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One-Pot C–N/C–C Cross-Coupling of Methyliminodiacetic Acid Boronyl Arenes Enabled by Protective Enolization

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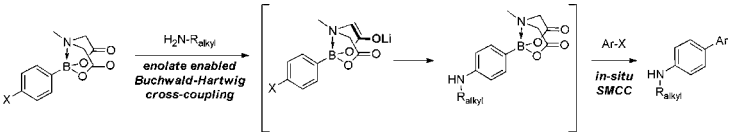
ABSTRACT



Iterative cross-coupling is a highly efficient and versatile strategy for modular construction in organic synthesis, though this has historically been demonstrated solely in the context of C–C bond formation. A C–N cross-coupling of haloarene methyliminodiacetic acid (MIDA) boronates with a wide range of aromatic and aliphatic amines is reported. Successful cross-coupling of aliphatic amines was realized only through protective enolization of the MIDA group. This reaction paradigm was subsequently utilized to achieve a one-pot C–N/C–C cross-coupling sequence.

Metal catalyzed cross-couplings have for decades been among the most practical and widely used methodologies in the synthesis of natural products and other biologically relevant small molecules.[1] In particular, the ubiquitous application of sp^2–sp^2 cross-couplings in the preparation of drug-like molecules in pharmaceutical research and development[2] has had a transformative impact on the synthetic strategies employed by medicinal chemists, which is reflected in the chemical space occupied by pharma compound collections and screening libraries.[3] This process often involves the application of a building block approach to target compound synthesis where shelf stable, commercially available intermediates can be installed in a modular and iterative fashion onto a core scaffold.[4] Cross-coupling methodology is uniquely suited to this application, and in recent years the possibility for iterative cross-couplings has been realized.[5] One especially noteworthy paradigm enabling such iterative applications of cross-couplings is the use of air-stable and reagent tolerant methyliminodiacetic acid (MIDA) protected boronates pioneered by Burke, the power of which has been demonstrated in several very efficient natural product syntheses.[6] We have also applied MIDA boronate chemistry in telescoped syntheses of drug-like compound arrays.[7]

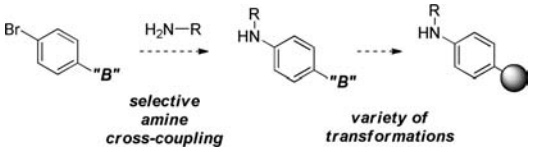


Figure 1. C–N cross-coupling approach to the preparation and diversification of boron-functionalized amino-aryls.

To date, iterative cross-coupling methodologies of boronate derivatives have focused exclusively on the formation

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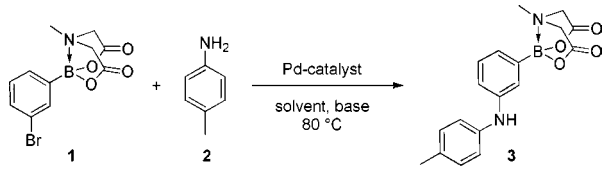
of C−C bonds. Advancing this iterative synthetic strategy to include C−N or C−O cross-couplings would substantially expand the chemical space that can be accessed with this highly modular approach, including that occupied by many pharmaceutically active compounds containing C(sp^2)−N bonds. Given the wide range of transformations achievable from boron-functionalized aryls,[8] this diversification strategy could take advantage of the well-established cross-coupling applications of boronates, as well as emerging methods in the fields of C−H functionalization[9] and metal catalyzed fluorination[10] and trifluoromethylation[11] that utilize boronic acid precursors (Figure 1).

As an initial investigation into the feasibility of this approach we assessed the reactivity and stability of a haloaryl MIDA boronate under standard Buchwald C−N cross-coupling conditions (Table 1).[12] While the C−N coupling failed to progress to full conversion, the MIDA boronate was completely stable under the reaction conditions. This early result, coupled with the known reagent tolerance,[13] ease of preparation,[14] and the ability of MIDA boronates to participate in slow release cross-couplings,[15] led us to further develop optimized conditions for this C−N cross-coupling.[16] Noteworthy observations from the optimization efforts (Table 1) include the significant improvement realized by applying the palladacyclic precatalyst *tert*-butyl X-Phos Pd G1 (entry 3) developed by the Buchwald group.[17] This system proved superior to other closely related biaryl phosphine precatalysts X-Phos (entry 2) and Brett-Phos (entry 4), which were only moderately successful. A variety of bases were also screened, though only tripotassium phosphate afforded high yields of the desired aminated MIDA boronate. While the strong base LiHMDS (entry 7) did promote the desired *N*-arylation at rt, the MIDA group was hydrolyzed under these conditions.

