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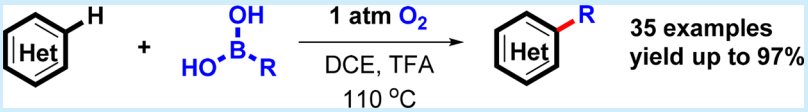
Molecular Oxygen-Mediated Minisci-Type Radical Alkylation of Heteroarenes with Boronic Acids

Lizhi Zhang[‡] and Zhong-Quan Liu*[,†,‡]

[†]State Key Laboratory Cultivation Base for TCM Quality and Efficacy, College of Pharmacy, Nanjing University of Chinese Medicine, Nanjing 210023, China

[‡]State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China

Supporting Information



ABSTRACT: The carbon−carbon bond formation via autoxidation of organoboronic acid using 1 atm of O_2 is achieved in a simple, clean, and green fashion. The approach allows a technically facile and environmentally benign access to structurally diverse heteroaromatics with medicinally privileged scaffolds. The strategy also displays its practicality and sustainability in the resynthesis of marketed drugs Crestor and pyrimethamine.

Synthesis of functional compounds such as drugs benefits human life worldwide but inevitably leads to a fast accumulation of pollutants in the environment. The development of greener or sustainable synthetic technology has historically been and remains a central topic of research in chemistry.[1] Organic transformations using molecular oxygen as the sole oxidant represent the most meaningful explorations since O_2 is the ideal oxidant. Considerable advances in aerobic oxidation of alcohol, aldehydes, amine, hydrocarbon, and organometallics, etc. have been made in the past decades.[2] However, transition-metal and/or organocatalysts along with electron-transfer mediators are usually required in most of these systems. In contrast, although it would be much simpler, cleaner and waste-minimizing developments on establishing efficient synthetic methods based upon autoxidation of organic molecules without any catalysts have remained stagnant.[3] Very few successful organic transformations, for instance, carbon−carbon bond formation using only O_2, have been explored in the past years.[4] Nevertheless, most processes in these cases are very slow because direct oxidation by molecular oxygen is usually kinetically unfavored. It seems that the sustainability is contradictory to the efficiency in these reactions. Hence, exploration of more efficient and highly chemoselective synthetic methods on account of autoxidation to solve this contradiction remains a great challenge.

A historical report on autoxidation of organoboranes by Frankland can be traced back to 1860.[5] One century later, organoboranes were introduced to studies of free-radical reactions.[6] Since then, together with organotin hydride and/or AIBN, R_3B/O_2 has become a powerful initiator system for radical reactions.[7] In comparison with trialkylboranes[8] and organotrifluoroborates,[9] however, organoboronic acids are rarely utilized as radical precursors to construct C−C bonds.[10] In 2010, Baran and co-workers developed an efficient Ag(I)/$S_2O_8^{2-}$-promoted arylation/alkylation of heteroaromatics and quinones with $Ar(R)B(OH)_2$.[11] Subsequently, a convenient access to phenanthridines via a Mn(III)-mediated radical cascade reaction of diaryl isonitriles with boronic acids was reported by Tobisu and Chatani in 2012.[12] One year later, Lei and co-workers described a Ni(II)/DTBP-promoted effective arylation of (sp^3)C−H using arylboronic acids.[13] Recently, Antonchick developed a facile metal-free arylation of quinoline *N*-oxides with aryl boronic acids under hot DMSO.[14] In 2016, a convenient Mn(III)-mediated alkylation of arenes with alkylboronic acids was discovered by Rodríguez et al.[15] Very recently, Chen explored an elegant Minisci C−H alkylation of *N*-heteroarenes with boronic acids via a Ru(II)/hypervalent iodine-promoted photoredox process.[16] Although these protocols allow facile access to diverse C−C bonds using boronic acids as the radical sources, they suffered from usage of excess metal and/or nonmetal chemical oxidants. Herein, we report a catalyst and metal-free C−H alkylation of heteroarenes with boronic acids using only 1 atm of O_2. To the best of our knowledge, this work represents the first applicable use of autoxidation of organoboronic acids to form C−C bonds (Scheme 1).

