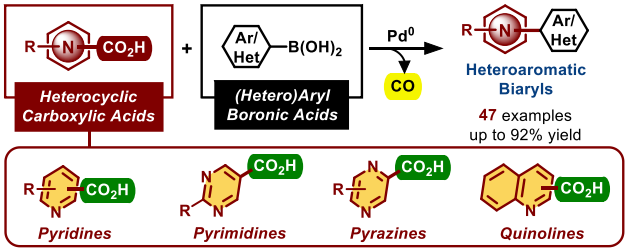
Decarbonylative Pd-Catalyzed Suzuki Cross-Coupling for the Synthesis of Structurally Diverse Heterobiaryls

Alejandro Cervantes-Reyes,[†] Aaron C. Smith,*[,§] Gary M. Chinigo,[§] David C. Blakemore,[§] and Michal Szostak*[,†]

[†]Department of Chemistry, Rutgers University, 73 Warren Street, Newark, New Jersey 07102, United States

[§]Medicine Design, Pfizer, Inc., Groton, Connecticut 06340, United States

Supporting Information



ABSTRACT: Heteroaromatic biaryls are core scaffolds found in a plethora of pharmaceuticals, however, their direct synthesis by the Suzuki cross-coupling is limited to heteroaromatic halide starting materials. Here, we report a direct synthesis of diverse nitrogen-containing heteroaromatic biaryls by Pd-catalyzed decarbonylative Suzuki cross-coupling of widely available heterocyclic carboxylic acids with arylboronic acids. The practical and modular nature of this cross-coupling enabled the straightforward preparation of >45 heterobiaryl products using pyridines, pyrimidines, pyrazines and quinolines in excellent yields. We anticipate that the modular nature of this protocol will find broad application in medicinal chemistry and drug discovery research.

Nitrogen-containing heteroaromatic biaryls are a cornerstone in the pharmaceutical industry as these core scaffolds exist widely in biologically active molecules.[1] For instance, Rosuvastatin (blood cholesterol lowering), AZD2858 (Alzheimer's disease therapy), Vismodegib (Hedgehog pathway inhibitor for treatment of basal cell carcinoma) or Etoricoxib (anti-inflammatory), are pyridine- and pyrazine-containing drug biaryls. Pyrimidine-derived molecules such as Osimertinib and Imatinib are kinase inhibitors for the treatment of chronic myelogenous leukemia, gastrointestinal tumors or non-small cell lung carcinoma among other diseases.[1c–f] The most general and widely used method for the synthesis of heterobiaryls is Suzuki cross-coupling between a boronic acid and a halide.[2] While the available halide set is large, there is key opportunity offered by other functional group sets, such as carboxylic acids.

An internal Pfizer analysis of the available monomer file and the Quick Building Blocks[3] workflow that is utilized to support parallel medicinal chemistry efforts highlights several heteroaryl subsets where greater availability exists for a carboxylic acid than for its corresponding halide (Figure 1). In this analysis, building blocks that are available as both halides and carboxylic acids were organized into commonly used heterocycles. Building blocks that were available as both halides and carboxylic acids were then filtered out to highlight those that are unique to each functional group. Notably from this analysis,