Table 1. Optimization of the C−N Cross-Coupling of Haloaryl MIDA Boronates



entry	solvent	Pd-source ligand	base	conversion[a]
1	MeCN	$Pd(OAc)_2$, X-Phos	K_3PO_4	42%
2	MeCN	X-Phos Pd G1	K_3PO_4	33%
3	MeCN	*t*-Bu-X-Phos Pd G1	K_3PO_4	95% (62%)[d]
4	MeCN	Brett-Phos Pd G1	K_3PO_4	60%
5	MeCN	*t*-Bu-X-Phos Pd G1	K_2CO_3	59%
6	MeCN	*t*-Bu-X-Phos Pd G1	Cs_3CO_3	76%
7	MeCN	*t*-Bu-X-Phos Pd G1	LiHMDS	95%[b,c]
8	DMF	*t*-Bu-X-Phos Pd G1	K_3PO_4	95%
9[e]	MeCN	*t*-Bu-X-Phos Pd G1	K_3PO_4	0%
10[f]	MeCN	*t*-Bu-X-Phos Pd G1	K_3PO_4	95%[c]

[a] All reactions were run with 1 equiv of aryl halide, 1.2 equiv of aniline, 5 equiv of base, and 5 mol % Pd-catalyst. Conversion was determined by UV-HPLC. [b] Free boronic acid product was observed. [c] Reaction run at 25 °C. [d] Isolated yield. [e] Ar−$B(OH)_2$ was used instead of MIDA boronate. [f] Ar−BF_3K was used instead of MIDA boronate.

With these optimized conditions we set out to evaluate the scope of the C−N couplings. Successful aminations were observed with a variety of aniline and heterocyclic amine nucleophiles as well as heteroaryl MIDA boronates (Figure 2). The versatility of the procedure is further underscored by the successful cross-coupling reactions in the presence of commonly encountered functionality, including ester (**6**), sulphone (**8**), pyridines (**4**−**7**), and a heterocyclic core structure (**4**). It bears mention, however, that this reaction is sensitive to steric demands on both the MIDA boronate (**9**) and the aryl amine (**10**) and is completely inoperable on both primary and secondary aliphatic amines (**13**, **14**) under these conditions.

To address this limitation we first considered base strength as a probable cause of lack of reactivity, as the only base successful in the aniline couplings was the strongest of the commonly available, non-nucleophilic, inorganic bases.[18] We hypothesized that the switch from aryl to aliphatic amines impacted the relative acidity of the

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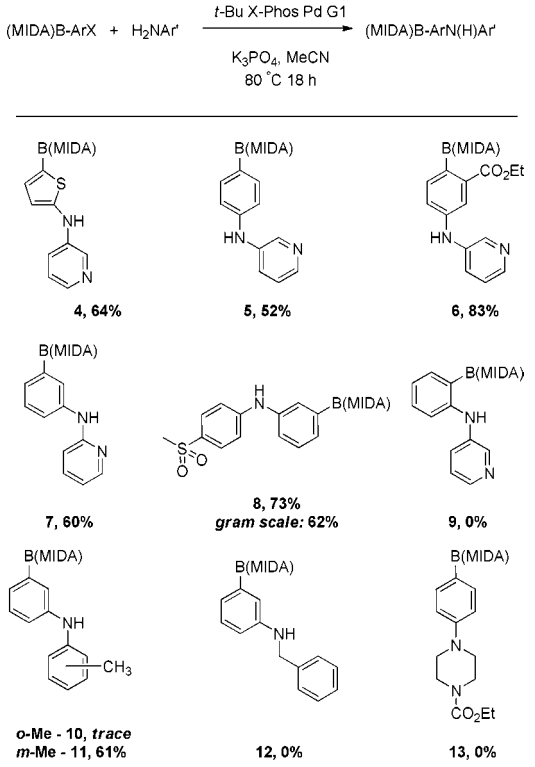
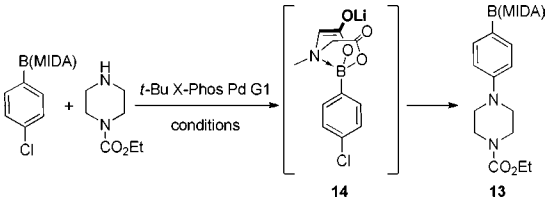


Figure 2. Investigation of substrate scope in the *N*-arylation of aryl amines. All reactions were run with 1 equiv of aryl halide, 1.2 equiv of amine, 5 equiv of K_3PO_4, and 5 mol % *t*-BuX-Phos Pd G1.

