Beneficial Effect of a Secondary Ligand on the Catalytic Difunctionalization of Vinyl Arenes with Boron and CO_2

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Abstract: The boracarboxylation of vinyl arenes catalysed by copper(I) is an alkene difunctionalization reaction that provides synthetically useful β-boryl-α-aryl propanoic acid derivatives. Drawbacks of the original reaction methodology are high catalyst loading and vinyl arene scope limited largely to electron-rich systems. Herein, we demonstrate that catalytic additives, specifically triphenylphosphine or electron-rich styrene, leads to improved catalyst efficiency and broadening of substrate scope. With the addition of PPh_3, comparable yields of previously reported boracarboxylated substrates as well as two novel β-boronated non-steroidal anti-inflammatory drugs (*bora*-fenoprofen and *bora*-flurbiprofen) were achieved at lower catalyst loading. Boracarboxylation of electron-deficient substrates could be achieved through superstoichiometric addition of vinyl arene or addition of secondary phosphine ligand. Reactivity optimization and competition experiments have provided preliminary insights into the ability of PPh_3 to aid in the catalytic cycle, specifically carboxylation of electron-rich benzyl-copper(I) intermediate. Additional competition studies revealed that a catalytic amount of an electron-rich vinyl arene could be used in addition to the copper(I) catalyst to promote boracarboxylation of an electron-deficient styrene derivative.

Introduction

Catalysis is one of the central and most important strategies to achieve chemical sustainability. The use of organic and inorganic catalysts in chemical synthesis has the potential to improve eco-efficiency, economic growth, and quality of life.[1] Transition metal catalysis has historically played a key role in solving many challenging problems in chemical synthesis, and in recent years, the community has recognized the need to develop chemistries utilizing earth-abundant metals as catalysts.[2] At the same time, sustainable chemical synthesis is achieved by utilizing renewable sources of carbon chemical feedstocks, such as biomass-based chemicals[3] and CO_2.[4] The utilization of CO_2 for the direct production of synthetically relevant, value-added products has yet to be achieved broadly due in part to the stability of CO_2 often necessitating harsh reagents or reaction conditions.

Over the last decade, researchers have sought to identify new catalytic methodologies that allow the installation of CO_2 into unsaturated organic molecules. Due to the medicinally relevant α-aryl propionic acid pharmacophore, the core motif for non-steroidal anti-inflammatory drugs (NSAIDs), there has been interest in developing hydrocarboxylation strategies of styrene derivatives to deliver NSAIDs directly from readily available vinyl arenes and CO_2. Highly regioselective hydrocarboxylation has been achieved using base-metal catalysts with a variety of sacrificial reductants including Grignard reagents,[5] organo-zinc reagents,[6] or Mn/water[7] (Figure 1A). An alternative strategy is the installation of C–X(E) bonds, that upon cleavage, react with CO_2.[8]

We envisioned that installation of both CO_2 and a second hetero(element) functional group (eg., B or Si) would be quite appealing; however, at the time such reactions were only known for alkynes and allenes.[9] In 2016, we reported that redox-neutral copper(I) catalysis in tandem with bis-pinacolatodiboron (B_2pin_2) and a balloon of CO_2 provided the first examples of vinyl arene boracarboxylation, affording functionalized carboxylic acids that included novel β-boryl-NSAID derivatives such as *pinB*-ibuprofen and *pinB*-naproxen (Figure 1B).[10], [11] Limitations with the redox-neutral copper catalyst system could not be overcome in our original vinyl arene boracarboxylation methodology optimization. Specifically, the method was limited to electron-rich vinyl arene substrates as well as necessitated relatively high catalyst loading. Exploring the primary literature revealed examples of reductive copper-catalysed processes that were aided by the addition of a

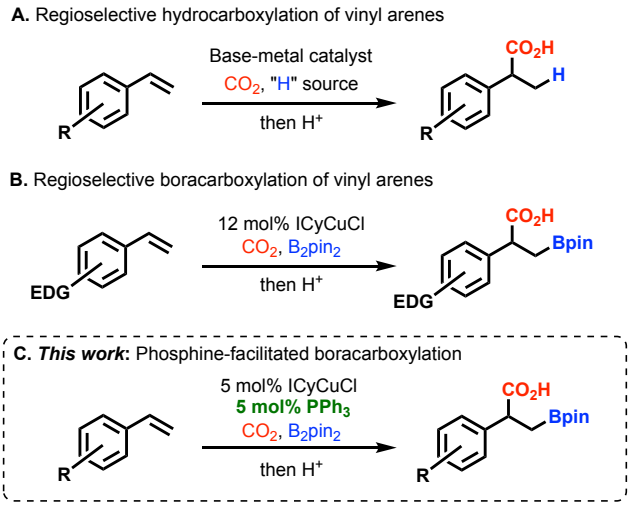

Figure 1. Strategies that employ CO_2 as a feedstock to prepare α-aryl carboxylic acids.

