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Copper-Mediated Synthesis of Monofluoro Aryl Acetates via Decarboxylative Cross-Coupling

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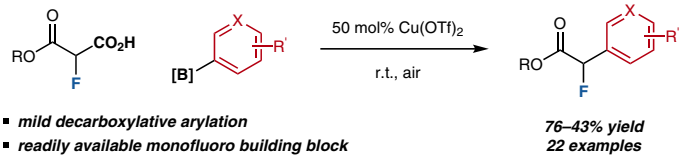
Dedicated to Victor Snieckus on the occasion of his 80th birthday.



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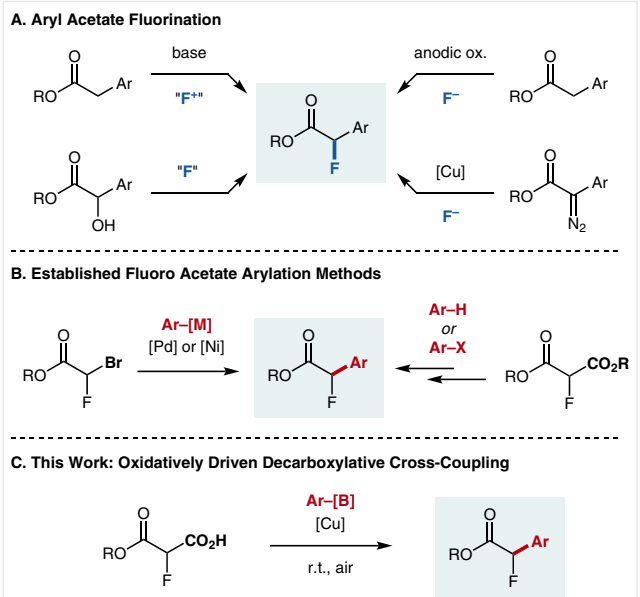
Abstract We report the Cu-promoted oxidative cross-coupling of α-fluoromalonate half-esters and aryl boron reagents to deliver monofluoro α-aryl acetates under mild conditions (in air at room temperature). The reaction uses a simple, readily available monofluorinated building block to generate arylated compounds with functional groups that are not easily tolerated by existing methods, such as aryl bromides, iodides, pyridines, and pyrimidines.

Key words arylation, cross-coupling, copper, aerobic catalysis, fluorine

The installation of fluorine atoms into bioactive molecules can have a profound impact on the physical and biochemical properties of the target compound. The ability to selectively incorporate fluorine into complex molecules or rapidly build structural complexity from available fluorinated chemical feedstocks is a wide spanning goal in synthetic methodology development because a strong need for such technology exists in the drug discovery and agrochemical sectors.[1] Challenges associated with enabling mild and general synthetic routes to prepare polyfunctionalized organofluorine compounds has motivated the development of new fluorination reactions and fluorinating reagents, and has led to increased availability of fluorine-containing synthetic building blocks.[2]

The preparation of α-fluoro aryl acetate derivatives typify the evolution of the field, whereby modern metal-catalyzed strategies and the use of novel fluorinating agents have emerged,[2b,3] offering the potential to supplant traditional methodologies such as electrophilic fluorination of enolates generated under strongly basic conditions,[4] electrochemical routes,[5] or the deoxyfluorination of α-hydroxy esters,[6,7] which require forcing reaction conditions with highly reactive fluorinating agents (Scheme 1A). Alternatively, the ability to arylate simple, readily available monofluoro acetate derivatives presents an attractive alternative route to polyfunctionalized fluorinated derivatives (Scheme 1B).[8] In this regard, the Pd- or Ni-catalyzed cross-coupling of α-bromo-α-fluoroacetates with aryl nucleophiles provides direct access to monofluoro aryl acetates.[9,10] Although these reports provide a useful strategy for preparing increasingly complex benzyl fluoride compounds, relatively high reaction temperatures (80–100 °C), the requirement



