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Authors: Patrick J Moon, Anis Fahandej-Sadi, Wenyu Qian, and Rylan J. Lundgren

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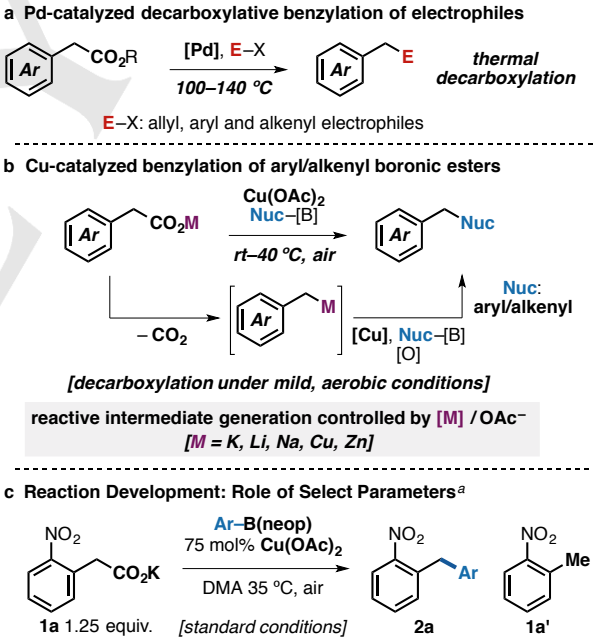
Decarboxylative Benzylation of sp^2-Organoboron Reagents

Patrick J. Moon, Anis Fahandej-Sadi, Wenyu Qian, Rylan J. Lundgren* [a]

Abstract: *The Cu-catalyzed decarboxylative benzylation of aryl and alkenyl boronic esters with electron-deficient aryl acetates is reported. The oxidative coupling proceeds under mild, aerobic conditions and tolerates a host of potentially reactive electrophilic functional groups that would be problematic with traditional benzylation protocols (aryl iodides and bromides, protic heteroatoms, aldehydes, Michael acceptors). A reaction pathway in which a benzylic nucleophile is generated via aryl acetate decarboxylation and in turn is intercepted by the catalyst to form diarylmethane products is supported by mechanistic studies.*

Carboxylic acids are ubiquitous functional groups found in organic molecules and can act as versatile building blocks in synthesis. A number of strategies have been developed to use carboxylates as reactive groups in carbon–carbon bond forming processes via the extrusion of CO_2. Approaches to enable decarboxylative functionalizations include nucleophile generation by enzymatic or organocatalytic activation;[1] thermally-promoted reactions at transition metals;[2] C–C bond homolysis induced by single-electron oxidation to generate radicals;[3] or by use of chemical pre-activation of the carboxylate in combination with transition metal or photoredox catalysts.[4] The astute application of these concepts has allowed for a myriad of valuable coupling reactions to be invented.[5] The reactivity patterns and functional group compatibility of decarboxylative transformations often compliment C–C bond forming methodologies that use more traditional electrophile/nucleophile pairs, expediting small molecule synthesis. Thus, expanding the scope of decarboxylative transformations remains an important challenge. This endeavor requires both improved approaches towards the decarboxylative generation of reactive intermediates and an expansion of the coupling manifolds that can productively engage such species.