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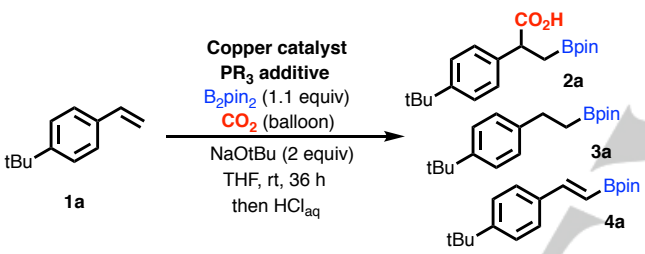
secondary ligand, triphenylphosphine (PPh_3), that was thought to ligate and deactivate catalytically promiscuous copper decomposition species while concurrently improving reaction yields.[12] In this communication, we discuss current efforts to address boracarboxylation limitations through the use of a secondary ligand approach to facilitate boracarboxylation catalytic turnover (Figure 1C).

Results and Discussion

In our original work, we noted significantly decreased boracarboxylation yields and high conversion of styrene upon reduced ICyCuCl catalyst loading (ICy = 1,3-bis(cyclohexyl)imadzol-2-ylidene).[10] We observed the same behaviour with *p*-tBu-styrene (**1a**), leading to boracarboxylation product (**2a**) as well as trace amounts of hydro/protoboration (**3a**)[13] and dehydrogenative borylation (**4a**) products; this substrate was chosen for screening purposes below (entry 1-2, Table 1). We reasoned that ICyCuCl catalyst was decomposing to promiscuous or inactive species at lower catalyst loading, promoting formation of unwanted borylation side products as well as polymerization as evidenced by near quantitative styrene conversion.[14] Similar behaviour was observed by Buchwald and co-workers in an asymmetric Cu(I)-catalysed reductive coupling of vinyl arenes, and they discovered that addition of exogenous PPh_3 rescued yields while not impacting reaction *ee*.[12a] Gratifyingly, the addition of equimolar ICyCuCl catalyst and PPh_3 (5 mol %) led to 89 % yield of **2a** with trace amounts of byproducts (entry 3). Control experiments with CuCl/PPh_3 or only PPh_3 showed, in the former case, precipitous drop in yield of **2a** with increased yields of **3-4a** and incomplete consumption of **1a** (entry 4), while in the latter case, no borylation products were detectable (entry 5).

Table 1. Boracarboxylation optimization with phosphine additive.[a]



Entry	Cu catalyst (mol %)	PR_3 additive (mol %)	yield (%)[b] 2a : 3a : 4a	convn (%)[b]
1	ICyCuCl (12)	—	92 : tr : tr	> 99
2	ICyCuCl (6)	—	60 : tr : tr	95
3	ICyCuCl (5)	PPh_3 (5)	89 : tr : tr	> 99
4	CuCl (12)	PPh_3 (13)	18 : 8 : 16	65
5	—	PPh_3 (5)	nr : nr : nr	30
6	ICyCuCl (5)	PCy_3 (5)	82 : tr : tr	> 99
7	ICyCuCl (5)	$P(OPh)_3$ (5)	44 : 28 : tr	> 99
8	ICyCuCl (5)	pyridine (5)	60 : tr : tr	> 99
9	ICyCuCl (5)	PPh_3 (10)	86 : tr : tr	95
10	ICyCuCl (2.5)	PPh_3 (10)	71 : tr : tr	90
11[c]	ICyCuCl (2.5)	PPh_3 (3)	78 : 15 : tr	> 99
12[c]	ICyCuCl (2.5)	PCy_3 (3)	69 : 8 : tr	85

[a] Limiting reagent – **1a** (0.25 mmol) in THF (4 mL). Reactions quenched with 1 M HCl_{aq}.. [b] Yields and conversions were determined by ^1H NMR spectroscopy using mesitylene as internal standard with respect to vinyl arene substrate. tr = < 5 % detected. nr = no reaction. [c] 40 °C

