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Oxidative Coupling of Aryl Boron Reagents with sp^3-Carbon Nucleophiles: The Enolate Chan–Evans–Lam Reaction

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Abstract: *Reported is a versatile new oxidative method for the arylation of activated methylene species. Under mild reaction conditions (RT to 40°C), $Cu(OTf)_2$ mediates the selective coupling of functionalized aryl boron species with a variety of stabilized sp^3-nucleophiles. Tertiary malonates and amido esters can be employed as substrates to generate quaternary centers. Complementing either traditional cross-coupling or S_NAr protocols, the transformation is chemoselective in the presence of halogen electrophiles, including aryl bromides and iodides. Substrates bearing amide, sulfonyl, and phosphonyl groups, which are not amenable to coupling under mild Hurtley-type conditions, are suitable reaction partners.*

Cross-coupling reactions between two distinct nucleophilic partners have emerged as valuable transformations which display reactivity and selectivity orthogonal to classical metal-catalyzed couplings of electrophiles with nucleophiles.[1] Oxidative coupling reactions often proceed under exceptionally mild reaction conditions, employ base-metal mediators or catalysts, and in ideal cases, tolerate electrophilic functionality useful for subsequent transformations. The copper-mediated union of aryl boronic acids and heteroatom nucleophiles exemplifies the power of such coupling manifolds.[2] First reported by Chan, Lam and co-workers,[3] and Evans et al.,[4] functionalized aniline and phenol derivatives can be prepared from stable, readily available aryl boron species at room temperature by employing simple copper salts and mild organic bases. In addition to N- and O-based nucleophiles, sulfur, selenium, tellurium, and halogen nucleophiles are also suitable partners in these reactions.[2,5,6]

Despite the success of Chan–Evans–Lam-type reactions in carbon–heteroatom bond construction processes, as well as an increasing appreciation for the mechanism of these transformations,[7] a general method for the copper-mediated arylation of stabilized sp^3-carbon-based nucleophiles with organoboron reagents has not been established. This is particularly noteworthy in light of the importance of α-aryl carbonyl compounds in synthetic organic and medicinal chemistry, and the considerable body of literature concerning transition-metal-based methods for their synthesis by the coupling of sp^2 electrophiles.[8–10] Indeed, in comparison to heteroatom nucleophiles, reports of copper promoting C–C bond-forming reactions with aryl boron reagents under oxidative conditions remain sparse.[11,12] To the best of our knowledge, enamine annulation[13] and vinylation[14] represent the closest known reports towards an enolate Chan–Evans–Lam reaction. Currently available oxidative arylation strategies employing organoboron reagents and activated methylenes require stoichiometric amounts of $Pb(OAc)_4$ in combination with mercury additives.[15] Motivated by this methodological gap and the opportunity to access compound classes not easily prepared by existing protocols, we report herein the first copper-mediated oxidative coupling reactions between either aryl boroxines or boronic esters and in situ formed enolates to generate α-aryl carbonyl compounds (Figure 1). The reaction is chemoselective in the presence of halogen electrophiles (including aryl iodides) and can be employed for substrate classes which are not amenable to Hurtley-type reactions under mild reaction conditions (< 70°C), such as amides and tertiary malonate esters.

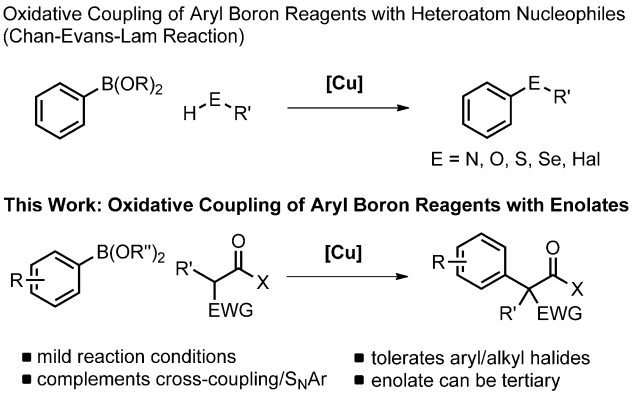

Figure 1. Overview of the copper-mediated oxidative coupling of heteroatom nucleophiles and the oxidative carbonyl α-arylation developed herein.

