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Direct Chan–Lam Amination and Etherification of Aryl BMIDA Reagents

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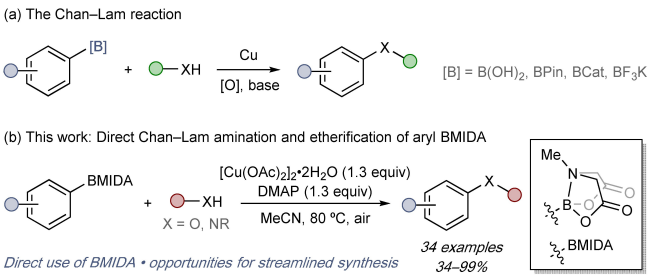
We report a method for the direct Chan–Lam coupling of arylboronic acid *N*-methyliminodiacetic acid esters (ArBMIDA) with amine and alcohol nucleophiles. A wide range of C–N and C–O cross-coupled products are obtained in 34–99% yield (34 examples). This method serves to expand the scope of organoboron components that can be used directly in this oxidative coupling reaction and provides opportunities for streamlining synthesis.

Introduction

The Chan–Lam reaction is a broadly useful methodology for the formation of C–X bonds under generally mild conditions (Scheme 1a).[1–8] The reaction uses an organoboron reagent with a heteroatomic coupling partner in the presence of a copper source and a terminal oxidant, usually oxygen. In terms of generality, the process is highly tolerant to the heteroatom coupling partner; however, the scope of the organoboron is more limited. Specifically, the reaction works most effectively with aryl organoboron reagents, with limited examples of alkyl coupling partners.[1–8] In addition, arylboronic acids dominate this area, with comparatively few examples of other organoboron reagents, such as arylboronic acid pinacol esters (ArBPin)[9–12] and aryltrifluoroborates ($ArBF_3K$).[13,14] In this latter case, based on the proposed mechanism of transmetalation, which involves a Lewis pairing of the Cu catalyst with the organoboron,[10,15] the $ArBF_3K$ reagent must first be hydrolyzed to a neutral organoboron, similar to that proposed for Suzuki–Miyaura cross-coupling with these reagents.[16]

The $ArBF_3K$ can therefore be considered as a protected arylboronic acid undergoing a one-pot deprotection/Chan–Lam reaction.

We have been interested in the use of arylboronic acid *N*-methyliminodiacetic acid esters (ArBMIDA) as components within selective cross-coupling processes.[17–30] Despite their widely appreciated utility in chemoselective synthesis, only one example of a Chan–Lam reaction using ArBMIDA has been disclosed, with no yield given.[31]



Scheme 1. (a) General overview of the Chan–Lam reaction. (b) This work: direct Chan–Lam amination and etherification of aryl BMIDA reagents.

Here, we report the development of a general approach for Chan–Lam amination and etherification of ArBMIDA. This allows the direct use of these reagents, allowing exploitation of their unique protecting group potential, and extending the scope of organoboron reagent that can be employed in Chan–Lam cross-coupling processes (Scheme 1b).

Results and Discussion

The direct amination reaction was first optimized using a model system using ArBMIDA reagent **1** and aniline (Table 1). An atmosphere of air was used throughout – O_2 was the requisite terminal oxidant.[1–8] Control experiments under strictly air-free conditions delivered lower yields (entry 2). It was quickly apparent that the use of low catalytic loadings of Cu was not possible (entry 3). Control experiments (see ESI Table S8) suggested that MIDA salts impede the reaction, presumably by coordinating Cu and therefore might be the cause of the poor turnover.[10] A series of Lewis acids were therefore screened as additives (see ESI Table S11) to attempt to scavenge MIDA and prevent deactivation of Cu; however, this was not successful. The reaction required stoichiometric Cu (1.3 equiv) for efficient bond formation, indicating very limited turnover from the mechanistic perspective. Organic bases were found to provide

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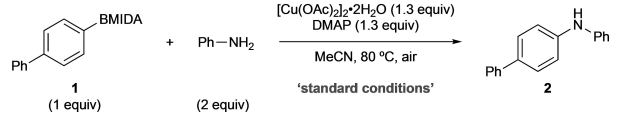
Table 1. Reaction development.



Entry	Deviation from 'standard conditions'	Yield **2** [%][a]
1	None	84%[b]
2	Strictly air-fee	52%
3	20 mol% $Cu(OAc)_2$	<5%
4	No DMAP	67%
5	Et_3N instead of DMAP	50%
6	Et_3N + DMAP	82%
7	Pyridine instead of DMAP	43%
8	K_2CO_3 instead of DMAP	59%
9	*N*-Methylpiperidine instead of DMAP	47%
10	Room temperature or 50 °C	<12%
11	$Cu(OAc)_2$	58%
12	$Cu(MeCN)_4PF_6$	0%
13	$Cu(OTf)_2$	0%
14	Addition of H_2O (2 equiv)	0%
15	$PhB(OH)_2$ instead of PhBMIDA	74%
16	$PhBF_3K$ instead of PhBMIDA	77%

[a] Determined by ^1H NMR analysis of crude reaction mixtures using an internal standard. [b] Isolated yield.