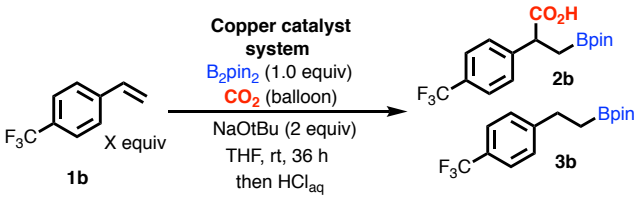
Since CuCl/PPh_3 was catalytically active, albeit poorly, we thought that a more electron-rich phosphine, such as PCy_3 paired with ICyCuCl, would produce a more competent secondary boracarboxylation catalyst upon primary catalyst decomposition.[10] To our surprise, addition of PCy_3 led to slightly diminished catalytic reactivity (entry 6, Table 1). The phosphite additive, $P(OPh)_3$, was ineffective leading to much lower yields of **2a** and significant yields of **3a**. The addition of pyridine, which showed no reactivity as a primary ligand in our original study, was tolerated in the reaction but did not lead to improved yields (entry 8, Table 1). Excess PPh_3 did not improve reaction yield with 5 mol % ICyCuCl (entry 9); however, at even lower ICyCuCl loading (2.5 mol %), we found that 4-fold excess was necessary to achieve moderate yield of **2a** (entry 10). Finally, we observed that 2.5 mol % ICyCuCl in the presence of phosphine additive as well as gentle heating of the reaction (40 °C) leads to slightly improved yields but also higher yields of hydro/protoborylated **3a** (entries 11-12).

Having demonstrated that catalytic efficiency could be improved with addition of PPh_3 for an electron-rich vinyl arene, we wanted to reassess the reactivity of strongly electron-deficient vinyl arenes that were unreactive in our original work.[10] Using *p*-CF_3-styrene (**1b**) as the limiting reagent, we observed only trace amounts of boracarboxylation products with our originally published conditions.[10] Upon addition of excess **1b** (5 equiv) and using 12 mol % ICyCuCl, we were pleased to find that boracarboxylation **2b** and hydro/protoboration **3b** products were obtained in respective yields of 40 and 44 % (entry 2, Table 2). Nearly equivalent yields of both products were achieved when reactions were performed with equimolar 5 mol % ICyCuCl/PPh_3 catalyst system, only 2 equiv of substrate **1b,** and/or mild heating to 40 °C (entries 3-6). Interestingly, we observed that by using a limiting amount of styrene at lower loading of ICyCuCl, an equimolar amount of PPh_3 could be added to the catalyst system to achieve a moderate yield of boracarboxylated product (entry 7). By increasing the catalyst and PPh_3 concentration (12 mol %) and performing the reaction at room temperature, the yields of **2b** and **3b** were maximized and minimized (53 and 20 %, respectively, entry 8). These two latter results demonstrate the importance of PPh_3 to act as a competent secondary ligand in this catalysis.

With lower catalyst loading conditions optimized as demonstrated in Table 1, we sought to revisit vinyl arene

substrate scope by comparing yields for the boracarboxylation of vinyl arenes with 5 mol% ICyCuCl/PPh_3 and 12 mol% ICyCuCl catalyst system (*Condition A and B*, respectively; Table 3). For styrene (**1c**) and aliphatic substituted vinyl arenes (*p*-tBu, **1a**; *p*-Me, **1d;** *p*-iBu,**1e**) comparable crude yields were obtained for

Table 2. Electron-deficient substrate boracarboxylation optimization.[a]



Entry	ICyCuCl (mol %)	PPh_3 additive (mol %)	1b (equiv)	yield (%)[b] 2b : 3b
1	12	—	1	9 : 18
2	12	—	5	40 : 44
3	5	5	5	22 : 51
4[c]	5	5	5	31 : 33
5	5	5	2	27 : 63
6[c]	5	5	2	36 : 35
7	5	5	1	28 : 13
8	12	12	2	53 : 20

