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Methodology to Control the Regioselective Installation of a Carboxylic Acid for the Synthesis of 2,3-Diarylpropionic Acids

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Abstract: A stepwise copper-catalyzed boracarboxylation then palladium-catalyzed Suzuki-Miyaura cross-coupling methodology was developed to access 2,3-diarylpropionic acid derivatives regioselectively by pre-setting the position of the carboxylic acid in the boracarboxylation reaction. This method provides access to a wide range of aryl and heteroaryl products in up to 80% isolated yield. Pharmaceutical potential was demonstrated by synthesizing a glucagon receptor antagonist drug in three steps (31% overall yield) from commercially available 4-*tert*-butylstyrene.

Keywords: C–C bond formation; Organoboron; Carboxylation; Palladium catalysis; Regioselectivity

Introduction

2,3-Diarylpropionic acids are interesting synthetic targets due to their prevalence as biologically active compounds. They have been shown to be active as VLA-4 antagonists, which are involved in cell adhesion, migration, and activation of leukocytes.[1] In addition, the propionic acid scaffold is present in the factor Xa inhibitor, DX-9065a, which has been shown to prevent several types of thromboses (Figure 1).[2] Amide derivatives of 2,3-diarylpropionic acids also have interesting physiological properties. The glucagon receptor antagonist shown in Figure 1 reduced the glucagon induced glucose excursion by 50% when delivered to rats intravenously.[3]

There are several recently reported catalytic routes to access 2,3-diarylpropionic acid derivatives.[4–7] A two-step method of hydroboration of stilbenes followed by copper-catalyzed carboxylation (Scheme 1A)[4] or cesium-mediated carboxylation,[5] using gaseous carbon dioxide, gave a mixture of regioisomers when electronically similar aryl rings were present on the stilbene reactant. Sterically or electronically differentiated aryl rings provide good regiocontrol in moderate to good yields. Palladium-catalyzed hydrocarboxylation, using formic acid as a source of carbon dioxide, also offered moderate regiocontrol through aryl ring electronic or *o*-substitution steric effects (Scheme 1B).[7]

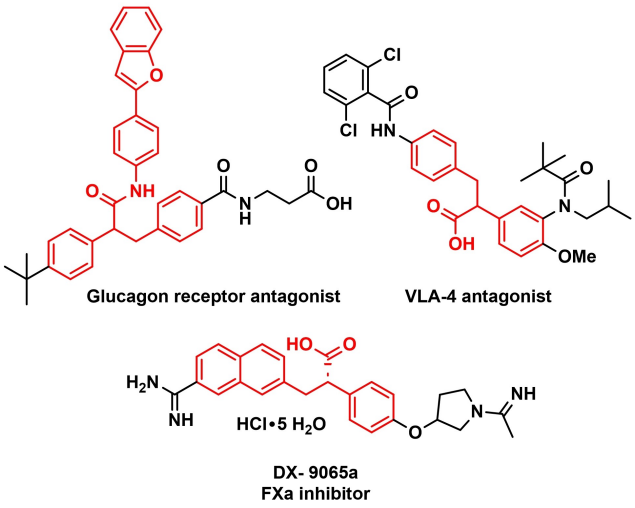

Figure 1. Biologically active 2,3-diarylpropionic acid derivatives.

We envisioned the regioselective installation of the carboxylic acid via a two-step methodology: copper-catalyzed boracarboxylation of a vinylarene[8–10] followed by Suzuki-Miyaura cross-coupling with an aryl halide (Scheme 1C).[11,12] The success of this method would rely on setting the regiochemistry of the carboxylic acid before employing the cross-coupling. Previous alkylboronic ester cross-coupling chemistries