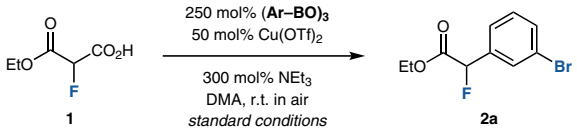
Scheme 1 Synthetic methods used for the preparation of monofluoro aryl acetates; (A) Fluorination of aryl acetates, α-hydroxy aryl acetates, or α-diazo esters; (B) Arylation of fluoroacetate and malonate derivatives; (C) Cu-promoted decarboxylative arylation of fluoromalonic half-esters with aryl boron reagents reported herein

for substrate bromination as a prefunctionalization step, and the lack of tolerance to reactive electrophilic functionality or substrates bearing basic nitrogen heterocycles remain a challenge for the general application of these approaches. Dialkyl fluoromalonate derivatives can be arylated via S_NAr[11] or metal-catalyzed cross-coupling methods;[12] however, these reactions proceed with limited substrate scope and with the requirement for subsequent dealkoxycarbonylation steps to generate the aryl acetate product (Scheme 1B).

We have recently developed Cu-mediated oxidative cross-coupling reactions to enable the functionalization of malonate derivatives with aryl boron reagents.[13,14] This reaction manifold provides an alternative to traditional organo(pseudo)halide / nucleophile carbon–carbon bond forming arylation processes, tolerating electrophilic functional groups that are reactive under typical coupling conditions. We report herein that fluorinated malonic acid derivatives can be employed as substrates in decarboxylative arylation processes promoted by Cu to enable an exceptionally mild route to high-value fluorinated compounds (Scheme 1C).

Monofluoro malonate half-esters present potentially confounding chemical properties for cross-coupling catalysis. The carboxylic acid moiety is rendered more acidic in comparison to the unsubstituted derivative via inductive effects; however, the malonyl C–H group is considerably *less* acidic due to fluorine's anion destabilizing α-effect, thus resulting in a more nucleophilic enolate species upon formation of a putative dianion.[15] Perhaps unsurprisingly, use of conditions established for the cross-coupling of monoethyl malonate[13b] resulted in a poor yield of the desired monofluoro aryl acetate product when using the fluorinated acid **1** (34% yield; Table 1, entry 1). In competition studies between protio- and fluoromalonic half-esters, the unsubstituted half-ester was seen to dramatically out-compete the fluorinated derivative, suggesting that the fluorine group induces a significant reduction in decarboxylative cross-coupling reactivity (see the Supporting Information for details). Undeterred, a range of experimental parameters were explored, ultimately resulting in the identification of mild conditions that resulted in good yields of product (50 mol% $Cu(OTf)_2$, 2.5 equiv aryl boroxine, room temperature in air: 78% yield; entry 2). Selected reaction parameters that are important for a productive process are outlined in Table 1. $Cu(OAc)_2$ was completely ineffective as a catalyst (<2% yield); however, Cu(I) species with noncoordinating counter anions, such as $Cu(MeCN)_4PF_6$ provided good yields of product (74%), presumably due to rapid oxidation under the reaction conditions. Ambient air provided the best conditions for reoxidation of copper; a pure O_2 environment resulted in 30% product yield, whereas reactions conducted under N_2 resulted at 14% yield (entries 5 and 6). Aryl boroxines were superior boron reagents; the use B(neop) derivatives resulted in acceptable yields (64%), but B(pin) or $B(OH)_2$ reagents performed poorly (entries 7–9). The amount of aryl boron could be reduced to 1.2 equivalents with a minor decrease in yield (58%; entry 10), and the corresponding potassium carboxylate of **1** could be used instead of the acid with only a slight reduction in product formation (62%; entry 11). The aryl boroxine can be used as the limiting reagent upon minor modifications to the reaction conditions (Scheme 2). Highlighting the importance of the half-ester structure to reactivity, diethyl fluoromalonate, fluoromalonic acid, and ethyl fluoroacetate failed to give more than 10% product under the standard reaction conditions (Figure 1).