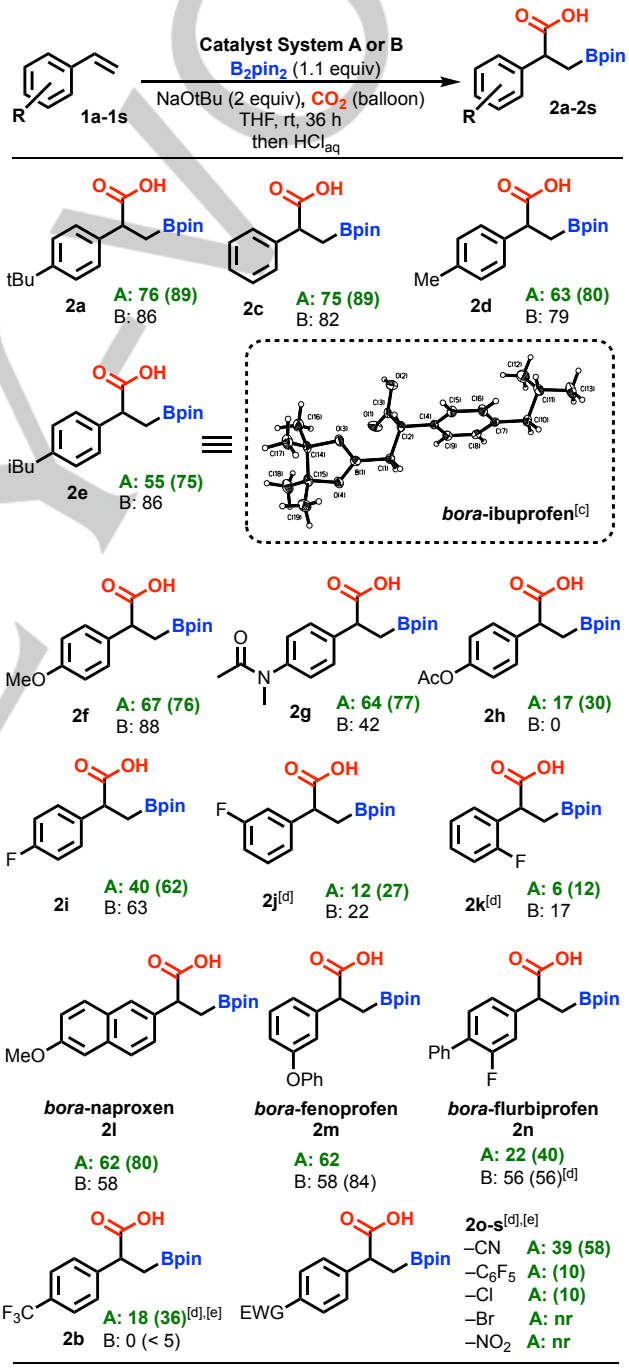
[a] Limiting reagent – B_2pin_2 (0.25 mmol) in THF (4 mL). Reactions quenched with 1 M HCl_{aq}. [b] Yields and conversions were determined by ^1H NMR spectroscopy using mesitylene as internal standard with respect to B_2pin_2. [c] 40 °C.

both catalyst systems. At lower catalyst loading, the boracarboxylation reaction becomes more attractive for significant reaction scale-up. Indeed, boracarboxylation of **1a** can be performed on 40 mmol scale with isolation of greater than 8 grams of product **2a** (~60% isolated yield). Isolation and purification of boracarboxylation products was achieved through multiple acid/base extraction steps due to the instability of borylated products on silica gel, and we have found that removal of PPh_3 generally leads to lower isolated yields. Notably, similar reaction scale-up efficiency is observed for *bora-ibuprofen*, **2e,** facilitating the acquisition of analytically pure crystals for solid-state structural characterization. Heteroatom-substituted methoxy, amide, and acetoxy vinyl arenes (**1f-h**) tolerated reduced catalyst loading conditions. Indeed, the new catalyst conditions led to a significantly improved isolated yield for *N*-methyl amide **2g** (64%) and enabled formation of acetoxy **2h** in low yield.

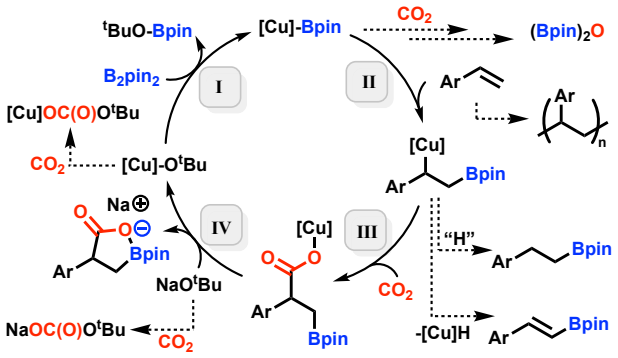
Electron-poor fluorine-substituted vinyl arenes (**1i-k**) have similar reactivity with crude products obtained in similar NMR yields. It is worth pointing out that mild heating (40 °C) is necessary to achieve low yields of electronically and sterically (*m*-F and *o*-F, respectively) unfavorable boracarboxylation substrates.

We also found that bora-naproxen (**2l**) could be obtained with slightly higher isolated yield (62%) at lower catalyst loading. Further, two new *bora*-NSAID derivatives, *bora*-fenoprofen (**2m**) and *bora*-flurbiprofen (**2n**) were prepared in good to excellent yields with both catalyst systems. Finally, other electron-poor vinyl arenes, similar to *p*-CF_3-styrene **1b**, that showed no reactivity with only ICyCuCl catalyst were re-examined with 5 mol % ICuCuCl/PPh_3. Sterically congested per-fluoroaryl (**1p**), halides

Table 3. Comparison of copper catalyst systems.[a],[b]



[a] Limiting reagent – styrene derivative (0.25 mmol) in THF (4 mL). *Catalyst system A*: ICyCuCl (5 mol %) and PPh_3 (5 mol %). *Catalyst system B*: ICyCuCl (12 mol %) originally reported in ref. 10 for compounds **2a-g**, **2i-l**. Reactions quenched with 1 M HCl_{aq}. [b] Isolated yields and NMR yields in parentheses. NMR yields were determined by ^1H NMR spectroscopy using mesitylene as the internal standard. [c] X-ray crystallographic structure (thermal ellipsoids at 50% probability). [d] 40 °C. [e] Limiting reagent – B_2pin_2 (0.25 mmol) and styrene derivative (2 equiv) in THF (4 mL). nr = no reaction.

