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Metal-free α-arylation of α-fluoro-α-nitroacetamides employing diaryliodonium salts†

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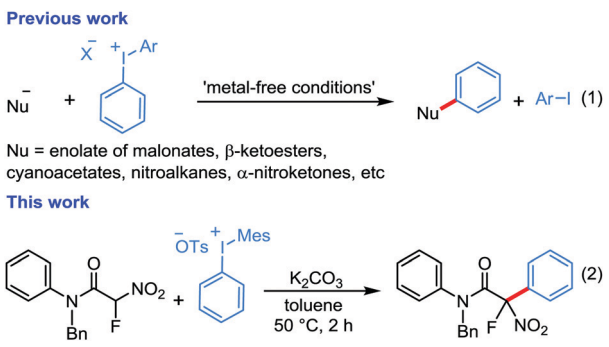
Herein, we present a mild and efficient metal-free arylation of α-fluoro-α-nitroacetamides employing diaryliodonium salts. A broad range of diaryliodonium salts and α-fluoro-α-nitroacetamides containing sensitive functional groups was successfully employed in this protocol to yield the arylated products in good yields. The synthetic value of this novel protocol was further highlighted by extending the α-arylation to α-cyano-α-fluoroacetamides.

The growing interest in fluorinated aromatic compounds in drug discovery research is attributed to the potential of the fluorine atom to fine tune biological properties such as metabolic stability and lipophilicity when it is strategically placed in a molecule.[1,2] Over the past two decades, there has been significant progress in the development of novel methods for the introduction of fluorine and fluoroalkyl groups into arenes.[3,4] The most frequently used strategies, particularly in the case of fluorocarbonyl compounds, rely on metal-catalyzed coupling between aryl halides and appropriately functionalized fluoroalkyl compounds.[5] Hence, a complementary method to introduce fluoroalkyl groups into arenes remains a relevant task.[6]

Hypervalent iodine compounds have received great attention over the last few decades as a versatile class of reagents useful for a wide variety of synthetic transformations.[7,8] Among them, diaryliodonium salts have emerged as mild, selective and robust reagents for both metal-catalyzed and metal-free electrophilic arylation reactions.[9,10] Recent studies have ascertained the versatile use of diaryliodonium salts in the installation of the arene moiety into a multitude of heteroatom nucleophiles such as alcohols, amines, amides, thiols, and enolizable carbon nucleophiles.[11,12] In addition to metal-catalyzed C-arylations, metal-free α-arylations of enolizable substrates such as ketones, α-ketoesters, malonates, nitroalkanes, α-nitroketones, and cyanoesters have also been documented in recent years (Scheme 1, eqn (1)).[13] However, to our knowledge, this strategy has not yet been exploited for fluorocarbon nucleophiles. Intrigued by the compatibility of diaryliodonium salts with enolizable substrates, we wondered about the possibility of using this strategy for the introduction of arenes into α-substituted fluoroacetamides, given their immense synthetic value as essential motifs in pharmaceuticals.[14] Herein, we report a novel metal-free protocol for the direct α-arylation of α-fluoro-α-nitroacetamides under mild basic conditions to generate a fully substituted benzylic fluoroalkyl center (Scheme 1, eqn (2)). Moreover, the process was found to be useful for the arylation of α-cyano-α-fluoroacetamides.

We selected *N*-benzyl-2-fluoro-2-nitro-*N*-phenylacetamide **1a** as a suitable enolizable substrate and the unsymmetrical mesityl(phenyl)iodonium salt **2a** (1.1 equiv.) as an arylating agent to optimize the reaction conditions. The high chemoselectivity observed in the selective transfer of aryl groups over the mesityl group in the C-arylation of carbon nucleophiles prompted us to choose the mesityl group as the dummy ligand in this study.[15] Pleasingly, the reaction conducted in the presence of Cs_2CO_3 gave the α-arylated product **3a** in 65% yield



Scheme 1 Electrophilic arylations using diaryliodonium salts.