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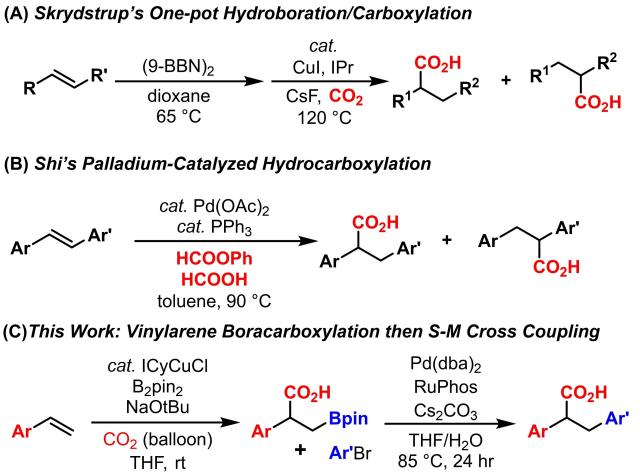


Scheme 1. Strategies to access 2,3-diarylpropionic acids.

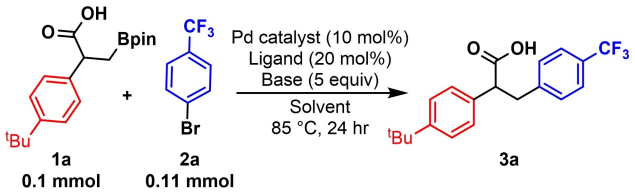
suggested this to be a viable route.[13–23] Herein, we report a new methodology to synthesize 2,3-diarylpropionic acids regioselectively via copper-catalyzed boracarboxylation followed by Suzuki-Miyaura cross-coupling.[24]

Results and Discussion

Initial catalyst screening was carried out on *p-tert*-butyl boracarboxylated product (**1 a**) with the electron-withdrawing aryl bromide, 4-bromobenzotrifluoride (**2 a**), as the coupling partner. We began our catalyst screening with two different palladium(0) pre-catalysts but neither catalyst afforded poor yields of 2,3-diarylpropionic acid **3 a** (Table 1, entries 1–2). Upon testing various base and solvent combinations, we determined that Cs_2CO_3 and a 10:1 mixture of THF:water were optimal (Table 1, entries 3–4). Upon switching to a palladium(II) pre-catalyst, no product was observed (Table 1, entry 5). With the addition of the Buchwald ligand, XPhos, we saw dramatic improvement with the highest product yield arising from $Pd(dba)_2$ (Table 1, entries 6–8).[25] RuPhos proved to be most effective in conjunction with $Pd(dba)_2$ (Table 1, entry 9).[25] Notably, no *ortho*-C–H activation/functionalization side products were observed.[26,27]

With the optimal catalyst and reaction conditions identified, 10 mol% of $Pd(dba)_2$ and 20 mol% of RuPhos producing 95% yield of **3 a** (Table 2, entry 1), we attempted to increase reaction efficiency. Decreasing the loading of base from 5 equivalents to 2.5 equivalents or catalyst from 10 mol% to 5 mol% led to a significantly decreased yield (Table 2, entry 2–3). Superstoichiometric loadings of aryl bromide did not impact yields, and reactant conversion was incomplete (entries 4–5). Yield rebounded to nearly 90% at lower catalyst loading by doubling the reaction time to 48 hr

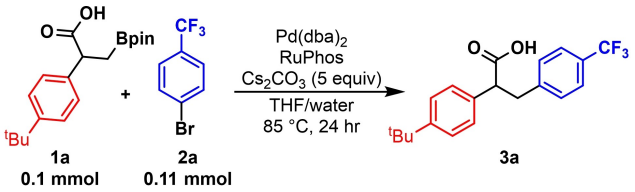
Table 1. Screening of catalyst conditions for the cross-coupling of organoboron substrate **1 a**.[a]



Entry	Catalyst	Base	Solvent	Yield[b]
1	$Pd(dba)_2$	K_2CO_3	Toluene/water	5%
2	$Pd(PPh_3)_4$	K_2CO_3	Toluene/water	17%
3	$Pd(PPh_3)_4$	K_2CO_3	THF/water	29%
4	$Pd(PPh_3)_4$	Cs_2CO_3	THF/water	38%
5	$Pd(OAc)_2$	Cs_2CO_3	THF/water	0%
6	$Pd(OAc)_2$ + XPhos	Cs_2CO_3	THF/water	24%
7	$Pd(PPh_3)_4$ + XPhos	Cs_2CO_3	THF/water	70%
8	$Pd(dba)_2$ + XPhos	Cs_2CO_3	THF/water	78%
9	$Pd(dba)_2$ + RuPhos	Cs_2CO_3	THF/water	95%

[a] Reactions ran in 10:1 toluene/water or 10:1 THF/water at a concentration of 0.022 M.
[b] Yields were determined by ^{1}H NMR spectroscopy using mesitylene as the internal standard.