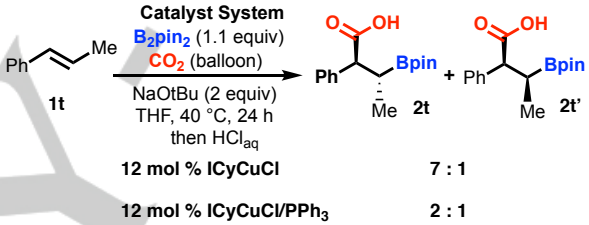


Scheme 1. Proposed boracarboxylation mechanism highlighting potential side reactions that may be influenced by PPh_3.

(**1q-r**), and nitro (**1s**) derivatives were incompetent boracarboxylation substrates, which is not surprising as these derivatives often are unsuccessful in copper(I) catalysis. However, we were happy to find that boracarboxylated *p*-CN-styrene (**2o**) could be obtained in good NMR and moderate isolated yield (58/39%), suggesting that future catalyst screening efforts may reveal conditions to improve the yields and scope of electron-deficient substrates.

A plausible mechanism for the boracarboxylation of vinyl arenes based on the mechanism advanced by Hou and co-workers for the boracarboxylation of alkynes is shown in Scheme 1 (Steps I⇨IV). [9a], [15] To begin to elucidate the role of PPh_3, we explored specific modifications to the reaction that would provide information about each elementary step. We began by probing the influence of different MOtBu bases (M = Li, Na, K) using both catalyst systems (Table S1). In general, the presence of PPh_3 does not impact product yield. We also reasoned that order of addition (eg., PPh_3 addition to catalyst/base solution vs. styrene/B_2pin_2 solution) or time of addition (eg., PPh_3 addition after 5–60 min) may influence reaction yields; however, no evidence of such behaviour was observed. These results suggest that salt metathesis (Step IV) and formation of [Cu]–Bpin (Step I) are not impacted by PPh_3. Preliminary evidence from in situ infrared spectroscopy supports the formation of metal-carbonate species during the reaction,[16] which was also suggested by Hou in a similar reaction with aldehyde substrates.[17] Thus, the role of PPh_3 may involve trapping of copper catalyst decomposition products as organic carbonates as observed by Saegusa 40 years ago.[18]

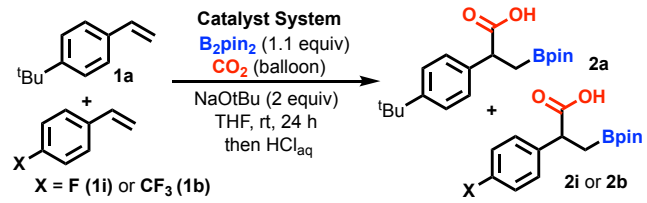
Stoichiometric studies of vinyl arene insertion into copper-boryl species (see, Step II, Scheme 1) by Sadighi, and confirmed computationally by Lin, showed that insertion occurred in exclusively *syn* fashion with electron-poor inserting faster than electron-rich styrene derivatives.[19] The resulting alkyl is carboxylated (Step III) through either direct insertion or an S_E–type pathway. In our original study, we used *trans*-β-methylstyrene (**1t**) as a mechanistic probe and found the boracarboxylation to be regioselective (*dr* 7:1) favouring a direct insertion pathway.[10] Interestingly, we re-examined this reaction in the presence of PPh_3 and found the direct insertion pathway still favored but with selectivity significantly eroded (*dr* 2:1, eq. 1). Control experiments in which the diastereo-enriched product was subsequently mixed with PPh_3 under the reaction conditions did not lead to erosion in diastereomer ratio. These results imply that PPh_3 directly impacts Step III and enables access to an alternative S_E-like carboxylation transition state, proceeding through a benzyl anion that is largely inaccessible with ICyCuCl catalyst alone.



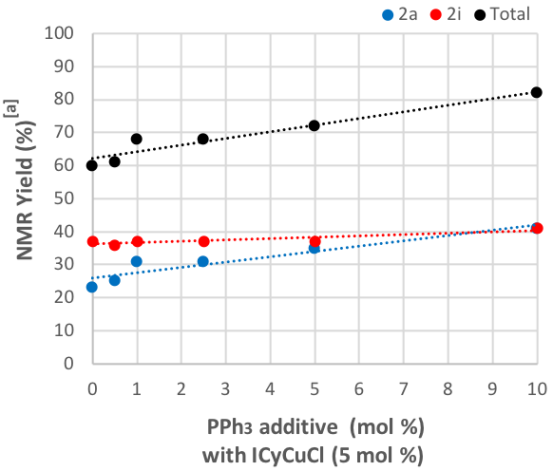
(1)

