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Decarbethoxylative Arylation Employing Arynes: A Metal-Free Pathway to Arylfluoroamides

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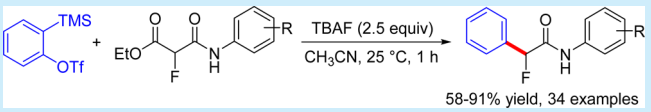
Supporting Information

ABSTRACT: An efficient, metal-free decarbethoxylative arylation protocol for the synthesis of α-aryl-α-fluoroamides from fluoromalonamates, under ambient reaction conditions using aryne as an electrophilic arylating agent, is reported. This decarbethoxylative arylation proceeds under mild conditions and provides a practical and effective entry to a wide range of α-aryl-α-fluoroacetamides. Interestingly, the use of the *tert*-butyl ester of fluoromalonamate prevented the otherwise rapid decarboxylation step, affording the arylated fluoromalonamate in moderate yield.



The strategic use of arynes as a synthetic platform for the access of densely functionalized arenes in carbon−carbon and carbon−heteroatom bond-forming reactions has seen phenomenal growth in the last decades.[1,2] Indeed, the convenient and mild generation of arynes by fluoride-induced 1,2-elimination of 2-(trimethylsilyl)aryl triflates, introduced by Kobayashi in 1983,[3] has prompted the exploration of arynes in manifold types of reactions such as multicomponent reactions (MCRs),[4] insertion reactions,[5] cycloaddition reactions,[6] and arylations (Figure 1).[7] Several elegant methodologies have been

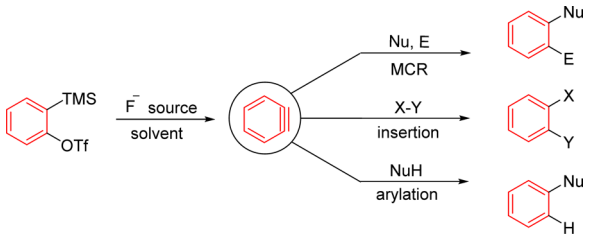


Figure 1. Reactivity of arynes.

reported wherein arynes served as a versatile structural unit for the synthesis of diversely substituted arenes. Importantly, too, arynes have found widespread use in natural product synthesis.[8] Despite the widespread use of arynes in various carbon−carbon bond-forming reactions, metal-free C-arylation reactions employing arynes remain sparse.[9] Currently, most of the reactions of arynes with 1,3-diactivated methylene substrates are C−C insertion reactions, and the studies of Mhaske[9a] and Rodriguez[9b] have shown that arylation can be achieved using malonamides and β-ketoamides, respectively.

Recent studies have shown that malonates, their derivatives, particularly malonic acid half thioesters (MAHTs) and their fluorinated analogues, are versatile building blocks for the metal- and organocatalyzed decarboxylative coupling reactions with various electrophiles to incorporate the (fluoro)acetate moiety into organic molecules in high yields and stereoselectivity.[10,11] Although this attractive feature of malonate derivatives has been successfully explored in a wide range of carbon−carbon bond-forming reactions, it still remains elusive for arylation reactions.[12,13] Undoubtedly, a strategy for the decarboxylative arylation of malonate derivatives to introduce aryl group would be of substantial synthetic utility. Encouraged by these attractive findings, we chose to examine the use of fluoromalonamates as a nucleophile for the decarboxylative arylation reaction with arynes. If successful, this strategy would offer new avenues for the development of mild strategies for the introduction of fluoroacetamides into arenes, an important subunit, which is present in a wide array of pharmaceuticals and agrochemicals.[14] Our efforts in this direction culminated in the development of the first decarbethoxylative arylation reaction that employs fluoromalonamate as a fluoroacetamide surrogate to generate α-aryl-α-fluoroamides in high yields.

Our studies commenced with the decarboxylative arylation of ethyl *N*-bromophenyl-α-fluoromalonamate **2a**, a substrate easily accessible in two steps from the corresponding aniline and diethyl malonate using amidation/fluorination conditions. Using this substrate and the standard conditions (CsF, CH_3CN) employed for the generation of aryne from 2-(trimethylsilyl)-phenyl trifluoromethanesulfonate **1a**, the reaction was carried out at room temperature, and pleasingly, the arylfluoroamide derivative **3a** was obtained in 50% yield. In attempts to improve the efficiency of the reaction, the malonamate substrate **2a** was subjected to various reaction conditions, and in all cases, fluoride source was required to be in excess to produce compound **3a** in reasonable yields (Table 1). When the reaction was carried out at elevated temperature using CsF, the product was obtained in