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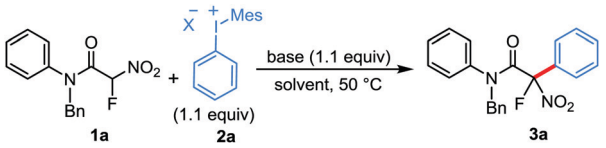
Table 1 Optimization of the reaction conditions[a]



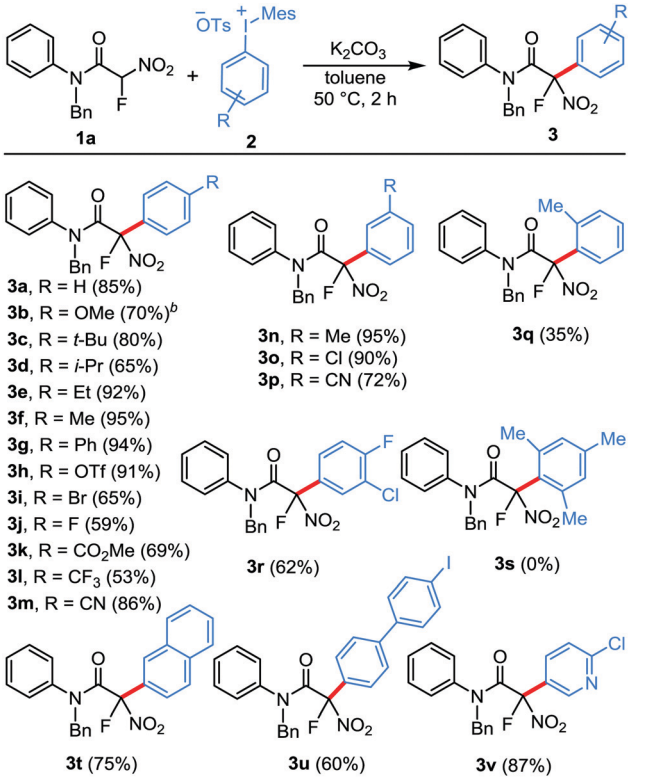
Entry	Anion X^-	Base	Solvent	Time (h)	Yield[b] (%)
1	OTs	Cs_2CO_3	THF	12	65
2	OTs	Cs_2CO_3	TBME	12	79
3	OTs	Cs_2CO_3	Dioxane	12	82
4	OTs	Cs_2CO_3	Toluene	6	86
5	OTs	Cs_2CO_3	Et_2O	6	—
6	OTs	Cs_2CO_3	DCM	6	50
7	OTs	Cs_2CO_3	DMF	12	77
8	OTs	K_2CO_3	Toluene	2	88
9	OTs	*t*-BuOK	Toluene	6	80
10	OTs	KOH	Toluene	6	82
11	OTs	NaH	Toluene	6	60
12	OTs	DABCO	Toluene	12	Trace
13	OTf	K_2CO_3	Toluene	6	80
14	BF_4	K_2CO_3	Toluene	6	55
15[c]	OTs	K_2CO_3	Toluene	2	90 (85)[d]
16[e]	OTs	K_2CO_3	Toluene	2	76

[a] General reaction conditions: **1a** (0.2 mmol), **2a** (0.22 mmol), and base (0.22 mmol) in 2 ml of solvent at 50 °C. [b] NMR yield using 1,3,5-trimethoxybenzene as an internal standard. [c] Reaction performed using 0.24 mmol of K_2CO_3. [d] Isolated yield after silica gel column chromatography. [e] Reaction carried out at 80 °C.

in THF at 50 °C (Table 1, entry 1). In attempts to improve the reaction efficiency, various solvents were screened (entries 2–7), and toluene proved to be an optimal solvent furnishing the expected product in 86% yield (entry 4). Further evaluation revealed that the reactions conducted using TBME, dioxane, DCM, and DMF as solvents were not as efficient as that of toluene, and no product formation was observed with Et_2O. We continued the optimization studies by examining various bases for this transformation, and K_2CO_3 was found to be the best choice giving the product in 88% yield and shortening the reaction time to 2 h (entries 8–12). The triflate and tetrafluoroborate salts were tried subsequently, but with no improvement in the efficiency (entries 13 and 14). Further increase in the stoichiometry of K_2CO_3 (1.2 equiv.) was found to be beneficial, enhancing the yield of **3a** to 90% (entry 15). The use of a higher reaction temperature of 80 °C afforded the product in lower yield (entry 16).

