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Regioselective Metal-Free Cross-Coupling of Quinoline *N*-Oxides with Boronic Acids

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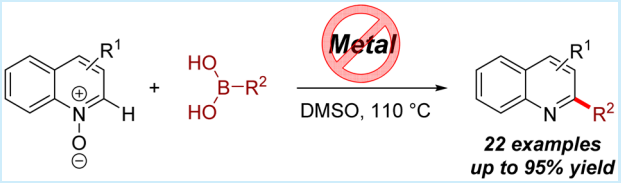
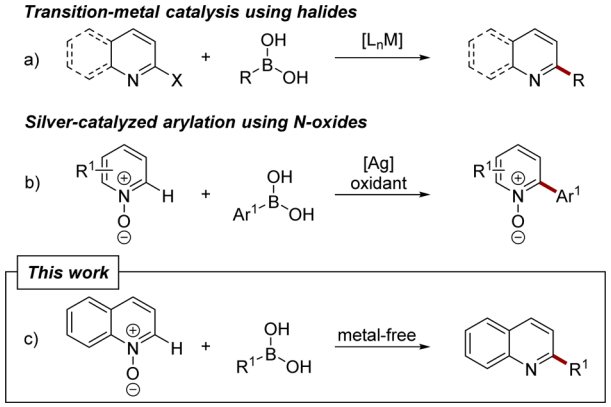
Supporting Information

ABSTRACT: A novel and operationally simple one-step C−H bond functionalization of quinoline *N*-oxides to 2-substituted quinolines was developed. This approach enables the regioselective functionalization under external oxidant- and metal-free conditions. The developed transformation represents the first application of the Petasis reaction in functionalization of heterocycles.



Heterocycles are important scaffolds for organic synthesis, natural bioactive compounds, and advanced materials.[1] Functionalized quinolines are prevalent compounds with medicinal benefits, especially with antimalarial and antimicrobial activities.[2] Consequently, the regioselective formation of C−C bonds, especially at the C2-position of quinolines, is an important strategy to functionalize nitrogenous heterocycles and represents a significant challenge.[3] Transition-metal-catalyzed coupling is the most common strategy (Scheme 1a), and widely employed among these reactions is the Pd-catalyzed cross-coupling of aromatic halides and boronic acids (Suzuki−Miyaura reaction).[4] Heteroaryl halides are accessible by synthesis from *N*-oxides or using *ortho*-metalation reactions.[5] However, the synthesis of these halides is generally associated with low yields and poor functional group compatibility.[6] To overcome the requirement of prefunctionalized starting materials, more recent methods were developed based on metal-catalyzed direct C−H bond functionalization in which heteroaromatic *N*-oxides are employed as versatile templates for C−H bond functionalization.[7] Employed as substrates, heteroaromatic *N*-oxides enable transformations including deoxygenative *ortho*-functionalization, nondeoxygenative C−H bond functionalization, or alternatively 1,3-dipolar cycloaddition.[8] Utilizing boronic acids, Baran and co-workers reported a silver catalyzed radical C−H bond arylation of electron deficient heterocycles and Mai et al. proved the arylation of pyridine *N*-oxides under comparable conditions (Scheme 1b).[9] Although the utilization of *N*-oxides achieved an improved regioselectivity and supersedes the use of a strong acid, an additional reduction of the nitrogen−oxygen bond after the coupling step is required.[9b] The useful physical properties of heteroaryl *N*-oxides result from the 1,2-dipolar nitrogen−oxygen bond, whereby the reactivity toward nucleophiles is enhanced on the C2- and C4-positions.[10] Our group is involved in developing novel methods for the synthesis and functionalization of heterocycles.[11] Therefore, heterocyclic *N*-oxides aroused our attention toward metal-free C−H bond functionalization of heterocycles. Complementary, boronic acids gained increasing interest for the development of metal-free C−C bond construction reactions since their employment in Petasis reaction and its variants.[12] Transition-metal-free reactions are of great interest in terms of atom economy, environmental impact, and cost reduction.[13] Herein, we report the first oxidant- and metal-free regioselective cross-coupling of quinoline *N*-oxides with boronic acids (Scheme 1c).