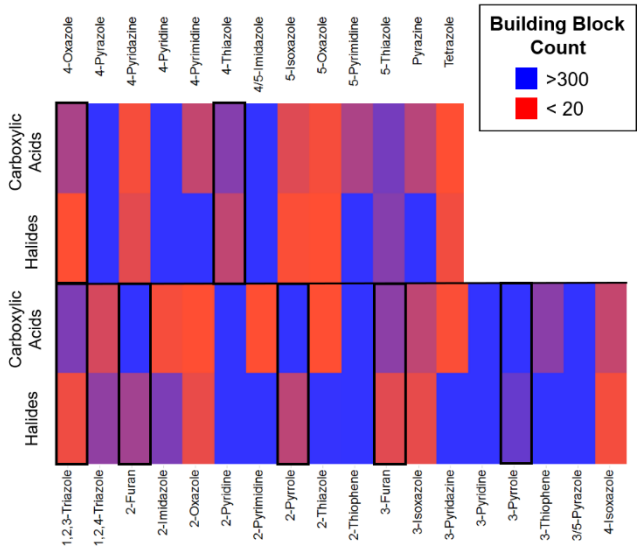


Figure 1. Analysis of Available Building Blocks at Pfizer. The Pfizer file and the Quick Building Block collection were sorted by heterocycle across the carboxylic acid and halide functional groups and a count was performed. Structures that were available as both functional groups were filtered out to highlight the unique space that each set offers. Blue represents a count of >300 unique building blocks while red represents <20 unique building blocks.

multiple substitution patterns of furans, pyrroles, and thiazoles were more available as carboxylic acids than their halide counterparts. This could be an artifact of instability of certain halide substitution patterns (another potential opportunity), could result from commonly-used ring-building reactions that may be more practical to perform with a carboxylic acid already in place, or for a variety of other reasons. Even within monomer sets that have good representation such as pyridines and pyrimidine halides, significant numbers are uniquely available with a pendant carboxylic acid. Some examples of these valuable building blocks are shown in Figure 2 and Figure 3A.

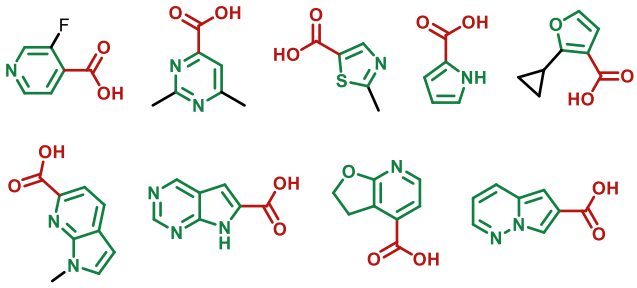


Figure 2. Selected Examples of Carboxylic Acid Monomers with Greater Availability.

Decarbonylative cross-couplings have emerged as an attractive alternative strategy to metal-catalyzed decarboxylative cross-couplings[4,5] and classic Suzuki-Miyaura cross-couplings[2] that allow for C(aryl)–C(aryl) bond construction. Nickel and palladium-catalyzed decarbonylative Suzuki-Miyaura cross-couplings[5] exploit the reaction of widely available aryl carboxylic acids,[6] aldehydes,[7] amides,[8] (acyl)halides,[9] esters,[10] anhydrides,[11] or other chemical feedstocks[12] with organoboron compounds, thus providing an orthogonal strategy to aryl halides and establishing a valuable new disconnection to form (un)symmetrical biaryl motifs (Figure 3B). The significance of heteroaromatic biaryls as potential pharmaceutical candidates and the relevance of decarbonylative Suzuki-Miyaura cross-coupling has driven the present investigation to employ widely available nitrogen heterocyclic carboxylic acids as cross-coupling partners.[13]

In our continuing interest in decarbonylative cross-coupling of carboxylic acids and derivatives,[6] in this collaborative study with Pfizer Medicine Design group, we report a palladium-catalyzed cross-coupling reactions that forge C(heteroaryl)–C(aryl/heteroaryl) bonds producing structurally diverse heterobiaryl motifs using nitrogen heterocyclic carboxylic acids as electrophilic coupling partners (Figure 3C).

Our investigations began by optimizing the reaction parameters using 3-pyridine carboxylic acid as the heterocyclic substrate and 4-methoxyphenyl boronic acid as nucleophile (Table 1). The screening of several phosphine-based ligands (Table 1, entries 1–7) showed that **L6** afforded the highest yield (90%) in the benchmark reaction (entry 1). The use of $Pd(TFA)_2$ afforded slightly lower yield (74%, entry 8), while the employment of $[Pd(allyl)Cl]_2$ complex was deleterious (6% yield, entry 9). By lowering the quantity of Piv_2O, activator (1.5 equiv), product **1** was delivered in good yield (86%, entry 10). However, replacing Piv_2O with Ac_2O (entry 11) or Boc_2O (entry 12), the yield