The catalytic impact of PPh_3 was also assessed by conducting vinyl arene competition studies. We began by reacting an equimolar amount of electronically similar **1a** and **1i** with B_2pin_2 (1.1 equiv) in the presence of increasing amounts of PPh_3 (Figure 2A). The results suggest that PPh_3 (0-10 mol %) has differential effects. Minimal impact on electron-poor boracarboxylation was observed (**2i** yield ~39 %). Conversely, the yield of **2a** increases linearly with increasing [PPh_3]. These results suggest that an alternative copper catalyst is formed with the PPh_3 additive that is selective for more electron-rich benzyl-copper carboxylation.[20] This explanation is consistent with the fact that low yields of boracarboxylation product are obtained with PPh_3 and CuCl alone (entry 4, Table 1). Examination of the reaction of **1i** with PPh_3 and CuCl alone revealed only trace yields of boracarboxylated product.

Finally, competitive boracarboxylation reactions were carried out between **1a** and **1b**, a more electron-deficient vinyl arene. Interestingly, only **2b** was observed in all experiments (Figure 2B). When lower copper loading with PPh_3 additive was employed, the yield was reduced, as was also observed in reaction screening with substrate **1b** in the absence of 1a (Table 2, entry 7). Nevertheless, electron-rich PPh3 or alkene 1a both allow for higher yields at lower catalyst loading as compared to the original conditions (c.f., Table 2, entry 1). Interestingly, we observed that a doubling of yield can also be obtained by performing the reaction with only 10 mol % **1a** (Figure 2b, entries 3-4). This suggests that **1b** selectively inserts into Cu-boryl species (Step II) and the additive enhances the reactivity of the resulting electron-deficient benzyl-copper species toward reaction with CO_2 (Step III).



A.



B.

Entry	Catalyst System	1a (equiv)	NMR yield (%)[a] 2a : 2b
1	ICyCuCl (12 mol %)	1.0	nr : 41
2	ICyCuCl (5 mol %) PPh_3 (5 mol %)	1.0	nr : 23
3	ICyCuCl (12 mol %)	0.1	nr : 18
4	ICyCuCl (12 mol %)	0.1[b]	nr : 9

[a] Yields and conversion were determined by ^1H or ^{19}F NMR spectroscopy using mesitylene as the mesitylene or fluorobenzene as internal standard. nr = no reaction. [b] 1.1 equiv. **1b** used.

Figure 2. Competitive boracarboxylation reactions to probe role of PPh_3. (**A**) Plot of competition reaction yields of substrates with similar electronic character using ICyCuCl (5 mol %) and PPh_3 (X mol %). (**B**) Table of competition reaction yields of substrates with significantly different electronic character.

Conclusions

We have developed a copper catalyst system for vinyl arene boracarboxylation that allows for a reduced loading of copper with the use of a secondary PPh_3 ligand. With this catalyst system, similar yields of many previously reported substrates as well as access to two new β-boronated NSAIDs (fenoprofen and flurbiprofen) was demonstrated. Boracarboxylation of electron-deficient substrates was also achieved through superstoichiometric addition of vinyl arene while reaction of electron-poor vinyl arene as the limiting reagent can be catalyzed by an electron-rich vinyl arene. Competition experiments and reaction of a diastereomeric probe substrate were used to elucidate the catalytic role of PPh_3 and the results suggest that the additive serves two main purposes: 1) yield a new PPh_3-bound copper catalyst that is kinetically competent for carboxylation of electron-rich benzyl-copper species and 2) allow access to an S_E-like carboxylation pathway. A more detailed kinetics investigation of the catalytic effects of both PPh_3 and electron-rich vinyl arene additives are underway.

Experimental Section

General information

Due to air and moisture sensitivity, all experiments were set up in a nitrogen-filled MBraun 200B dual-port glovebox. Dry tetrahydrofuran was used for all experiments from a Glass Contour solvent purification system and $CDCl_3$ was purchased from Cambridge Isotope Laboratories, Inc. NMR spectra were recorded on either a 400 MHz Agilent or JEOL NMR spectrometer. ^1H NMR and ^{13}C NMR experiments were acquired in $CDCl_3$ using tetramethylsilane or $^{13}CDCl_3$, respectively, as reference. ^{19}F and ^{11}B NMR experiments were also run in $CDCl_3$ with ^{11}B NMR spectra recorded using quartz NMR tubes and referenced to an external $BF_3{\cdot}OEt_2$ standard. High-resolution mass spectra were recorded on a Thermo Fisher Scientific Q-Exactive Mass Spectrometer with samples dissolved in 1:1 methanol/acetonitrile.