Having identified the optimal conditions, we proceeded with the evaluation of the scope for this arylation strategy. First, we examined the structural diversity possible for unsymmetrical diaryliodonium salts keeping the mesityl group as the dummy ligand to achieve the requisite chemoselectivity. As shown in Table 2, the transformation was effective for diaryliodonium salts containing a broad series of substituents, and the aryl groups were selectively transferred to the fluoroacetamide moiety in excellent yields. Notably, substrates bearing various alkoxy, alkyl and phenyl substituents at the *p*-position of the aryl group generated the corresponding arylated fluoroacetamides in good to excellent yields (**3a**–**3g**). Importantly, diaryliodonium salts containing bromo, fluoro, triflate, carbalkoxyl,

Table 2 Substrate scope of aryl(mesityl)iodonium salts[a]

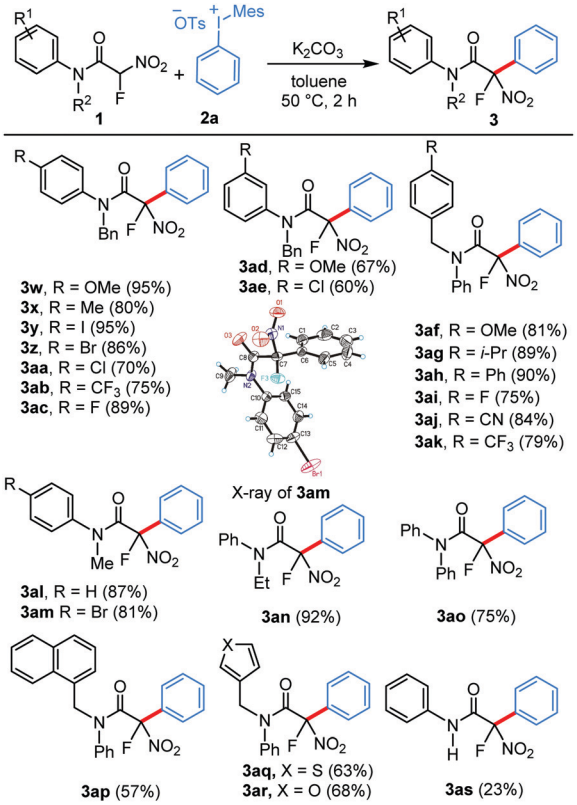


[a] General reaction conditions: **1a** (0.2 mmol), **2** (0.22 mmol), and K_2CO_3 (0.24 mmol) in 2 ml of toluene at 50 °C for 2 h. Isolated yield after silica gel column chromatography. [b] The reaction performed using K_2CO_3 (0.3 mmol) for 3 h.

trifluoromethyl, and cyano substituents at the *p*-position were competent for this arylation, illustrating the advantage of this strategy in producing these compounds which are often difficult to achieve through metal-catalyzed coupling reactions (**3h**–**3m**). Additionally, the reactions carried out using electronically varied functional groups at the *m*-position of the aryl ring proceeded smoothly to afford the arylated products in moderate yields (**3n**–**3p**). A substituent at the *o*-position was also tolerated to afford the product, albeit in lower yield (**3q**). In addition to the monosubstituted diaryliodonium salts, a disubstituted diaryliodonium salt was also found to be viable for this transformation, and product **3r** was obtained in 62% yield. Our further evaluation of the scope revealed that a sterically demanding aryl group such as mesityl could not be transferred under the present reaction conditions. Pleasingly, 2-naphthyl and 4-iodobiphenyliodonium salts could also be effectively employed in this conversion (**3t** and **3u**). Regarding the introduction of heteroaryls, 2-chloropyridine-derived diaryliodonium salt was successfully transformed to the corresponding product **3v** in excellent yield.