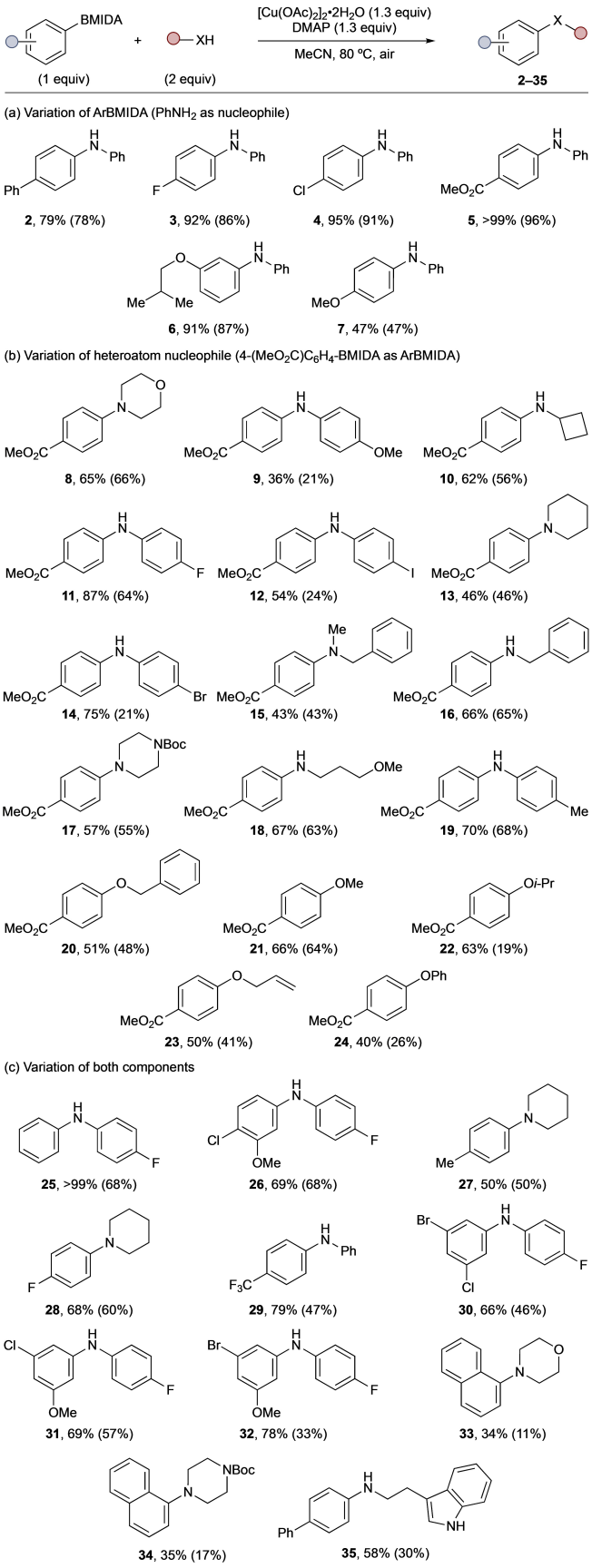
greater efficiency than inorganic, with 4-dimethylaminopyridine (DMAP) proving to be most effective (entries 4–9). Furthermore, lower reaction temperatures were not accommodated (entry 10). Finally, $[Cu(OAc)_2]_2 \cdot 2H_2O$ was found to be optimal, with all other Cu sources less efficient (entries 11–13).

With regards reaction mechanism, we considered that the ArBMIDA is hydrolyzed *in situ*, possibly by H_2O present from $[Cu(OAc)_2]_2 \cdot 2H_2O$, allowing transmetalation to proceed as previously established.[4–8] Control experiments revealed low levels of ArBMIDA hydrolysis in the presence of the same quantity of H_2O as provided by $[Cu(OAc)_2]_2 \cdot 2H_2O$ (*i.e.*, 2.6 equiv. H_2O) but hydrolysis is accelerated in the presence of aniline and DMAP (see ESI Scheme S2 and Figures S1–S5); however, use of additional H_2O was deleterious (entry 14). This possibly explains the comparative lack of reactivity of other Cu sources. It is likely that DMAP is likely to act as a ligand for Cu in this system,[32] possibly offsetting some Cu poisoning by MIDA released during the reaction. Lastly, the standard conditions were also effective for the coupling of $PhB(OH)_2$ and $PhBF_3K$ (entries 15 and 16).

With optimized conditions developed for this model system, a substrate scope was designed to assess reaction generality (Scheme 2). Gratifyingly, a range of electron-rich and electron-poor ArBMIDA were tolerated (Scheme 2a).

