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Ambient Decarboxylative Arylation of Malonate Half-Esters via Oxidative Catalysis

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Supporting Information

ABSTRACT: We report decarboxylative carbonyl α-arylation by coupling of arylboron nucleophiles with malonic acid derivatives. This process is enabled by the merger of aerobic oxidative Cu catalysis with decarboxylative enolate interception reminiscent of malonyl-CoA reactivity in polyketide biosynthesis. This method enables the synthesis of monoaryl acetate derivatives containing electrophilic functional groups that are incompatible with existing α-arylation reactivity paradigms. The utility of the reaction is demonstrated in drug intermediate synthesis and late-stage functionalization.

In the biosynthesis of polyketides and fatty acids, carbon−carbon bond formation proceeds via decarboxylative cross-condensation between malonic acid derivatives such as malonyl-CoA and enzyme-bound acyl electrophiles.[1] A variety of conceptually related metal- or organocatalyzed reactions have been developed in which malonates and related species undergo decarboxylation and coupling with carbonyl or allylic electrophiles.[2] These reactions obviate the need for high temperatures, strongly basic mediators, or prior stoichiometric manipulations to generate the enolate component (Figure 1a).[3] By contrast, there are limited reports of decarboxylative coupling reactions of malonate derivatives with aryl electrophiles. Pd-catalyzed coupling of malonic acid derivatives with aryl halides requires pre-deprotonation of the acid and high temperatures (≥120 °C), presumably in order to generate a Pd enolate via thermal decarboxylation.[4] The development of mild and robust methods for decarboxylative α-arylation would find broad appeal, as the preparation of polyfunctionalized monoaryl acetic acids via cross-coupling of simple acetate derivatives remains a significant challenge in synthetic chemistry.

Unstabilized acetates can be arylated via in situ enolization under strongly basic conditions incompatible with protic or electrophilic functionality[5] or subjected to stoichiometric manipulations to generate preformed silyl or metal enolates.[6] These strategies significantly reduce synthetic efficiency and utility in complex molecule synthesis. Common methods used in medicinal chemistry campaigns requiring α-aryl carbonyl compounds remain traditional S_NAr or metal-catalyzed coupling reactions involving dialkyl malonates, followed by hydrolysis and thermal decarboxylation. Thus, access to complex monoaryl acetic acids (such as those in Figure 1d) generally requires multistep substrate-specific processes.[7] The dearth of mild malonic acid decarboxylative arylation reactions stands in contrast to the burgeoning fields of radical arylative decarboxylations of α-heteroatom-substituted acids via platinum-group metal photoredox catalysis[8] or the use of redox-active esters functionalized with activators to promote bond cleavage.[9]

