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Journal:	*Organic Chemistry Frontiers*
Manuscript ID	QO-RES-08-2023-001246.R1
Article Type:	Research Article
Date Submitted by the Author:	27-Sep-2023
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Organic Chemistry Frontiers

Research Article

Carboxylic Acids as Double Aryl Group Donors for Biaryl Synthesis

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

The synthesis of biaryl compounds by employing carboxylic acids as double aryl group donors is reported. Naturally present and benign carboxylic acids have been applied as double aryl group donors by sequential decarbonylations for the construction of unsymmetrical biaryls. This method represents an orthogonal approach for the synthesis of valuable biaryl compounds. Aryl carboxylic acids were first converted to aryl boronic esters via palladium-catalyzed decarbonylative borylation. Next, aryl boronic esters were transformed to aryl boronic acids via hydrolysis. Biaryl compounds were generated through decarbonylative coupling between aryl carboxylic acids and aryl boronic acids. Broad substrate scope and excellent functional group tolerance have been demonstrated. Furthermore, a range of pharmaceutical motifs can be readily engaged in excellent yields by this approach. The present method successfully achieves the synthesis of highly valuable biaryls using readily available and inexpensive carboxylic acids as a single class of precursors to access cross-coupling synthons of central importance to the synthetic community.

Introduction

The biaryl motif is a structural architecture of central importance in chemical synthesis.[1-3] The importance of biaryl compounds is underscored by the fact that biaryls have found key applications in medicine, agriculture and materials science, affecting the quality of life and societal well-being.[1-3] The synthesis of biaryls have represented an important endeavor in the development of chemical methodologies.[1-5] Among methods available, at present, Suzuki–Miyaura cross-coupling represents the most powerful and reliable approach to the synthesis of biaryl compounds.

The two essential raw precursors for the Suzuki–Miyaura cross-coupling are aryl halides and aryl boronic acids. Aryl boronic acids for industrial synthesis are routinely prepared by the borylation of aryl halides to generate aryl boronic esters, which are then hydrolyzed to furnish aryl boronic acids.[1] Thus, aryl halides are two-fold essential raw precursors deployed for the Suzuki–Miyaura cross-couplings (Figure 1A). However, aryl halides are not naturally present in nature, and are typically synthesized by electrophilic halogenation of aromatic hydrocarbons through the Friedel–Crafts reaction. Thus, the traditional sequence of preparing biaryls through the Suzuki–Miyaura cross-coupling involves four steps: 1) Friedel–Crafts halogenation of aromatic hydrocarbons to prepare aryl halides, 2) the borylation of aryl halides to furnish aryl boronic esters, 3) the hydrolysis of aryl boronic esters to afford aryl boronic acids, 4) the reaction of aryl boronic acids with aryl halides to synthesize biaryls (Figure 1A). Furthermore, there are safety concerns involving the use of halogens, which pose certain safety hazards. The prepared aryl halides also entail toxicity risks. The development of methods for the synthesis of biaryls using benign and naturally present substrates that can replace aryl halides and can be easily employed under the powerful Suzuki–Miyaura cross-coupling regimen is highly desirable from the societal, industrial and academic standpoints.

Carboxylic acids are readily available and inexpensive raw precursors, which are naturally present in nature.[6-7] Following the wide use of aryl halides in cross-coupling reactions,[1-5] chemists turned their attention to carboxylic acids as cross-coupling substrates, which led to the development of decarboxylative cross-coupling reactions of carboxylic acids (Figure 1B).[6] Compared to aryl halides, the advantages of carboxylic acids are plentiful, including their stability, non-toxicity and orthogonality.[6] However, despite advantages of carboxylic acids over aryl halides, there are several major drawbacks of the decarboxylative cross-coupling reaction mode of carboxylic acids. Most notably, decarboxylative cross-couplings of carboxylic acids typically feature narrow substrate scope and poor functional group tolerance. In general, only ortho-functionalized carboxylic acid substrates or substrates containing strongly electron-withdrawing groups are compatible.[6] In addition, decarboxylative cross-coupling reactions of carboxylic acids generate aryl nucleophiles and require oxidants in the cross-coupling with aryl boronic acids.[8] At present, there are very few examples where carboxylic acids are used as double aryl group donors to achieve the synthesis of biaryl compounds.[9,10] These methods are limited by the synthesis of symmetrical biaryls, specific substitution patterns, limited substrate scope and functional group tolerance, and are not viable for the synthesis of broadly useful biaryl compounds.