In order to clarify the mechanisms for autoxidation of organometallic compounds, Davies and Roberts investigated the reaction of boronic acid with O_2 for the first time in 1966.[17] Through extensive studies on oxidation of optically pure 1-phenylethylboronic acid by oxygen leading to racemic peroxides, they postulated a radical-chain mechanism for the autoxidation of organoboranes. Fifty years have passed by since the discovery of autoxidation of organoboronic acid; however, not a single applicable use of the autoxidation in organic synthesis has been reported. Of particular interest is the exploration green radical systems;[18] therefore, we began to envision whether the autoxidation of boronic acids could be utilized to develop

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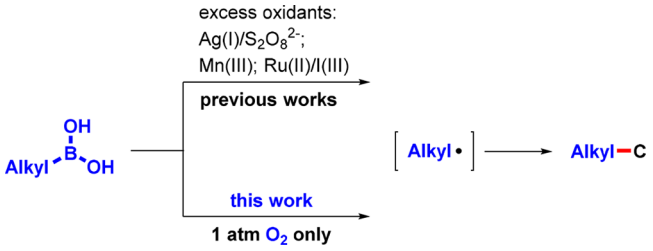
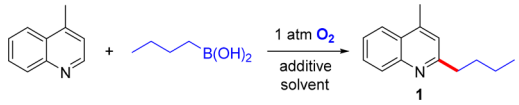
Scheme 1. Radical C−C Bond Formation Using Alkylboronic Acid as Precursor



efficient synthetic methods, for instance, forming C−C bonds. Initially, a Minisci-type reaction[19,20] of 4-methylquinoline with butylboronic acid under oxygen atmosphere was designed to test our hypothesis (Table 1). Table 1 shows that addition of acid,

Table 1. Optimization of the Reaction Conditions[a]



entry	additive (equiv)	solvent (mL)	temp (°C)	yield[b] (%)
1[c]	TFA (2)	DCE (2)	90	
2[c]	TFA (2)	DCE (2)	110	25
3[c]	TFA (2)	CH_3CN (2)	110	14
4	TFA (2)	DCE (2)	110	58
5	H_2SO_4 (1)[d]	DCE (2)	110	10
6	TFA (2)	DCE (5)	110	
7	TFA (2)	DCE (0.5)	110	77

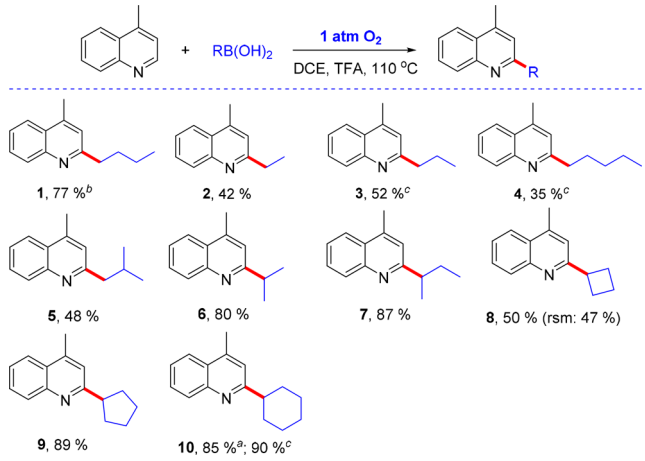
[a]Reaction conditions: 4-methylquinoline (0.2 mmol, 1 equiv), *n*-BuB(OH)$_2$ (1 mmol, 5 equiv), 1 atm of O_2 (air bag); 12 h, unless otherwise noted. [b]Isolated yields. [c]6 h. [d]2 M of H_2SO_4 used.

solvent, and temperature critically affected the efficiency of this reaction. No reaction occurred at 90 °C or lower (entry 1). By increasing the temperature to 110 °C, the desired product was obtained in 25% (entry 2). Acetonitrile as solvent gave lower yield than dichloroethane (DCE) (entry 3). To our delight, a 58% yield of the expected products was isolated by extension of reaction time to 12 h (entry 4). H_2SO_4 as an alternative to TFA afforded only 10% yield of the product (entry 5). Furthermore, we evaluated the cage effect of this system (entries 6 and 7, see also the Supporting Information). We found it is critical for this process. Finally, this oxygen-promoted alkylation of heteroaromatics with boronic acid produced the corresponding product in good yields under the following conditions: 1 equiv of heterocycle, 5 equiv of alkylboronic acid, 2 equiv of TFA, 1 atm O_2, 0.5 mL of DCE, 110 °C, refluxing for 12 h.

With the modified conditions in hand, we began to evaluate the generality of this reaction. As demonstrated in Scheme 2, an array of alkylboronic acids are compatible with this system. Acyclic substrates including primary and secondary boronic acids afforded the desired alkylated heteroarenes in 35%−87% yields (**1**−**7**). It was found that 2° boronic acids gave higher yields than 1°. In addition, cyclic aliphatic boronic acids are also effective substrates, and led to the products in 50−90% yields (**8**−**10**).