amine proton in the amine-Pd(II) complex and, therefore, that the less acidic Pd−N(R)−H proton in the case of aliphatic amines might require a stronger base to promote reductive elimination.[19] However, given the presumed incompatibility of the MIDA protecting group with strong bases, balancing these reactivities appeared to be a formidable challenge. We consequently revisited our original optimization (Table 2) and focused on the reaction with LiHMDS (Table 1, entry 7), which had previously provided successful C−N coupling of an aniline, albeit with the destruction of the MIDA group. These conditions applied to an aliphatic amine under anhydrous conditions did afford the desired product as a 1:1 mixture of MIDA boronate and free boronic acid despite the strict exclusion of water. We hypothesized that a further degree of protection could be imparted if the MIDA group were enolized, rendering it impervious to nucleophilic attack. We generated the enolate under controlled conditions at low temperature which yielded the desired MIDA boronate containing product with little evidence of hydrolysis. This result combined with further NMR spectroscopic

(19) By analogy to the Pd(II) precatalysts reported by the Buchwald group[16] which are activated by reductive elimination from the Pd(II) center. The 2-amino biphenyl derived second generation precatalyst is activated by K_3PO_4 at ambient temperature, whereas the phenethylamine derived first generation precatalyst requires NaO*t*-Bu for ambient temperature activation.

Table 2. Effect of Enolization on C−N Couplings of Aliphatic Amines



entry	solvent	temp	base	conversion[a]
1	MeCN	80 °C	K_3PO_4	0%
2	MeCN	25 °C	LiHMDS	>95%[b]
3[c]	THF	25 °C	LiHMDS	>95%[d]
4[c]	THF	−30 to +25 °C	LiHMDS	>95% (80)

[a] All reactions were run with 1 equiv of arylbromide, 1.2 equiv of amine, 5 equiv of base, and 5 mol % *t*-BuX-Phos Pd G1. Conversion was determined by UV-HPLC. Isolated yield in parentheses. [b] Free boronic acid product was observed. [c] Anhydrous conditions. [d] A ratio of 1:1 MIDA boronate to free boronic acid was observed.

evidence of enolate formation[20] validated our hypothesis and thus enabled the cross-coupling of aliphatic amines and MIDA boronates which was completely inoperable under all other conditions.

These conditions proved to be quite general[21] (Figure 3) and enabled access to a variety of amine functionalized boron containing building blocks primed for further derivatization. Of particular interest is the range of heterocyclic coupling partners that participate in the amination reaction, as well as the regioselective amination of dichloropyridine substrate (**15**), presumably due to the extreme steric demand imposed by the MIDA boronate on the *ortho*-halide.

Aware that the Buchwald precatalysts utilized in the transformations developed above are also capable of catalyzing Suzuki−Miyaura cross-couplings (SMCCs),[22] we set out to explore the potential for developing a one-pot sequence to effect both cross-coupling steps, in keeping with efforts aimed at developing efficient step-economical, greener methods for medicinal and process chemistry applications.[23] We noted the lack of literature precedent for the use of *tert*-butyl X-Phos in SMCCs, so we chose to introduce the second generation X-Phos derived precatalyst at the second step of this two-step one-pot procedure. In the event we were gratified to observe successful SMCC, realized merely by dosing the C−N coupling reaction mixture with an aryl halide, aqueous base, and the X-Phos Pd G2 (Figure 4).[24]

(20) See Supporting Information for evidence in support of the enolate formation.

(21) The improved conditions were ineffective on the aryl amines.

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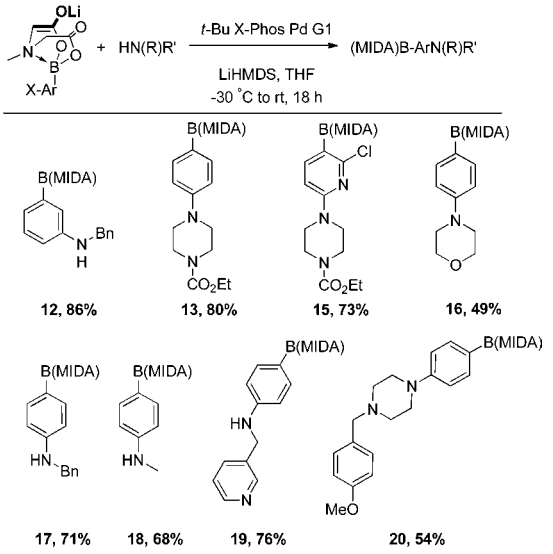

Figure 3. C−N couplings with aliphatic amines. All reactions were run with 1 equiv of aryl halide, 1.2 equiv of amine, 5 equiv of LiHMDS, and 5 mol % *t*-BuX-Phos Pd G1. All yields are for isolated materials and are reported relative to the MIDA boronate.