Oxidative cross-coupling reactions can enable selective bond-formation between two distinct nucleophilic partners.[6] The inherent compatibility towards electrophilic functional groups displayed by oxidative coupling processes provides a significant benefit in comparison to traditional cross-coupling reactions. The Cu-promoted coupling of aryl boronic acids and N- or O-heteroatom nucleophiles illustrates the practical utility of oxidative coupling reactions, finding widespread use in synthetic and medicinal chemistry.[7] We discovered that activated methylenes undergo efficient Cu-promoted arylation using organoboronic esters.[8] Malonic half-esters are oxidatively coupled with a decarboxylation event occurring from the arylated intermediate to yield aryl acetic acid derivatives.[9] We were inspired by the work of Tunge,[10] Lui,[11] and Zhu[12] who demonstrated that nitrophenyl acetates could be decarboxylatively trapped with allyl, aryl, and alkenyl electrophiles under Pd-catalysis at high temperatures (100–140 °C) (Figure 1a). A mild oxidative method to prepare diarylmethane structures[13] from aryl acetic acids could provide a useful alternative strategy to Friedel-Crafts,[14] electrophile/nucleophile cross-coupling,[15] and radical benzylations.[16] Herein, we report an oxidative coupling reaction between aryl or alkenyl boronic esters and nitrophenyl acetates (Figure 1b). The decarboxylation event precedes oxidative C–C bond formation, with the Cu catalyst assuming a dual role in mediating the oxidative coupling process and stabilizing substrate



c Reaction Development: Role of Select Parameters[a]

entry	deviation from standard conditions	conv. **1a** (%)[b]	**2a**	**1a'** (%)
1	**none**	**113**	**75**	**31**
2	acid instead of K-salt, 3 equiv. NEt_3	30	<2	26
3	acid instead of K-salt, 1.5 equiv. K_2CO_3	>123	29	96
4	rt instead of 35 °C	65	32	9
5	under N_2 instead of air	93	25	36
6	$Cu(OTf)_2$ instead of $Cu(OAc)_2$	<2	<2	<2
7	30% $Cu(OAc)_2$ instead of 75%	>123	27	51
8	Ar–B(pin) instead of Ar–B(neop)	>123	31	38
9	Pd, Co, Ni, Fe, or Zn instead of Cu	31-119	<2	23-76

Figure 1. (a) Pd-catalyzed coupling of electrophiles with aryl acetates. (b) Oxidative arylation of aryl acetates (this work). (c) Effect of select reaction parameters on the coupling. [a]0.20 mmol scale, 0.2 M, 21 h, yields and conv. determined by calibrated ^{1}H NMR [b]Conv. **1a** out of 125%, Ar = 3-Br-C_6H_4.

[a] P. J. Moon, A. Fahandej-Sadi, W. Qian, Prof. R. J. Lundgren
Department of Chemistry
University of Alberta
Edmonton, Alberta, T6G 2G2, Canada
E-mail: rylan.lundgren@ualberta.ca

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in DMA solvent. These insights can be applied to other metal-catalyzed reactions of carboxylates to enable reactivity under mild conditions.

Reaction development studies focused on enabling the oxidative cross-coupling of 2-nitrophenyl acetate (**1a**) and an electrophile-functionalized aryl boronic ester derivative (Figure 1c). Optimal conditions were achieved using the K-aryl acetate salt and neopentyl boronic ester, with 75 mol % $Cu(OAc)_2$ in DMA under air to yield the desired diarylmethane **2a** in 75% yield (entry 1). Under other conditions, considerable hydrodecarboxylation of the acid was observed to form nitrotoluene **1a'**. This was surprising in light of the aggressive reaction conditions typically used to promote decarboxylation from electron-poor aryl acetates.[11-12] Use of the K-carboxylate salt was essential; when the free acid was used in combination with NEt_3 or K_2CO_3, or when reduced amounts of $Cu(OAc)_2$ were employed, formation of nitrotoluene outpaced product formation (entries 2, 3, and 7). Under N_2, less than one turnover of Cu catalyst was observed (entry 5, 25% yield **2a**).[17] $Cu(OAc)_2$ outperformed other Cu-catalysts tested (see the SI for details). Other metal (II) acetates (Pd, Co, Ni, Fe and Zn) were ineffective in promoting the coupling process, with varying amounts of non-productive substrate decarboxylation observed (entry 9).

