Copper-Catalyzed Aminoboration from Hydrazones To Generate Borylated Pyrazoles

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Supporting Information

ABSTRACT: Herein we report an aminoboration reaction that employs inexpensive, Earth-abundant, and commercially available $Cu(OTf)_2$ as an effective catalyst in the direct addition of B–N σ bonds to C–C π bonds, generating borylated pyrazoles, which are useful building blocks for drug discovery. By nature of the mechanism, the reaction produces exclusively one regioisomer and tolerates groups incompatible



with alternative lithiation/borylation and iridium-catalyzed C–H activation/borylation methods. The reaction can be scaled up, and the resulting isolable pyrazole pinacol boronates can be further functionalized through palladium-catalyzed Suzuki cross-coupling reactions.

A minoboration of alkynes by $B-N \sigma$ bond addition would be a useful synthetic method to provide alternative routes to borylated *N*-heterocycles that can be further functionalized through metal-catalyzed cross-coupling reactions.¹ Yet there were only limited reports of direct addition of $B-N \sigma$ bonds to $C-C \pi$ bonds prior to a report by our group in 2015, demonstrating this aminoboration strategy for the synthesis of borylated indoles.² That reaction employed a precious-metal catalyst IPrAuTFA. Replacement of this precious-metal catalyst with an Earth-abundant metal catalyst is however desirable from cost and sustainability standpoints, as is extension of this chemistry to new substrate classes.

Subsequent to our report, there were two additional reports of aminoboration reactions^{3,4} in which boron trichloride was used to activate the C–C π bonds toward cyclization without a catalyst. However, due to its high reactivity, boron trichloride might not tolerate other active sites on the same substrate. We herein report the first example of copper as a catalyst in the direct addition of B–N σ bonds to C–C π bonds. Cost effective Cu(OTf)₂ is an efficient catalyst obviating the need for complicated organic ligands, further reducing catalyst cost and increasing availability.

This aminoboration method is tolerant of a variety of functional groups and generates exclusively the 4-borylated regioisomer in one synthetic step, without the need to preform the heterocyclic core. Products of this reaction are building blocks toward potent medicinal scaffolds that exhibit a full spectrum of biological activities, such as antimicrobial,⁵ antifungal,⁶ antiinflammatory,⁷ anticancer,⁸ and many others.⁹ Pyrazoles are present in several FDA-approved drugs, for example celecoxib (Celebrex),¹⁰ sildenafil citrate (Viagra),¹¹ tepoxalin (Zubrin),¹² and also in pesticides.¹³ Currently, borylated pyrazoles can be accessed through [3 + 2] cycloaddition/retrocycloaddition of sydnones (Scheme 1a).¹⁴ or Ir-catalyzed borylation of pyrazoles (Scheme 1b).¹⁵ However, these methods are limited due to poor regioselec-

Scheme 1. Comparison of Previous Methods (a-c) and This Aminoboration Method (d) with Earth-Abundant Copper Catalyst



tivity. Alternatively, a sequential lithiation/borylation of 4bromopyrazoles¹⁶ has been used to access 4-borylated pyrazoles (Scheme 1c), but this method does not tolerate bromides and electrophilic functional groups.

On the basis of our previous borylative heterocyclization reactions, $^{2,17-23}$ we hypothesized that an analogous route to borylated pyrazoles from hydrazones 1 may be amenable to a

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direct borylation pathway.²² The aminoboration reaction developed here starts from readily available hydrazones and does not require isolation of synthetic intermediates (Scheme 1d).

The reaction was developed through a series of optimization studies. We first investigated the formation of the requisite B– N σ bond (Table S1, Supporting Information) through the screening of different boron sources and bases using phenyl hydrazone (R³ = Ph) and tosyl hydrazone (R³ = Ts) as initial nitrogen substitution patterns. We determined that *B*-chloro-catecholborane (ClBcat) and triethylamine together were sufficient in forming the desired B–N σ bond in 2 (R³ = Ts) at room temperature with complete consumption of 1. The byproduct of this reaction, triethylammonium chloride, was removed from the reaction mixture by filtration to prevent the formation of the undesired protonated pyrazole 3a'.