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

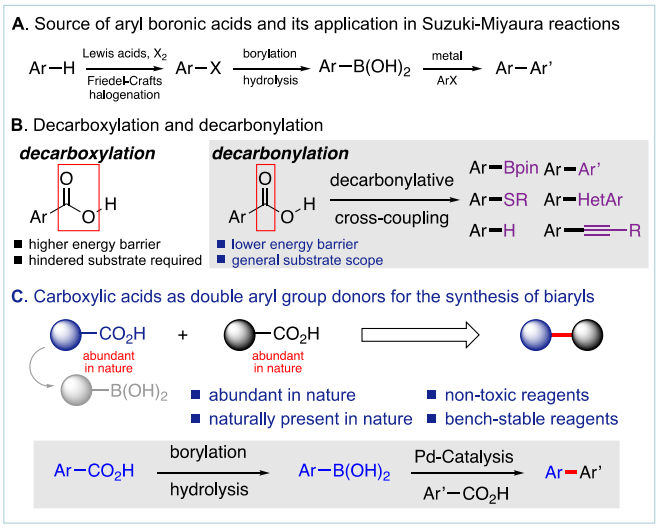


Figure 1. The synthesis of biaryls using carboxylic acids.

In contrast, decarbonylative cross-coupling of carboxylic acids represents an exceedingly robust reaction mode, where the powerful Pd(0)/Pd(II) cycle shows the inherent broad substrate scope and excellent functional group tolerance (Figure 1B). Most crucially, carboxylic acids applicable to decarbonylative cross-coupling are not limited to substrates with ortho-substituents or substrates with strongly electron-withdrawing groups, which results in broad compatibility of diverse aryl carboxylic acids to this reaction mode.[11]

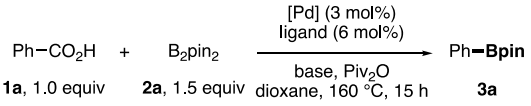
In 1998, de Vries and co-workers reported decarbonylative cross-coupling of carboxylic acid anhydrides with olefins establishing the first decarbonylative Heck reaction.[12a] Afterwards, this reaction was extended to in situ activation of carboxylic acids.[12b] These methods were based on precedents in decarbonylative *β*-hydride elimination of alkyl carboxylic acids.[13-14] In 2013, the Shi group reported rhodium-catalyzed aryla-tion of aromatic hydrocarbons via C–H bond activation using carboxylic acids as aryl donors.[15] It was not until 2018 that decarbonylative borylation of carboxylic acids was reported, marking the first time carboxylic acids were used as coupling reagents for the formation of carbon–heteroatom bonds via decarbonylative pathway.[16] In 2019, the first decarbonylative arylation of carboxylic acids was reported, which represented a general and practical method for the synthesis of biaryls using carboxylic acids as arylating reagents.[17] Thereafter, a series of methods to generate carbon–carbon and carbon–heteroatom bonds through decarbonylative cross-coupling of carboxylic acids were developed.[18-24]

Based on our interest in decarbonylative cross-coupling, we envisioned the use of carboxylic acids as double aryl donors to synthesize biaryl compounds. The specific steps of this approach involve 1) decarbonylative borylation of carboxylic acids to generate aryl borate esters, 2) hydrolysis of aryl borate esters to furnish aryl boronic acids, and 3) decarbonylative Suzuki–Miyaura cross-coupling of the generated aryl boronic acids with carboxylic acids to generate biaryls (Figure 1C). Noteworthy features of this approach involve 1) the use of benign carboxylic acids that are naturally present and orthogonal to aryl halides, 2) the first use of carboxylic acids as double aryl functional group donors for the synthesis of biaryl compounds, and 3) broad functional group tolerance, including functionalization of pharmaceutical motifs that can be readily synthesized via the present approach.