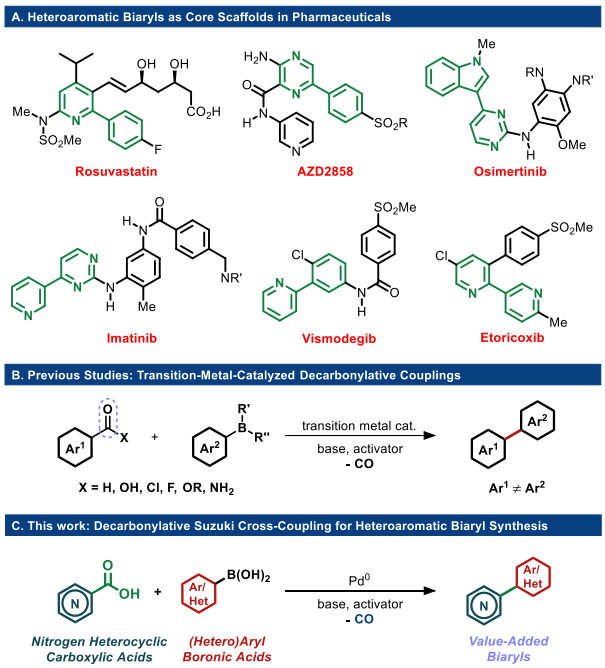
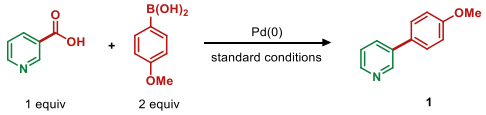


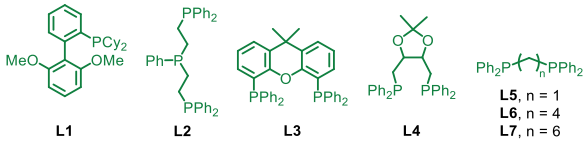
Figure 3. (A) Selected examples of pharmaceuticals containing heteroaromatic biaryls. (B) Decarbonylative cross-coupling reactions of arene carboxylic acids. (C) Present work: heterocyclic carboxylic acids.

Table 1. Optimization of the Reaction Conditions[a]

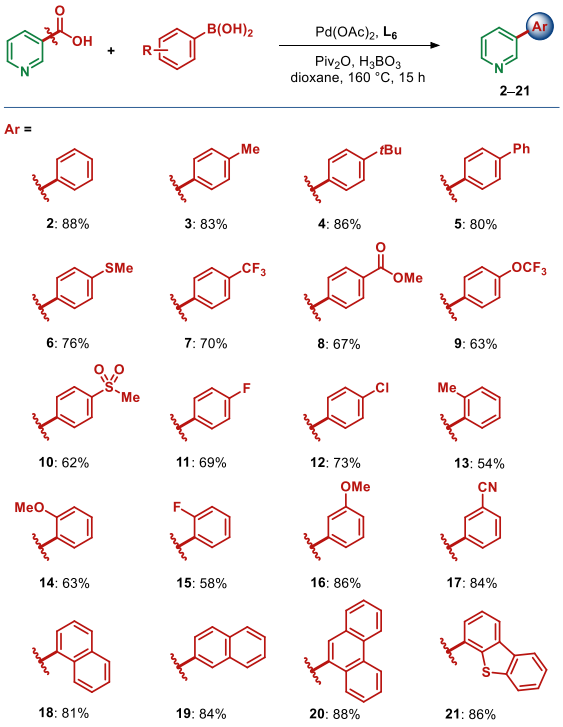


entry	deviation from standard conditions[a]	yield (%)
1	None	90
2[b]	**L1** instead of **L6**	<2
3	**L2** instead of **L6**	10
4	**L3** instead of **L6**	50
5	**L4** instead of **L6**	61
6	**L5** instead of **L6**	52
7	**L7** instead of **L6**	60
8	$Pd(TFA)_2$ instead of $Pd(OAc)_2$	74
9	$[Pd(allyl)Cl]_2$ instead of $Pd(OAc)_2$	6
10	Piv_2O (1.5 equiv) used	86
11	Ac_2O instead of Piv_2O	64
12	Boc_2O instead of Piv_2O	42
13	DIPEA instead of Et_3N	27
14	[0.1M] instead of [0.2M]	56
15	No H_3BO_3 added	38

