Communication

Mild Rhodium(III)-Catalyzed C–H Activation and Annulation with Alkyne MIDA Boronates: Short and Efficient Synthesis of Heterocyclic Boronic Acid Derivatives

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Mild Rhodium(III)-Catalyzed C–H Activation and Annulation with Alkyne MIDA Boronates: Short and Efficient Synthesis of Heterocyclic Boronic Acid Derivatives

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Supporting Information Placeholder

ABSTRACT: Taking advantage of Rh(III)-catalyzed C–H activation reactions, we have developed a mild, short and efficient method for the synthesis of bench-stable 3-isoquinolone MIDA boronates. The reaction is practical and scalable. The product formed has been applied in the Suzuki-Miyaura reaction with high efficiency. This strategy has also been successfully expanded to the synthesis of MIDA boronate functionalized heterocycles such as isoquinoline, pyrrole and indole.

Organoboron compounds are among the most important and valuable building blocks in organic synthesis due to their versatility in cross-coupling reactions to construct various carbon-carbon, carbon-oxygen, and carbon-nitrogen bonds.[1] However, in contrast to the versatility of phenyl boronic acid and its derivatives, the application of heterocyclic boron reagents, especially those where boron is located adjacent to the ring heteroatom, frequently encounter a lot of problems.[2] This is due to: 1) their inherent instability, which makes the purification and long term storage difficult; 2) their inefficiency in cross-coupling reactions; and 3) the lack of efficient methods for their preparation. This is demonstrated by the striking fact that 3-isoquinolone[3] and 3-isoquinoline[4] boron reagents have seldom been utilized for synthesis, even though these two skeletons are undoubtedly important in natural products and pharmaceutical agents.

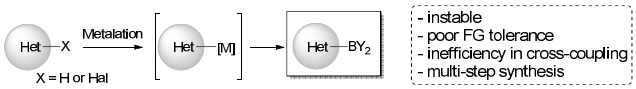
Typically, the synthesis of heterocyclic boron reagents relies heavily on borylation of the metalated heterocycles.[2a,5] The requisite prefunctionalization on a preformed heterocycle and the low functional group tolerance dramatically limit their applications.

The past years have witnessed considerable progress in the field of transition metal catalyzed C–H functionalization reactions.[6] Notably, rhodium(III)-catalyzed C–H activation[7] followed by annulation reaction with alkynes has been frequently used as a powerful tool to construct various heterocycles.[8] Nevertheless, there are still limitations: For example, most of these methods suffer from harsh reaction conditions. In addition, the formation of a single specific product, without valuable handle (for instance, halogen or boron) on the newly-formed ring for further derivatization restricts their applicability to a large extent. However, in medicinal chemistry wherein complexity and diversity based on a core molecule is crucial for lead discovery and optimization, the construction of heterocycles[9] with a versatile handle for divergent synthesis is highly desirable for rapid library development.

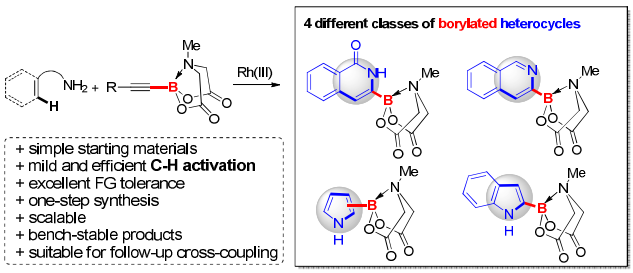
In the past years, the group of Burke introduced MIDA (*N*-methyliminodiacetic acid) boronates as a stable, reliable surrogate of boronic acids, which renders the late stage modification of organoboron reagents feasible under various reaction conditions.[10]

Scheme 1. Heterocyclic Boron Reagent Synthesis

(a) Classic preparation of heterocyclic boron reagent:



(b) This work (heterocycle formation/boron incorporation):