Table 1 Effect of Reaction Parameters on the Cu-Promoted Oxidative Cross-Coupling of α-Fluoromalonic Half Esters and Aryl Boron Reagents



Entry	Variation from standard conditions[a]	Conv. (%)[b]	Yield (%)[b]
1	from ref.[13b] (malonate half ester conditions)	68	34
2	none	>95	78
3	$Cu(OAc)_2$ instead of $Cu(OTf)_2$	50	<2
4	$Cu(MeCN)_4PF_6$ instead of $Cu(OTf)_2$	>95	74
5	O_2 atmosphere instead of air	65	30
6	N_2 instead of air	55	14
7	Ar–B(neop) instead of boroxine	88	64
8	Ar–B(pin) instead of boroxine	70	14
9	Ar–$B(OH)_2$ instead of boroxine	20	<2
10	1.2 equiv boroxine	82	58
11	K-carboxylate instead of free acid	>95	62

[a] 0.2 M in DMA, 48 hours.
[b] Conversions and yields determined by calibrated ^1H NMR.

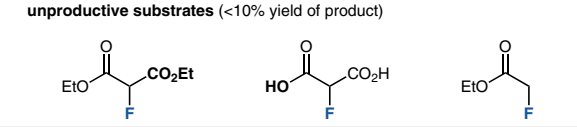
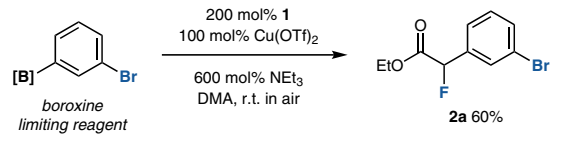


Figure 1 Unproductive substrates (<10% yield of product)

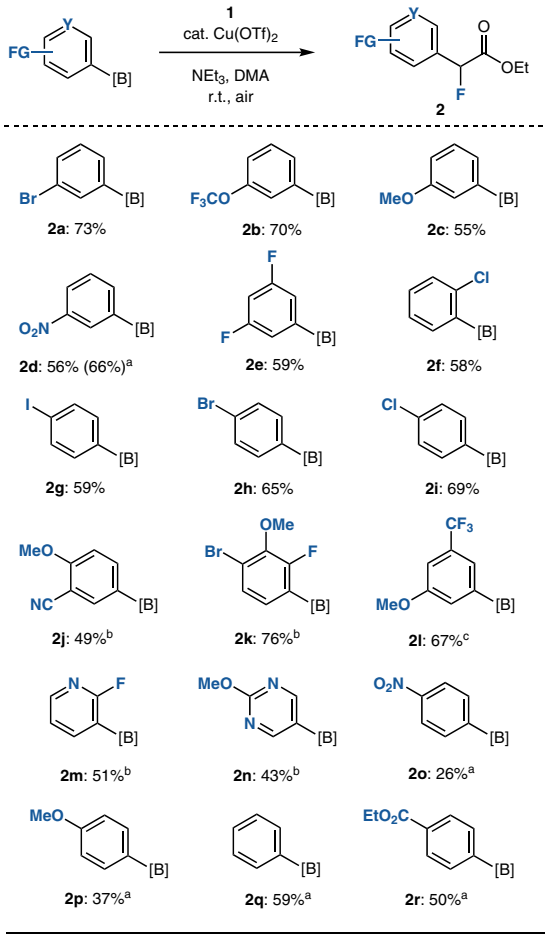


Scheme 2 Preparation of a monofluoro aryl acetate using the arylating species as the limiting reagent

The scope of the oxidative cross-coupling reaction between monofluoromalonate half ester **1** and a structurally diverse series of aryl boron substrates was explored (Scheme 3). The reaction proceeds with synthetically useful yields under the standard conditions for aryl boroxines containing halogens (**2a**, **2e–i**), including an aryl iodide (**2g**), trifluoromethoxy (**2b**), nitro (**2d**), methoxy (**2c**), trifluoromethyl (**2l**), cyano (**2j**), and ester groups (**2r**), including substrates with polysubstitution (**2e**, **2j–l**). Pyridine and pyrimidine heterocycles can be alkylated in moderate yields (**2j**, **2k**). For more complex substrates in which boroxine generation is less convenient (such as heteroaryl substrates), the corresponding aryl B(neop) reagent could be employed (**2j–n**). The use of highly electron-deficient coupling partners such as 4-NO_2 aryl boroxine (**2o**) led to lower yields owing to the formation of diarylated product; this was presumably because of the high acidity of the monofluoro aryl acetate product. The electron-rich substrate 4-OMe aryl boroxine delivered the product in modest yield due to sluggish reactivity (**2p**; 37%). The reaction was not compatible with NH amides, aldehydes or bulkier *ortho*-substituted boroxines (2-tolyl). Whereas the scope of the reactivity is not universal with respect to the arylating reagent, the tolerance to potentially reactive aryl iodides and bromides and ability to generate electron-poor heterocyclic monofluoro aryl acetates addresses reactivity problems found when using α-bromo-α-fluoroacetates under Ni or Pd catalysis or Cu-catalyzed fluorination reactions of α-diazo esters.[3a,9,16]

