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

Honggen Wang, Christoph Grohmann, Corinna Nimphius, and Frank Glorius*

Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, Corrensstrasse 40, 48149 Münster, Germany

Supporting Information

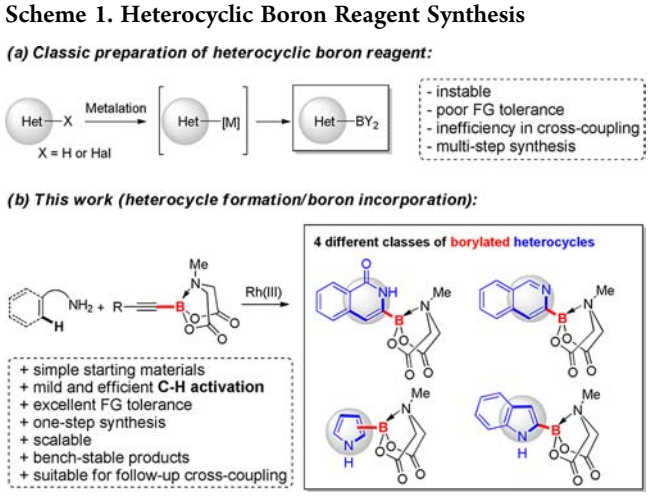
ABSTRACT: Taking advantage of Rh(III)-catalyzed C−H activation reactions, we have developed a mild, short, and efficient method for the synthesis of bench-stable 3-isoquinolone MIDA boronates. The reaction is practical and scalable. The product formed has been applied in the Suzuki−Miyaura reaction with 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 C−C, C−O, and C−N 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 encounters many problems.[2] This is due to (1) their inherent instability, which makes purification and long-term storage difficult; (2) their inefficiency in cross-couplings; 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 (Scheme 1).[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, Rh(III)-catalyzed C−H activation[7] followed by an annulation reaction with alkynes has been frequently used as a powerful tool to construct various heterocycles.[8] Nevertheless, limitations still exist. For example, most of these methods suffer from harsh reaction conditions. Also, the formation of a single specific product, without a 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.

Scheme 1. Heterocyclic Boron Reagent Synthesis



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

Also, the MIDA boronates are capable of undergoing efficient Suzuki−Miyaura couplings under a controlled slow-release strategy.[11] Yet, 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, 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 of **1a** and ethynyl MIDA boronate **2a**.[16] Unfortunately, under the 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 focused on the screening of different solvents. Indeed, acetonitrile was found to be an ideal solvent for this transformation, delivering borylated isoquinolone **3a** in 50%

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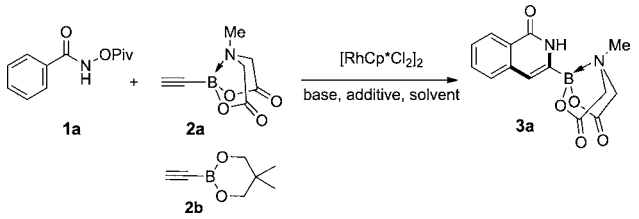
Table 1. Reaction Optimization[a]



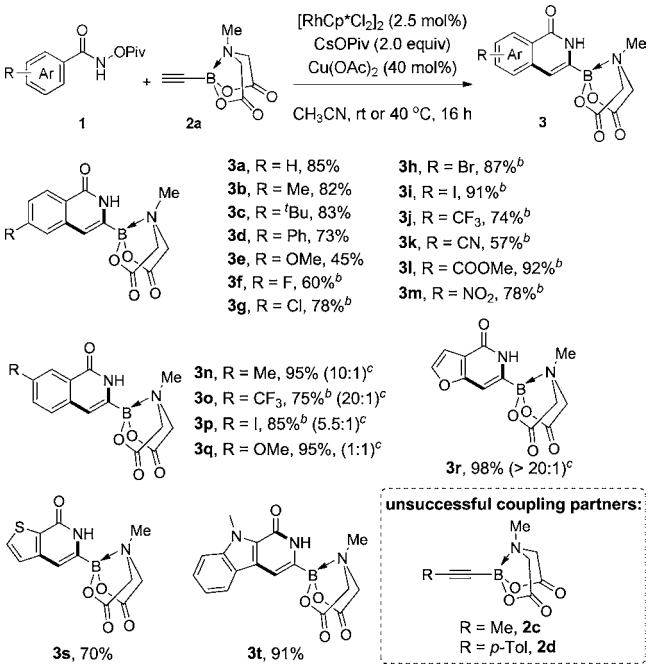
entry	2	base	additive (mol %)	solvent	yield[b] (%)
1	**2a**	CsOAc	–	MeOH	0
2	**2a**	CsOAc	–	CH_3CN	50
3	**2a**	CsOPiv	–	CH_3CN	63
4	**2a**	CsOPiv[c]	–	CH_3CN	48
5	**2a**	CsOPiv	AgOAc (50)	CH_3CN	45
6	**2a**	**CsOPiv**	**$Cu(OAc)_2$ (40)**	**CH_3CN**	**85**
7	**2a**	CsOPiv	Cu(2-ethyl hexanoate)$_2$ (40)	CH_3CN	74
8	**2b**	CsOPiv	$Cu(OAc)_2$ (40)	CH_3CN	0[d]

[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.24 mmol, 1.2 equiv), $[RhCp^*Cl_2]_2$ (2.5 mol %), base (2.0 equiv), solvent (2 mL), rt, 16 h. [b]Isolated yields. [c]1.0 equiv. [d]Yield of the corresponding borylated product; instead, 9% of the protodeboronated isoquinolin-1(2*H*)-one were formed.

