Published in final edited form as:

J Am Chem Soc. 2010 September 29; 132(38): 13194–13196. doi:10.1021/ja1066459.

Direct C–H Arylation of Electron-Deficient Heterocycles with Arylboronic Acids

Ian B. Seiple, Shun Su, Rodrigo A. Rodriguez, Ryan Gianatassio, Yuta Fujiwara, Adam L. Sobel, and Phil S. Baran

Department of Chemistry and Chemical Biology, The Scripps Research Institute, 10550 N. Torrey Pines Rd

Phil S. Baran: pbaran@scripps.edu

Abstract

A direct arylation of a variety of electron-deficient heterocycles with arylboronic acids has been developed. This new reaction proceeds readily at room temperature using inexpensive reagents: catalytic silver(I)nitrate in the presence of persulfate co-oxidant. The scope with respect to heterocycle and boronic acid coupling partner is broad, and sensitive functional groups are tolerated. This method allows for rapid access to a variety of arylated heterocycles that would be more difficult to access with traditional methods.

Methods for the cross-coupling of heterocycles with aryl groups are of fundamental importance in nearly all areas of chemical science. Among these, the Pd-catalyzed coupling of arylboronic acids with aromatic halides (Suzuki reaction) is widely employed.¹ A far less studied and underappreciated coupling reaction is the Ag-catalyzed addition of nucleophilic, alkyl-centered radicals to electron-deficient heterocycles (Minisci reaction).² One drawback of the Minisci reaction is the limited access to nucleophilic radicals, especially of the aryl variety.³ Our recent studies involving chemoselective silver-mediated oxidation reactions on highly complex alkaloids such as palau'amine⁴ led us to reexamine this gap in the scope of the classic Minisci reaction. Herein we report the development of a silver(I)-catalyzed addition of arylboronic acids to a range of electron-deficient heterocycles (see Figure 1A). This net C–H arylation proceeds at room temperature and is operationally simple, scalable, and has broad functional group compatibility and substrate scope.

The most common method to arylate electron-deficient heterocycles is by the direct addition of an arylmetallate followed by rearomatization.⁵ However, this method often furnishes products in low to moderate yield, is only effective on electron-deficient heterocycles, and has low functional group compatibility. Due to these drawbacks, several powerful alternative methods have arisen in the literature to functionalize heterocycles.⁶ The direct coupling of heterocycles to aryl halides has been accomplished using palladium,⁷ rhodium,⁸ gold,⁹ and copper¹⁰ catalysis. Additionally, pyridine has been coupled to arylzinc reagents under nickel catalysis in good yield,¹¹ and directed metallation of pyridine derivatives followed by Negishi coupling to aryl halides has demonstrated unique selectivity.¹² Finally, pre-activation of heterocycles as their *N*-oxides has been shown to allow heterocycles to be directly arylated under palladium catalysis with a broad range of aryl halides.¹³

Correspondence to: Phil S. Baran, pbaran@scripps.edu.

Supporting Information Available: Detailed experimental procedures, copies of all spectral data and full characterization. This material is available via the Internet at <http://pubs.acs.org>.

In principle, a mild C–H arylation of heterocycles that paralleled the Minisci reaction (Figure 1A) would require a facile route to aryl radicals. Specifically, mild generation of these reactive intermediates from stable, readily available starting materials would be greatly enabling, obviating the need for harsh, impractical or environmentally hazardous reaction conditions commonly employed to access these reactive intermediates.^{3,14} Unfortunately, Minisci's conditions for the oxidative decarboxylation of alkylcarboxylates fails on their aryl counterparts (Figure 1B). It was surmised that homolytic cleavage of the C–B bond in an arylboronic acid could be induced in a manner similar to decarboxylation. The widespread availability and unique reactivity patterns of boronic acids has inspired many groups to explore chemistry beyond the Suzuki reaction.¹⁵ However, to the best of our knowledge, a mild protocol for the generation of aryl radicals from arylboronic acids is unknown.¹⁶ By employing conditions similar to those used in the Minisci reaction with alkyl carboxylic acids (catalytic silver(I)nitrate in the presence of persulfate), it was found that arylboronic acids can directly unite with protonated electron-deficient heterocycles at room temperature (Figure 1B). As opposed to prior work on aryl radical coupling to pyridines, the heterocycles can be used as limiting reagents rather than as solvent.^{14,16}