[a]Conditions: Pyridine-3-carboxylic acid (1.0 equiv), 4-MeO-$C_6H_4B(OH)_2$ (2 equiv), Piv_2O (2.0 equiv), $Pd(OAc)_2$ (10 mol%), **L6** (5 mol%), H_3BO_3 (2 equiv), Et_3N (1.75 equiv), dioxane (0.20 M), 160 °C, 15 h.



Scheme 1. Decarbonylative Cross-Coupling of Pyridine-3-Carboxylic Acid with Various Aryl Boronic Acids[a]

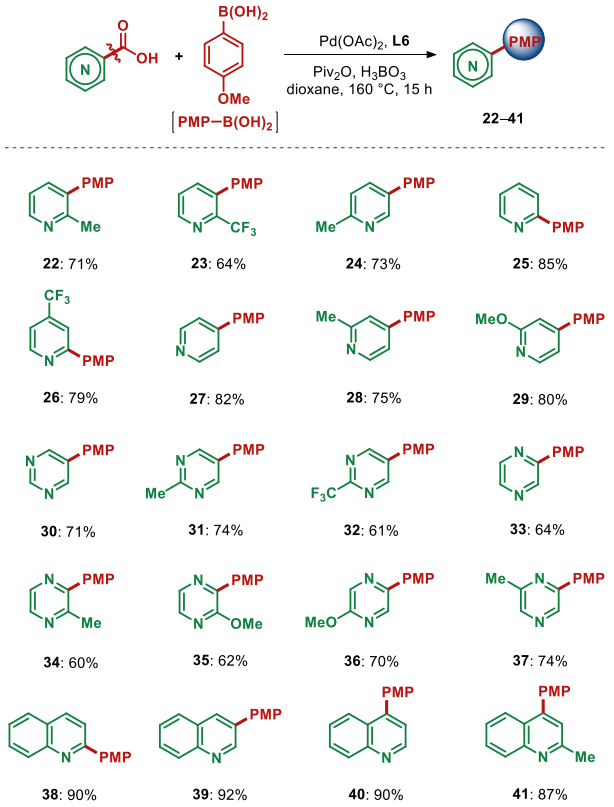


[a]Conditions: Pyridine-3-carboxylic acid (1.0 equiv), Ar-B(OH)$_2$ (2 equiv), Piv_2O (2.0 equiv), $Pd(OAc)_2$ (10 mol%), **L6** (5 mol%), H_3BO_3 (2 equiv), Et_3N (1.75 equiv), dioxane (0.20 M), 160 °C, 15 h.

decreased to 64% and 42%, respectively. The use of DIPEA in lieu of Et_3N (entry 13) as a base, resulted in 27% yield, while a low concentration (0.1 M, entry 14) also gave a low yield. Finally, the addition of H_3BO_3 (entry 15) was crucial for the successful reaction outcome; the role of H_3BO_3 may involve slowing down protodeboronation or activating the carbonyl group towards oxidative addition.[8d]

With the optimized reaction conditions in hand, we next explored the scope of the reaction. As shown in Schemes 1-3, the scope of the reaction is remarkably broad accommodating a wide variety of substituents on the boronic acid and heterocyclic components. Thus, different heteroaromatic biaryls can successfully be synthesized with the use of various arylboronic acids (Scheme 1). Products bearing electronically neutral unsubstituted (**2**), *p*-Me (**3**), *p*-*t*Bu (**4**), *p*-Ph (**5**) and electron-donating *p*-SMe (**6**) substituents were obtained in 80–88% yields. Heterobiaryls containing electron-withdrawing groups at the aromatic ring were delivered in good yields (**7**–**12**). Furthermore, boronic acids bearing substituents at the ortho-position reacted to afford products **13**–**15** in 54%-63% yields, thus showing that sterics is also tolerated at the ortho-position. Products containing either electron-donating (-OMe, **16**) or electron-withdrawing (-CN, **17**) groups at the meta-position were obtained in excellent yields. It is noteworthy that when we employed polyaromatic boronic acids, they performed well and provided the corresponding biaryl products **18**–**20** in high yields (81–88%). Dibenzothiophene-4-boronic acid was also suitable for the transformation, affording product **21** in 63% yield.