Results and Discussion

The decarbonylative borylation of carboxylic acids was first investigated using benzoic acid (**1a**) and bis(pinacolato)diborane (**2a**) as model substrates (Table 1). The use of base was first screened, and we found that 4-(dimethylamino)pyridine (DMAP) is the optimal base for this reaction (entries 1-3). Furthermore, various phosphine ligands were evaluated (entries 3-14), and we found that DPPP, XantPhos and DPPB gave the highest conversion under the tested conditions. The effect of temperature was also investigated (entries 15-16), and we determined that the reaction can still maintain 71% yield at 120 °C under these conditions.

Table 1. Optimization of borylation of carboxylic acids.[a]



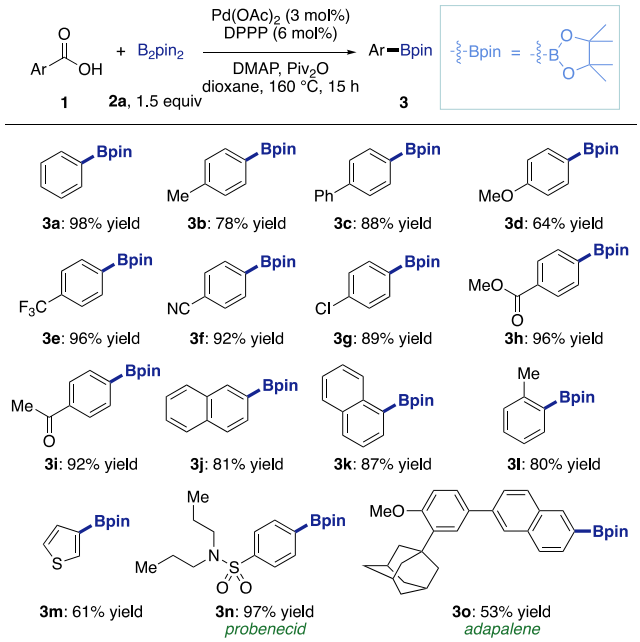
entry	catalyst	ligand	base	yield
1	$Pd(OAc)_2$	DPPB		77
2	$Pd(OAc)_2$	DPPB	Et_3N	88
3	$Pd(OAc)_2$	DPPB	DMAP	96
4	$Pd(OAc)_2$	DPPP	DMAP	98
5	$Pd(OAc)_2$	DPPPent	DMAP	90
6	$Pd(OAc)_2$	DPPF	DMAP	90
7	$Pd(OAc)_2$	BINAP	DMAP	41
8	$Pd(OAc)_2$	XantPhos	DMAP	97
9	$Pd(OAc)_2$	DavePhos	DMAP	13
10	$Pd(OAc)_2$	XPhos	DMAP	<2
11	$Pd(OAc)_2$	SPhos	DMAP	7
12	$Pd(OAc)_2$	PCy_3HBF_4	DMAP	29
13	$Pd(OAc)_2$	$PCyPh_2$	DMAP	37
14	$Pd(OAc)_2$	PPh_3	DMAP	53
15[b]	$Pd(OAc)_2$	DPPP	DMAP	88
16[c]	$Pd(OAc)_2$	DPPP	DMAP	71

[a]Conditions: **1a** (1.0 equiv), **2a** (1.5 equiv), $Pd(OAc)_2$ (3 mol%), ligand (6 mol%), base (1.5 equiv), Piv_2O (1.5 equiv), dioxane, 160 °C, 15 h; [b]140 °C; [c]120 °C.