Table 2. Screening of reaction conditions for the cross-coupling of organoboron substrate **1 a**.[a]

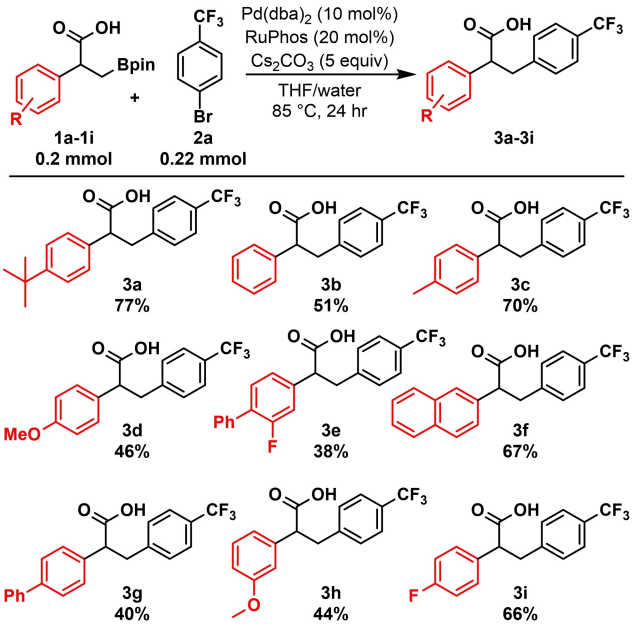


Entry	Pd(dba)2	RuPhos	Variation	Yield[b]
1	10 mol%	20 mol%	None	95%
2	10 mol%	20 mol%	2.5 eq Cs_2CO_3	72%
3	5 mol%	10 mol%	–	62%
4	5 mol%	10 mol%	1.5 eq. aryl bromide	69%
5	5 mol%	10 mol%	2 eq. aryl bromide	68%
6	5 mol%	10 mol%	48 hr	88%
7	5 mol%	5 mol%	48 hr	77%

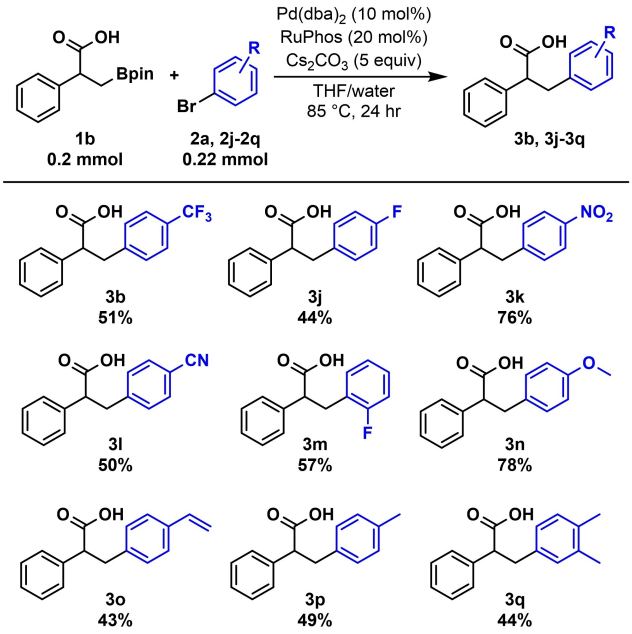
[a] Reactions ran in 10:1 THF/water at a concentration of 0.022 M.
[b] Yields were determined by ^{1}H NMR spectroscopy using mesitylene as the internal standard.

though a two-fold excess of RuPhos relative to $Pd(dba)_2$ remained necessary (entries 6–7).