Scheme 2. Scope of Heterocyclic Carboxylic Acids in the Pd-Catalyzed Suzuki–Miyaura Biaryl Synthesis

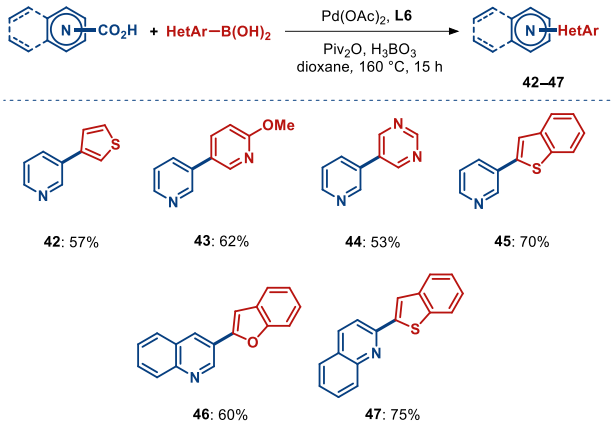


[a]Conditions: Carboxylic acid (1.0 equiv), 4-MeO-$C_6H_4B(OH)_2$ (2 equiv), Piv_2O (2.0 equiv), $Pd(OAc)_2$ (10 mol%), **L6** (5 mol%), H_3BO_3 (2 equiv), Et_3N (1.75 equiv), dioxane (0.20 M), 160 °C, 15 h.

Next, we investigated the scope of the heterocyclic carboxylic acids. As depicted in Scheme 2, a broad plethora of nitrogen-containing heterocyclic rings could be applied to the current reaction conditions. 3-Pyridine carboxylic acids bearing neutral (Me) or electron-withdrawing (CF_3) substituents at C2 or C6 positions reacted well, delivering products **22**–**24** in 64–73% yields. Unsubstituted 2- and 4-pyridine carboxylic acids smoothly produced biaryls **25** and **27** in 85% and 82% yields, respectively. In this context, Yamaguchi and co-workers reported a decarbonylative cross-coupling of preactivated phenolic esters with arylboronic acids, which is limited to 2-azinecarboxylates, thus demonstrating that our present protocol is not limited to precoordinating heterocycles and uses carboxylic acids directly.[15] In the case of biaryl product **26**, bearing a CF_3 group at the C4 position, the obtained (79%) yield was also high compared to its unsubstituted counterpart. Further, the use of substituted 4-pyridine carboxylic acids exerted a negligible impact in the yield (products **28**–**29**) with regard to the unsubstituted 4-pyridine carboxylic acid.