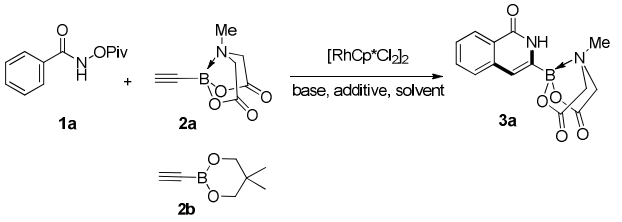


Additionally, the MIDA boronates are capable to undergo efficient Suzuki-Hiyama coupling reactions under a controlled slow-release strategy.[11] On the other hand, we have been focusing on Rh(III)-catalyzed C–H functionalization reactions under mild reaction conditions.[12-14] We thus reasoned that alkyne MIDA boronates would be compatible with the mild reaction conditions, thereby delivering interesting borylated heterocycles.[15] Herein, we report that 3-isoquinolone MIDA boronates can efficiently be constructed by a Rh(III)-catalyzed annulation of *N*-(pivaloyloxy)benzamides[8s,13] and alkyne MIDA boronates. Furthermore, this concept was successfully extended to the synthesis of three other types of privileged B-containing *N*-heterocycles.

We commenced our study by investigating the coupling reaction of **1a** and ethynyl MIDA boronate **2a**.[16] Unfortunately, under the reaction conditions reported previously by others[8s] and us[13], the desired product **3a** was not observed (Table 1, entry 1). Realizing that MIDA boronates would be labile in basic alcoholic solution,[17] we turned our efforts to the screening of different solvents. Indeed, acetonitrile was found to be an ideal solvent for this transformation, delivering borylated isoquinolone **3a** in 50% yield with complete regioselectivity, the boron being attached next to the heteroatom nitrogen (entry 2). Notably, **3a** is a bench-stable off-white solid, which can be easily purified by silica gel chromatography without detectable decomposition. Replacing CsOAc with CsOPiv resulted in a higher yield of 63% (entry 3). An attempt to lower the base loading failed as a decreased yield of 48% was obtained (entry 4). Interestingly, extensive experimentation revealed that the addition of a sub-stoichiometric amount of $Cu(OAc)_2$ facilitated this reaction, improving the yield to 85% (entry 6). The dimerization of **2a** caused by $Cu(OAc)_2$ was not

significant since a slight excess of ethynyl MIDA boronate (1.2 equivalents) was sufficient to ensure a high yield.[18] The role of $Cu(OAc)_2$ is unknown at this point.[19] The use of AgOAc or $Cu^{II}(2\text{-ethylhexanoate})_2$[20] was proven to be less efficient (entry 5 and 7). Furthermore, the failure of boronate **2b** (entry 8), leading only to protodeboronated isoquinolin-1(2*H*)-one product in 9% yield, was testimony for the importance of the MIDA boronate group.

Table 1. Reaction Optimization[a]

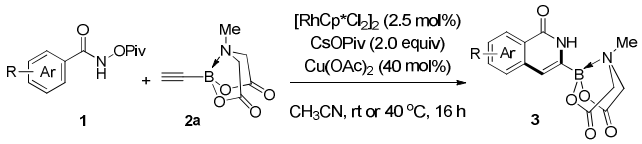


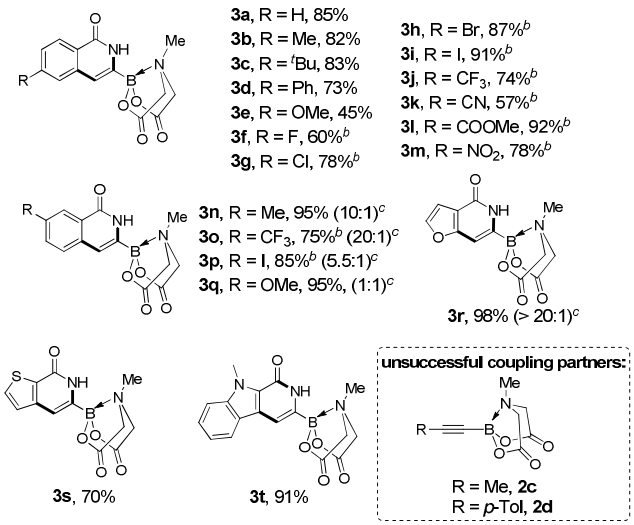
Entry	2	Base (equiv)	Additive (mol%)	Solvent	Yield[b] (%)
1	**2a**	CsOAc (2.0)	-	MeOH	0%
2	**2a**	CsOAc (2.0)	-	CH_3CN	50%
3	**2a**	CsOPiv (2.0)	-	CH_3CN	63%
4	**2a**	CsOPiv (1.0)	-	CH_3CN	48%
5	**2a**	CsOPiv (2.0)	AgOAc (50)	CH_3CN	45%
6	**2a**	**CsOPiv (2.0)**	**$Cu(OAc)_2$ (40)**	**CH_3CN**	**85%**
7	**2a**	CsOPiv (2.0)	Cu(2-ethyl hexanoate)$_2$ (40)	CH_3CN	74%
8	**2b**	CsOPiv (2.0)	$Cu(OAc)_2$ (40)	CH_3CN	0%[c]