We next targeted the aminoboration step for optimization. A series of gold and copper catalysts with varying oxidation states, counterions, and ligands were examined with **2a** as the model substrate. Previously, our group developed oxyboration and aminoboration methods with IPrAuTFA as the optimal catalyst.^{2,17,18,24} However, when IPrAuTFA was used in this reaction, only a trace amount of **3a** was observed by ¹H and ¹¹B NMR spectroscopy (Table 1, entry 1). We switched to

Table 1. Selected Optimization Study for the Formation of Borylated Pyrazole $3a^{a}$



"Reactions were carried out on a 0.10 mmol scale. ^bPercent conversion was determined based on the amount of desired product formed with respect to the amounts of starting material and byproduct 3a'.

Et₃N

40

0

10

TfOH

7

study Cu(I) and Cu(II) catalysts due to an initial unpublished hit in the oxyboration study of borylated isoxazoles¹⁸ and found the inexpensive and commercially available Cu(OTf)₂ to be the optimal catalyst, with 70% conversion to **3a** at 40 °C in 24 h (Table 1, entries 2–5). Control experiments without a catalyst and with triflic acid were performed at 110 and 40 °C, respectively (Table 1, entries 6 and 7). These control reactions confirmed the vital role of the catalyst.

Under the optimized reaction conditions (Table 1, entry 5), the substrate scope was examined (Scheme 2). Previously unreported pyrazole catechol boronic esters 3a-3k were generated and then transesterified to afford bench-stable and silica-gel-column-chromatography-stable pyrazole pinacol boronic esters 4a-4k. In Scheme 2, the numbers inside the parentheses denote the ¹H NMR spectroscopy yields of pyrazole catechol boronic esters 3 relative to phenanthrene as





^aIsolated yield of 4 (¹H NMR yield of 3). ^b110 °C.

the internal standard. The numbers outside the parentheses correspond to the isolated yields of **4**. The blue color in Scheme 2 indicates compounds that would be incompatible with previous lithiation or iridium-catalyzed synthetic methods due to chemo- or regioselectivity.

The aminoboration reaction provided 4 in moderate-togood ¹H NMR spectroscopy and isolated yields. The reaction was compatible with a variety of electron-rich (1b and 1k) and electron-poor (1h) aryl substituents in \mathbb{R}^1 and \mathbb{R}^2 . Aliphatic (1c, 1g, and 1j) and heteroaryl (1e and 1f) substitution were also tolerated with the reaction conditions. Thiophenesubstituted 4e and 4f demonstrated the complementary bond disconnections that avoided potential competing ortho borylation of the thiophene²⁵ under the alternative lithiation/borylation method (73% and 80% ¹H NMR spectroscopy yields of 3e and 3f, respectively; and 60% and 74% isolated yields of 4e and 4f, respectively).

In addition, aryl bromide 1i smoothly undergoes aminoboration to produce borylated pyrazole 3i (78% ¹H NMR yield, 68% isolated yield of 4i). Aryl bromides would not be tolerated under an alternative lithiation/borylation sequence¹⁶ because of competitive lithium-halogen exchange. Substrates 1d and 1j required an elevated reaction temperature (110 °C), which may be caused by steric hindrance from the *tert*-butyl and the silyl groups. Consistent with competing formation of byproduct 3a, resumably due to the acid sensitivity of the B–C bond. Replacement of the tosyl on nitrogen with phenyl resulted in no or incomplete deprotonation of the nitrogen from the requisite B–N bond by HBcat, ClBcat/NaH, or ClBcat/NEt₃ presumably due to the higher pK_a of the N–H bond (see Supporting Information Table S1 for details); however, *N*-tosylpyrazoles can be detosylated after downstream coupling of the pinacol boronate if desired, using known procedures.²⁶

We propose a plausible catalytic cycle for the coppercatalyzed aminoboration reaction in Scheme 3. The Lewis

Scheme 3. Proposed Mechanism



acidic Cu(OTf)₂ activates the C–C π bond^{27,28} to form intermediate 5, to which the N–B σ bond is subsequently added to generate intermediate 6, which then separates into a neutral organocopper intermediate 7 and electrophilic boron intermediate 8. The organocopper intermediate is primed for transmetalation with 8 in the next step to produce the desired boronate 3 and regenerate Cu(OTf)₂, which would be an early example of organocopper-to-boron transmetalation reaction. Organocopper-to-boron transmetalation is not well-established, but the reverse reaction from organoboron-to-copper is better studied.^{29,30}