Using the optimized $Pd(dba)_2$/RuPhos catalyst system, we began investigating the organoboron substrate scope (**1**) with 4-bromobenzotrifluoride (Scheme 2). The screening reaction product **3 a**, bearing a *tert*-butyl group in the *para*-position, was isolated in 77% yield. The electron-neutral organoboron substrate, **1 b**, derived from styrene, afforded the cross-



Scheme 2. Organoboron substrate scope for cross-coupling.[a,b] [a] Reactions ran in 10:1 THF/water at a concentration of 0.045 M. [b]Isolated yields.■■Please check scheme captions 2, 3, 4 and 5 if captured and presented correctly.■■

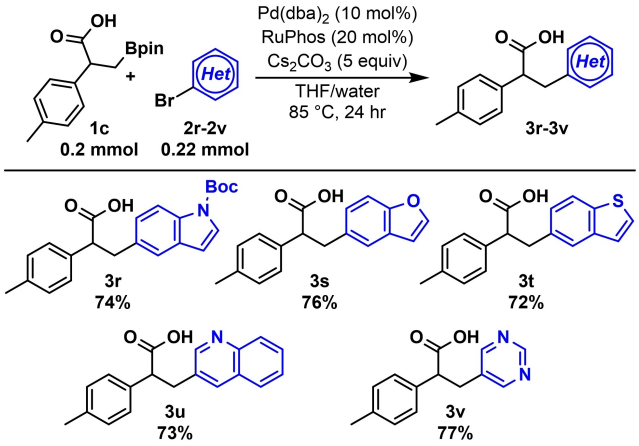


Scheme 3. Substrate scope of aryl halides for cross-coupling.[a,b] [a] Reactions ran in 10:1 THF/water at a concentration of 0.045 M. [b] Isolated yields.

coupled product in 51% yield (**3 b**). It is important to note that not only do aryl bromides undergo cross-coupling for this reaction, but aryl iodides are also suitable coupling partners. The coupling reaction between **1 a** and 4-iodobenzotrifluoride was successful, albeit with a slightly lower yield of 42% as assessed by ^{1}H NMR spectroscopy. Furthermore, the carboxylic acid moiety is essential for the cross-coupling reaction, as using the methyl ester variant of the organoboron substrate, **1 b**, led to no conversion of the starting material. The electron-rich *p*-methyl and *p*-methoxy organoboron substrates were obtained in 70% and 46% yield, respectively (**3 c-3 d**). The cross-coupling procedure is also applicable to extended π-systems such as napthyl and biphenyl, affording moderate-to-good yields (**3 e-3 g**). Finally, electron-poor *m*-methoxy and *p*-fluoro organoboron substrates afford 2,3-diarylpropionic acid products in 44% and 66%, respectively (**3 h-3 i**).

After examining the scope of organoboron substrates, we began exploring the scope of aryl bromide substrate that would undergo cross-coupling with electron-neutral organoboron **1 b** (Scheme 3). In general, the cross-coupling protocol afforded moderate-to-good yields with electron-poor *para*-substituted aryl bromides (**2 j-2 l**). With a fluorine substituent in the *ortho*-position (**2 m**), we saw no notable decrease in yield compared to the *p*-fluoro derivative. The electron-donating 4-bromoanisole substrate (**2 n**) afforded 78% yield, and *p*-bromostyrene (**2 o**) gave the cross-coupling product in a good yield of 43%. Lastly, methyl substituted aryl bromides, *p*-methyl bromobenzene (**2 p**) and 4-bromo-*o*-xylene (**2 q**) provide the respective products in 49% and 44% yield. Notably, this cross-coupling protocol shows good tolerance to potentially reactive functional groups (e. g., –NO_2, **2 k**; –CN, **2 l**; –$CHCH_2$, **2 o**).

Heterocycles were next screened to further demonstrate synthetic versatility and functional group tolerance of the cross-coupling protocol (Scheme 4). All screening started from organoboron compound **1 c**.