Next we turned our attention to a variety of heterocycles that are extremely valuable for library design and drug discovery.[21] As illustrated in Scheme 3, we discovered that this new autoxidation method allows facile alkylation of a broad range of heteroaromatics by using boronic acids with 1 atm of O_2 only. A series

Scheme 2. Molecular Oxygen-Mediated Alkylation of Lepidine with Boronic Acids[a]



[a]Reaction conditions: 4-methylquinoline (1 equiv, 0.2 mmol), alkyl boronic acid (5 equiv, 1 mmol), TFA (2 equiv, 0.4 mmol), DCE (0.5 mL), 1 atm of O_2 (air bag), 110 °C, 12 h, unless otherwise noted. [b]Isolated yields. [c]HOAc/CH_3CN (1:1, 0.5 mL) as alternative solvent.

of quinoline and its derivatives were examined first. The expected alkylated heteroarenes were successfully obtained in moderate to excellent yields (**11**−**18**). It is noteworthy that various sensitive functional groups can be tolerated in this protocol. For example, cinchonine gave the corresponding product in 44% isolated yields with recovery of 50% of starting material (**18**). Subsequently, other *N*-heteroaromatics such as isoquinoline, pyridine, phenanthridine, and phthalazine were screened (**19**−**24**). Gratifyingly, the alkylated heterocycles were synthesized in good to nearly quantitative yields. Furthermore, monoalkylation compounds were isolated as the major products. More interestingly, 4-*tert*-butylpyridine and pyridin-4-ylmethanol afforded the unique monoalkylated pyridines in 91% and 72% yield, respectively, and no difunctionalized products were observed (**21** and **22**). Both benzo[*d*]imidazole and benzo[*d*]-thiazole were also proven to be effective substrates (**25**−**27**). Finally, an array of DNA base analogues were subjected to this autoxidative alkylation (**28**−**32**). To our delight, these bioactive compounds were found to be amenable to this system. Notably, pentoxifylline, a medicine primarily used to reduce pain, led to its alkylated analogue in 40% yield (**32**). Pyridine 1-oxide was found to be an effective substrate in this reaction (**33**). These results show that this unique alkylation protocol has broad substrate scope, which could be potentially applied in the synthesis of pharmaceuticals.

To verify its application in drug synthesis, we synthesized several drugs using this autoxidative alkylation strategy. Scheme 4 shows a valuable alternative access to a worldwide best-selling drug, rosuvastatin, commercially named Crestor. Starting from 1-(4-fluorophenyl)ethan-1-one, the heterocycle ethyl 2-amino-4-(4-fluorophenyl)pyrimidine-5-carboxylate was obtained by known processes.[22] Subsequently, the unprotected amino-pyrimidine was directly subjected to our oxygen-mediated alkylation with isopropyl boronic acid. The core skeleton **34** was smoothly isolated in 62% yield. Followed by known steps,[22] the target drug could then be prepared. Compared with previous approaches to **34**, this method would be more sustainable and represents a valuable alternative route.

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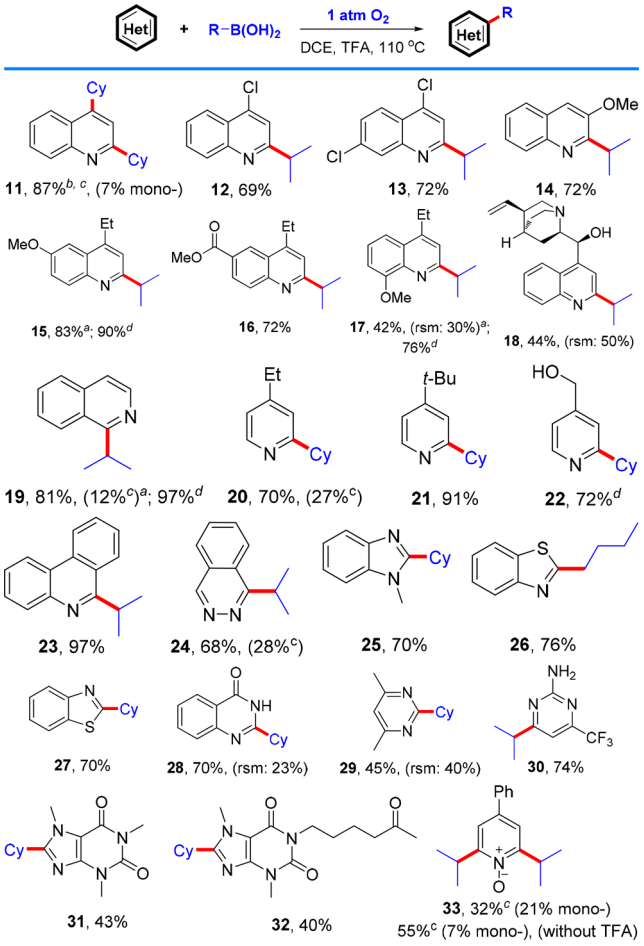
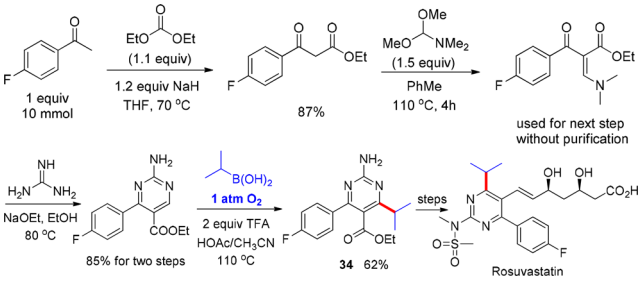
Scheme 3. Molecular Oxygen-Mediated Alkylation of Heterocycles with Boronic Acids[a]