With respect to heteroatom nucleophile variation (Scheme 2b), a variety of anilines were tolerated with various substitution patterns. The reaction also translated well to alkyl amines (*e.g.*, **8**, **10**, **13**, **15**–**18**), with yields generally lower than for anilines, possibly indicating a preference for electron-deficient nucleophiles.

Alcohols could be employed as nucleophiles to yield aryl ether products in good yields but generally lower than *N*-nucleophiles (**20**–**24**). Variation of both components (ArBMIDA and heteroatom nucleophile) was generally successful, but highlighted some clear limitations, such as the naphthyl BMIDA



Scheme 2. Example scope of the direct Chan–Lam process. Determined by ^1H NMR. Isolated yields in parentheses (see ESI).

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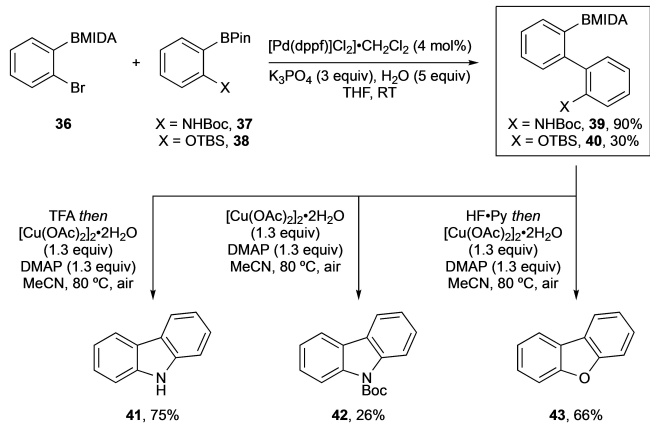

Scheme 3. Heterocycle synthesis via Suzuki–Miyaura and direct Chan–Lam cross-coupling reactions or aryl BMIDA reagents.

being a poor substrate (**33** and **34**). Some chemoselectivity was possible, for example, tryptamine underwent *N*-arylation exclusively at the primary amine with no indole *N*-arylation observed (**35**). Several other couplings were explored, including heterocyclic variants; however, these were unsuccessful (see ESI Scheme S1). Lastly, the benefits of the oxidative Chan–Lam coupling were highlighted with accommodation of haloaromatics (**4**, **12**, **26**, **30**, **31**, and **32**), providing a useful functional handle for subsequent reactions, *e.g.*, Pd-catalyzed cross-couplings.

To demonstrate the utility of this method, we prepared several heterocycles by exploiting the BMIDA unit in chemoselective cross-coupling (Scheme 3). Chemoselective cross-coupling of aryl bromide and aryl BPin reagents **37** and **38**, under reaction conditions that retain the BMIDA unit,[24] delivered the expected products **39** and **40**, respectively. This allowed direct intramolecular amination to provide carbazoles **41** and **42**, and etherification to give dibenzofuran **43**. Regarding the amination processes, this was more effective using the free aniline, obtained by TFA-mediated deprotection prior to the cross-coupling, giving **41**, with the coupling significantly less efficient using **39** directly.

Conclusion

In summary, we have developed a method for the direct Chan–Lam coupling of arylboronic acid methyliminodiacetic acid esters (ArBMIDA) with amine and alcohol nucleophiles to deliver the expected cross-coupled products in good to excellent yield. We have also shown how this method can be applied in the context of chemoselective synthesis of heterocyclic scaffolds by using the unique attributes of the BMIDA protecting group. Overall, this method expands the scope of organoboron component that can be used in the Chan–Lam reaction and offers opportunities for streamlining chemical synthesis.[33]

Experimental Section

General experimental procedure. For example, synthesis of compound **2**: An oven-dried 20 mL microwave vial was charged with 4-biphenyl BMIDA (**1**; 155 mg, 500 μmol, 1.00 equiv), [Cu-$(OAc)_2]\cdot 2H_2O$ (118 mg, 650 μmol, 1.30 equiv), and DMAP (79.4 mg, 650 μmol, 1.30 equiv). The vial was capped before addition of anhydrous MeCN (1.00 mL, 500 mM) followed by aniline (90.4 μL 1.00 mmol, 2.00 equiv). The reaction mixture was heated to 80 °C for 36 h before allowing to cool to RT. The reaction mixture was filtered through Celite®, eluting with CH_2Cl_2. The filtrate was the treated with 10% aq. ammonia (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude product, which was purified by flash column chromatography (silica gel, 0–5% EtOAc in petroleum ether) to give the desired product as an orange solid (95.4 mg, 78%).

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are openly available in University of St Andrews at https://doi.org/10.17630/f842a14f-2843-4266-aa37-64edc78433b9.

Keywords: Amination · Boron · copper · Cross-coupling · Etherification

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