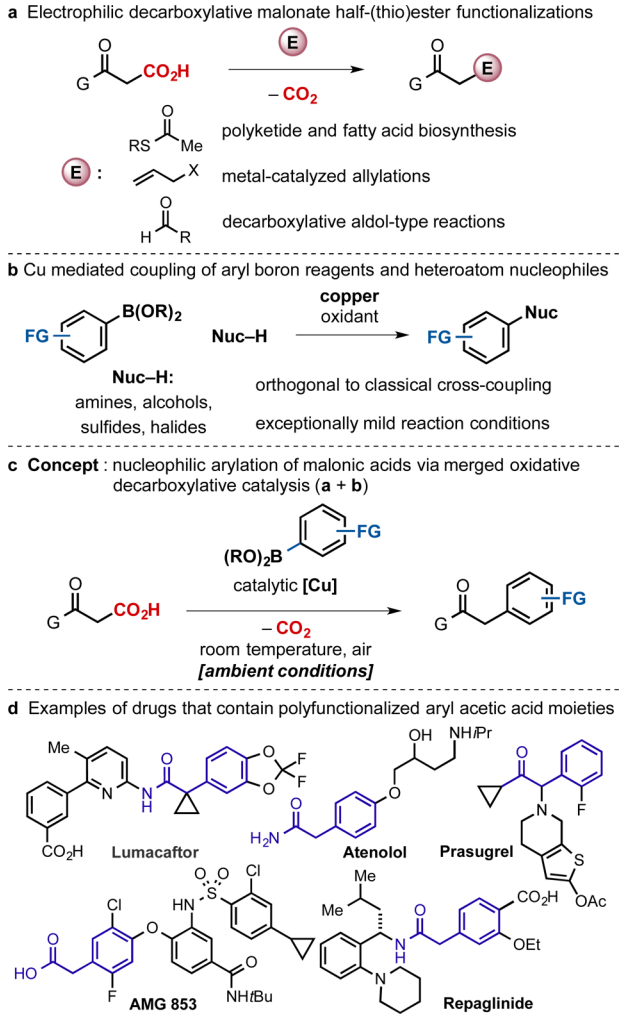

Figure 1. Reactivity of malonic acid derivatives, oxidative coupling, and α-aryl carbonyl structures in bioactive molecules.

We were inspired by the exceptionally mild conditions under which Cu(II)-catalyzed decarboxylative aldol-type reactions occur[3a,10] and hypothesized that combining the use of a Cu(II) (pre)catalyst, a malonic acid derivative, and an appropriate aryl

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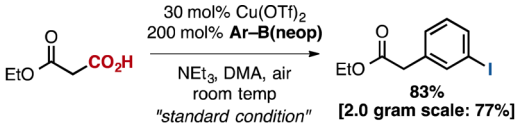

Deviations from standard conditions [y: yield, c: conversion]

Ar–B	y (%)	(% c)	Cu Source	y (%)	(% c)	Conditions	y (%)	(% c)
$(ArBO)_3$	68	(98)	$Cu(OAc)_2$	14	(74)	O_2 instead of air	31	(99)
$ArB(OH)_2$	19	(59)	$CuSO_4$	20	(42)	RCO_2K half ester	36	(39)
ArBpin	40	(99)	$Cu(MeCN)_4PF_6$	73	(99)	no Et_3N	0	(0)
$ArBF_3K$	0	(42)	**CuI**	**70**	**(99)**	**1.2 equiv Ar-B**	**74**	**(99)**

Figure 2. Overview of reaction discovery and optimization.

coupling partner could allow for decarboxylative C−C bond formation without the detriments of thermal activation and strongly basic conditions. We were encouraged by the mild and robust nature of oxidative copper(II)-catalyzed cross-coupling reactions of two nucleophilic partners.[11] The Cu-catalyzed oxidative arylation of heteroatom nucleophiles with arylboronic acids for the preparation of anilines and phenols (Figure 1b)[12] occurs under mild conditions using the O_2 present in ambient air as the oxidant. This reactivity has been extended to the arylation of carbon-based nucleophiles, including the stoichiometric arylation of activated methylenes.[13] Thus, a new reactivity platform that merges ambient decarboxylation of malonic acids and aerobic copper catalysis could allow enolate arylation to occur with unprecedented tolerance toward reactive functional groups, providing a solution to the difficulties associated with synthesizing aryl acetates (Figure 1c). The abundance of α-aryl carbonyl units found embedded in the cores of pharmaceuticals, ranging from relatively simple nonsteroidal anti-inflammatory drugs like naproxen to structurally complex, densely functionalized bioactive molecules such as lumacaftor, prasugrel, and repaglinide, provided clear motivation for the development of such a method (Figure 1d).

We were cognizant of the potential difficulties associated with realizing an oxidative decarboxylative arylation reaction involving malonic acids, particularly as carboxylic acids themselves are viable partners for copper-catalyzed O-arylation[14] and irreversible decarboxylation or protodeborylation would result in unreactive substrates. Attempts to oxidatively couple enolate equivalents with arylboron reagents mediated by copper involving in situ deprotonation or the use of preformed silyl ketene acetals were not successful. These results highlight an inherent difficulty in oxidative coupling reactions,[15] as the use of preformed enolates resulted in the exclusive formation of homocoupling products derived from both reaction partners without detectable cross-coupling. However, monoethyl malonate was observed to engage in highly selective catalytic decarboxylative cross-coupling with 3-iodophenyl boronic neopentyl ester [B(neop)] in air at room temperature with $Cu(OTf)_2$ to give the desired product in 83% yield (Figure 2). No cross- or homocoupling at the reactive electrophilic aryl iodide site or competing arylation of the carboxylic acid was observed. The process can be scaled up to deliver gram quantities of aryl acetate product by using an uncapped round-bottom flask (77% yield, 1.6 g of product). To briefly describe key experimental parameters in reaction development, neopentyl glycol-derived boronic esters were superior to pinacol ester, boroxine, or free boronic acid forms. Alternative Cu(II) salts performed poorly, but Cu(I) species, such as $Cu(MeCN)_4PF_6$ or CuI, could be used as catalysts; in these cases a significant induction period was observed.[16] These results suggest that the