With the aim of developing copper-mediated oxidative C–C bond formation between an aryl boron species and an activated sp^3-nucleophile, reaction conditions similar to those established for heteroatom arylations were investigated, generally without success. Typical side products arising from protodeborylation, aryl–aryl homocoupling, and acetoxylation were observed under standard Chan–Evans–Lam conditions.[2,14] The use of aryl boronic anhydrides (boroxines), however, provided a breakthrough in reactivity (Table 1 A). Under standard reaction conditions, both aryl boronic acids

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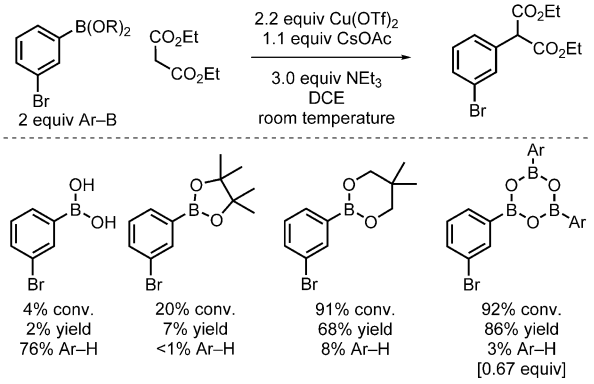
Table 1: The enolate Chan–Evans–Lam reaction: effect of aryl boron and reaction parameters.

A) Effect of boron group

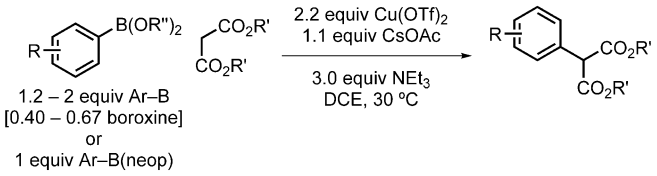


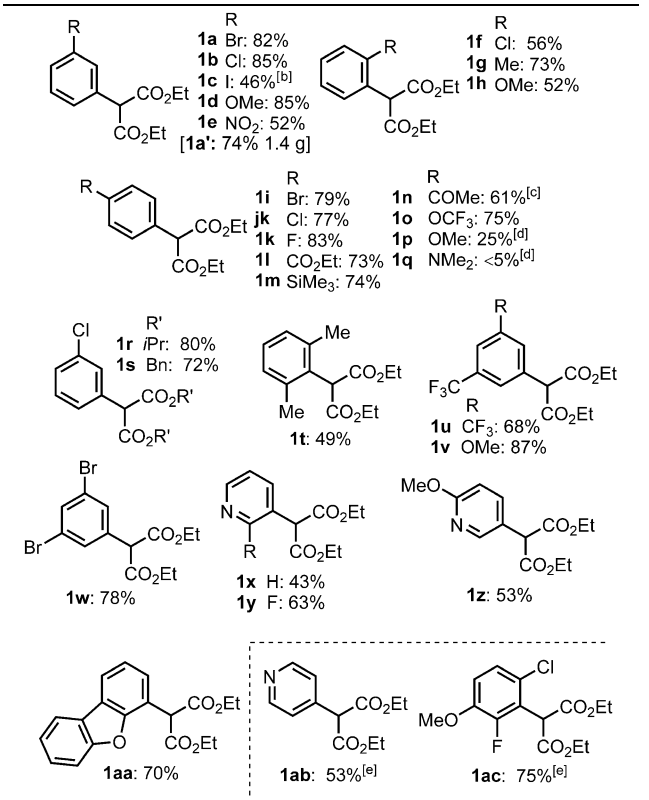
B) Effect of copper source and reaction parameters.[a]