Scheme 1. Cross-Coupling of *N*-Heterocycles with Boronic Acids



Our studies toward the cross-coupling of quinoline *N*-oxides and boronic acids were initiated by a hypothesized analogy between an iminium-ion in a Petasis−Borono Mannich multicomponent reaction and heteroaromatic *N*-oxides (Figure

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1).[14] The Petasis reaction is a convenient method for the preparation of α-amino acids, mostly simplified by means of a

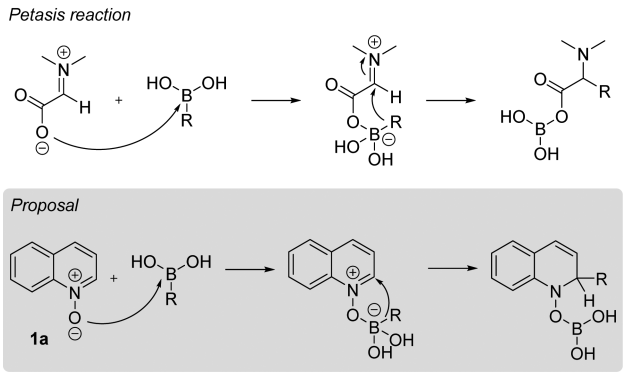


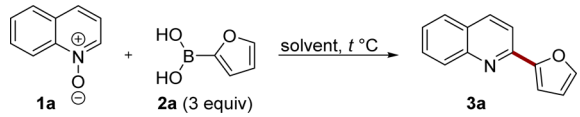
Figure 1. Reaction design.

reaction among a glyoxylic acid, an amine, and a boronic acid.[15] According to density functional theory (DFT) studies by Gois and co-workers, the Petasis reaction proceeds via formation of an iminium-ion followed by the coordination of boronic acid to the carboxylic acid, which finally undergoes an aryl migration and leads to a C−C bond formation (Figure 1).[16] Considering that heterocyclic *N*-oxides simultaneously contain a formal iminium-ion and a coordination site for boronic acids, a heteroaryl Petasis reaction was expected. In this process coordination of boronic acid would lead to an aryl migration, which occurs via a nucleophilic attack on C2-position of quinolines, followed by elimination of boric acid.

Initially, the reaction between quinoline *N*-oxide (**1a**) and 2-furanylboronic acid (**2a**) was examined in DMF under heating conditions. According to our hypothesis the desired product **3a** was formed smoothly within 3 h in 41% yield (Table 1, entry 1). To our delight the reaction proceeded in a deoxygenative and regioselective manner, although first attempts of cross-coupling suffered from an incomplete conversion and partial nitrogen−oxygen bond cleavage of the starting material. To improve the cross-coupling reaction, a broad range of solvents was screened. By changing the solvent to NMP, an increase of yield was observed (Table 1, entry 2). In contrast, the use of nonpolar solvents yielded solely traces of **3a**, due to low solubility of reactants (Table 1, entries 3 and 4). In addition, the reaction showed a high sensitivity toward the presence of hydroxyl group bearing solvents (Table 1, entries 5−8). Acidic and basic conditions inhibited the reaction as well (Table 1, entries 13 and 14). Finally, the use of polar aprotic solvents yielded product **3a** in all cases (Table 1, entries 9−12), from which DMSO led to the most significant increase of product formation with 73% yield in a short reaction time. Highly polar aprotic solvents turned out to be most advantageous for the course of reaction, respectively. Furthermore, different temperatures and equivalents of boronic acid **2a** were tested, but provided no beneficial effect (Table 1, entries 15−17 and Supporting Information for details). In an attempt to improve the yield, selected additives were tested. Unfortunately, the use of common additives led to a dramatic decrease of product formation (see Supporting Information for details).

Having the optimized reaction conditions in hand, the scope of this novel metal-free cross-coupling was examined by investigating the reaction between quinoline *N*-oxides (**1**) and boronic acids **2** (Scheme 2). The scope of boronic acids was limited to electron-rich aromatic and alkenyl boronic acids,

Table 1. Screening of Reaction Conditions[a]



entry	solvent	time (h)	yield[b] (%)
1	DMF	3	41
2	NMP	3	58
3[c]	toluene	8	traces
4[c]	chlorobenzene	8	traces
5[c,d]	EtOH	14	25
6[c]	water	24	traces
7[c]	ethylene glycol	24	n.d.[e]
8	diethylene glycol	24	traces
9	diglyme	24	48
10	1,4-dioxane	6	38
11	**DMSO**	**3**	**73**
12	sulfolane	8	27
13	acetic acid	24	n.d.
14[c]	pyridine	24	traces
15[f]	DMSO	12	33
16[g]	DMSO	3	66
17[h]	DMSO	2	56

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), solvent (0.6 M), under argon atmosphere, 110 °C. [b]Yields are given for isolated products after column chromatography. [c]Concentration = 0.4 M. [d]Reflux. [e]n.d. = not detected. [f]*T* = 90 °C. [g]*T* = 100 °C. [h]*T* = 120 °C.

which yielded the desired products in moderate to good yield (Scheme 2, products **3a−f**). This observation was consistent with the analogy to the Petasis reaction, which is known to be most efficient for this type of boronic acids.[17] The application of cyclohexylboronic acid, thiophen-2-ylboronic acid, and alkyl substituted vinylboronic acid did not yield the desired product.

