 mg) were combined in a 50 mL oven-dried sealing tube. The vessel was evacuated and backfilled with N_2 (repeated for 3 times), and aryl bromine **1** (1.0 equiv, 0.2 mmol, if liquid), **2** (2 equiv, 0.4 mmol, 58.2 mg), DMA (1.4 mL) and THF (0.6 mL) were then added into the reaction system subsequently via syringe. The tube was sealed with a Teflon lined cap and heated in a preheated oil bath at 80 ˚C. After stirring for 16 h, the reaction mixture was cooled to room temperature, diluted with EtOAc and filtered through a pad of Celite. The filtrate was added into brine and extracted with EtOAc, the combined organic phase was dried over Na_2SO_4, filtrated and concentrated under vacuum and purified by flash column chromatography (PE/EA = 30:1) to give the desired product **3**.

Acknowledgements

We gratefully acknowledge the National Science Foundation of China (21971228, 21772187) and China Postdoctoral Science Foundation (2019M653580) for financial support.

Conflict of interest

The authors declare no conflict of interest.

Keywords: monofluoroacetation • aryl halides • ethyl chlorofluoroacetate • nickel • cross-coupling

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10.1002/asia.202100348

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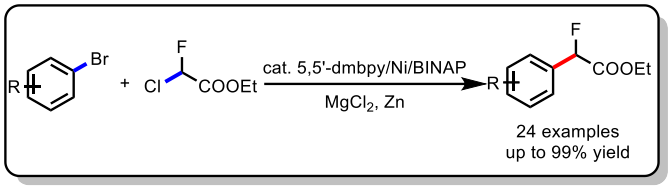

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