The scope of reactivity with alternative α-fluoro carboxylic acids was also briefly explored. Isopropyl, benzyl, α,α,α-trifluoroethyl, and allyl half-esters could be arylated under the standard conditions with acceptable yields (**3a–d**, 56–74%; Scheme 4). An α-fluoro-α-keto acid substrate was not a productive reaction partner, forming less than 10% product (**3e**). In a competition study between the Et-(**1**) and CF_3CH_2-(**3c**) substituted malonate half-esters, the α,α,α-trifluoroethyl derived substrate was observed to form the product at approximately twice the rate of the ethyl substrate (see the Supporting Information for a plot). These results confirm the empirical trend that increasing the C–H acidity of the malonic half-ester results in an increased rate of reaction, and suggest that the generation of a Cu/malonic dianion intermediate is a key step in the reaction.

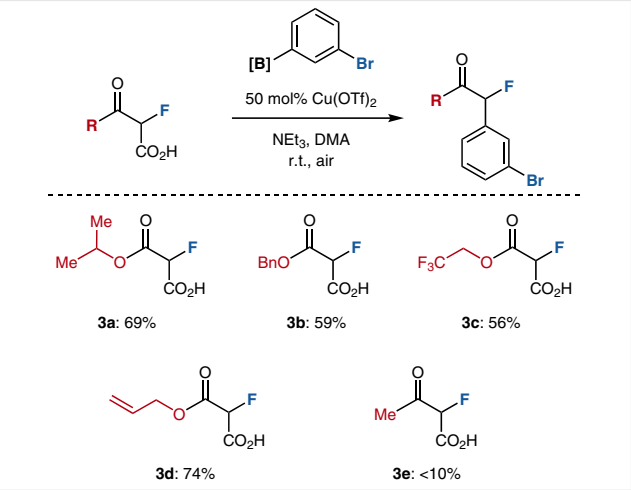
A potential series of mechanistic steps for the cross-coupling reaction is given in Scheme 5. Transmetalation of the substrates and disproportion between two Cu(II) species would generate a Cu(III) aryl malonate intermediate. These steps are similar to those proposed for related Cu-catalyzed oxidative coupling reactions of aryl boron reagents (the Chan–Evans–Lam reaction).[17] The Cu(III) species, similar to those postulated in Hurtley-type cross-couplings of aryl electrophiles and malonates,[18] would be capable of undergoing facile carbon–carbon bond-forming reductive elimination to form an aryl carboxylate. Molecular oxygen



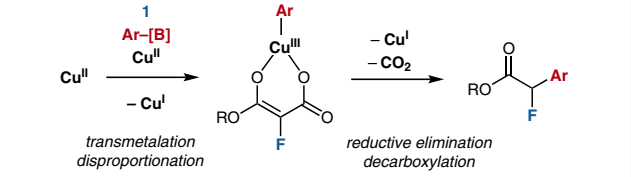
Scheme 3 Aryl boron substrate scope for the Cu-mediated oxidative coupling of fluoromalonate half esters. *Reagents and conditions*: aryl boroxine (250 mol%), $Cu(OTf)_2$ (50 mol%), NEt_3 (300 mol%), 0.2 M; [a] Yield based on $^1H/^{19}F$ NMR spectroscopic analysis; [b] Obtained using ArB(neop); [c] Aryl[B] (200 mol%) was used.

in ambient air then reoxidizes the two equivalents of Cu(I) generated in the reaction back to Cu(II). Given that α-fluoro ethyl acetate is not observed as a side product in the reaction, we favor a process in which carbon–carbon bond formation precedes decarboxylation;[19] however, additional studies are required to provide a more accurate mechanistic description of the reaction.

