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View Article Online
DOI: 10.1039/C9CC03737C

COMMUNICATION

Nickel-Catalyzed Monofluoromethylation of (Hetero)aryl Bromides via Reductive Cross-coupling

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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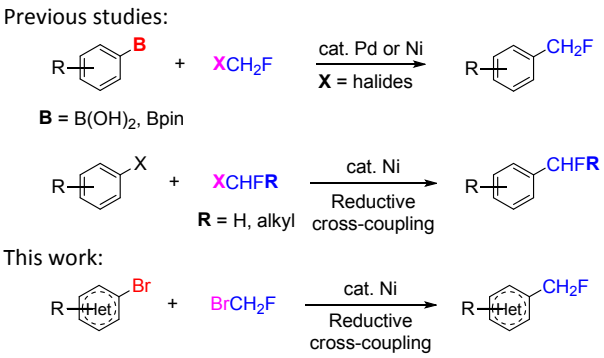
A mild and efficient Nickel-catalyzed direct monofluoromethylation of (hetero)aryl bromides by reductive cross-coupling has been developed. This method exhibits good efficiency, wide functional-group compatibility, and suitable for aryl and heteroaryl bromides with abundant industrial raw material $BrCH_2F$. This strategy provides an efficient way to synthesize monofluoromethylated molecules for drug discovery.

Fluorinated organic compounds have been widely used in pharmaceuticals and agrochemicals because fluorine or fluorinated moieties could remarkably enhance the lipophilicity, metabolic stability and bioavailability of the parent molecules.[1] Accordingly, the selective incorporation of fluorine atom or fluorinated moieties into organic molecules has attracted extensive interest of synthetic chemists.[2] Among all fluorinated functional groups, monofluoromethylene (CH_2F) has emerged as an important motif due to its widespread existence in many biologically active molecules, such as Afloqualone, Loflupane and Florfenicol. Actually, the traditional methods for the synthesis of monofluoromethyl arenes ($ArCH_2F$) were nucleophilic monofluorination from benzylic alcohols[3] or halides.[4] However, the limited availability of the corresponding benzylic precursors restricted the application of such functional group conversion processes in organic synthesis.[5] As an alternative, the monofluoromethyl functional group, known as a large class of fluorine-containing building block, could be introduced into arenes as a whole.[2e-f] During the past decades, the indirect monofluoromethylation methods[6] which usually use monofluoromethylating reagents installed with easily removed protective groups, including phosphoryl ester,[6b-c] carboxylic ester[6d-f] and phenylsulfonyl,[6g-j] have been developed rapidly.



Scheme 1 Direct Monofluoromethylation by Cross-Coupling

As results for the development of direct and regiospecific monofluoromethylation methods, transition-metal mediated or catalyzed incorporation of monofluoromethyl group (CH_2F) into aryl substrates have been well established in the past decade. Starting from the first example of stoichiometric amount of palladium-mediated cross coupling of aryl boronates with monofluoromethyl halides in 2009 by the Suzuki group,[7] the direct monofluoromethylations of aryl boron compounds with fluoromethyl halides have been successfully developed via palladium and nickle-catalysis by Hu[8] and Zhang.[9] Due to its high atom- and step-economy and straightforward handling by avoiding the use of organometallic reagents, nickel-catalyzed reductive crossing-coupling has been used for fluoroalkylation of aryl halides by Zhang[10] and our group[11a] recently. However, none of these methods could be compatible with heteroarenes, which definitely hampered their application on drug design and development. As one part of our continuous efforts[11a-b] to develop high efficient monofluoroalkylation, herein, we describe a nickel-catalyzed reductive cross-coupling between heteroaryl halides and abundant industrial raw material bromofluoromethane. This method has demonstrated high efficiency, mild conditions, and good functional-group

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x
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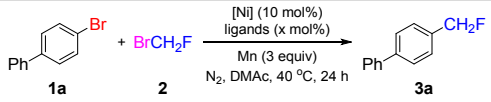
compatibility for both aryl and heteroaryl bromides. The key to success was the combination of readily available bidentate and monodentate pyridine-type nitrogen ligands with nickel[9,11a,12] to in situ generate efficient catalysts which promote the monofluoromethylation for broad scope of (hetero)aryl bromides.[13]

Table 1 Optimization of the reaction conditions [a]