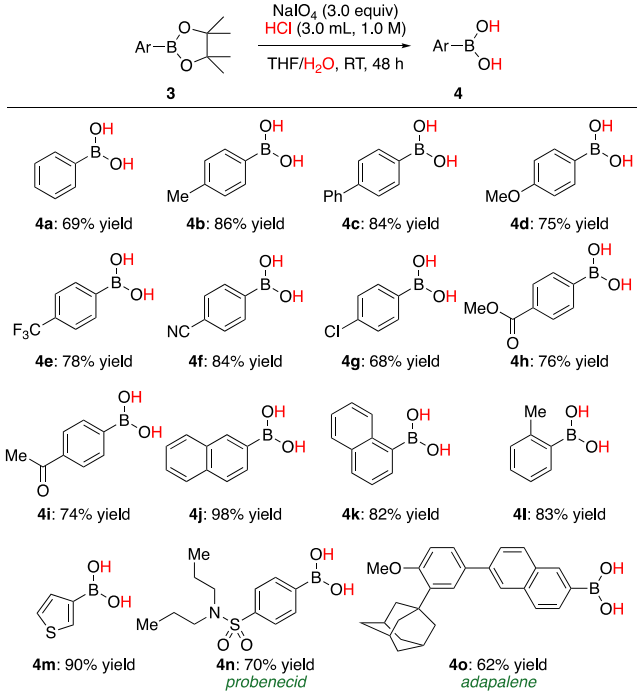
With the optimized reaction conditions in hand, the scope of decarbonylative borylation of carboxylic acids was investigated (Scheme 1). As shown in Scheme 1, carboxylic acids bearing diverse electron-neutral (**3a–3c**), electron-donating (**3d**), and electron-deficient (**3e**) substituents are well tolerated in this approach. Furthermore, substrates containing sensitive cyano (**3f**), chloro (**3g**), ester (**3h**), ketone (**3i**) groups are compatible with this method. Naphthyl substrates (**3j–3k**) could also be converted to the desired borylation products in excellent yields. Furthermore, sterically-hindered (**3l**) and heterocyclic (**3m**) substrates could also be readily employed in this process. Notably, bioactive carboxylic acids, such as found in

pharmaceuticals (**3n–3o**), were also compatible with this reaction.

Scheme 1. Decarbonylative borylation of carboxylic acids.

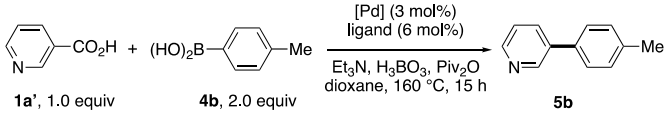


Scheme 2. Hydrolysis of aryl boronic esters.



Having achieved the conversion of a series of carboxylic acids to aryl boronic esters, we next focused on the next step to hydrolyze aryl boronic esters to aryl boronic acids (Scheme 2). We established that these obtained aryl boronic esters could be hydrolyzed under mild conditions using $NaIO_4$/HCl.[25] As shown in Scheme 2, aryl boronic esters bearing electron-neutral (**4a–4c**), electron-rich (**4d**), and electron-withdrawing (**4e**) substituents were converted to aryl boronic acids in excellent yields. Substrates containing cyano (**4f**), chloro (**4g**), ester (**4h**), ketone (**4i**) groups were well-tolerated. Naphthyl substrates (**4j–4k**), sterically-hindered (**4l**), and heterocyclic (**4m**) precursors were also well-suitable. Importantly, substrates derived from pharmaceuticals (**4n–4o**) were also compatible with this mild hydrolysis approach.

Table 2. Optimization of arylation of carboxylic acids.[a]