The procedure for the direct arylation is very simple: to a solution of the in situ-generated heterocycle•TFA salt (1.0 equiv) and arylboronic acid (1.5 equiv) in DCM:H₂O (1:1 v:v) at room temperature was added silver(I)nitrate (0.2 equiv) and K₂S₂O₈ (3.0 equiv) followed by a basic workup after 3–12 hours. Trifluorotoluene can be substituted for dichloromethane as an environmentally friendly alternative and an inert atmosphere or purification of solvents/reagents is unnecessary. Irrespective of isolated yield, analysis of the crude mixtures by NMR spectroscopy reveal only product(s) and unreacted starting material (the byproducts are easily removed during aqueous workup) – suggesting that this reaction would be amenable to library synthesis. Performing the reaction without the silver catalyst or persulfate failed to produce any product, while TFA improved rate and conversion,³ but was not essential to achieve the desired reactivity in some cases. These standard conditions could be applied to a range of heterocycles as shown in Table 1, using *p*-tolylboronic acid as a standard aryl coupling partner.

The reaction proved fairly general for several classes of electron-poor heterocycles of varying substitution, with yields ranging from 30% to >90%. Regioselectivity on the heterocycle was predominantly for the 2- and 4- positions, and bis-addition proved to be minimal. Diazines such as pyrimidine, pyridazine, and pyrimidine (**4–6**) all proved to be viable substrates, as well as benzannulated derivatives (**13–18**). Aryl halides were tolerated (e.g. **9**, **11**), providing handles for further functionalization (e.g. with a Suzuki reaction). Electron-withdrawing groups (including ketone functionalities) appeared to enhance the reactivity of the substrate, but sometimes with the loss of selectivity (e.g. **10** and **11**). 2-halogenated pyrazine derivatives did not perform well (**19**), and neither did electron rich heterocycles such as indole or imidazole (**21** and **22**). In this regard, the current reaction is orthogonal to other C–H arylation approaches.^{6–10} The reaction proved scalable, with pyrimidine (**4**) performing well on gram scale, delivering 96% of the desired product. It should be noted that oxidative dimerization of the boronic acid is observed, but the rate appears to be much slower than that of the desired transformation.

The scope of arylboronic acid was explored and the results are displayed in Table 2. Several electron-poor to electron-rich arylboronic acids were tolerated, with the more electron-rich substrates demonstrating shorter reaction times. Many of the more electron-poor boronic acids required a second addition of AgNO₃/K₂S₂O₈ to drive the reaction to completion. Halogenated arylboronic acids performed well (**27–30**, **33**), as well as alkoxy- and aryloxyphenylboronic acids (**32–33**). *Ortho*-substitution was tolerated, but only with electron-donating substituents (e.g. **23**, **31**), and in reduced yield.

Perhaps the most notable example of the generality and functional group tolerance of the title reaction is the direct arylation of quinine (**39**, Scheme 1). This natural product contains an oxidizable benzyl alcohol, an electron-rich monosubstituted alkene, and a highly-nucleophilic quinuclidine-type nitrogen. However, under the reported reaction conditions, *p*-phenoxyphenylboronic acid can be directly coupled to 2-position of this natural product in 40% isolated yield, obviating the need for multistep sequences involving protecting groups and prefunctionalization of the heterocycle. The direct arylation of a natural product such as quinine displays the utility of this reaction in the functionalization and diversification of sensitive late-stage intermediates.

A postulated mechanistic scenario that is consistent with experimental data and literature precedent is summarized in Figure 2. It has been shown² that in the presence of silver(I)-salts, persulfate anion disproportionates into sulfate dianion and sulfate radical anion. This radical could react with the boronic acid through an unexplored process (to be the subject to future investigations), providing an aryl radical. It is probable that this aryl radical reacts with protonated heterocycle **41** to form radical cation **42**, which is reoxidized by silver(II), delivering the desired product **43** and regenerating the silver(I) catalyst.² It is worth noting that this reaction fails with the use of stoichiometric silver(II) as the sole oxidant, or with the use of persulfate in the absence of silver catalyst. Further, product distributions are similar to those seen previously for phenyl radical addition to pyridine,³ strongly suggesting the same reactive intermediate.

Despite the generality and practicality of the title reaction, there are several apparent limitations: First, the regioselectivity (like the Minisci reaction) is not governed by the reagents but by the inherent reactivity of the substrates. Second, the yields are mediocre in some cases and do not necessarily follow a predictable trend. Finally, *ortho*-substitution on the boronic acid greatly hinders the reaction, limiting the scope of the arylboronic acid coupling partner. In addition to a detailed exploration of the mechanism of this reaction, future studies will be aimed at overcoming these limitations.