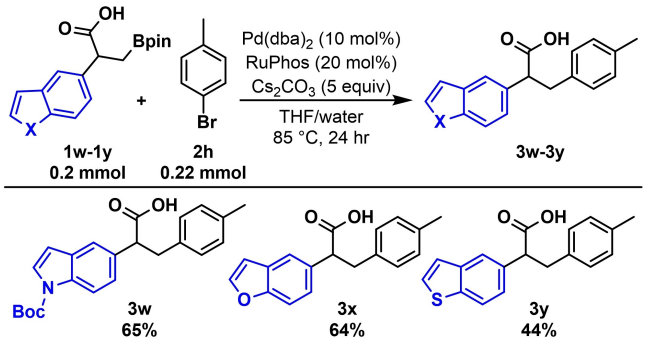
Scheme 4. Substrate scope of heterocyclic bromides.[a,b] [a] Reactions ran in 10:1 THF/water at a concentration of 0.045 M. [b] Isolated yields.

Reaction with electron-rich heteroaromatic bromides (*N*-boc-5-bromoindole, **2 r**; 5-bromobenzofuran, **2 s**; bromobenzothiophene, **2 t**) gave similarly excellent yields of 72–76%. Likewise, coupling with more electron-deficient 3-bromoquinoline (**2 u**) and 5-bromopyrimidine (**2 v**) afforded excellent yields.

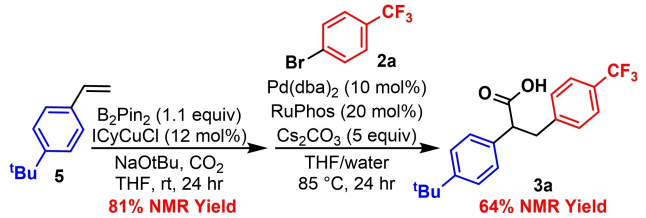
We then aimed to obtain the opposite regioisomer for these heterocyclic 2,3-diarylpropionic acids to further establish the utility of the catalytic method. In our previous scope, *p*-methyl organoboron substrate **1 c**, was reacted with heterocyclic bromides to afford a product bearing the carboxylic acid moiety in the β-position relative to the heterocycle. To generate the opposite regioisomer, we instead boracarboxylated the requisite vinylated heterocycle, installing the carboxylic acid in the α-position relative to the heterocycle with subsequent cross-coupling that yields β-arylation product (Scheme 5). Cross-coupling of *N*-boc indole organoboron substrate **1 w**, yielded product **3 w** in 65% yield. Additionally, benzofuran (**1 x**) and benzothiophene (**1 y**) organoboron substrates afforded yields of 64% and 44%, respectively. Boracarboxylation of electron deficient 3-vinylquinoline and 5-vinylpyrimidine were unsuccessful.

We also explored the feasibility of a one-pot boracarboxylation/cross-coupling process within our current protocol (Scheme 6). Starting from *p-tert*-butylstyrene, we applied our previously published boracarboxylation conditions to install the α-aryl carboxylic acid and β-arylboronic ester moieties.[8] After 24 hours, we achieved an 81% yield of the *p-tert*-butyl organoboron susbstrate **1 a**, as assessed by ^{1}H NMR spectroscopy. The reaction was then directly subjected to the standard cross-coupling conditions without additional intermediate workup. After an additional 24 hours, the desired 2,3-diarylpropionic acid product (**3 l**) was obtained a in slightly lower yet still good yield of 64% by ^{1}H NMR spectroscopy.