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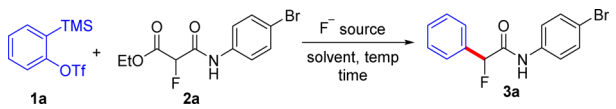
Table 1. Optimization of the Reaction Conditions[a]



entry	F⁻ source	solvent	temp (°C)	time (h)	yield[b] (%)
1	CsF	CH_3CN	25	12	50
2	CsF	CH_3CN	60	12	60
3	KF/18C-6	CH_3CN	25	4	81
4	KF/18C-6	THF	25	12	73
5	KF/18C-6	DMF	25	24	<5
6	TBAF	THF	25	4	72
7	**TBAF**	**CH_3CN**	**25**	**1**	**83**

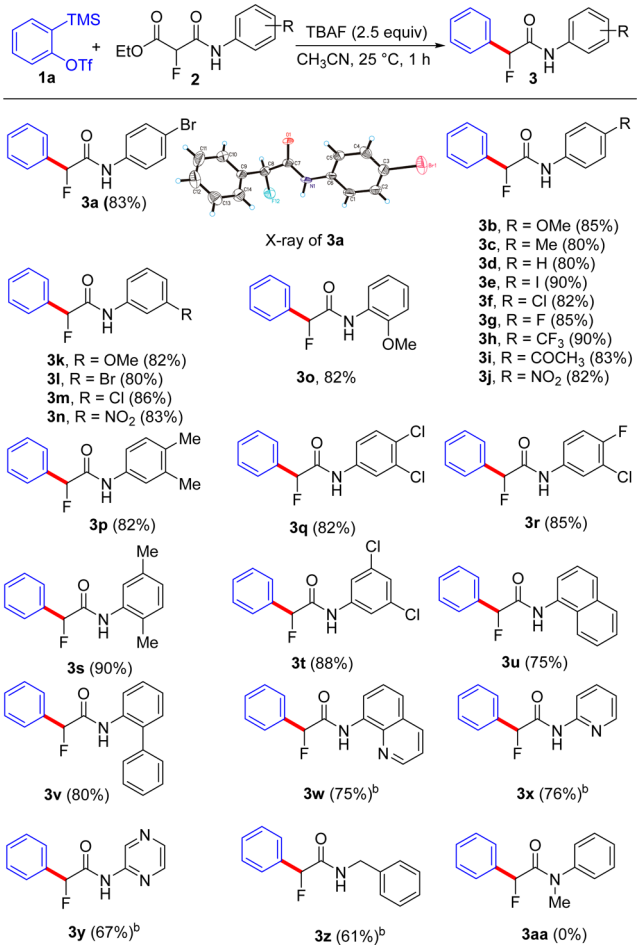
[a]General conditions: **1a** (0.24 mmol), **2a** (0.20 mmol), fluoride source (0.50 mmol), solvent (2.0 mL). [b]Isolated yield after silica gel column chromatography.

60% yield. The reaction conducted using KF/18C-6 as fluoride source provided **3a** in 81% yield. The best result (83%, 1 h, entry 7) was obtained with TBAF-CH_3CN conditions.

Having identified the optimal conditions for this new decarboxylative arylation strategy, we next turned our attention to the evaluation of the scope of this reaction for the amide component. As shown in Scheme 1, a wide variety of functional groups on the phenyl ring of malonamate coupling partner were first investigated. In general, electronically varied *N*-arylmalonamate derivatives underwent this decarboxylative arylation reaction in high yields. The reaction tolerates various functionalities including methoxy, halo, alkyl, trifluoromethyl, enolizable ketone, and nitro moieties at 4-position of the aryl group (**3a**–**j**). The structure of the product was unambiguously confirmed by X-ray analysis of compound **3a**.[15] Subsequently, the electronic effects of the substituents at *m*- and *o*- positions were examined. To our delight, both the electron-rich and electron-withdrawing substituents were well-tolerated, and the corresponding substrates were transformed to arylated products in good to excellent yields (**3k**–**o**). Pleasingly, the malonamate substrates bearing disubstituted aryl group reacted readily with aryne to yield the corresponding arylfluoroamides in excellent yields (**3p**–**t**). The substrates bearing a naphthyl as well as biphenyl ring can also be successfully employed in the reaction (**3u**,**v**). Given the interesting medicinal chemistry applications of this class of compounds, it is important to note that heteroaryl amides can also take part in the reaction. Malonamates bearing heteroarenes including quinoline, pyridine, and pyrazine performed well in the reaction to afford the fluoroamide derivatives in good to excellent yields (**3w**–**y**). Our attempts to further expand the generality of this reaction proved to have little scope with aliphatic amides. Except for *N*-benzyl malonamate (**3z**), other aliphatic amides either failed to react or decomposed under the reaction conditions. We subsequently examined the scope of using *N*,*N*-disubstituted malonamates in this reaction and found tertiary amides unviable for this transformation.