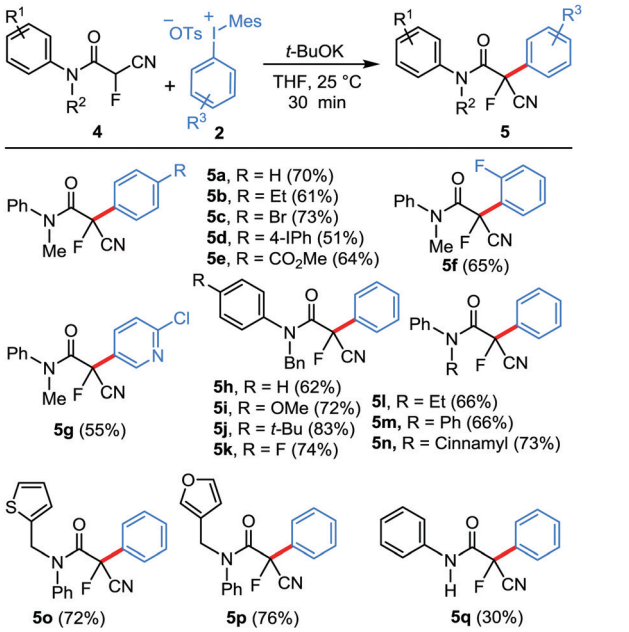
We next turned our attention to the scope of the amide component for this practical arylation strategy. Notably, a diverse range of electronically varied tertiary amides can be used for this new protocol to deliver these arylated products in good to excellent yields (Table 3). Fluoronitroacetamides bearing electron-withdrawing and electron-donating substituents at the *p*-position of

Table 3 Substrate scope for α-fluoro-α-nitroacetamides[a]



[a] General reaction conditions: **1** (0.2 mmol), **2a** (0.22 mmol), and K_2CO_3 (0.24 mmol) in 2 ml of toluene at 50 °C for 2 h. Isolated yield after silica gel column chromatography.

Table 4 Substrate scope for α-arylation of α-cyano-α-fluoroacetamides[a]



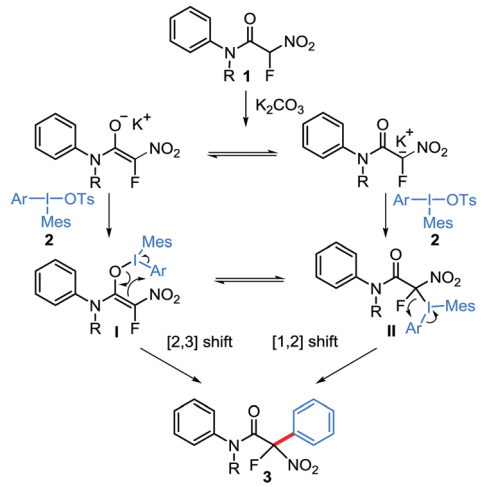
[a] General reaction conditions: **5** (0.2 mmol), **2** (0.22 mmol), and *t*-BuOK (0.24 mmol) in 2 ml of THF at 25 °C for 30 min. Isolated yield after silica gel column chromatography.