In summary, we have reported a mild and efficient route to monofluoro aryl acetates by the oxidative cross-coupling of fluoromalonic acid derivatives and aryl boron reagents.[20] The reaction serves as a useful complement to both aryl acetate fluorination protocols and cross-coupling reactions that use halogenated fluoroacetates. The demonstrated tolerance towards electrophilic aryl halide functionality and nitrogen-containing heterocycles aids in addressing challenges associated with traditional cross-coupling methods. Future efforts will focus on developing a clear



Scheme 4 Scope of alternative α-fluoro carboxylic acid derivatives in the Cu-mediated decarboxylative cross-coupling reaction with aryl boron reagents



Scheme 5 Potential mechanistic steps in the Cu-mediated cross-coupling of α-fluoromalonic half esters and aryl boron reagents

mechanistic understanding of the process and expanding the diversity of α-fluorinated acids that can be used a coupling partners.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588516.

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(20) **General Procedure for the Copper-Mediated Synthesis of Monofluoro Aryl Acetates via Decarboxylative Cross-Coupling; Procedure A (0.50 mmol scale):** In an atmosphere controlled glovebox, $Cu(OTf)_2$ (90.4 mg, 0.250 mmol, 0.50 equiv) and aryl boronic ester (1.25 mmol, 2.5 equiv) or aryl boroxine (0.42 mmol, 2.5 equiv Ar-B) were added sequentially to a 1 dram screw-top vial containing a stir bar. The fluoromalonic half ester (0.50 mmol, 1.0 equiv) was added as a solution in anhydrous DMA (1.0 mL). Additional DMA (2 × 0.6 mL) was used to quantitatively transfer the solution to the reaction mixture. The solution was stirred until the majority of the solid had dissolved, followed by the addition of NEt_3 (0.2 mL, 1.5 mmol, 3.0 equiv). The vial was sealed with a PTFE-lined cap, removed from the glovebox, and the PTFE septum was pierced with an 18 gauge needle. The reaction mixture was gently stirred at room temperature. Upon reaction completion (24 to 72 h), the reaction mixture was diluted with EtOAc (60 mL), and washed sequentially with NH_4Cl (60 mL), 0.5 M NaOH (2 × 60 mL), and brine (60 mL). The organic layer was dried with Na_2SO_4, concentrated in vacuo, and purified by silica gel chromatography. Note, the needle gauge and vial size can influence the reaction rates and overall efficiency, see the Supporting Information for more detail. Reactions conducted without the use of a glovebox gave similar results. $Cu(OTf)_2$ and aryl boroxines are hydroscopic and should be stored under inert gas.

Synthesis of 2b: Prepared according to Procedure A from the corresponding aryl boroxine (229 mg, 0.42 mmol, 2.5 equiv Ar–B) and fluoromalonic half ester (75 mg, 0.50 mmol, 1.0 equiv), 49 h. Isolated in 73% yield after purification by column chromatography (10:1, Hex/EtOAc) as a light-yellow oil. ^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.63–7.61 (m, 1 H), 7.54–7.51 (m, 1 H), 7.41–7.38 (m, 1 H), 7.29–7.26 (m, 1 H), 5.72 (d, *J* = 47.4 Hz, 1 H), 4.30–4.20 (m, 2 H), 1.26 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 176 MHz): δ = 167.9 (d, *J* = 27.1 Hz), 136.3 (d, *J* = 21.3 Hz), 132.6, 130.3, 129.5 (d, *J* = 6.7 Hz), 125.0 (d, *J* = 6.2 Hz), 122.8, 88.4 (d, *J* = 187.6 Hz), 62.1, 14.0; ^{19}F NMR ($CDCl_3$, 377 MHz): δ = –182.3 (d, *J* = 47.4 Hz); HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{10}H_{10}BrFO_4$: 259.9848; found: 259.9846