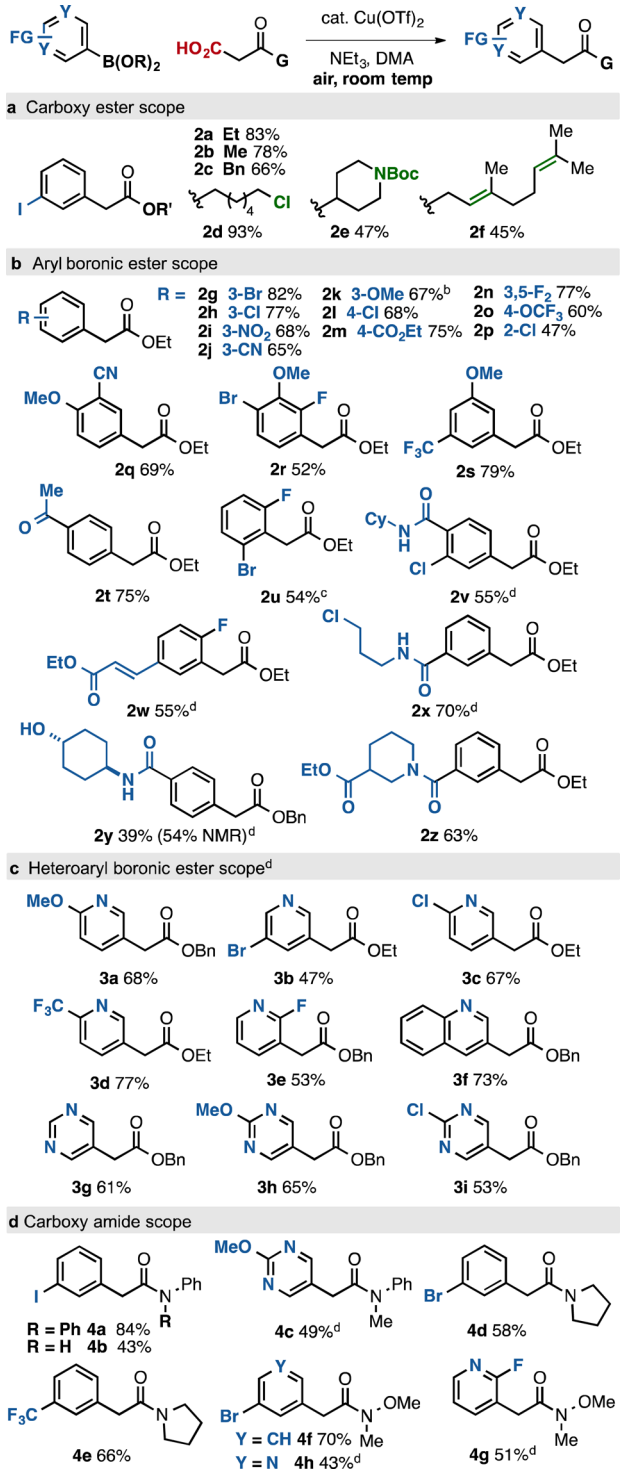

Figure 3. Scope of the Cu-catalyzed decarboxylative cross-coupling of malonate derivatives and arylboronic esters. Notes: [a]Conditions: 0.3 M in DMA or DCE, 24−72 h, 30 mol % $Cu(OTf)_2$, 1.5−2.0 equiv of arylboronic ester, in air at room temperature. [b]100 mol % Cu. [c]3 equiv of ArB(neop). [d]50 mol % Cu. See the Supporting Information (SI) for full details.

nature of the counterion of the Cu (pre)catalyst influences the reactivity more than the initial oxidation state.