These conditions were then applied to a range of coupling partners with varying electronics and sterics, as well as heterocyclic substrates, affording access to a wide product scope in good overall yields. The one-pot procedure worked well on both electron-rich haloaromatic coupling partners (**27**, **28**) and electron-deficient haloaromatics (**35**). Heterocyclic systems performed equally efficiently (**25**, **26**, and **29**). Aryl amines behave in a similar way, where after the C−N coupling (as in Figure 2) the reaction mixture is subjected to *in situ* SMCC and desired products are obtained for both electron-rich (**30**) and electron-poor aryl halides (**31**). To further highlight the utility of this approach in a medicinal chemistry context we applied this procedure to the synthesis of a histamine H3 receptor agonist (**37**),[25] which was prepared in good overall yield from commercially available materials in a single synthetic operation.

We have developed a general approach to selective C−N cross-coupling of bifunctional arenes and report an efficient and versatile application of Buchwald−Hartwig couplings in the presence of boronic acid derivatives. In the course of our investigation we discovered a novel mode of protection for MIDA boronates. This enolization strategy uniquely enables access to the products of C−N cross-coupling of aliphatic amines and aryl halides bearing a MIDA boronate. We have further demonstrated the power of this methodology in a one-pot, two-step, iterative

(24) Our initial attempts to perform this reaction with a single dose of Pd-catalyst resulted in limited success. Cross-coupling sequences were low yielding and/or narrow in scope.

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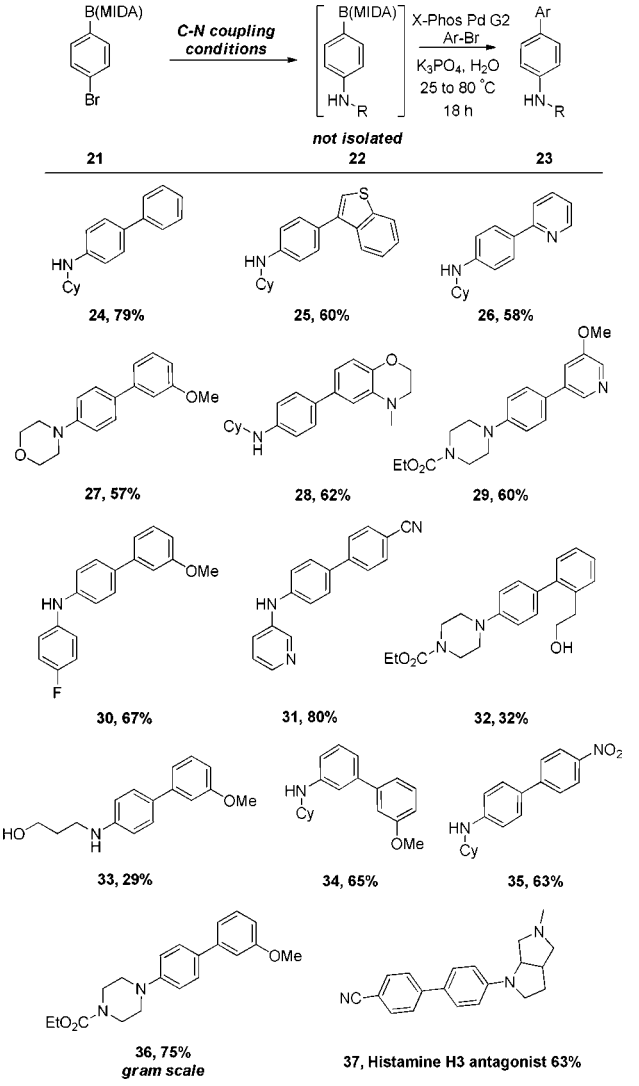

Figure 4. Two-step, one-pot cross coupling sequence. The *in situ* SMCC used 1.5 equiv of aryl halide, 3 equiv of base, and 5 mol % X-Phos Pd G2. Yields are reported over two steps relative to the MIDA boronate. For **31** and **37**, X-Phos Pd G1 was used for the C−N coupling and no second addition of Pd was required. The SMCC was run at 50 °C for **32** and **33** and at 80 °C for **31**.

C−N/C−C cross-coupling sequence utilizing *in situ* release of the masked boronic acid. Future investigations will seek to develop the paradigm of protective enolization of MIDA boronates in varied contexts.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.