1a 2 3a

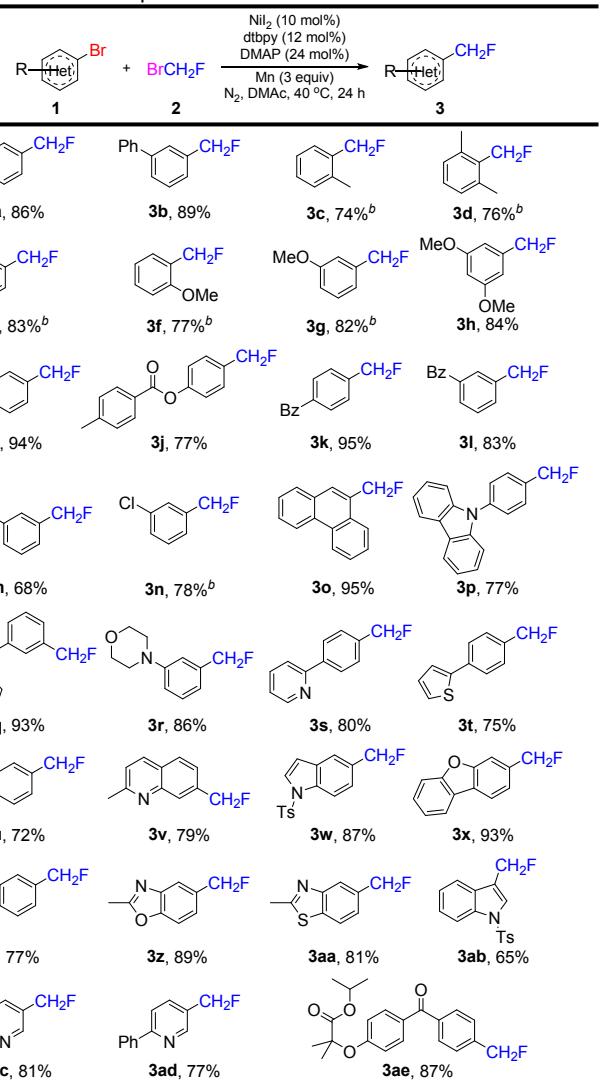
Entry	[Ni]	Ligand(mol%)	Yield(%)[b]
1	NiI_2	4-CN-Py(24)	0
2	NiI_2	DMAP(24)	15
3	NiI_2	2,6-lutidine(24)	0
4	NiI_2	PPh_3(24)	0
5	NiI_2	dmbpy(12)	64
6	NiI_2	dtbpy(12)	71
7	NiI_2	dombpy(12)	79
8	NiI_2	phen(12)	52
9	NiI_2	dppe(12)	12
10	NiI_2	dombpy(12)/DMAP(24)	76
11	**NiI_2**	**dtbpy(12)/DMAP(24)**	**85 (86)[c]**
12	NiI_2	dmbpy(12)/DMAP(24)	72
13	NiI_2	phen(12)/DMAP(24)	69
14	NiI_2	dtbpy(12)/2,6-lutidine(24)	78
15	NiI_2	dtbpy(12)/4-CN-Py(24)	74
16	NiI_2	dtbpy(12)/PPh_3(24)	50
17	$NiCl_2$	dtbpy(12)/DMAP(24)	39
18	$Ni(OAc)_2$	dtbpy(12)/DMAP(24)	19
19	$Ni(acac)_2$	dtbpy(12)/DMAP(24)	68
20[d]	NiI_2	dtbpy(12)/DMAP(24)	41
21[e]	NiI_2	dtbpy(12)/DMAP(24)	76
22	NiI_2	none	0
23	none	dtbpy(12)/DMAP(24)	0

[a] Standard reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2** (2.5 equiv), [Ni] (10 mol%), Mn (3.0 equiv), DMAc (1 mL), 40 ℃, under N_2 atmosphere, 24 h. [b] Yields determined by ^{19}F NMR using $PhCF_3$ as an internal standard. [c] Isolated yield. [d] MeCN. [e] 60 ℃.

