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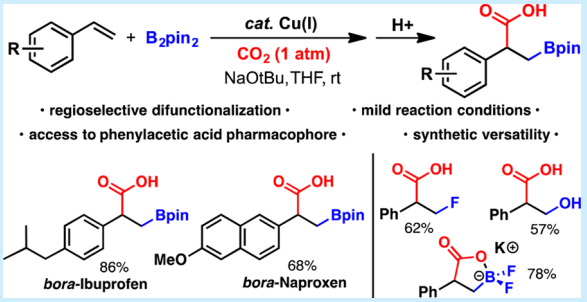
Regioselective Copper-Catalyzed Boracarboxylation of Vinyl Arenes

Trevor W. Butcher, Edward J. McClain, Tyler G. Hamilton, Trina M. Perrone, Kayla M. Kroner, Gregory C. Donohoe, Novruz G. Akhmedov, Jeffrey L. Petersen, and Brian V. Popp*

C. Eugene Bennett Department of Chemistry, West Virginia University, Morgantown, West Virginia 26505, United States

Supporting Information

ABSTRACT: Regioselective copper-catalyzed boracarboxylation of vinyl arenes with bis(pinacolato)diboron and carbon dioxide has been achieved. New boron-functionalized α-aryl carboxylic acids, including nonsteroidal anti-inflammatory drugs (NSAIDs), are obtained in moderate to excellent yields. The synthetic utility of the transformation was shown through subsequent derivatization of the carbon−boron bond yielding formal hydroxy- and fluorocarboxylation products as well as anionic difluoroboralactones.



Carbon dioxide is an appealing C_1 synthon in chemical synthesis due to its abundance, availability, nontoxicity, and inherent renewability; however, it is underutilized and undervalued due in large part to its thermodynamic and kinetic stability.[1] Due to the importance of carboxylic acid substrates in the preparation of fine chemicals and in medicinal chemistry applications,[2] new transition-metal-catalyzed reductive carboxylation strategies have emerged in recent years.[3] Many of these strategies utilize earth abundant metal catalysts and rely upon substrates with prefunctionalized C−X bonds,[4] while fewer strategies have been established for unsaturated C−C bonds.[5]

Hydrocarboxylation represents the most prominent strategy to carboxylate unsaturated substrates (Figure 1A).[5a−g] The intermediacy of M−H species and the use of reactive sources of hydride (e.g., Grignard reagents), though, has hampered broader development of catalytic hydrocarboxylation by limiting functional group tolerance. Transition-metal-catalyzed difunctionalization represents an attractive approach because reactive M−H species are avoided while also delivering densely functionalized carboxylic acid products.[6] Hetero(element)carboxylations are exceedingly rare, however, and remain limited to alkynyl and allenyl substrates (cf., Figure 1B−C).[5h−l] Extension of boracarboxylation to less reactive olefinic substrates would be highly valuable to the synthetic community because the reaction produces an alkylborane product, a versatile functionality for C−C cross-coupling,[7] oxidation,[8] fluorination,[9] amination,[10] and carboxylation chemistries.[3,11]

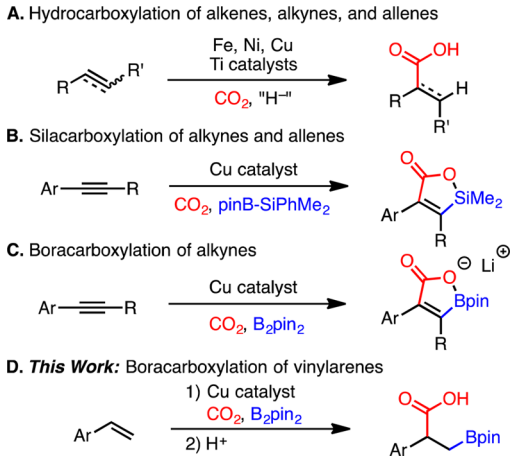


Figure 1. Examples of reductive carboxylation of unsaturated C−C bonds.

We envisioned that catalytic boracarboxylation of olefins (Figure S1) could be achieved by redox-neutral copper catalysis. The success of the reaction would hinge upon (1) olefin borylcupration by a Cu-boryl species and (2) CO_2 insertion into a Cu-alkyl species. Olefin borylcupration has been proposed in a variety of contexts[12] and observed directly by Sadighi and coworkers for ethylene and styrene derivatives;[13] however, we were concerned with insertion regioselectivity and competing CO_2 borylation.[14] Carboxylation of Cu-alkyls has been observed in stoichiometric studies,[15] and it is a probable step in the catalytic carboxylation of alkylboranes.[11b] Nevertheless, this step appeared problematic because β-hydride elimination[14] and protodecupration[17] could be kinetically competitive due to the relative instability of Cu−C_{sp^3} bonds. Given the high reactivity and insertion regioselectivity of Cu-boryl species toward styrene,[13] we reasoned that activated olefins offered the highest potential for success. Herein, we report the first hetero(element)carboxylation of alkenes, providing access to novel, functionalizable α-aryl carboxylic acid derivatives that have potential medicinal value.