Entry	Deviation from above	Conv. [%]	Yield [%]	Ar-H [%]
1	none	92	86	3
2	$Cu(OAc)_2$ instead of $Cu(OTf)_2$	30	11	61
3	$Cu(OMe)_2$ instead of $Cu(OTf)_2$	15	13	84
4	$CuSO_4$ instead of $Cu(OTf)_2$	5	0	30
5	pyridine instead of NEt_3	3	0	92
6	K_2CO_3 instead of NEt_3	5	0	104
7	no NEt_3	0	0	104
8	NaOAc instead of CsOAc	86	78	6
9	no CsOAc	71	48	2
10	6 equiv of H_2O	17	15	43

[a] Conversion (based on malonate) and yields determined by calibrated GC analysis using dodecane as the internal standard, 0.2 M 48 h. Ar = 3-BrC_6H_4, DCE = 1,2-dichloroethane, Tf = trifluoromethanesulfonyl.

Table 2: Scope of the copper-mediated oxidative arylation of malonate esters with aryl boroxines.[a]





[a] 0.20 M in DCE, 19-48 hours, see the Supporting Information for details. Unless noted otherwise, yields are those of isolated material using 2.0 equiv of ArB (0.67 equiv boroxine). Run on 0.5 mmol scale. [b] 1.2 equiv of ArB at RT. [c] 1.2 equiv of ArB at 30 °C. [d] Yield determined by calibrated ^{1}H NMR spectroscopy; >95% conv. of malonate. [e] 1 equiv ArB(neop), 2 equiv malonate at 35 °C.

and pinacol boronic esters provided only trace conversion into the desired arylated malonate product (2% and 7%, respectively), while the aryl boroxine provided excellent yields (86%) and minimal side-product formation.[16a] The corresponding neopentyl boronic ester also provided lower, but acceptable conversion into the product (68%). The transformation proceeded smoothly at room temperature with no observable side reactions at the electrophilic aryl bromide site.

$Cu(OTf)_2$ is the preferred copper source, as the use of other reagents provided lower yields and increased amounts of protodeborylation (Table 1B, entries 2–4). Triethylamine was essential to the reaction, as other bases were not effective (entries 5–7). Acetate salts provided acceleration in reaction rate, but were not essential to product formation (entries 8 and 9).[16b] Water had a deleterious effect on the reaction, thus providing some insight into the poor reactivity observed with aryl boronic acids, which are in equilibrium with the anhydride form and water (entry 10).

The scope of the copper-mediated oxidative coupling of aryl boroxines and malonate esters is demonstrated in Table 2. Aryl fluorides, chlorides, bromides, and highly reactive iodides (**1c**) were tolerated under the standard reaction conditions. In traditionally employed malonate arylation methods, such as S_NAr or cross-coupling, these functional groups are typically reactive. The reaction can be conducted open to air on the gram scale without decrease in efficiency (**1a**′ 74% yield, 1.4 grams of product). Substitution at either the 2- or 3-position with electron-withdrawing nitro or chloro groups (**1b**, **1e**, **1f**) or electron-donating methyl or methoxy groups (**1d**, **1g**, **1h**) led to moderate to excellent yields of product. The reaction tolerated aryl boroxines with potentially reactive ester (**1l**), ketone (**1n**), and silyl functionality (**1m**), as well as CF_3 (**1u**, **1v**) and OCF_3 (**1o**) substitution. For electron-rich, 4-substituted aryl boroxines, low yields were observed as the arylated malonate products undergo further oxidative coupling reactions with malonate (**1p**, **1q**). These electron-rich arene derivatives, however, can be readily accessed from the bromo-containing products **1a** and **1i** in greater than 60% overall yield by a sequential oxidative coupling/palladium-catalyzed cross-coupling protocol.[16c] Isopropyl or benzyl malonate esters (**1r**, **1s**), polysubstituted aryl boroxines (**1u**, **1v**, **1w**), and bulky 2,6-disubstituted (**1t**) reagents could be employed under the standard