Because of the mild, ambient nature of the transformation, the oxidative decarboxylative α-arylation reaction is amenable to coupling of substrates containing a host of functional groups that would be potentially complicating with established methods

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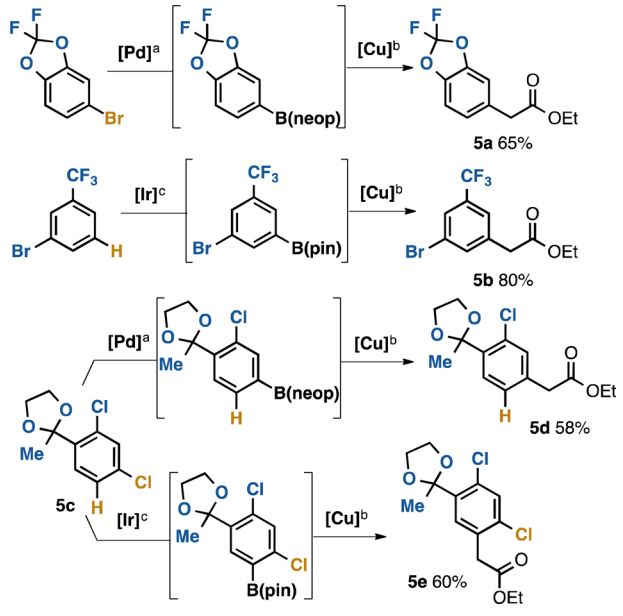

Figure 4. Sequential arene borylation/decarboxylative coupling reactions. Notes: [a]1.1 equiv of $B_2(neop)_2$, 5 mol % $PdCl_2MeCN_2$, 6 mol % DiPPF, KOAc. [b]Standard conditions (see Figure 2). [c]0.52 equiv of B_2pin_2, 1.5–5 mol % $[IrCOD(OMe)]_2$, 3–10 mol % dtbpy. See the SI for full details.

(Figure 3a). The reaction tolerates alkyl halides (**2d**, **2x**), aryl halides (**2a**–**h**, **2l**, **2p**, **2r**, **2u**, **2w**), enolizable ketones (**2t**) and esters (**2z**), Michael acceptors (**2w**), electron-rich olefins (**2f**), and nitriles (**2j**, **2q**) as well as protic nitrogen (**2v**, **2y**, **4b**) and oxygen (**2y**) groups. The ester moiety can range from relatively simple, easy to dealkylate groups such as methyl or benzyl to species containing more complex functional groups (**2d**–**f**). Heteroaryl boronic esters such as substituted pyridines (**3a**–**e**), quinolines (**3f**), and pyrimidines (**3g**–**l**), including halogenated examples, are smoothly cross-coupled to give heteroaryl acetate adducts. Malonic monoamides undergo decarboxylative (hetero)arylation under the standard conditions, including NH amides (**4b**), aryl–alkyl amides (**4c**) and dialkyl amides (**4d**, **4e**). While β-keto acids are not currently viable cross-coupling partners, Weinreb amides, versatile ketone surrogates, can be employed with both halogenated arenes and pyridines (**4f**–**h**).

A large range of arylboronic acids and esters are commercially available; however, in cases where the arylboron reagent is not immediately available, the oxidative coupling can be conducted in tandem with an arene borylation step (Figure 4). Aryl halides can be subjected to Pd-catalyzed borylation[17] to generate the corresponding aryl–B(neop) reagent, which can be used after extractive workup without chromatographic purification to give **5a**. Ir-catalyzed C–H borylation[18] can be used to generate products of formal carbonyl α-C–H arylation (**5b**). The combined power of metal-catalyzed borylation and Cu-catalyzed decarboxylative malonate arylation can be leveraged to achieve regiocontrolled alkylation of substituted aromatics such as chloroarene **5c** in a straightforward and predictable manner to give two distinct compounds (**5d** and **5e**) from a common starting material.