Reaction Conditions: [a]**1a** (0.2 mmol), **2** (0.24 mmol, 1.2 equiv), $[RhCp^*Cl_2]_2$ (2.5 mol%), solvent (2 mL), rt, 16 h. [b]Isolated yields. [c]Yield of the corresponding borylated product; instead, 9% of the protodeboronated isoquinolin-1(2*H*)-one were formed.

With the optimized conditions in hand, we sought to investigate the generality of this reaction (Table 2). Many substituents regardless of electron-donating or electron-withdrawing properties on the aromatic ring were well tolerated, providing the products in moderate to excellent yields (45-95%). It should be mentioned that electron-withdrawing groups somewhat retarded the reaction. However, by slightly elevating the reaction temperature to 40 °C, these reactions underwent smoothly. Importantly, functional groups like methoxy, fluoro, chloro, bromo, iodo, trifluoromethyl, ester, cyano, and nitro are commonly encountered in organic synthesis, thus giving ample opportunity for further elaboration. When *meta*-substituted substrates were applied, good regioselectivities favoring activation of the less hindered C–H bond were usually observed (**3n-p**). However, the *m*-OMe substrate was an exception as a 1:1 ratio of inseparable regioisomers was obtained(**3q**).[21] Gratifyingly, several heterocyclic derivatives like furan, thiophene and indole were suitable substrates for this transformation, delivering the cyclization products in good to quantitative yields (**3r**, **3s**, **3t**). The C–H activation took place exclusively at the α position of the furan when **1r** was subjected. Notably, products **3g**, **3h**, **3i** and **3p**, wherein halogen and boron

Table 2. Rh(III)-catalyzed C–H Coupling of *N*-(pivaloyloxy)benzamides with Ethynyl MIDA Boronate[a]

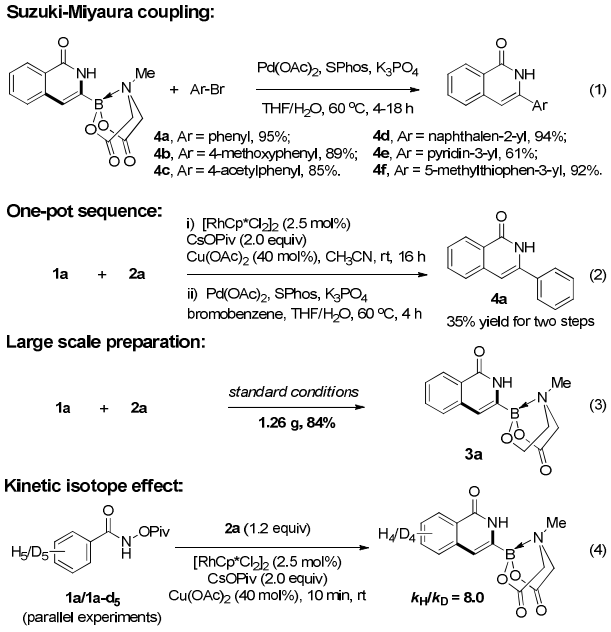




[a]**1** (0.2 mmol), **2a** (0.24 mmol). [b]40 °C was used. [c]Ratio of regioisomers (major isomer shown).

were installed in the same molecule, provide an ideal platform for iterative cross-coupling and orthogonal functionalization.[22] Unfortunately, attempts to utilize internal alkyne MIDA boronates **2c** and **2d** failed. Giving the fact that internal alkynes are predominantly used in C–H functionalization reactions[8,23], we presumed that the presence of the bulky MIDA boronate may impart a significant steric demand thus rendering this reaction sensitive to additional steric interference.