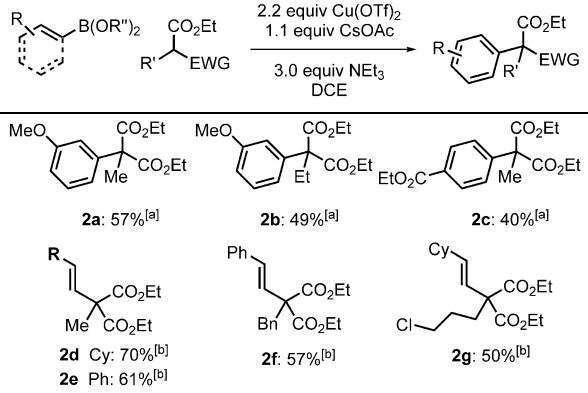
reaction conditions to give consistently high yields of products. Heterocycles, such as substituted pyridines (**1x**, **1y**, **1z**) and dibenzofuran (**1aa**), could also be oxidatively coupled to malonate derivatives. The tolerance of the reaction was accessed further by conducting an intermolecular functional group tolerance screen as outlined by Glorius and coworkers (see Table S6 in the Supporting Information).[17]

Under the standard reaction conditions two equivalents of the aryl boron reagent (0.67 equiv boroxine) were generally employed, which could be a drawback if the arylating reagent is particularly valuable. To address this issue, it was found that under modified reaction conditions, aryl or heteroaryl neopentyl boronic esters could be used as the limiting reagent to afford good yields of the desired oxidative coupling product (Table 2). Examples of successful aryl groups include bromide- (**1a**; 87%) and iodide-containing substrates (**1c**; 51%), a pyridine (**1ab**), and a polyfunctionalized trisubstituted aryl partner (**1ac**).

This oxidative coupling strategy also allowed the generation of quaternary carbon centers by arylation or vinylation of tertiary sp^3-nucleophiles under remarkably mild reaction conditions (Table 3).[18,19] Preliminary experiments, with both aryl boroxines and alkenyl neopentyl boronic ester reagents, demonstrated the ability of malonates to undergo copper-mediated C–C bond formation under reaction conditions similar to those described above.[20,21] The cross-coupling reaction tolerates benzylic substitution (**2f**) and a potentially reactive alkyl chloride group (**2g**). This type of reactivity to generate quaternary carbon centers with diester substrates is without precedent in copper-promoted cross-coupling.[22]