Afterward, the scope of the cross-coupling reaction was explored between various quinoline *N*-oxide derivatives (**1**) and 2-furanylboronic acid (**2a**). Starting from C3 functionalized quinoline *N*-oxides, a great compatibility for cross-coupling was found. Notably, substituents with an electron withdrawing effect led to the desired products with high yields, whereas electron-rich groups provided the products in good yields (Scheme 2, products **3g,h**). Substituents on C3 position enhanced the reactivity toward nucleophiles by decreasing the electron density in the tested quinolines. Phenanthridin 5-oxide could be employed in the cross-coupling providing product **3k** with 88% yield. Further decorations with electron withdrawing groups on the quinoline scaffold were well tolerated in every tested position (Scheme 2, products **3m−o**). Moreover, the introduction of aliphatic groups was examined on position C4, 7, and 8 (Scheme 2, products **3l**, **3p**, **3q**). Surprisingly, only product **3q** was formed in a short time and with good yields among these compounds. In the next experiments, we tested polysubstituted quinoline derivatives. The application of those derivatives provided the cross-coupled products in good yields (Scheme 2, products **3r−t**). Finally, quinoxaline *N*-oxide (Scheme 2, product **3u**) was found to be an exception for utilization of alternative nitrogenous heterocycles in the cross-coupling reaction and provided the desired product with moderate yield. Unfortunately, isoquinoline, pyridine, and quinazoline *N*-oxides were not compatible with the developed reaction.

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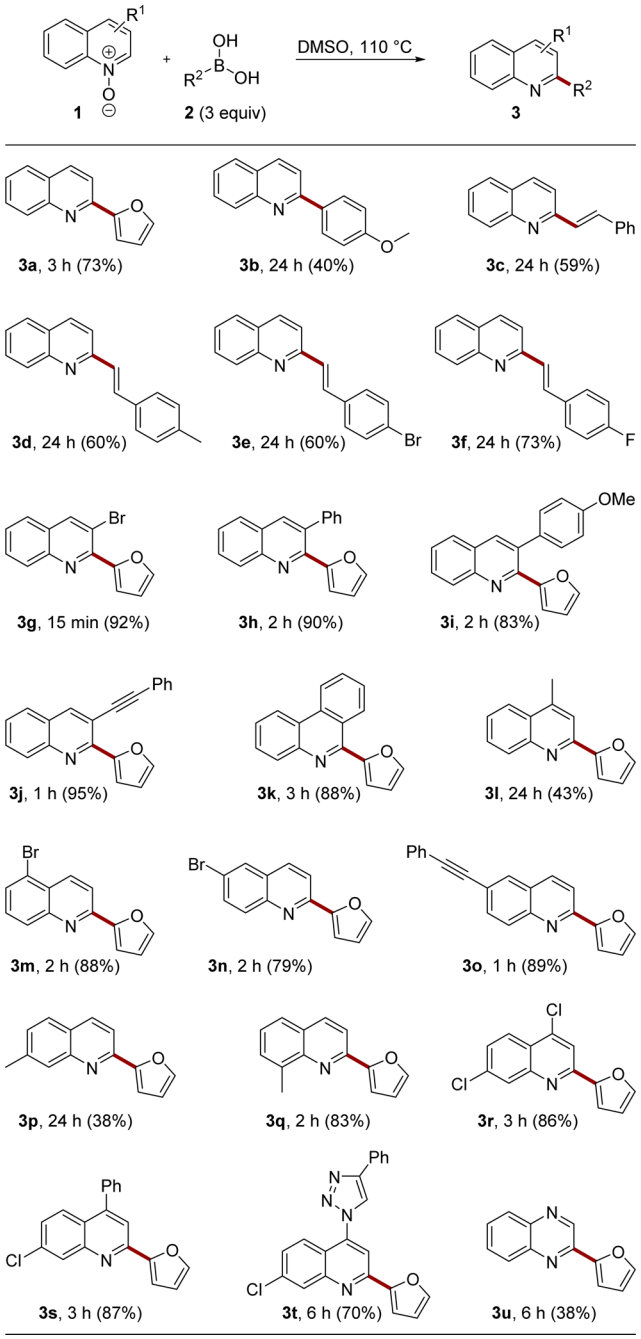
Scheme 2. Substrate Scope[a,b]