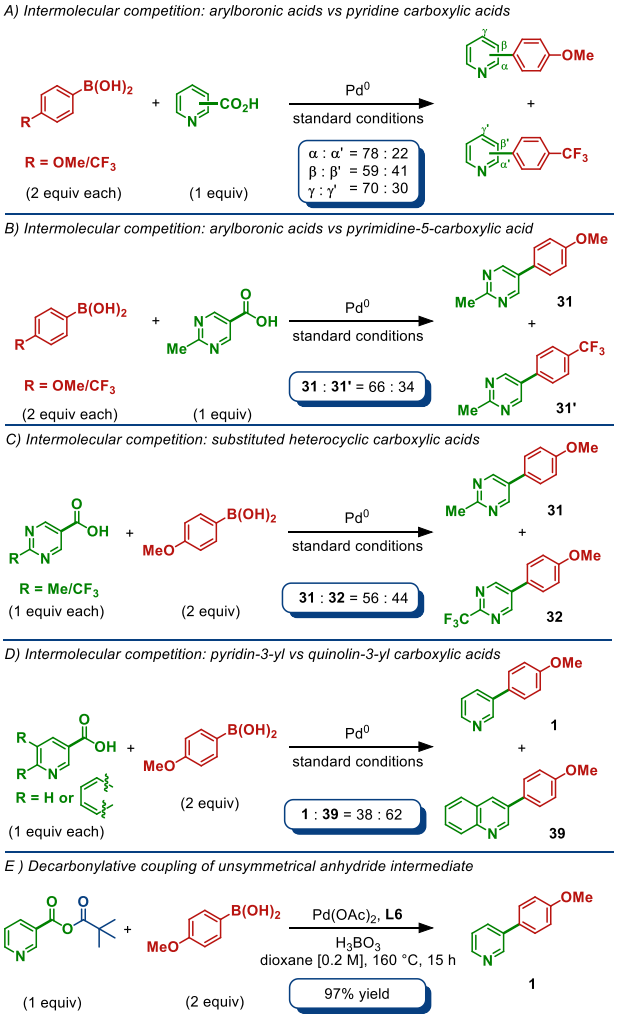
Importantly, pyrimidine carboxylic acids were also suitable for the decarbonylative coupling. We found that unsubstituted and 2-Me substituted substrates afforded products **30** and **31** in 71-74% yield, respectively. The introduction of a CF_3 group at the heterocyclic ring was tolerated (**32**, 61%). Pyrazine carboxylic acids produced biaryl derivatives **33**–**37** in 60–74% yields.

Scheme 3. Scope of (Hetero)Aryl Boronic Acids in the Pd-Catalyzed Suzuki–Miyaura Biaryl Synthesis



[a]Conditions: HetAr–CO_2H (1.0 equiv), Ar–$B(OH)_2$ (2 equiv), Piv_2O (2.0 equiv), $Pd(OAc)_2$ (10 mol%), **L6** (5 mol%), H_3BO_3 (2 equiv), Et_3N (1.75 equiv), dioxane (0.20 M), 160 °C, 15 h.

Scheme 4. Mechanistic Studies



Further, it is noteworthy that various heteroaryl boronic acids, such as thiophen-3-yl, pyridin-3-yl, pyrimidin-5-yl, benzo[*b*]furan-2-yl and benzo[*b*]thiophen-2-yl, reacted with the benchmark carboxylic acids to give the challenging heteroaryl–heteroaryl products (**43**–**48**) in good yields (Scheme 3).

To gain preliminary insight into the nature of this cross-coupling reaction using heterocyclic carboxylic acids, mechanistic experiments were performed (Scheme 4). Most importantly, we probed the reaction of unsymmetrical anhydride with 4-$MeOC_6H_4B(OH)_2$ under the standard reaction conditions, which afforded the biaryl product in 97% yield (Scheme 4E). This is consistent with the mechanism involving activation of the carboxylic acid by Piv_2O and previous DFT studies on the cross-coupling of similar unsymmetrical anhydrides.[6a-e] *Crucially, only traces of the ketone side product resulting from acyl 3-pyC(O)– coupling (cf. decarbonylative 3-py–coupling) were detected (<2%), indicating high chemoselectivity of the present protocol.*

In conclusion, we have reported a direct synthesis of diverse nitrogen-containing heteroaromatic biaryls by Pd-catalyzed decarbonylative Suzuki cross-coupling of widely available heterocyclic carboxylic acids with arylboronic acids. The method employs a broad array of nitrogen heterocyclic carboxylic acids and (hetero)arylboronic acids to assemble a collection of relevant heteroaromatic biaryl building blocks. Given the importance of heterobiaryls in pharmaceutical industry and drug development, the current protocol provides new avenues for broad applications in discovering new bioactive molecules.

ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

aron.smith2@pfizer.com
michal.szostak@rutgers.edu

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