Our study commenced with 4-bromobiphenyl **1a** as the pilot substrate, and bromofluoromethane **2** as the coupling partner in the presence of a catalytic amount of NiI_2 (10 mol%) and Mn (3 equiv) in DMAc (1 mL) at 40 ℃ for 24 hours. Different kinds of nitrogen and phosphine ligands were first examined (entries 1-9; see the SI for details) and three kinds of bidentate pyridine-type nitrogen ligands gave the desired monofluoromethylated product **3a** in approximate yields (64%-79%, entries 5-7). Inspired by our previous results on combinatorial nickel catalysis[11], we then investigated various combinations of N/P and N/N ligands. To our delight, a mixture of DMAP and dtbpy (N/N) as a simple ligand combination further improved the yield to 85% (entry 11), whereas other kinds of ligand combinations were ineffective (entries 10-16; see the SI for details). Additionally, careful screening of solvents, nickel sources and temperature indicated DMAc, NiI_2 and 40 ℃ were the best choices (entries 17–21; see the SI for details). Lastly, it was confirmed that none of the desired product **3a** was detected in the absence of nickel catalyst or ligands when conducting the corresponding control experiments (entries 22-23).

View Article Online DOI: 10.1039/C9CC03737C

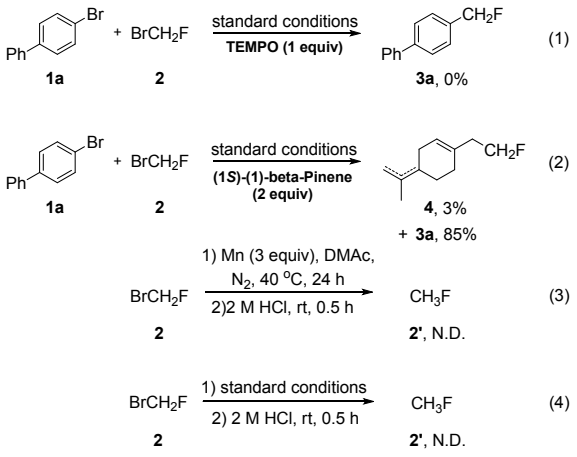
Table 2 Substrate scope [a]



[a] Standard reaction conditions: **1** (0.2 mmol, 1.0 equiv), **2** (2.5 equiv), NiI_2 (10 mol%), dtbpy (12 mol%), DMAP (24 mol%), Mn (3.0 equiv), DMAc (1 mL), 40 ℃, under N_2 atmosphere, 24 h. Isolated yields. [b] Yield determined by ^{19}F NMR using $PhCF_3$ as an internal standard.

With the optimal conditions in hand, we then probed the scope of aryl and heteroaryl bromides **1** with substrate **2**. As shown in table 2, the substituent groups on the phenyl ring, including electron-donating groups such as Ph (**3a**, **3b**) Me (**3c**, **3d**), OMe (**3f-h**), OBn (**3i**) and OCOR (**3j**), and electron-withdrawing groups such as ketones (**3k-m**) at different positions on the phenyl ring of aryl bromides, were monofluoromethylated smoothly in good to excellent yields (68–94%). Meanwhile, aryl bromides installed with Cl (**3n**) or polycyclic aryl group (**3o**) were also suitable for this transformation. After the successful monofluoromethylation of aryl bromides, our next concern was the direct monofluoromethylation of heteroaryl compounds by reductive cross-coupling that has never been achieved before.[10-11,15] To our delight, several heterocyclic substituents on the aryl

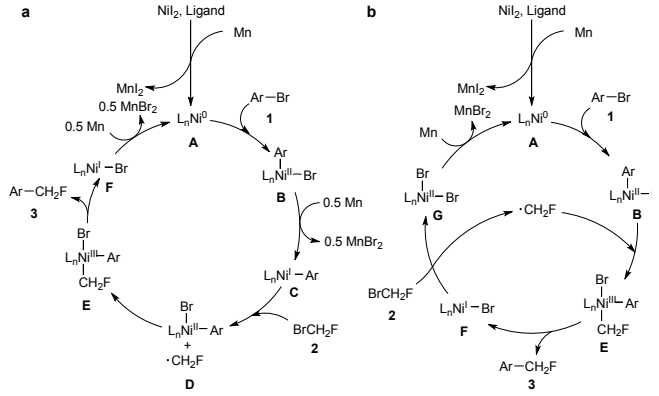
bromides, such as carbazole (**3p-q**), morphine (**3r**), pyridyl (**3s**) and thiophene (**3t**), were also well tolerated in this catalytic reaction, providing the desired products in satisfactory yields (75%-93%). Various kinds of heteroaryl bromides, such as quinolyl (**3u-v**), indolyl (**3w**), dibenzofuryl (**3x**), dibenzothienyl (**3y**), benzoxazolyl (**3z**) and benzothiazolyl (**3aa**) were also compatible with this reaction, which thus paved the way for incorporation of monofluoromethyl group into such heteroaryl rings. It was worth noting that even cross-coupling with bromides on heteroaryl-rings, such as indolyl (**3ab**), quinolyl (**3ac**) and pyridyl (**3ad**), which to the best of our knowledge had never been achieved before due to the miscellaneous byproducts it might generate, afforded the expected products in good to excellent yields (65%-81%). Indeed, we believe this protocol might offer a solution for direct introduction of fluorine-containing building blocks into heteroaryl rings. To demonstrate the synthetic potential and the functional group tolerance of this transformation, this catalytic system has been applied to the late-stage monofluoromethylation of fenofibrate-derived aryl bromide (**3ae**), which afforded the corresponding monofluoromethylated product in excellent yield (87%).