All styrene derivatives were purchased from commercial sources and degassed prior to storage in the glovebox. *N*-methyl-4-vinylacetanilide (**1g**) was prepared according to previous literature methods.[21] 4-isobutylstyrene (**1e**) and 3-phenyoxystyrene (**1m**) were synthesized by subjecting the commercially obtained aldehyde precursor to Wittig conditions.[5b] 2-methoxy-6-vinylnaphthalene (**1l**) and 3-fluoro-4-phenylstyrene (**1n**) were prepared by performing Suzuki cross-coupling between commercially available aryl bromide and vinyl-Bpin[8b]. The preparation and isolation of ICyCuCl complex was based on literature precedent.[22]

Experimental procedures

General boracarboxylation procedure: In a nitrogen-filled glovebox, a vial was charged with ICyCuCl (4.0 mg, 0.012 mmol, 5 mol %), PPh_3 (3.0 mg, 0.011 mmol, 5 mol%), sodium tert-butoxide (48.0 mg, 0.50 mmol, 2.0 equiv), and anhydrous, dry, degassed THF (0.90 mL). The vial was sealed and stirred for at least 15 minutes to afford a clear, pale yellow solution. In a separate 25 mL round-bottom flask, B_2pin_2 (70.0 mg, 0.275 mmol, 1.1 equiv) and 3.1 mL of THF were added. To the solution, vinyl arene (0.25 mmol, 1.0 equiv) was added. The flask was charged with a stir bar, sealed with a septum, and taped. The catalyst solution was loaded in a 1.0 mL syringe and the needle with capped into a septum. The syringe containing catalyst solution and the 25 mL round-bottom flask containing vinyl arene were removed from the glovebox. The catalyst/base solution was added to the round-bottom and the vessel was fitted with a

double-walled CO_2 balloon. The reaction was stirred at room temperature for 36 hours, replacing the balloon when deflated. Upon reaction completion, the reaction was quenched with 20 mL of 1.0 M aqueous HCl and extracted with dichloromethane (15 mL x 3). The combined organic layers were collected in a 100 mL round-bottom flask and concentrated under vacuum to give the crude product. Mesitylene (20 mol%) was added to the crude mixture as an internal standard and dissolved in $CDCl_3$ to be analyzed by ^1H NMR spectroscopy (NMR yield). The crude product was then taken up in 6 mL of diethyl ether and extracted with saturated $NaHCO_3$ (6 mL x 3). The combined aqueous layers were collected and acidified with 12 M HCl and extracted with dichloromethane (15 mL x 3).

Initial reaction conditions with substrates bearing electron-withdrawing groups were altered: bis(pinacolato)diboron (63.0 mg, 0.25 mmmol) and vinyl arene (0.50 mmol, 2.0 equiv). Reactions were heated to 40°C.

Characterization Data

^1H, ^{13}C, ^{11}B, and ^{19}F NMR shifts for compounds **2a, 2c-g, 2i-l** matched previously reported spectra.[10]

3-boronic acid pinacol ester-2-(4-trifluoromethylphenyl) propionic acid **2b.** white solid, yield 18% ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, J = 7.9 Hz, 2H), 7.43 (d, J = 7.9 Hz, 2H), 3.93 (t, J = 8.0 Hz, 1H), 1.56 (dd, J = 15.9, 9.1 Hz, 1H), 1.29 (dd, J = 15.9, 7.5 Hz, 1H), 1.13 (s, 6H), 1.13 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 179.65, 144.29, 129.47 (q, J = 32.3 Hz), 128.29, 125.42, 124.05 (q, J = 272.7 Hz), 83.52, 46.75, 24.55, 24.47, 15.87; ^{11}B NMR (128 MHz, $CDCl_3$): δ 33.04 (br s) ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.61 (s). The ^{13}C NMR resonance at 15.87 (methylene carbon signal) has very low intensity due to ^{11}B quadrupolar broadening; HRMS (ESI) m/z calc. for $C_{16}H_{19}BF_3O_4^-$ $[M-H]^-$ 343.13230, found 343.13226

3-boronic acid pinacol ester-2-(4-acetoxyphenyl) propionic acid **2h.** white solid, yield 17% ^1H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J = 8.0 Hz, 2H), 7.00 (d, J = 7.8 Hz, 2H), 3.85 (t, J = 8.1 Hz, 1H), 2.27 (s, 3H), 1.53 (dd, J = 16.0, 9.3 Hz, 1H), 1.27 (dd, J = 16.0, 7.2 Hz, 1H), 1.14 (s, 6H), 1.13 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 179.87, 169.39, 149.69, 137.89, 128.89, 121.49, 83.40, 46.22, 24.61, 24.52, 21.09, 16.02; ^{11}B NMR (128 MHz, $CDCl_3$): δ 33.14 (br s). The ^{13}C NMR resonance at 16.02 (methylene carbon signal) has very low intensity due to ^{11}B quadrupolar broadening; HRMS (ESI) m/z calc. for $C_{17}H_{22}BO_6^-$ $[M-H]^-$ 333.15094, found 333.15070