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 substoichiometric 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 equiv) 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-ethylhexanoate)$_2$[20] was proven to be less efficient (entries 5 and 7). Furthermore, the failure of boronate **2b** (entry 8), leading only to a protodeboronated isoquinolin-1(2*H*)-one product in 9% yield, evidenced the importance of the MIDA boronate group.

With the optimized conditions in hand, we investigated the generality of this reaction (Table 2). Many substituents regardless of electron-donating or -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 proceeded smoothly. Importantly, functional groups such as 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, e.g. furan, thiophene, and indole, were suitable substrates for this transformation, delivering the cyclization products in good to quantitative yields (**3r**, **3s**, **3t**).

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).

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 a halogen and boron 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. Given 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 (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). Yet, previous observations have revealed the larger substituent is preferentially positioned far from the bulky Cp* ligand when electronically similar disubstituted alkynes were used.[8c,g–i] Thus, it is more reasonable to assume that the electronic bias of the ethynyl

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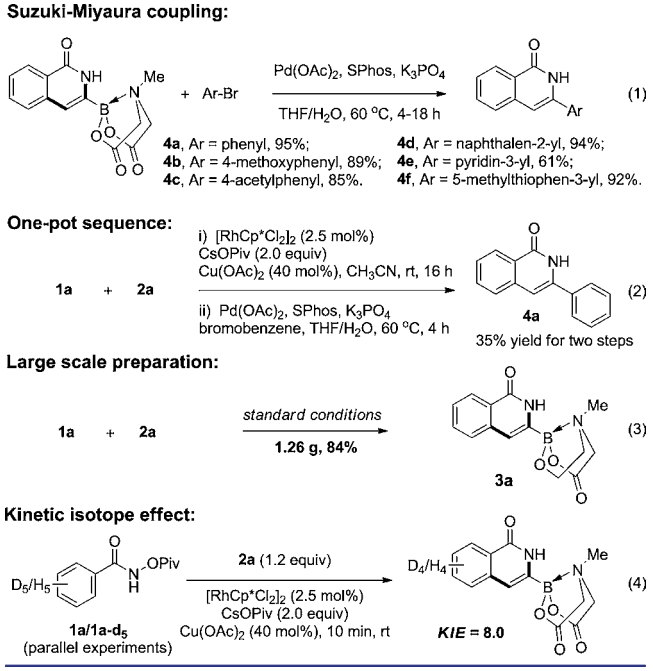
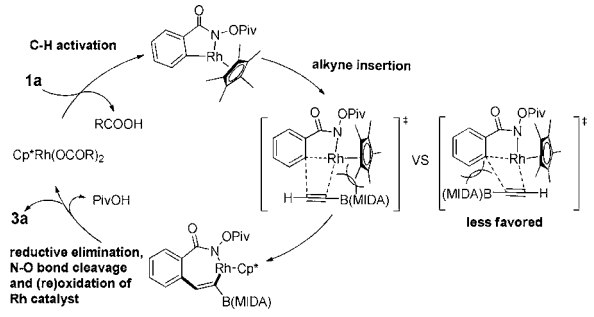


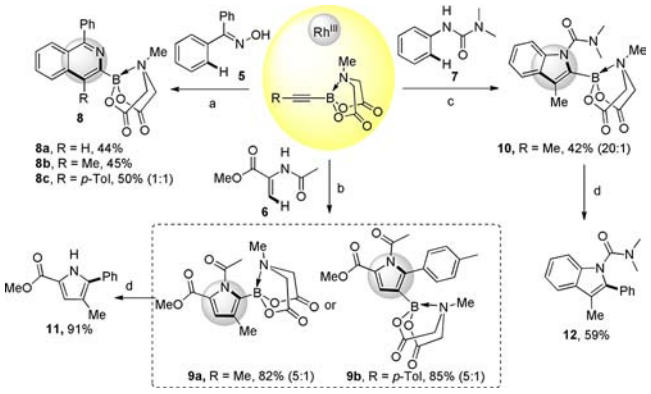
Scheme 2. Mechanistic Proposal



MIDA boronate governs the regioselectivity.[27] Reductive elimination delivers the product and concomitantly regenerates the Rh(III) catalyst.[28]

To further highlight the versatility of this strategy, we next focused on the synthesis of MIDA boronates of other privileged heterocycles. The results were 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 makes the products highly functionalized and diversified, even though a low regioselectivity (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 the major product. Again, the Suzuki−Miyaura coupling of **9a** with bromobenzene delivered the arylated pyrrole **11** in excellent yield, with concomitant removal of the 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 urea protected aniline

Scheme 3. Synthesis of Other Heterocyclic MIDA Boronates[a]



[a]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.

7. **10** was transformed to the corresponding 2-phenylindole **12** in reasonable yield.

In summary, by using a C−H activation/alkyne MIDA boronate annulation strategy under Rh(III) catalysis, 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 in accessing their corresponding 2-heterocyclic boron reagents by other methods, this methodology should 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.

■ AUTHOR INFORMATION

Corresponding Author

glorius@uni-muenster.de

Notes

The authors declare no competing financial interests.

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