In summary, a reaction to achieve the direct coupling of arylboronic acids to electron-deficient heterocycles using an inexpensive silver catalyst (<\$1.00/g) and co-oxidant (ca. 1 cent/g) has been invented. The reaction proceeds under ambient conditions, displays a broad scope with respect to both the heterocycle and boronic acid partners, and does not require prefunctionalization of the heterocycle. It has a high functional group tolerance, is operationally trivial to execute, scalable, and can be used to directly functionalize sensitive natural products such as quinine (**39**). These features will likely render it a useful tool in the retrosynthetic analysis of arylated heterocycles. Finally, this work sets a precedent for the mild generation of highly reactive species (tentatively assumed to be radicals) from arylboronic acids, a platform that may find use in other areas of reaction design.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to Dr. Raju Mohan (Exelixis) for a generous donation of boronic acids. Financial support for this work was provided by the NIH/NIGMS (GM-073949), the NSF (predoctoral fellowships for I.B.S. and R.A.R.), Japan Society for the Promotion of Science (JSPS, post-doctoral fellowship for Y.F.), Amgen, and Bristol-Myers Squibb (postdoctoral funding for S.S. and unrestricted research support).

References

1. Suzuki, A.; Brown, HC. *Organic Synthesis Via Boranes*. Vol. Volume 3. Milwaukee, WI: Aldrich; 2003.
2. For selected reviews on the Minisci reaction, see: (a) Minisci F, Vismara E, Fontana F. *Heterocycles*. 1989; 28:489. (b) Minisci F, Fontana F, Vismara E. *J. Heterocycl. Chem.* 1990; 27:79. (c) Harrowven DC, Sutton BJ. *Prog. Heterocycl. Chem.* 2004; 16:27.
3. Minisci F, Vismara V, Fontana F, Morini G, Serravalle M, Giordano C. *J. Org. Chem.* 1986; 51:4411.
4. Seiple IB, Su S, Young IS, Lewis CA, Yamaguchi J, Baran PS. *Angew. Chem. Int. Ed.* 2010; 49:1095.
5. For general reviews, see: (a) Boulton, AJ.; McKillop, A. *Comprehensive Heterocyclic Chemistry*. Katrizky, AR.; Rees, CW., editors. Vol. Vol. 2. New York: Pergamon; 1984. p. 262-270. (b) Joule, JA.; Mills, K. *Heterocyclic Chemistry*, Fourth Edition. Malden, MA: Blackwell; 2000. For a recent example with potassium *t*-Butoxide, suggested to be proceeding through a radical mechanism, see: Yanagisawa S, Ueda K, Tanaguchi T, Itami K. *Org. Lett.* 2008; 10:4673. [PubMed: 18816127]
6. For a review on direct aryl-aryl bond formation, see: Alberico D, Scott ME, Lautens M. *Chem. Rev.* 2007; 107:174. [PubMed: 17212475]
7. For an excellent article including the history of the non-directed palladium-catalyzed arylation of heterocycles, see: (a) Liégault B, Lapointe D, Caron L, Vlassova A, Fagnou K. *J. Org. Chem.* 2009; 74:1826. (and references therein). [PubMed: 19206211] For examples of arylation of indoles with boronic acids under palladium catalysis, see: (b) Yang S-D, Sun C-L, Fang Z, Li B-J, Li Y-Z, Shi Z-J. *Angew. Chem. Int. Ed.* 2008; 47:1473. (c) Zhao J, Zhang Y, Cheng K. *J. Org. Chem.* 2008; 73:7428. [PubMed: 18702549] For a carboxy-directed palladium-catalyzed heterocycle arylation, see: (d) Wasa M, Worrell B, Yu J-Q. *Angew. Chem. Int. Ed.* 2010; 49:1275.
8. Berman AM, Lewis JC, Bergman RG, Ellman JA. *J. Am. Chem. Soc.* 2008; 130:14926. [PubMed: 18855360]
9. Li M, Hua R. *Tetrahedron Lett.* 2009; 50:1478.
10. Do H-Q, Khan RMK, Daugulis O. *J. Am. Chem. Soc.* 2008; 130:15185. [PubMed: 18855471]
11. Tobisu M, Hyodo I, Chatani N. *J. Am. Chem. Soc.* 2009; 131:12070. [PubMed: 19663443]
12. Jaric M, Hang BA, Unsinn A, Karaghiosoff K, Knochel P. *Angew. Chem. Int. Ed.* 2010; 49:5451.
13. Campeau L-C, Stuart DR, Leclerc J-P, Bertrand-Laperle M, Villemure E, Sun H-Y, Lasserre S, Guimond N, Lecavallier M, Fagnou K. *J. Am. Chem. Soc.* 2009; 131:3291. [PubMed: 19215128]
14. For a review of the reaction of diazo derivatives and aroyl peroxides in neat pyridine at 105 °C, see: (a) Hey DH, Stirling CJM, Williams GH. *J. Chem. Soc.* 1955:3963. For generation of aryl radicals from arylbromides with TTMSS and AIBN at 80 °C in neat pyridine, see (b) Núñez A, Sánchez A, Burgos C, Alvarez-Builla J. *Tetrahedron*. 2004; 60:6217. For a phenylation in neat pyridine at 85 – 115 °C in the presence of palladium, see: (c) Mukhopadhyay S, Rothenberg G, Gitis D, Baidossi M, Ponde DE, Sasson Y. *J. Chem. Soc., Perkin Trans.* 2000:1809. For the the generation of aryl radicals from aryl halides in refluxing heterocycles using tin hydrides and an initiator, see (d) McLoughlin PTF, Clyne MA, Aldabbagh F. *Tetrahedron*. 2004; 60:8065. (e) Crich D, Patel M. *Tetrahedron*. 2006; 62:7824. For a review on the generation of aryl radicals from arenediazonium ions, see: (f) Galli C. *Chem. Rev.* 1988; 88:765.
15. For a comprehensive review on the various uses of boronic acids, see: Hall, DG. *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*. Weinheim, Germany: Wiley-VCH; 2005.
16. For arylations with boronic acids in refluxing neat heterocycle using 3 equivalents of Mn(OAc)₃, see: Demir AS, Reis Ö, Emrullahoglu M. *J. Org. Chem.* 2003; 68:578. [PubMed: 12530885] For similar conditions using 10 equivalents of boronic acid at 170 °C, see: Guchhait SK, Kashyap M, Saraf S. *Synthesis*. 2010; 7:1166.