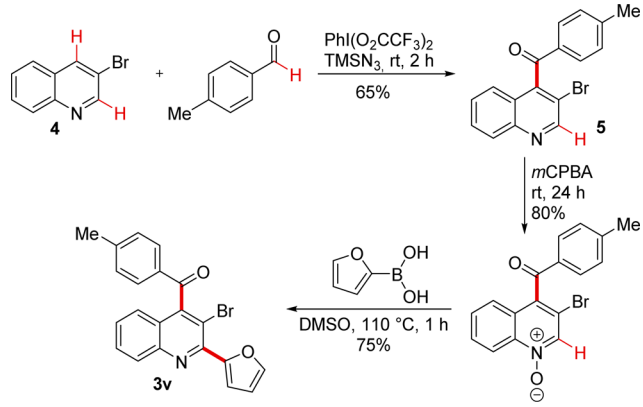


[a]Reaction conditions: **1** (0.3 mmol), **2** (0.9 mmol), DMSO (0.6 M), under argon atmosphere, 110 °C. [b]Yields are given for isolated products after column chromatography.

A highlight in our studies toward the selective substitution of quinolines was found in the stepwise C−H bond functionalization of 3-bromoquinoline (**4**) using the methods developed in our group.[3c] Quinoline **3v** was obtained by means of cross-dehydrogenative coupling followed by *N*-oxidation and cross-coupling with boronic acid **2a** (Scheme 3). Functionalized quinoline **3v** was straightforwardly obtained without the utilization of any metal containing reagent.

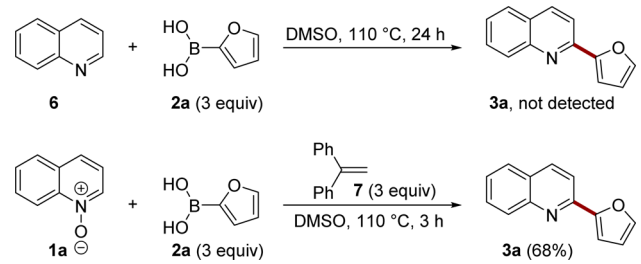
As proof of concept, we further examined the reaction between quinoline *N*-oxide (**1a**) and furanylboronic acid (**2a**). The absence of any product formation while using quinoline

Scheme 3. Sequence for Regioselective Stepwise C−H Bond Functionalization of 3-Bromoquinoline



(**6**) instead of the corresponding *N*-oxide clearly showed the need of preactivated heterocyclic starting materials via oxidation (Scheme 4). Additionally, to exclude a radical mechanism

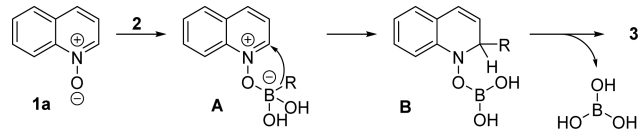
Scheme 4. Control Experiments



pathway, the cross-coupling of **1a** and **2a** was repeated in the presence of radical trap **7**. As expected, the desired product was formed without any changes in the reaction behavior.

Taking the previously mentioned DFT calculation from Gois and co-workers[17] into account and reconciling them with the results of our study, a reaction mechanism was proposed and outlined in Scheme 5. Starting from quinoline *N*-oxide (**1a**),

Scheme 5. Proposed Reaction Mechanism



coordination of boronic acid **2** takes places and enhances the proximity of both reactants. Similar to a Petasis reaction, aryl migration of the boronic acid proceeds via a nucleophilic attack at the C2 position (Scheme 5). This step is followed by a concerted rearomatization and elimination of boric acid, whereupon the functionalized quinoline is formed in a plausible deoxygenative manner.

In summary, a novel and metal-free method for the regioselective cross-coupling of quinoline *N*-oxides with boronic acids has been developed under reagent-less reaction conditions. A broad range of 2-substituted quinolines was obtained in up to 95% yield. The regioselective cross-coupling revealed a good functional group tolerance and proceeded especially well when using electron demanding heterocyclic *N*-oxides.

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■ ASSOCIATED CONTENT

Supporting Information

General experimental procedure, characterization of quinoline *N*-oxides, and products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01456.

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Notes

The authors declare no competing financial interest.

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