The oxidative benzylation process tolerates electronically diverse aryl boronic ester partners and a host of reactive functional groups that would be poorly compatible with traditional cross-coupling manifolds or thermally-driven decarboxylations (Figure 2a). Diarylmethanes featuring aryl bromides (**2a, 2w**) and iodides (**2j**), nitriles (**2b**), NH-amides (**2e**, **2u**), alcohols (**2aa**), esters (**2h, 2i**), ketones (**2m**), aldehydes (**2l**), and Michael acceptors (**2i**) can be smoothly generated under the standard conditions. Substrates with Lewis-basic nitrogen-heterocycles (**2r**, **2s**, **2u**, **2x**) or those featuring multiple functional groups (**2q**, **2z**, **2aa**) can be used without significant complication. Decarboxylative alkenylation of the aryl acetate can also be achieve using vinyl boronic ester partners (**2ab**, **2ac**).[17b]

A range of 2- and 4-nitrophenyl acetates engage in productive cross-coupling reactions (**3a-3j**, Figure 2b). For these substrates, it was more convenient and economical to employ the corresponding Cu bis(carboxylate) salts with KOAc additives (see below for a discussion). Under mild conditions, a series of polysubstituted diarylmethanes can be generated featuring electron-donating and withdrawing groups, including bromides, chlorides, and fluorides, as well as nitrogen and sulfur-containing heterocycles.

The aerobic coupling can be scaled to deliver grams of product (Figure 3a). It was beneficial and more cost-effective to react the carboxylic acid with $CuSO_4 \cdot 5H_2O$ and to subject the resultant Cu(II)bis(carboxylate) salt to the standard reaction conditions with the addition of KOAc. The Cu reagent can be isolated by simple filtration and is less hydrolytically sensitive than the corresponding K-species.[17c]