Scheme 2 Mechanism studies

To gain some insight into the mechanism of this transformation, we next carried out a series of control experiments. First, the reaction was completely quenched when 1.0 equivalent of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added into the reaction, indicating that this reaction might process via a radical path.[14] To further confirm this speculation, radical scavenger (1S)-(1)-beta-Pinene (2 equiv) was subjected into the standard conditions, which give the cycle-opening product **4** smoothly, albeit with a pretty low yield. Both findings demonstrate that a free monofluoromethyl radical is generated in the catalytic cycle.[6g, 15] Finally, several verification experiments were performed to rule out the possibility that this nickel-catalyzed transformation proceeded through cross coupling of aryl bromides with monofluoroalkyl manganese species, which was generated in situ between $BrCH_2F$ (**2**) and Mn. Neither monofluoromethyl manganese species were detected upon the treatment of **2** with manganese power in DMAc, nor the subjection of **2** to standard conditions in the absence of aryl bromide. Not surprisingly, no hydrogenated product was detected in either case.

On the basis of the results of the above experiments and previous reports[9b-c, 11a], two reaction mechanisms, radical cage rebound process (Path a) and radical chain mechanism (Path b), were proposed for this transformation. For Path a (Scheme 3a), NiI_2 was reduced to Ni^0 (**A**) firstly, and an oxidative addition with (hetero)aryl bromides **1** occurred to form Ni(II) complex $[(Ar)Ni^{II}(L_n)Br]$ (**B**) next. Then Ni(II) complex **B** was reduced to produce nickel complex $[(Ar)Ni^{I}(L_n)]$ (**C**), which underwent the second oxidative addition with $BrCH_2F$ to produce $[(Ar)Ni^{III}(L_n)CH_2FBr]$ (**E**) through a radical cage rebound process, in which the monofluoromethyl radical was generated via a single electron transfer pathway. Finally, reductive elimination of **E** provided the desired product and released the $[BrNi^{I}(L_n)]$ (**F**), which was further reduced by Mn to regenerate complex **A**. Alternatively, a radical chain mechanism (Path b) was also possible in this transformation. The intermediate **B** could be oxidated by monofluoromethyl radical, which was generated by reaction of $[BrNi^{I}(L_n)]$ with $BrCH_2F$ diffused to the solution, to produce $[(Ar)Ni^{III}(L_n)CH_2FBr]$ (**E**). Ni(III) complex **E** underwent reductive elimination to provide the monofluoromethylated arene and released $[Ni^{II}(L_n)Br_2]$, which could be reduced by Mn to regenerated complex **A**.



Scheme 3 Proposed reaction mechanism. **a** radical cage rebound process. **b** radical chain process

In conclusion, we have developed a nickel-catalyzed monofluoromethylation of aryl and heteroaryl bromides by reductive cross-coupling. Compared with the known direct monofluoromethylation methods,[7-9, 11a] our designed system stands out with its facile operation, economic choice of readily available substrates, and excellent functional groups tolerance, especially for a variety of heteroaromatics and pharmaceutical. Further exploration of the mechanistic details and the application of this method to the modification of complex biologically active molecules with fluorine groups are still ongoing in our laboratory.

We gratefully acknowledge the National Basic Research Program of China (973 Program 2015CB856600), the National Science Foundation of China (21772187, 21522208) for financial support.

Conflicts of interest

There are no conflicts to declare.

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