A. (Overview)

B. (Initial Findings)

Figure 1.

(A) Overview of the addition of arylboronic acids to electron-deficient heterocycles. (B) Initial findings with respect to arylboronic acid reactivity.

Figure 2.
A mechanism consistent with previous studies by Minisci.

Scheme 1. Direct arylation of quinine.^a

^a Quinine (0.125 mmol), arylboronic acid (0.25 + 0.125 mmol), TFA (0.375 mmol), AgNO₃ (0.025 mmol), K₂S₂O₈ (0.25 mmol), 23 °C, 3–24 h; isolated yield of chromatographically and spectroscopically pure product displayed.

Table 1 Scope of the coupling of arylboronic acids to heterocycles.^a

^a Heterocycle (0.25 mmol), *p*-tolylboronic acid (0.375 mmol), TFA (0.25 mmol), AgNO₃ (0.05 mmol), K₂S₂O₈ (0.75 mmol), 23 °C, 3–12 h; isolated yields of chromatographically and spectroscopically pure products yields displayed. (NH₄)₂S₂O₈ also suitable as an oxidant.

^b 2-hydroxyethyl ester byproduct arising from oxidation of the benzylic position and hydrolysis.

^c Reaction run at 0.02 M to prevent formation of dimeric byproducts.

Table 2 Scope of boronic acids for the arylation of 4-*tert*-butylpyridine.^a

^a 4-*Tert*-butylpyridine (0.25 mmol), arylboronic acid (0.375 mmol), TFA (0.25 mmol), AgNO₃ (0.05 mmol), K₂S₂O₈ (0.75 mmol), 23 °C, 3–24 h; isolated yields of chromatographically and spectroscopically pure products displayed. For reactions over 3 h, a second addition of AgNO₃ (0.05 mmol) and K₂S₂O₈ (0.75 mmol) were added after 3 h. (NH₄)₂S₂O₈ also suitable as an oxidant.

^b Reaction was performed on 1.0 grams of 4-*tert*-butylpyridine with a modified procedure; 23% starting material was recovered. See Supporting Information for details.