The applicability of this new copper-catalyzed decarboxylative arylation reaction was demonstrated in the preparation of **6a**, the α-aryl cyclopropyl ketone core of prasugrel (Figure 5a), which was synthesized in 51% yield in two steps via decarboxylative arylation of the Weinreb amide derivative followed by treatment

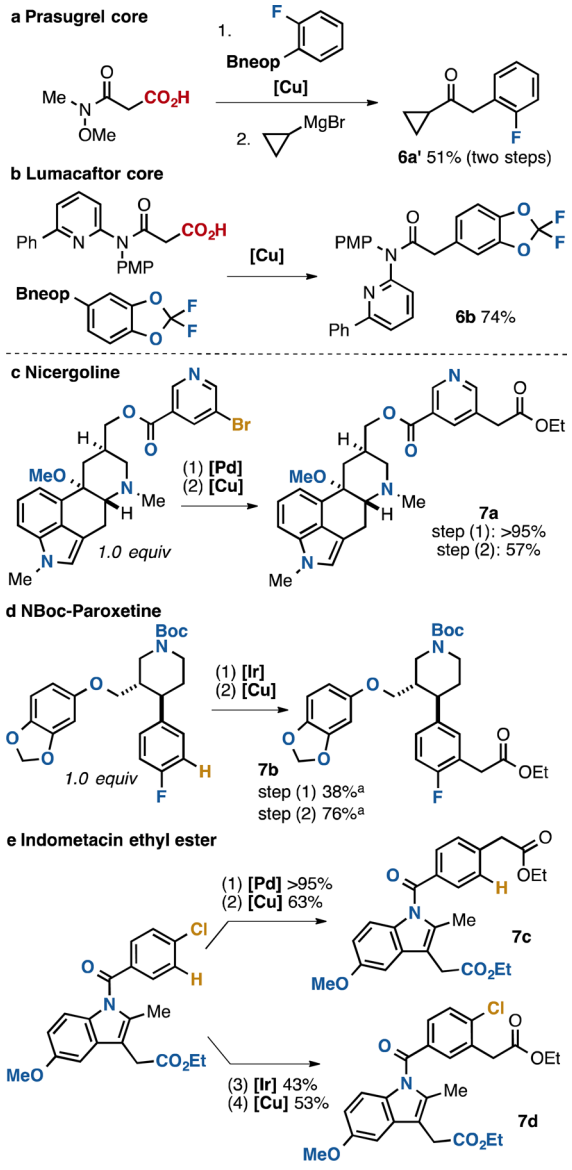

Figure 5. Applications of Cu-catalyzed decarboxylative malonate arylation in complex molecule synthesis and functionalization. Note: [a]Based on recovered starting material. See the SI for full experimental details.

with cyclopropyl Grignard reagent. The arylated core of lumacaftor was prepared by coupling the *p*-methoxyphenyl-protected pyridyl α-carboxy amide and a functionalized aryl B(neop) reagent (Figure 5b) to deliver the target **6b** in 74% yield.

The potential to functionalize complex molecules using this ambient decarboxylative strategy was tested on a variety of arene-containing drug molecules. The complex alkaloid nicergoline could be borylated quantitatively and cross-coupled to monoethyl malonate in 57% yield (**7a**).

N-Boc-paroxetine could be selectively alkylated at one of the five aryl C–H positions to deliver **7b** via an Ir-catalyzed diborylation/monodeborylation strategy followed by decarboxylative cross-coupling. Indometacin ethyl ester could be diversified into two unique derivatives by employing either Pd-catalyzed aryl chloride borylation followed by oxidative coupling (**7c**) or Ir-catalyzed C–H borylation followed by oxidative coupling (**7d**) to give the aryl acetate derivatives in synthetically

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useful yields (oxidative coupling yields of 63% and 53%, respectively). These results support the prospect that malonic half-esters may be used as two-carbon units to synthesize and diversify druglike molecules in medicinal chemistry campaigns by employing the reactivity platform described herein.

We have reported a new oxidative coupling method for the mild and efficient construction of sp^2–sp^3 carbon–carbon bonds.[19] This decarboxylative α-arylation of malonic half-esters and amides proceeds at room temperature in air under mildly basic conditions and employs both a simple copper catalyst and stable arylboronic esters. In contrast with existing enolate arylation chemistry, this oxidative strategy is compatible with protic and electrophilic functional groups, facilitating applications in late-stage functionalization. We have demonstrated that biomimetic decarboxylative trapping of malonate derivatives can provide new routes to the cores of drug molecules, and it should find immediate use in the preparation of aryl acetates and related derivatives in the context of functional molecule synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08906.

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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