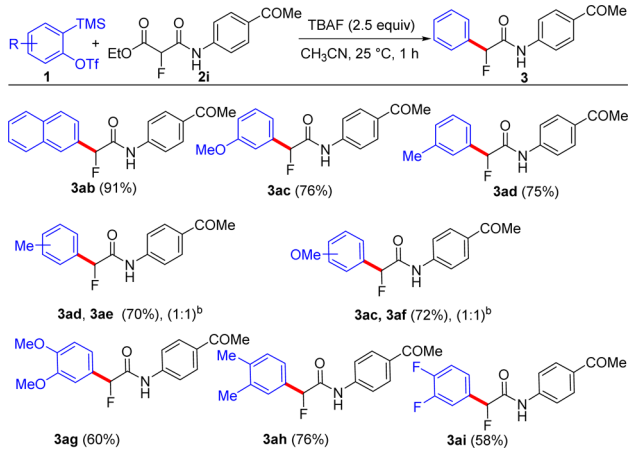
We next sought to evaluate the scope of variously substituted arynes in the decarboxylative arylation. Interestingly, electronically different symmetrical and unsymmetrical arynes also served as effective arylating agents and exhibited high levels of regiocontrol with respect to substitutions on arynes (Scheme 2). For instance, the reaction carried out using 1,2-naphthyne resulted in the formation of the *β*-addition product as a single regioisomer in 91% yield, presumably due to the preferred attack

Scheme 1. Substrate Scope for the Decarbethoxylative Arylation: Variation of Malonamates[a]



[a]General conditions: **1a** (0.24 mmol), **2** (0.20 mmol), TBAF (0.50 mmol), CH_3CN (2.0 mL). Isolated yield after silica gel column chromatography. [b]Reaction time: 12 h.

Scheme 2. Substrate Scope for the Decarbethoxylative Arylation: Variation of Arynes[a]



[a]General conditions: **1** (0.24 mmol), **2i** (0.20 mmol), TBAF (0.50 mmol), CH_3CN (2.0 mL). Isolated yield after silica gel column chromatography. [b]The ratio of regioisomers was determined by ^1H NMR analysis.

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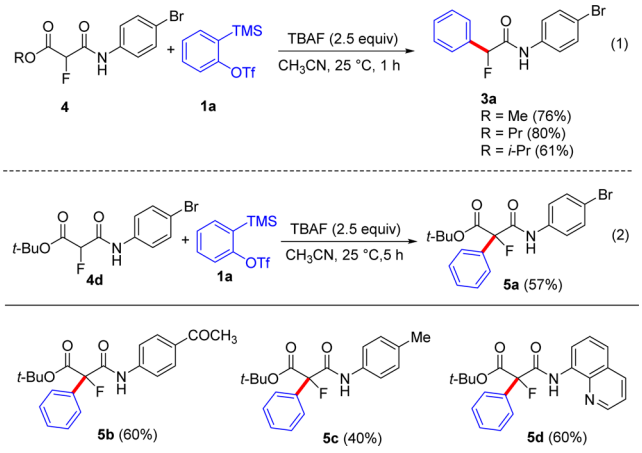
at sterically less demanding position (**3ab**). Similarly, 3-methoxy-1,2-benzyne provided compound **3ac** as a single regioisomer. Moreover, a high level of regiocontrol was observed when aryne having methyl substitution at the 3 position was used (**3ad**). However, the reaction conducted using 4-methylbenzyne resulted in the formation of an inseparable mixture of regioisomers **3ae** and **3ad** in 70% yield. The reaction using 4-methoxybenzyne also afforded the product as an inseparable mixture of regioisomers in 72% yield. The protocol was also compatible for disubstituted arynes such as dimethoxy, dimethyl, and difluoroarynes, thus rendering the arylfluoroacetamides in reasonable to good yields (**3ag–ai**).