The viability of copper catalysis in this reaction was considered further. Interestingly, this direct borylative heterocyclization did not proceed with IPrAuTFA as the catalyst, in contrast to four examples of oxyboration and aminoboration to make borylated benzofurans,¹⁷ indoles,² isoxazoles,¹⁸ and dihydrofurans.²⁴ The origin of this difference remains unclear. In an unpublished result from borylated isoxazoles, we found that $Cu(OTf)_2$ could also catalyze this oxyboration, albeit with a much slower rate than IPrAuTFA. Isoxazoles¹⁸ and pyrazoles are the only two substrate classes from this set that contain two consecutive heteroatoms in each of their core structures. This structural similarity may play a role in their susceptibility toward copper catalysis. We hypothesize that copper might coordinate to the far-left nitrogen atom (highlighted in a red box, Scheme 3) and activate the system toward B–N σ bond addition across the C–C π bond (shown in alternative intermediate 9). In order to test this hypothesis, LiOTf (5 mol %) was examined as a catalyst for the aminoboration reaction instead of $Cu(OTf)_2$.

This salt, LiOTf, is capable of coordinating nitrogen;³¹ therefore, any catalytic activity observed with LiOTf might indicate an alternative mode of activation for this type of reaction. However, we did not observe any boronate **3a** formation after heating **2a** with LiOTf at 40 °C for 24 h. This result does not eliminate the possibility of nitrogen activation by the copper catalyst entirely, and future mechanistic study is planned to provide insight into the role of the copper catalyst.

Synthetic Utility. The scale-up experiment of the aminoboration reaction of **1f** was successful to afford 816 mg of pinacol boronate **4f** on a 3 mmol scale (eq 2). This convenient scalability demonstrates the efficiency of the method, in which large quantities of these heterocyclic boronic ester building blocks could be prepared for multistep downstream syntheses.



The pinacol boronate **4f** could be further functionalized via Suzuki cross-coupling to add more structural complexity to the pyrazole core, showcasing the applicability of the aminoboration products. This coupling reaction afforded **11** in 63% yield (eq 3). Pinacol boronate **4i** could be transformed into bromide **12** (63%),³² the detosylation of which yielded **13** (54%) using standard procedures²⁶ (eq 4).



The aminoboration reaction also provides complementary regioselectivity to the alternative Ir-catalyzed C-H activation/ borylation reaction sequence,^{15,33} as highlighted in the reaction shown in eq 5. Protonated pyrazole 3f', a byproduct from the aminoboration reaction of 1f, was reacted with pinacolborane in the presence of [Ir(COD)OMe]₂ (3 mol %) and 4,4'-di-tertbutyl-2,2'-dipyridyl (3 mol %) at 25 °C, which are the literature conditions for the C-H activation/borylation proceedure.³³ After 1 h, the crude reaction mixture was examined by ¹H NMR spectroscopy, which showed formation of only one new product plus unreacted starting material 3f'. Purification of this mixture resulted in a 30% yield of 12 and 46% recovery of unreacted 3f'. The borylation reaction occurred exclusively at the thiophene instead of the pyrazole in contrast to the aminoboration reaction to yield 4f. Thus, borylated pyrazoles that are not accessible by this previous iridium-catalyzed route can be accessed in a straightforward manner by copper-catalyzed aminoboration.



In conclusion, a new copper-catalyzed aminoboration reaction was developed, which generates borylated pyrazoles, an important heterocyclic core for drug discovery. The reaction tolerates functional groups that are incompatible with alternative methods and produces only one regioisomer. This is the first report of Earth-abundant copper as the catalyst in a direct borylative heterocyclization reaction from a B-X bond. No complicated organic ligands are needed to attenuate the catalyst reactivity, with $Cu(OTf)_2$ as the optimal catalyst. The reaction scales up successfully. Downstream functionalization of 4f successfully added complexity, and an alternative Ircatalyzed C-H activation/borylation reaction sequence highlighted the complementary regioselectivity available through aminoboration. Further mechanistic studies are underway to aid in a better understanding of the reaction mechanism and the origin of catalytic activation by copper.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b04038.

Full experimental procedures, characterization data, and ¹H, ¹¹B, ¹³C, and ¹⁹F NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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