the aryl ring underwent the reaction smoothly to afford the arylated products in excellent yields (**3w–3ac**). Moreover, these mild metal-free conditions are compatible for substrates bearing methoxy and chloro substituents at the *m*-position of the aryl ring (**3ad** and **3ae**). Subsequently, we examined the electronic effects of the benzyl substitution of the fluoronitroacetamides, and all the substrates used were found to be competent nucleophiles in this transformation (**3af–3ak**). Furthermore, the reaction scope was evaluated by varying the *N*-substituent of the aniline moiety. Pleasingly, the amides having the most commonly used *N*-substituents such as Me, Et and Ph underwent arylation smoothly to furnish the corresponding products in excellent yields (**3al–3ao**). The structure of the product was unambiguously confirmed by the X-ray analysis of compound **3am**.[16] Similarly, α-fluoronitroacetamides bearing *N*-(naphthalen-1-ylmethyl), *N*-(thiophen-3-ylmethyl), and *N*-(furan-3-ylmethyl) groups displayed reasonable efficiency in this reaction (**3ap–3ar**). Pleasingly, though in a moderate yield, a substrate bearing a secondary amide also participated in this reaction (**3as**).

The cyanide group is one of the most important functionalities in organic synthesis as it can be easily converted to various functional groups such as an amine, acid, aldehyde and ester. Encouraged by the versatile chemistry involving the cyanide moiety, we decided to check whether this new protocol can be extended to a cyano-containing fluoroacetamide nucleophile.

In a preliminary experiment, α-cyano-α-fluoroacetamide **4a** derived from cyanoacetic acid was tested for its compatibility with diaryliodonium salt **2a** under identical reaction conditions, and the arylated product **5a** was obtained, albeit only in 37% yield. This result prompted us to carry out a brief optimization study which concluded that *t*-BuOK/THF at 25 °C suits best for this reaction affording the product in 70% yield.[17] As shown in Table 4, a brief survey of the substrate scope was conducted, and it was pleasing to find that electronically varied substituents at the *p*-position of iodonium salts were well tolerated in the α-arylation of α-cyano-α-fluoroacetamides, affording the products in moderate to good yields (**5a–5e**). Of note, the *o*-fluorophenyl group was successfully transformed to the product in 65% yield (**5f**). A heteroaryliodonium salt was also successfully employed in the transformation to incorporate a heteroarene into a fluoroacetamide substrate (**5g**). Subsequently, we focused our attention on the variation of α-cyano-α-fluoroacetamides. We were pleased to find that *N*-benzyl-*N*-aryl-substituted acetamides bearing methoxy, *t*-butyl, and fluoro substituents at the *p*-position of the phenyl ring were readily transformed to the corresponding arylated products (**5h–5k**). Moreover, the scope of this novel protocol was demonstrated by varying the *N*-substituent of the tertiary amide (**5l–5p**). Of note, the arylation of the secondary amide was also feasible under the present reaction conditions (**5q**).

Generally, the metal-free α-arylation is presumed to take place *via* a T-shaped intermediate formed by the coordination of the enolate generated by the base.[18] Either of the T-shaped intermediates (**I** or **II**) formed by the coordination of the enolate through the O–I or C–I bond subsequently undergoes a rapid ligand coupling process to afford the α-arylated α-fluoro-α-nitroacetamide derivative (Scheme 2).



Scheme 2 Reaction mechanism.

Furthermore, the possibility of a radical process was ruled out after performing the reactions in the presence of well-known radical scavengers TEMPO and 1,1-diphenylethylene (DPE). In both the reactions conducted using α-fluoro-α-nitroacetamide **1a**, the desired product **3a** was obtained in 80% and 74% respectively.

In conclusion, the use of diaryliodonium salts as arylating agents has enabled the development of a convenient metal-free protocol for the α-arylation of synthetically valuable α-fluoro-α-nitroacetamides for the creation of a quaternary benzylic fluorocarbon center. Unlike the other metal-free arylation strategies, the present reaction could be used for the selective transfer of a wide range of electronically varied arenes, thereby representing a new complementary approach for sp^3 C arylation. The strategy was further shown to be useful for the α-arylation of α-cyano-α-fluoroacetamides.

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Conflicts of interest

There are no conflicts to declare.

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16 Crystallographic data for **3am**: CCDC 1940141 (**3am**) contains the supplementary crystallographic data for this paper†.

17 For details, see the ESI†.

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