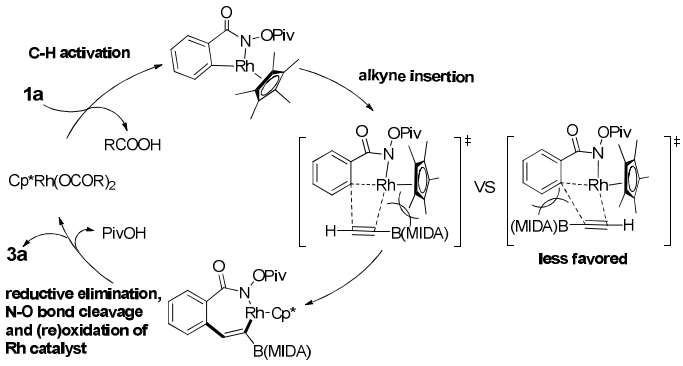
It should be mentioned that the MIDA boronate within the products is a valuable synthetic handle, being transformable to various functionalities.[10] In order to elucidate this, Suzuki-Miyaura reactions were conducted under slow release reaction



conditions.[11] We were pleased to observe the smooth formation of arylation products **4**, with differently substituted aryl and heteroaryl bromides being well tolerated (eq 1).[24] In line with green chemistry principles, a one-pot C–H functionalization/Suzuki-Miyaura coupling sequence was also realized and a low but promising overall yield of 35% was obtained (eq 2).[25] In addition, the reaction is scalable and practical since equal efficiency was observed when the reaction was performed on a gram scale (eq 3).

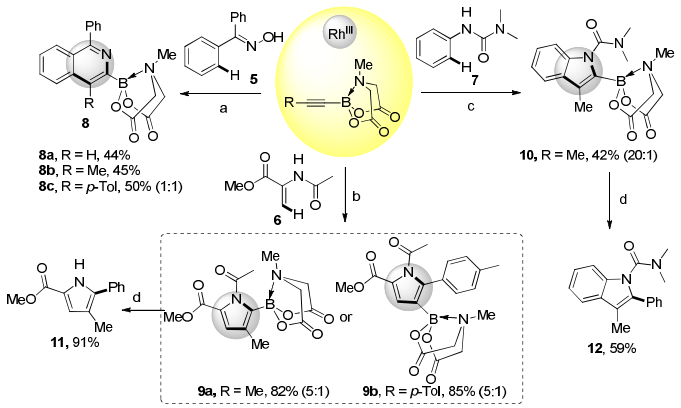
Consistent with previous observations,[8s,13] a large primary kinetic isotope effect value of 8.0 was obtained (eq 4), indicating the C–H activation to be involved in the rate-limiting step.[26] The observed insertion outcome would be rationalized by the more pronounced steric interaction of the boron motif with the aryl ring than that with the metal center (Scheme 2). However, previous observations have revealed the larger substituent is preferentially positioned far away from the bulky Cp* ligand when electronically similar disubstituted alkynes were used.[8c,g-i] Therefore, it is more reasonable to assume that the electronic bias of the ethynyl MIDA boronate governs the regioselectivity.[27] Reductive elimination delivers the product and concomitantly regenerates the Rh(III) catalyst.[28]

Scheme 2. Mechanistic Proposal



To further highlight the versatility of this strategy, we next turned our attention to the synthesis of MIDA boronates of other privileged heterocycles. The results turned out to be extremely encouraging (Scheme 3). For example, treatment of oxime **5** with both terminal and internal alkyne MIDA boronates under Rh(III) catalysis gave the corresponding cyclized isoquinoline products **8** bearing a boron handle in modest yields. Importantly, the success of using internal alkyne MIDA boronate as a coupling partner make the products highly functionalized and diversified, even though a low regioselectivitiy (1:1) is observed when *p*-tolylethynyl MIDA boronate **2d**[29] was applied. Furthermore, by a vinylic C–H activation/internal alkyne MIDA boronate annulation sequence, we were able to construct borylated pyrroles **9**[30] with good efficiency.[31] Interestingly, the coupling of **2d** resulted in a reverse of regioselectivity, giving 3-borylated pyrrole **9b** as major product.[32] Again, the Suzuki-Miyaura coupling of **9a** with bromobenzene delivered the arylated pyrrole **11** in excellent yield, with the concomitant removal of acetyl group. The use of stoichiometric amounts of external oxidant $Cu(OAc)_2$ probably prohibits the coupling of terminal ethynyl MIDA in this case.[18] Similarly, the formation of indole MIDA boronates **10** was also achieved by the C-H functionalization of an urea protected aniline **7**.[33] **10** was transformed to the corresponding 2-phenylindole **12** in reasonable yield.