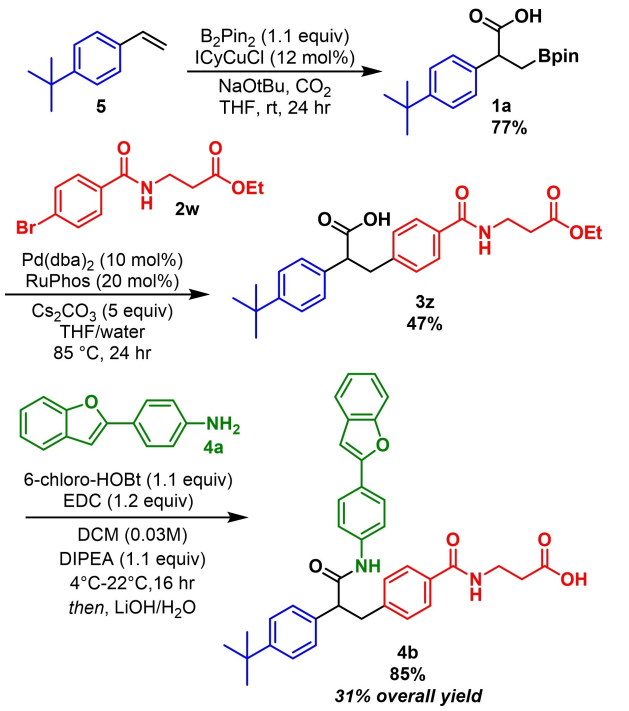
Lastly, to demonstrate the pharmaceutical utility of this novel methodology, we sought to synthesize a biologically active 2,3-diarylpropionic acid derivative (Scheme 7). Inspired by Kurukulasuriya and colleagues, we aimed to synthesize a glucagon receptor antagonist. Their synthetic route required seven steps and yielded the final product in a 42% overall yield.[3] We began our synthesis with commercially available *p-tert*-butyl styrene. Boracarboxylation of the styrene was achieved in 77% yield (**1 a**). Next, our cross-coupling protocol was carried out with *N*-(4-bromobenzoyl)-β-alanine ethyl ester **2 w**, affording the 2,3-diarylpropionic acid **3 z** in a 47% yield. Finally, an amide coupling[28] of the free carboxylic acid with 4-(benzofuran-2-yl)aniline **4 a**, followed by *in situ* ester hydrolysis, afforded the desired glucagon receptor antagonist **4 b** in an 85% yield. The overall yield of the three linear steps from starting styrene was 31%.



Scheme 5. Substrate scope of heterocycles with the carboxylic acid α- to the heterocycle.[a,b] [a] Reactions ran in 10:1 THF/water at a concentration of 0.045 M. [b] Isolated yields.



Scheme 6. One-pot boracarboxylation/cross-coupling.



Scheme 7. Synthesis of a biologically active glucagon receptor antagonist.

Conclusion

In summary, we have developed a novel two-step protocol to control the regioselectivity of 2,3-diarylpropionic acids. With this approach, the position of the carboxylic acid is predetermined through a regioselective copper-catalyzed boracarboxylation. Subsequent Suzuki-Miyaura cross-coupling with either aryl bromide (or aryl iodide) affords the single regioisomeric 2,3-diarylpropionic acid product. This method also provides independent access to both regioisomers, whereas traditional catalytic strategies typically yield a mixture of regioisomers in sterically or electronically unbiased substrates. Additionally, we have demonstrated the ability to access several interesting biaryl and heterocyclic 2,3-diarylpropionic acids. The protocol exhibits excellent functional group tolerance, as evidenced by the successful coupling of nitro, nitrile and vinyl substituted aryl bromides. Further, we have demonstrated the efficiency and synthetic utility of this methodology through a one-pot synthesis of 2,3-diarylpropionic acids, starting from inexpensive, commercially available styrene derivatives. Lastly, the pharmaceutical relevance was showcased by synthesizing a glucagon receptor antagonist in four fewer steps than the previously reported method, while achieving similar overall yields.