3-boronic acid pinacol ester-2-(3-phenoxyphenyl) propionic acid **2m.** clear oil, yield 58% ^1H NMR (400 MHz, $CDCl_3$): δ 7.31 (dd, J = 8.6, 7.4 Hz, 2H), 7.24 (t, J = 7.9 Hz, 1H), 7.10-7.03 (m, 2H), 7.00-6.98 (m, 3H), 6.86 (ddd, J = 8.2, 2.4, 0.9 Hz, 1H), 3.83 (dd, J = 9.3, 7.1 Hz, 1H), 1.53 (dd, J = 16.0, 9.4 Hz, 1H), 1.26 (dd, J = 16.0, 7.1 Hz, 1H), 1.16 (s, 6H), 1.14 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 180.32, 157.29, 156.97, 142.35, 129.71, 123.27, 122.59, 118.90, 118.46, 117.39, 83.45, 46.75, 24.66, 24.53, 15.90 ^{11}B NMR (128 MHz, $CDCl_3$): δ 33.55 (br s). The ^{13}C NMR resonance at 15.90 (methylene carbon signal) has very low intensity due to ^{11}B quadrupolar broadening; HRMS (ESI) m/z calc. for $C_{21}H_{24}BO_5^-$ $[M-H]^-$ 367.17168, found 367.17152

3-boronic acid pinacol ester-2-(3-fluorobiphenyl) propionic acid **2n.** white solid, yield 22% ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, J = 7.8 Hz, 2H), 7.44-7.35 (m, 4H), 7.17-7.12 (m, 2H), 3.91 (t, J = 8.2 Hz, 1H), 1.58 (dd, J = 16.0, 9.2 Hz, 1H), 1.32 (dd, J = 16.0, 7.3 Hz, 1H), 1.16 (s, 6H), 1.15 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 180.08, 160.78, 158.31, 141.63 (d, J = 7.8 Hz), 135.50, 130.70, 128.92, 128.39, 127.93, 127.79, 127.60, 123.85, 115.63 (d, J = 23.7 Hz), 83.55, 46.33, 24.63, 24.53, 16.00 ^{11}B NMR (128 MHz, $CDCl_3$): δ 33.02 (br s) ^{19}F NMR (376 MHz, $CDCl_3$): δ -117.76 (t, J = 9.8 Hz). The ^{13}C NMR resonance at 16.00 (methylene carbon signal) has very low intensity due to ^{11}B quadrupolar broadening; HRMS (ESI) m/z calc. for $C_{21}H_{23}BFO_4^-$ $[M-H]^-$ 369.16679, found 369.16695

3-boronic acid pinacol ester-2-(4-cyanophenyl) propionic acid **2o.** white solid, yield 39% ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 7.7 Hz, 2H), 7.42 (d, J = 7.7 Hz, 2H), 3.92 (t, J = 8.2 Hz, 1H), 1.55 (dd, J = 16.1, 8.7 Hz, 1H), 1.30 (dd, J = 16.1, 7.8 Hz, 1H), 1.13 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 178.77, 145.62, 132.27, 128.81, 118.63, 111.10, 83.61, 47.04, 24.56, 24.52, 15.58 ^{11}B NMR (128 MHz, $CDCl_3$): δ 33.22 (br s). The ^{13}C NMR resonance at 15.58 (methylene carbon signal) has very low intensity due to ^{11}B quadrupolar broadening; HRMS (ESI) m/z calc. for $C_{16}H_{19}BNO_4^-$ $[M-H]^-$ 300.14071, found 300.14047

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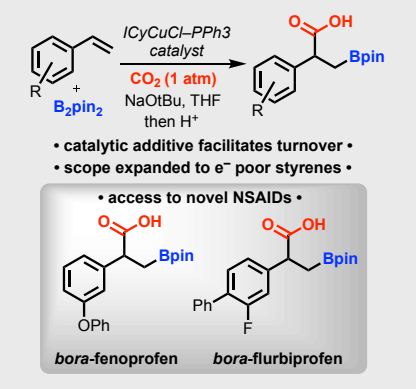
FULL PAPER

The boracarboxylation of vinyl arenes is a useful alkene difunctionalization reaction that provides synthetically useful β-boryl-α-aryl propanoic acid derivatives. Here we show that catalytic additives, specifically triphenylphosphine or electron-rich styrene, leads to improved catalyst efficiency and broadening of substrate scope. Preliminary experiments are described that begin to clarify the role of ligand additive in the catalytic reaction.



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Beneficial Effect of a Secondary Ligand on the Catalytic Difunctionalization of Vinyl Arenes with Boron and CO_2