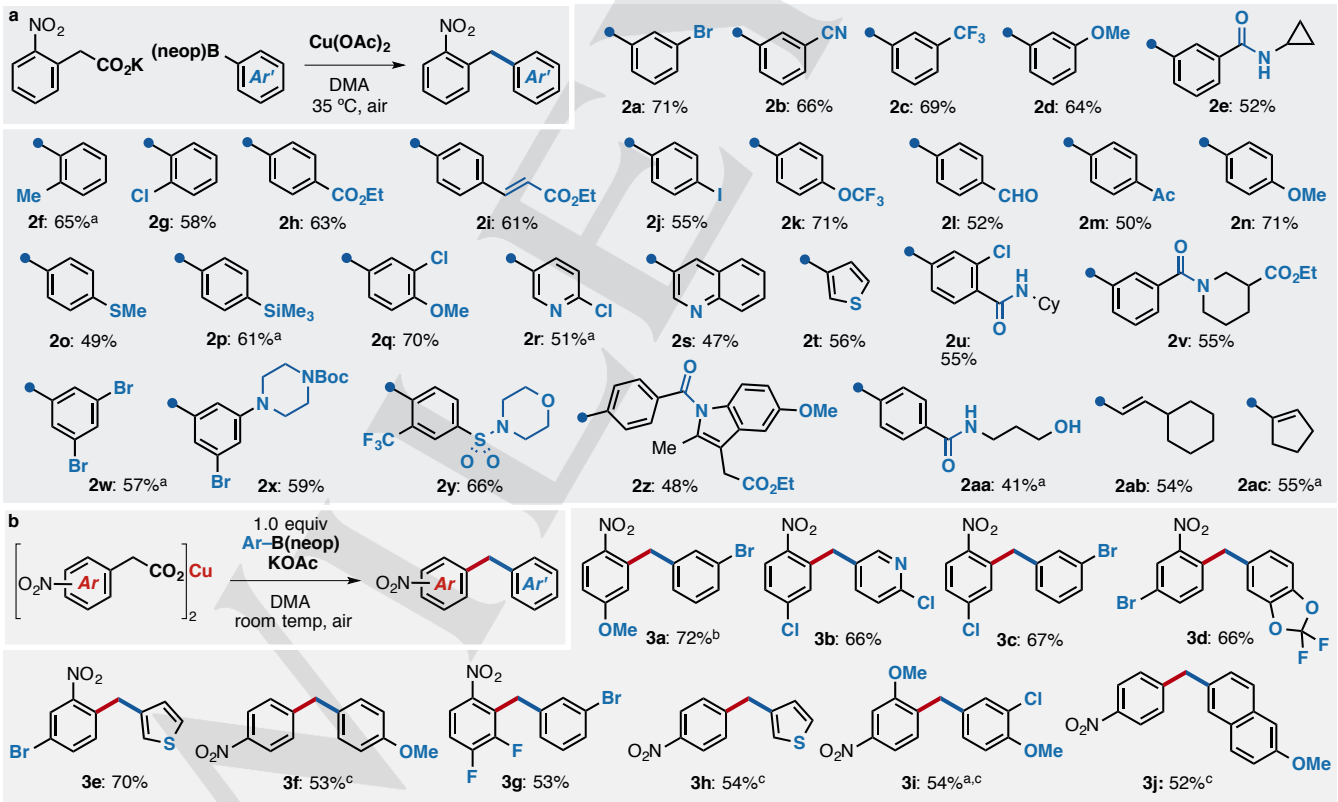

Figure 2. Cu-promoted decarboxylative benzylation: (a) Aryl/alkenyl boronic ester scope (b) Nitrophenyl acetate scope, see Fig 1c for condition. [a]calibrated 1H NMR yield. [b]at 40 °C. [c]0.5 equiv. carboxylate, 1.5-2.0 equiv. Ar–B(neop), 0.5 equiv. KOAc. See SI for full details.

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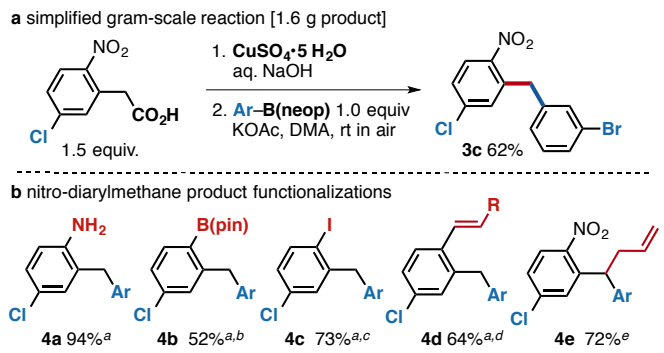

Figure 3. (a) Gram-scale cross-coupling. (b) Product functionalizations. Ar = 3-Br-C_6H_4 R = CO2Me. [a]Zn, NH_4Cl. [b]$NaNO_2$, B_2pin_2. [c]$NaNO_2$, KI. [d]*t*BuONO, methyl acrylate, $Pd(OAc)_2$, $MeSO_3H$. [e]allyl bromide, KO*t*Bu, 18-C-6. See SI for details.

A range of useful product classes can be derived from the requisite aryl nitro group.[18] Reduction to an amino group, borylation, halogenation, olefination, and methylene allylation can be accomplished to deliver polyfunctionalized diarylmethanes in a straight-forward fashion (**4a-4e**, Figure 3b).

Two general potential pathways for the decarboxylative arylation exist. One route consists of nitrophenyl acetate oxidative arylation followed by decarboxylation (Path I, Figure 4a). An alternative pathway involves a decarboxylation event to generate a benzyl nucleophile which undergoes subsequent oxidative trapping (Path II, Figure 4a). We found both nitrophenyl acetate decarboxylation and arylation to be dependent on the nature of the cation and solvent polarity. In DMA at 35 °C, the free acid or the corresponding Cu(II) or Zn(II) salts were stable, while rapid decarboxylation was observed for the K-salt (Figure 4b).[17d] No decarboxylation or cross-coupling was observed in less polar solvents. Decarboxylation from the K-carboxylate was not impeded by the addition of $Cu(OAc)_2$, however $Cu(OTf)_2$ completely suppressed reactivity, as did $Zn(OTf)_2$ and to a lesser extent $Zn(OAc)_2$ (Figure 4b).