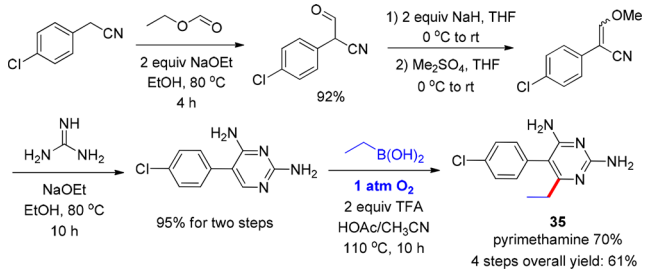
[a]Reaction conditions: heterocycle (1 equiv, 0.2 mmol), alkyl boronic acid (5 equiv, 1 mmol), TFA (2 equiv, 0.4 mmol), DCE (0.5 mL), 1 atm of O_2 (air bag), 110 °C, 12 h, unless otherwise noted. [b]Isolated yields. [c]Bis-alkylation product. [d]HOAc/CH_3CN (1:1, 0.5 mL) as alternative solvent.

Scheme 4. Synthesis of Rosuvastatin Using This Autoxidative Alkylation Strategy



Another application in the synthesis of pyrimethamine, an antimalarial drug, further elucidates the reliability and predictability of this method. Direct ethylation of 5-(4-chlorophenyl)-pyrimidine-2,4-diamine with ethylboronic acid under 1 atm of O_2 afforded the desired medicine in 70% yield (Scheme 5). In contrast to previous methods,[23] the present protocol is more concise and environmentally friendly. Overall, although arylboronic acids are not compatible with the current conditions, the features of metal-free, broad substrate scope, and

Scheme 5. Synthesis of Pyriethamine Using this O_2-Mediated Alkylation



sustainability make this method very attractive to synthetic organic chemists.

Ultimately, experiments were carried out to investigate the mechanism for this reaction. No alkylated heterocycle was detected by addition of TEMPO as a radical scavenger into the reaction of 4-methylquinoline with cyclohexylboronic acid under the typical conditions. A radical trapping adduct 1-(cyclohexyloxy)-2,2,6,6-tetramethylpiperidine was obtained in 75% yield, which indicates that an alkyl radical should be formed in this process. Furthermore, a large amount of cyclohexanol was produced that would be due to autoxidation of cyclohexyl radical by molecular oxygen. In accordance with the widely accepted mechanism, this autoxidative alkylation of heterocycles by boronic acids would conduct a radical-chain process.[6,17,24]

In summary, a catalyst-free facile carbon−carbon bond formation via autoxidation of organoboronic acid was developed. It allows efficient alkylation of diverse heterocycles by using aliphatic boronic acids and 1 atm of oxygen only. In contrast to the previous Minisci alkylation reactions requiring stoichiometric chemical oxidants and/or transition-metal salts, the present method is metal-free, environmentally benign, and tolerates sensitive functional groups. Additionally, compared with unstable and potentially explosive trialkylboron, alkylboronic acid used as radical precursor is far more stable and safe. Finally, this discovery might open the door to long-desired revolutions in green and sustainable chemistry by incorporation of organoboronic acid autoxidation into synthetic organic chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03297.

Experimental procedures, mechanistic studies, and characterization and spectral data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: liuzhq@lzu.edu.cn.

ORCID

Zhong-Quan Liu: 0000-0001-6961-0585

Notes

The authors declare no competing financial interest.

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