entry	catalyst	ligand	base	yield
1[b]	$Pd(OAc)_2$	DPPB		14
2[b]	$Pd(OAc)_2$	DPPB	Et_3N	22
3	$Pd(OAc)_2$	DPPB	Et_3N	92
4	$Pd(OAc)_2$	DPPB	DMAP	36
5	$Pd(OAc)_2$	DPPB	pyridine	74
6	$Pd(OAc)_2$	DPPB	DIPEA	96
7[c]	$Pd(OAc)_2$	DPPB	DIPEA	75
8[d]	$Pd(OAc)_2$	DPPB	DIPEA	56
9	$Pd(OAc)_2$	DPPP	DIPEA	47
10	$Pd(OAc)_2$	DPPPent	DIPEA	69
11	$Pd(OAc)_2$	DPPF	DIPEA	35
12	$Pd(OAc)_2$	BINAP	DIPEA	27
13	$Pd(OAc)_2$	XantPhos	DIPEA	80
14	$Pd(OAc)_2$	DavePhos	DIPEA	5
15	$Pd(OAc)_2$	XPhos	DIPEA	7
16	$Pd(OAc)_2$	SPhos	DIPEA	6
17	$Pd(OAc)_2$	PCy_3HBF_4	DIPEA	72
18	$Pd(OAc)_2$	$PCyPh_2$	DIPEA	67
19	$Pd(OAc)_2$	PPh_3	DIPEA	27

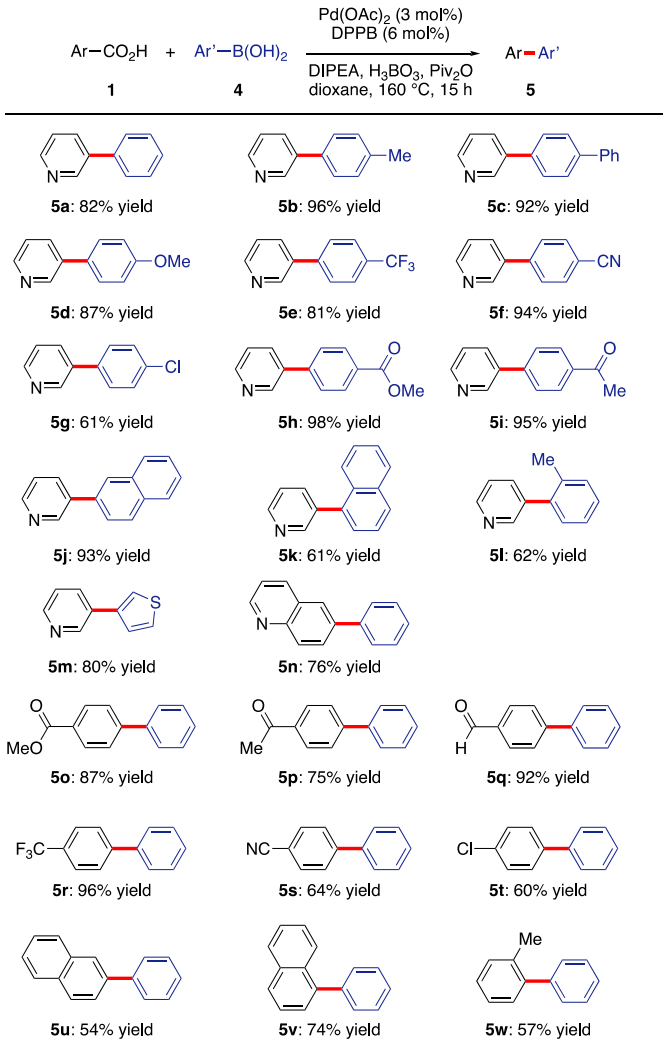
[a]Conditions: **1a** (1.0 equiv), **3b** (2.0 equiv), $Pd(OAc)_2$ (3 mol%), ligand (6 mol%), base (2.0 equiv), H_3BO_3 (2.0 equiv), Piv_2O (2.0 equiv), dioxane, 160 °C, 15 h; [b]without H_3BO_3; [c]**3b** (1.5 equiv), base (1.5 equiv), H_3BO_3 (1.5 equiv), Piv_2O (1.5 equiv); [d]**3b** (1.2 equiv), base (1.2 equiv), H_3BO_3 (1.2 equiv), Piv_2O (1.2 equiv).