Moreover, the reaction was possible with various alkyl esters of malonamate, and the corresponding product was obtained in reasonably good yields (Scheme 3, eq 1). Interestingly, the

Scheme 3. Substrate Scope for the Arylation of *tert*-Butyl Malonamates: Variation of Amides

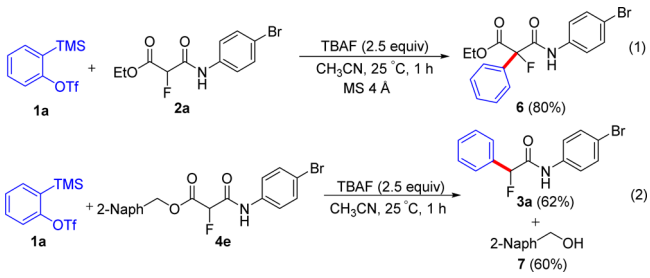


anticipated decarbalkoxylative arylation reaction did not take place when the *tert*-butyl malonamate **4d** was used; instead, the reaction generated arylated product exclusively (Scheme 3, eq 2). This reaction, though in moderate yields, offers an efficient strategy for the formation of fluorine-containing quaternary C-center, and hence, a brief evaluation on the scope was carried out (Scheme 3). Pleasingly, the reactions conducted using the *tert*-butyl ester of various malonamates furnished the arylated products in moderate yields (**5a–d**).

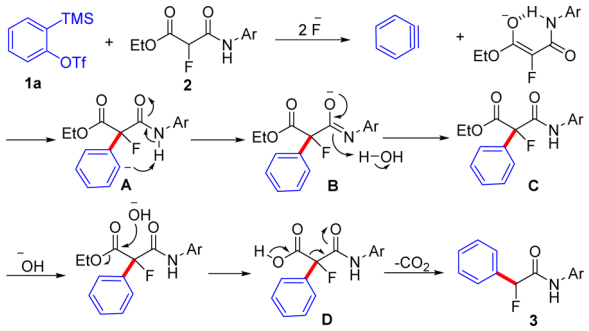
After the scope and limitations of the methodology were established, a few mechanistic experiments were performed to probe the reaction mechanism. The arylation reaction carried out in the presence of 4 Å molecular sieves afforded exclusively arylated product **6**, suggesting that the decarboxylation step most likely involves hydrolysis of the ester moiety by the residual water present in the media (Scheme 4, eq 1). This was further confirmed by carrying out a reaction using malonamate naphthyl ester **4e** where we could isolate the byproduct, naphthyl alcohol, in 60% yield along with 62% of the decarboxylative arylation product **3a** (Scheme 4, eq 2). These results show that the reaction involves the hydrolysis of the ester moiety followed by decarboxylation.

On the basis of the aforementioned experiments and literature reports, a plausible mechanism is proposed (Scheme 5). The reaction is likely initiated by the fluoride-induced generation of aryne and the enolate of compound **2**. The enolate subsequently undergoes nucleophilic addition to aryne to generate tetrasubstituted malonamate **B** after the intramolecular protonation of

Scheme 4. Mechanistic Experiments



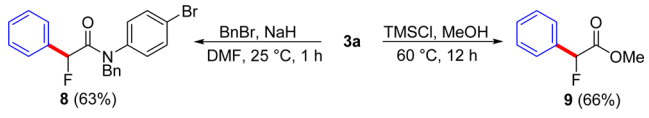
Scheme 5. Proposed Mechanistic Pathway



aryl anion by the amide moiety. Protonation of intermediate **B** by residual water generates the arylated malonamate **C**. Finally, the hydrolysis of the ester moiety by hydroxide ion followed by decarboxylation produces the arylfluoroacetamides **3**. This spontaneous decarbalkoxylation may be attributed to the increased electrophilicity of the α-carbon center rendered by fluorine as well as the newly installed aryl group. The exclusive formation of arylated malonamate in the case of malonamate *tert*-butyl esters and failed attempts using *N,N*-disubstituted malonamates further supports the proposed mechanism.

We next explored the synthetic utility of arylfluoroacetamides. The arylfluoroamide derivatives can be readily converted to the corresponding esters using alcoholysis conditions. Moreover, alkylation of **3a** using benzyl bromide under basic conditions provided the corresponding *N*-benzylated fluoroamide **8** in 63% yield (Scheme 6).

Scheme 6. Synthetic Transformations



In summary, a practical, metal-free, and efficient decarbethoxylative arylation of fluoromalonamates yielding synthetically valuable arylfluoroacetamides has been developed. The generality of this reaction has been illustrated by employing a wide range of fluoromalonamates including aryl, heteroaryl, and aliphatic amides, and substituted arynes. Unlike the other reports on α-arylation of fluoroacetic acid derivatives, this new process works under mild and operationally simple conditions. We have further demonstrated that the use of bulky *tert*-butyl ester of malonamates can prevent the decarbalkoxylation step to exclusively furnish the arylated products. Subsequently, it was demonstrated that these arylfluoroamides could be readily converted to their corresponding fluoroesters.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03072.

Detailed experimental procedures, complete characterization data, and NMR spectra (PDF)
X-ray data for compound **3a** (CIF)

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Notes

The authors declare no competing financial interest.

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(15) Crystallographic data for **3a** (CCDC 1543377) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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