Experimental Section

General Procedure for the Synthesis of 2,3-Diarylpropionic Acids

Working in a nitrogen-filled glovebox, a 20-mL scintillation vial was charged with a stir bar, $Pd(dba)_2$ (11.6 mg, 0.02 mmol, 0.10 equiv.), RuPhos (18.6 mg, 0.04 mmol, 0.20 equiv.), and 4.0 mL of THF. The heterogeneous suspension was swirled for 10–30 seconds until all solids dissolved. The vial was transferred from the glovebox and boracarboxylated product **1 a** (0.2 mmol, 66.5 mg, 1.0 equiv.), Cs_2CO_3 (326 mg, 1.0 mmol, 5.0 equiv.), 4-bromobenzotrifluoroide **2 a** (0.22 mmol, 30.8 µL, 1.1 equiv.), and 0.4 mL of deionized water were added to the reaction vial. A septum cap was secured tightly on the vial with electrical tape. The septum cap was punctured with a needle to purge the reaction mixture with argon for 5 minutes with an outlet to a bubbler. The puncture was taped over to prevent any evaporation of solvent. The reactions were stirred in an oil bath at reflux (85 °C) for 24 hours. Upon reaction completion, the crude mixture was allowed to cool to room temperature and added to a separatory funnel that contained 1 M HCl (10 mL). The organic layer was extracted with dichloromethane (15 mL×3). The combined organic layers were dried with Na_2SO_4 and collected in a 100 mL round-bottom flask and concentrated under vacuum to give the crude product. The crude product was purified via flash column chromatography on silica gel using hexane:EtOAc (20:1 and 1% HOAc) as the eluent. The combined product fractions were collected in a 500 mL round-bottom flask and concentrated under vacuum. The product was then transferred to a 1-dram vial and recrystallized in a minimal amount of *n*-heptane to give purified 2,3-diarylpropionic acid **3 a**.

One-Pot Synthesis of 2,3-Diarylpropionic Acid 3 a

Working inside a nitrogen-filled glove box, a 20-mL scintillation vial was charged with ICyCuCl (10.0 mg, 0.030 mmol, 0.12 equiv.), sodium tert-butoxide (48.0 mg, 0.75 mmol, 2.0 equiv.), and a magnetic stir bar. Anhydrous, degassed THF (0.90 mL) was added, the vial was capped, and the resulting suspension was stirred under nitrogen for 30 minutes at room temperature to give a clear, colorless solution. The catalyst solution was pulled into a 2 mL syringe and capped with a septum. In a separate 25 mL round-bottomed flask, bis(pinacolato)diboron (70.0 mg, 0.375 mmol, 1.1 equiv.) and 3.1 mL THF were added. To this solution, vinylarene (0.25 mmol, 1.0 equiv.) was added. The round-bottomed flask was charged with a magnetic stir bar, sealed with a septum, taped, and taken out of the glove box along with the catalyst filled syringe. The pre-prepared catalyst solution was transferred to the 25 mL round-bottomed flask outside of the glovebox. Immediately after catalyst addition, the reaction vessel was fitted with a double-walled CO_2 balloon and the reaction was stirred at ambient temperature for 24 hours. After 24 hours, the 25 mL round-bottom flask was purged with argon for 5 minutes. Next, working in a nitrogen-filled glovebox, a separate 20-mL scintillation vial was charged with $Pd(dba)_2$ (14.4 mg, 0.025 mmol, 0.10 equiv.), RuPhos (23.3 mg, 0.05 mmol, 0.2 equiv.) and 1 ml anhydrous, degassed THF. The vial was transferred from the glovebox and Cs_2CO_3 (407 mg, 1.25 mmol, 5.0 equiv.), 4-bromobenzotrifluoride **2 a** (38.5 µL, 0.275 mmol, 1.1 equiv.), and 0.4 mL of deionized water were added. A septum cap was secured tightly on the vial with electrical tape. The septum cap was punctured with a needle to purge the reaction mixture with argon for 5 minutes with an outlet to a bubbler. After 5 minutes, the cross-coupling solution was pulled into a syringe and added to the original boracarboxylation 25 mL round-bottom flask. The punctures in the septum were taped over to prevent any evaporation of solvent. The reaction was stirred in an oil bath at reflux (85 °C) for 24 hours. Upon reaction completion, the crude mixture was allowed to cool to room temperature and added to a separatory funnel that contained 1 M HCl (10 mL). The organic layer was extracted with dichloromethane (15 mL×3). The combined organic layers were collected in a 100 mL round-bottom flask and concentrated under vacuum to give the crude product. Yields were directly determined by ^{1}H NMR analysis of the crude products using mesitylene as an internal standard.

Author Contributions

M.D.H. and T.M.P performed all experiments, carried out product isolation/characterization, analyzed data, and composed the original draft. B.V.P and M.D.H. edited the manuscript. B.V.P was responsible for project conceptualization, supervision, data analysis, and funding acquisition.

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RESEARCH ARTICLE

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