Having secured access to aryl boronic acids, we then screened the conditions for the critical decarbonylative arylation of carboxylic acids using 3-py-CO_2H carboxylic acid as the model substrate (Table 2). We found that boric acid is an essential additive for this reaction (entries 1-3). *N*,*N*-Diisopropylethylamine (DIPEA) was identified as the optimal base for this decarbonylative arylation (entries 3-6). We established that stoichiometry is a crucial parameter for the arylation to ensure the optimal equivalency ratio (entries 6-8). Furthermore, different phosphine ligands were evaluated (entries 6, 9-19), and DPPB was identified as the optimal ligand. The first conditions (Scheme 1) are optimized for borylation, while the second are optimized for the Suzuki coupling (Table 2). The key difference is the use of triethylamine as a base to form more reactive acyl ammonium and boric acid.

Having identified the optimal conditions, the scope of the biaryl synthesis via decarbonylative arylation of carboxylic acids was next investigated (Scheme 3). As shown, aryl boronic acid substrates bearing electron-neutral (**5a-c**), electron-donating (**5d**), and electron-withdrawing (**5e**) substituents

were well compatible with this biaryl synthesis method, furnishing 3-pyridyl biaryls. Furthermore, aryl boronic acid substrates containing cyano (**5f**), chloro (**5g**), ester (**5h**), ketone (**5i**) functional groups were well-tolerated in this decarbonylative arylation. Moreover, naphthyl (**5j–5k**), sterically-hindered (**5l**), and heterocyclic (**5m**) aryl boronic acids were also well-compatible, affording the desired biaryl products in good to excellent yields. Interestingly, quinoline-6-carboxylic acid could also be applied to this reaction (**5n**), furnishing medicinally-relevant products. Next, we extended the scope of carboxylic acid substrates to benzoic acids. As shown in Scheme 3, carboxylic acid substrates containing sensitive ester (**5o**), ketone (**5p**), aldehyde (**5q**) functional groups were well-tolerated in this reaction, providing electrophilic handles for further functionalization. Moreover, carboxylic acids containing medicinally-relevant trifluoromethyl (**5r**), cyano (**5s**) and chloro (**5t**) substituents could be employed in good yields. Furthermore, naphthyl (**5u–5v**) substrates were readily amenable by this approach, furnishing conjugated biaryls. Finally, the sterically-hindered substrate (**5w**) was also well-tolerated in this method.

Scheme 3. Substrate scope of arylation of carboxylic acids.



Considering the benefits of carboxylic acids as double aryl donors, we next evaluated the rapid application of this method for the direct functionalization of bioactive molecules (Scheme 4A). As shown, this approach was successfully utilized for the arylation of pharmaceuticals and natural products, such as probenecid (**5x**, **5aa**), adapalene (**5y**), febuxostat (**5z**) and estrone (**5ab**). Crucially, this approach utilizes the inherent presence of the carboxylic acid moiety as a synthetic handle for decarbonylation. Furthermore, gram scale reaction has been implemented and a high conversion has been obtained (Scheme 4B).

Conclusions

In summary, we have reported the synthesis of biaryl compounds using carboxylic acids as double aryl group donors. This approach exploits sequential decarbonylations for the synthesis of unsymmetrical biaryls. The advantages of the method include the natural presence of carboxylic acids, their benign properties as well as orthogonal and ready availability, which provides an alternative approach to the traditional synthesis of biaryls using aryl halides. The approach features excellent functional group tolerance and broad substrate scope, demonstrating that this method represents an efficient pathway for the construction of biaryls using carboxylic acids as raw substrates. The utility has been further demonstrated in the direct functionalization of pharmaceutical molecules. This method provides new avenues for the synthesis of biaryl compounds using a single class of readily available and inexpensive precursors to access cross-coupling synthons of central importance to the synthetic community. Ongoing studies in our laboratories are focused on the development of one-pot decarbonylative processes of carboxylic acids and derivatives, and these results will be reported in due course.