It is likely that stable Cu-carboxylates are in equilibrium with reactive K-carboxylates under the standard reaction conditions and that decarboxylation precedes C–C bond formation (Path II). We propose a benzylic nucleophile is generated and trapped by Cu in the presence of aryl boronic ester in a series of steps similar to those in the Chan-Evans-Lam reaction (Figure 4c).[19] No product formation or decarboxylation is observed when a $Cu(carboxylate)_2$ salt of the standard substrate is added to aryl boronic ester, providing evidence that such species cannot access productive intermediates in the reaction. The addition of KOAc to mixtures of $Cu(carboxylate)_2$ and aryl boronic ester induces product formation with increasing rate and reaction productivity as KOAc loading is increased (Figure 4d). When a diarylmethyl carboxylate is subjected to the standard conditions oxidative dimerization is dominant over diarylmethane product formation. This indicates it is unlikely diarylated acids are formed under standard condition (Figure 4e). D-labelling studies of the nitrophenyl acetate also support a decarboxylation event prior to C–C coupling (see the SI for full details).

Given that $Cu(OAc)_2$ plays a dual role, both enabling aerobic oxidative coupling and stabilizing the reactive nitrophenyl acetate substrate, the necessity for high Cu-loadings (75 mol %) becomes

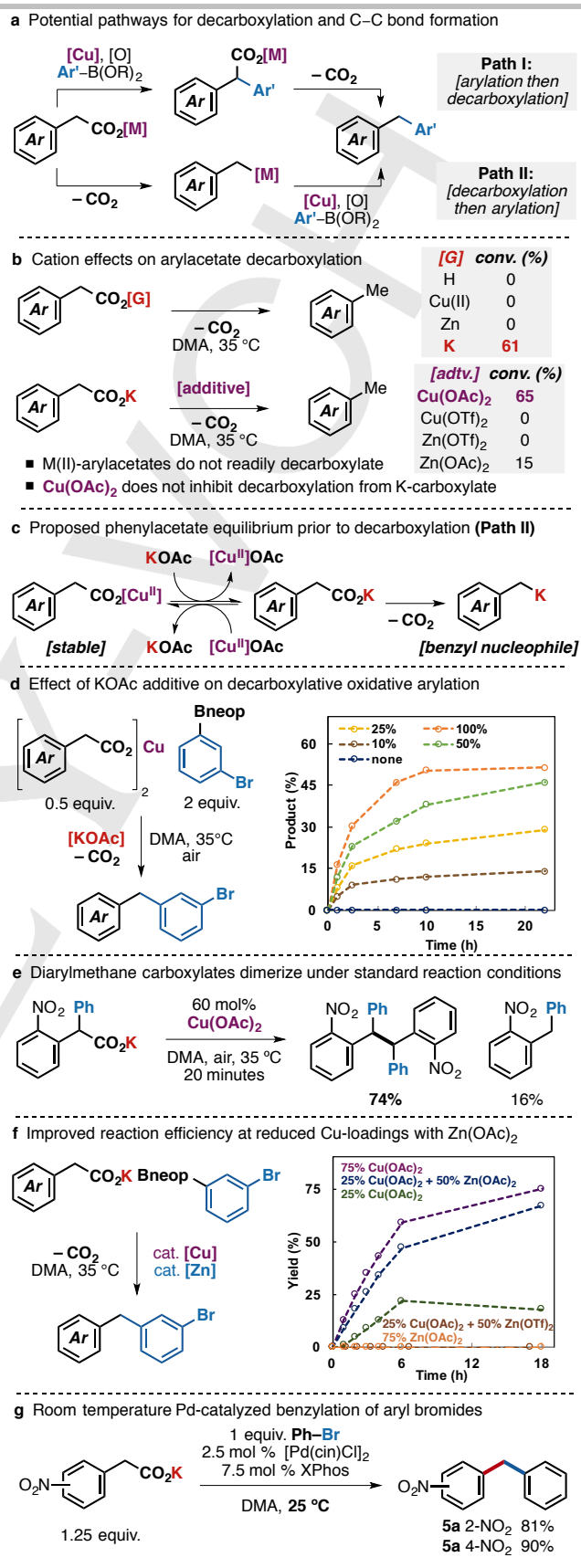

Figure 4. Mechanistic studies and process improvements.

evident. At 25 mol % $Cu(OAc)_2$ a terminal yield of <25% is observed under otherwise standard conditions due to unproductive decarboxylation of the nitrophenyl acetate (Figure 4f). A reduction in Cu catalyst could be achieved by simply adding Zn salts to modulate the rate of substrate decarboxylation. The use of 25% $Cu(OAc)_2$ in combination with 50% $Zn(OAc)_2$ closely mirrored reactions using 75 mol% $Cu(OAc)_2$, a dramatic improvement to reactions conducted with similar $Cu(OAc)_2$ loading in the absence of Zn (Figure 4f).