Scheme 3. Synthesis of Other Heterocyclic MIDA Boronates



Reaction conditions: (a) $[RhCp^*Cl_2]_2$ (10 mol%), CsOAc or K_2CO_3 (2.0 equiv), CH_3CN, 60 °C, 18 h. (b) $[RhCp^*Cl_2]_2$ (5 mol%), $Cu(OAc)_2$ (2.2 equiv), acetone, 60 °C, 18 h. (c) $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (10 mol%), $Cu(OAc)_2$ (2.2 equiv), acetone, 80 °C, 18 h. (d) $Pd(OAc)_2$ (10 mol%), SPhos (20 mol%), bromobenzene, K_3PO_4, THF/H_2O, 60 °C, 18 h.

In summary, by using C–H activation/alkyne MIDA boronate annulation strategy under the catalysis of Rh(III), we have identified a new method for the efficient, short and straightforward access to four important classes of 2-heterocyclic MIDA boronates: isoquinolone, isoquinoline, pyrrole, and indole. The boron substituent attached can serve as a synthetically valuable handle for further transformations, as demonstrated by successful Suzuki-Miyaura coupling reactions. Given the prevalence of these heterocycles in pharmaceuticals, natural products and materials, and the inherent challenges to access their corresponding 2-heterocyclic boron reagents by other methods, we believe this methodology will find broad applications.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures; characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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(25) Control experiments indicate that remaining $Cu(OAc)_2$ and CsOPiv are the main factors responsible for the low efficiency of the Suzuki-Miyaura coupling in this one-pot process. See SI for more details.

(26) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066.

(27) Li, L.; Jiao, Y. Z.; Brennessel, W. W.; Jones, W. D. *Organometallics* **2010**, *29*, 4593.

(28) Xu, L.; Zhu, Q.; Huang, G.; Cheng, B.; Xia, Y. *J. Org. Chem.* **2012**, *77*, 3017.

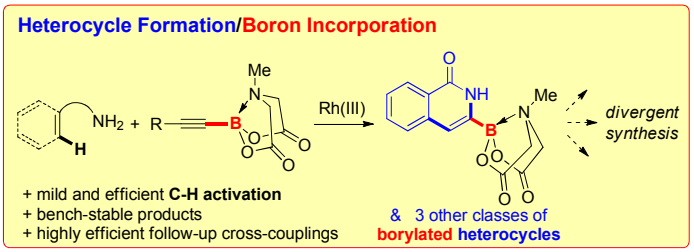
(29) **2d** was synthesized efficiently by a Sonogashira coupling reaction, see supporting information for details.

(30) For recent applications: (a) Smithen, D. A.; Baker, A. E. G.; Offman, M.; Crawford, S. M.; Cameron, T. S.; Thompson, A. *J. Org. Chem.* **2012**, *77*, 3439. (b) Asano, S.; Kamioka, S.; Isobe, Y. *Tetrahedron* **2012**, *68*, 272.

(31) Similar to the use of boronate **2b** (Table 1, entry 8), the coupling of 1-heptynylboronic acid pinacol ester with **6** under otherwise identical reaction conditions gave no corresponding product. Instead, the dimerization of the alkynylboronate resulted in the formation of the 1,3-diyne, together with the recovery of **6**.

(32) For a similar switch of regioselectivity when TMS substituted alkynes were used as coupling partners, see ref 8g.

(33) For recent applications: (a) Reilly, M. K.; Rychnovsky, S. D. *Synlett* **2011**, 2392. (b) Thakur, A.; Zhang, K.; Louie, J. *Chem. Commun.* **2012**, *48*, 203.


Heterocycle Formation/Boron Incorporation
Me
N
NH2 + R
B
O
O
O
H
Rh(III)
O
NH
Me
N
B
O
O
O
O
divergent
synthesis
+ mild and efficient C-H activation
+ bench-stable products
+ highly efficient follow-up cross-couplings
& 3 other classes of
borylated heterocycles