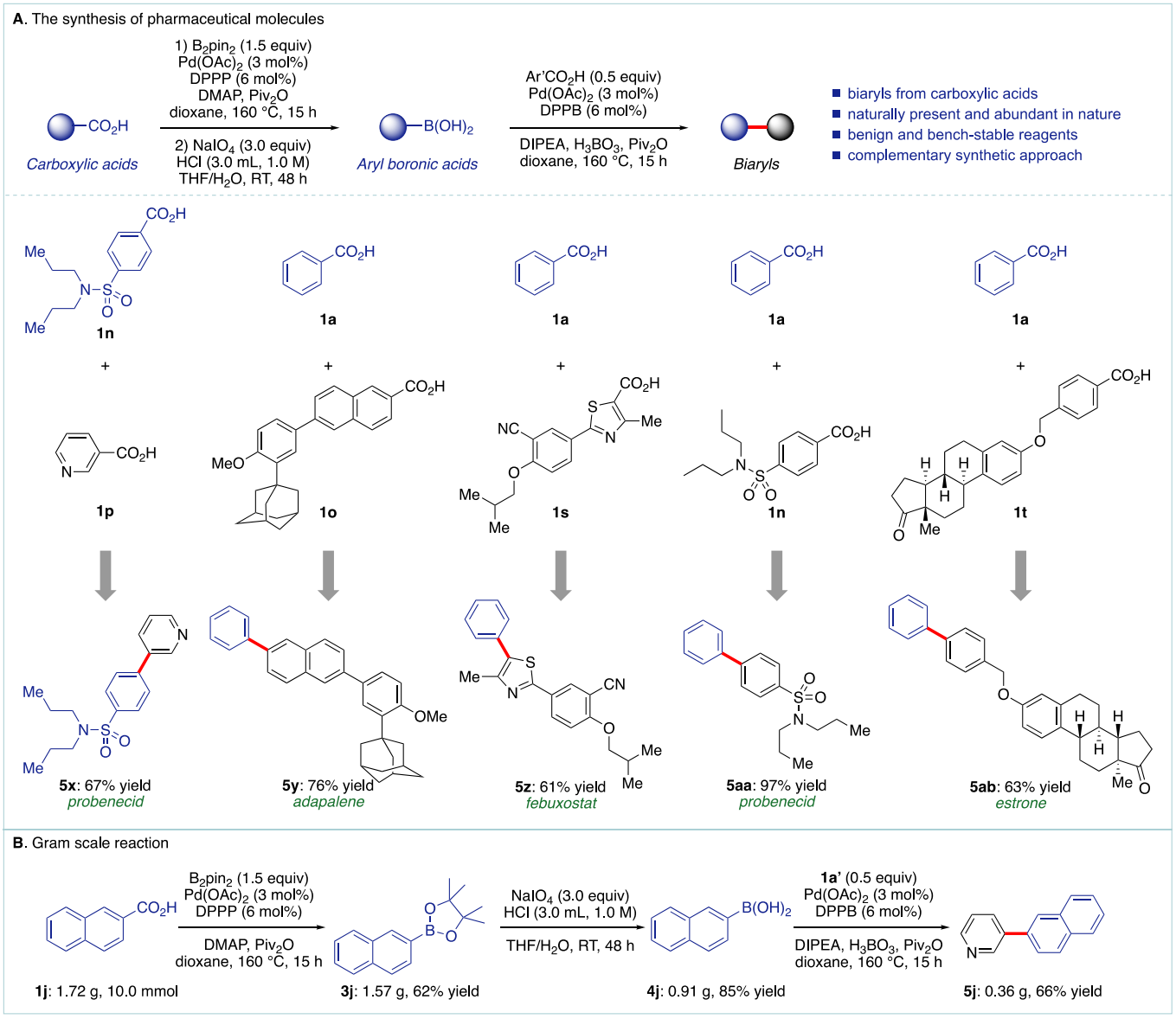
Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank Shanghai University (C. L.), Overseas High-Level Talents Introduction Program of Shanghai (C. L.), Rutgers University (M. S.), the NSF (CAREER CHE-1650766, M. S.), Zaozhuang University (W. Z.) for generous support. Additional support was provided by the Rutgers Graduate School in the form of Dean's Dissertation Fellowship (C. L.).

Scheme 4. Versatile applications and gram scale reaction.



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