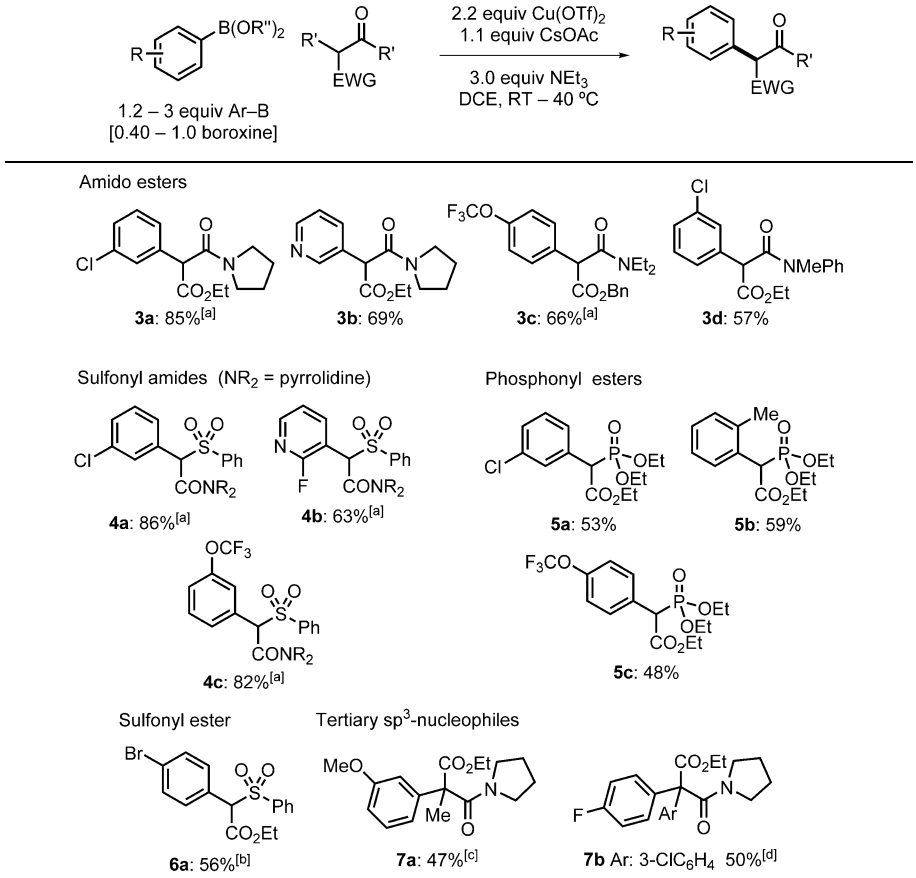
Copper-mediated oxidative coupling can be applied to activated methylene substrates which have not been reported to undergo Hurtley-type arylation under mild reaction conditions (< 70 °C),[9d] such as stabilized amides, sulfonyls, and phosphonyls (Table 4).[23,24] Both cyclic and acyclic alkyl 1,3-amido esters (**3a–c**), and aryl/alkyl 1,3-amido esters (**3d**) can be used as reaction partners, as well as 1,3-sulfonyl amides (**4a–c**). In both cases, halogenated and heterocyclic boroxines were smoothly arylated in high yield under mild reaction conditions (RT–30 °C). 1,3-Phosphonyl esters (**5a–c**) and a sulfonyl ester (**6a**) undergo oxidative coupling with similar efficiency to 1,3-diesters. Of note, each of these classes of compounds, made accessible by this copper-mediated oxidative arylation strategy, represents an important fragment in medicinal chemistry, such as in β-lactam antibiotics, tyrosine phosphatase inhibitors, and histone deacetylase inhibitors.[25]

Table 3: Copper-mediated oxidative arylation and vinylation of tertiary sp^3-nucleophiles.



0.20 M in DCE, 25–72 hours, see the Supporting Information for details. [a] Using 3 equiv ArB(1 equiv boroxine) at room temperature. [b] Using 1 equiv ArB(neop), 2 equiv malonate at 35 °C.

Table 4: Scope of the copper-mediated oxidative arylation with sp^3-nucleophiles.



0.20 M in DCE, 2.5–72 hours, see the Supporting Information for details. Unless noted otherwise, yields are those of isolated material using 2 equiv of aryl boron reagent (0.67 equiv boroxine) at 30 °C. 0.5 mmol scale. [a] 1.2 equiv of ArB at RT. [b] 1.5 equiv ArB at 40 °C. [c] 3 equiv ArB at RT. [d] 1.2 equiv ArB at 40 °C.

Finally, without modification to the standard conditions, tertiary 1,3-amido esters can be arylated using our method in moderate yield (Table 4). The reaction proceeds on both alkyl (**7a**) and aryl (**7b**) substituted sp^3-nucleophiles to deliver products which are not accessible by established copper-mediated reactions of aryl electrophiles.

We have yet to obtain conclusive information regarding the mechanism of the transformation. However our current hypothesis is that the steps mirror that of the Chan–Evans–Lam reaction as outlined by Stahl and co-workers.[7] Future work will aim to cast light on this issue.

In summary, we have reported a powerful new strategy for the arylation of activated sp^3-nucleophiles by a copper-mediated oxidative coupling. This enolate Chan–Evans–Lam reaction allows for the installation of sensitive and densely functionalized aryl units under mild reaction conditions from readily available aryl boron species. Given the broad scope of reactivity, the ability to form quaternary centers, and tolerance of electrophilic groups, this methodology should find broad appeal as an alternative to either traditional cross-coupling or S_NAr reactions of aryl electrophiles with activated methylene species.

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moderate yields (58% calibrated GC) are observed because of non-selective oxidative degradation of the starting materials and product. For tertiary malonates moderate yields are observed because of sluggish reactivity. f) Acetophenone and 1,3-diketones are not viable substrates.

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