[20] In line with the proposal that acetate is also vital to enable the exchange of metal carboxylates, the use of $Zn(OTf)_2$ with 25% $Cu(OAc)_2$ provided no diarylmethane product, as with $Zn(OAc)_2$ alone. Finally, we reconsidered the established protocols for thermally-driven Pd-catalyzed decarboxylative benzylation of aryl electrophiles that proceed only with forcing conditions (140 °C in mesitylene).[11] Remarkably, conducting reactions in DMA allowed for smooth formation of diarylmethane product at room temperature (Figure 4g).

In conclusion, a Cu-catalyzed oxidative cross-coupling of nitrophenyl acetates and sp^2-organoboronic esters has been developed. Diarylmethanes containing a number of potentially reactive electrophilic groups can be prepared via this method. The nitro functional group of the benzylic partner can be readily modified to gain access to a diverse range of arylated products. Process optimization and mechanistic studies uncovered an important relationship between reaction solvent and metal cations with aryl acetate decarboxylation in the context of this and related sp^2–sp^3 couplings.

Acknowledgements

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Keywords: cross-coupling • decarboxylation • aerobic catalysis • boron

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[17] Notes: a) Two equiv. of Cu(II) are required per oxidative bond forming event assuming a Chan-Evans-Lam type mechanism. b) See the SI for less successful substrates. c) $CuSO_4$•5 H_2O: \$18 USD/mol vs $Cu(OAc)_2$ \$170/mol, prices from Merck Dec. 20, 2017 for largest available quantity, compare to $Pd(OAc)_2$: \$5000/mol. d) Li, Na, and Cs-nitrophenyl acetates undergo decarboxylation and arylation under similar conditions. e) Pivalate can be used instead of acetate, see the SI for details. f) Batey has reported the Chan-Evans-Lam reaction of carboxylic acids, we do not observe C–O coupling: F. Huang, T. D. Quach, R. A. Batey, *Org. Lett.* **2013,** *15*, 3150-3153.

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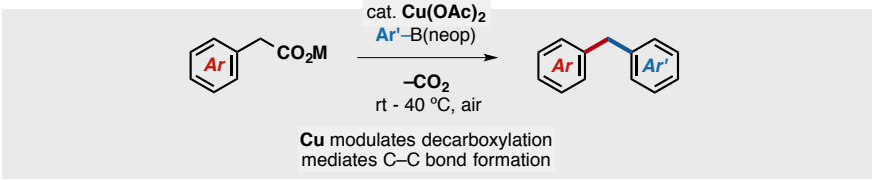

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