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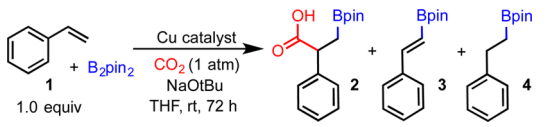
We began our studies by examining the reactivity of styrene, **1**, with bis(pinacolato)diboron (B_2pin_2) using a CuCl catalyst with different phosphine, nitrogen, and N-heterocyclic carbene ligands under 1 atm of CO_2 (Table 1). Three major products were identified: boracarboxylation product **2**, C−H borylation product **3**, and protoboration product **4**. We were pleased to observe only the α-carboxy-β-boryl regioisomer of **2**. A clear trend emerged in which more electron-donating monophosphine ligands gave higher yields of **2** (Table 1, entries 1−4). We hypothesize that this trend reflects a challenging carboxylation step that requires a strongly nucleophilic Cu-alkyl intermediate. Attempts to use bisphosphine ligands (entries 5−7), which are generally successful in Cu-catalyzed hydroamination[17] and aminoboration,[18] resulted in inferior yields. Strongly σ-donating *N*-heterocyclic carbene ligands were most efficient for boracarboxylation of **1** (entries 8−11), with ICyCuCl providing **2** in excellent yield (92%). The borane reagent and base loading could be dropped to 1.1 and 2.0 equiv, respectively, with no detrimental effects (entry 14).[19] Lowering the catalyst loading below 12 mol %, however, led to a significant decline in yield (entry 16).

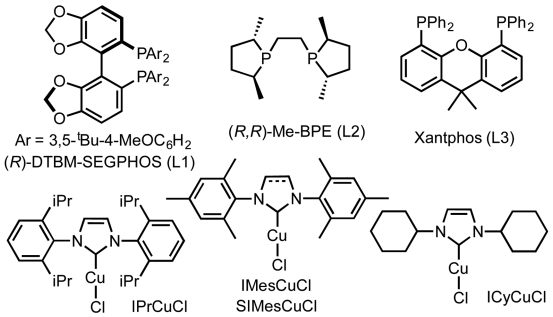
With optimized conditions in hand, we investigated the vinyl arene scope (Scheme 1). Owing to the poor stability of the products during flash chromatography, a multistep extraction protocol was developed in order to isolate and purify the carboxylic acid products.[20] The reactions of styrene derivatives with aliphatic and aromatic substituents in the *meta*- and *para*-positions proceeded to give excellent yields of boracarboxylated products (**2b**−**2e**). The reaction of *p*-*tert*-butylstyrene could be scaled to 3.75 mmol to provide more than a gram of **2b** with negligible change in yield (84%). Product **2b** was amenable to crystallization, and subsequent X-ray structural analysis confirmed its identity (Figure 2). Sterically hindered substrates provided lower yields of boracarboxylated product. A slightly decreased yield was obtained with *o*-methylstyrene (**1f**), and elevated temperatures were necessary to reach even a low yield with 2,4,6- trimethylstyrene (**1m**). Notably, steric bulk on the arene ring did not influence the regioselectivity of the reaction.

In general, less electron-rich substrates required higher temperatures or provided the boracarboxylated product in lower yields than more electron-rich substrates. For example,

Table 1. Optimization of the Boracarboxylation of Styrene[a]

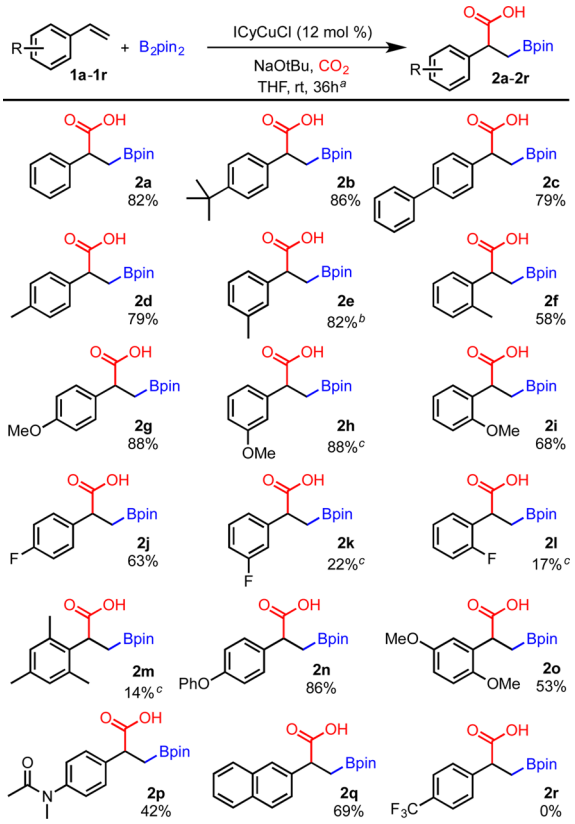


entry	Cu catalyst[b]	B_2pin_2 (equiv)	NaOtBu (equiv)	yield (%)[c] 2	3	4	convn (%)[c] 1
1	PPh_3 + CuCl	1.5	3.0	1	22	13	99
2	$PMePh_2$ + CuCl			21	11	17	98
3	PEt_3 + CuCl			58	14	11	100
4	PCy_3 + CuCl			79	5	14	99
5	L1 + CuCl			0	6	2	94
6	L2 + CuCl			11	41	12	100
7	L3 + CuCl			20	8	17	98
8	IPrCuCl			17	< 1	< 1	99
9	IMesCuCl			85	8	< 1	100
10	SIMesCuCl			< 70	< 1	4	100
11	ICyCuCl			92	< 1	3	100
12[d]	ICyCuCl	1.1		91	1	6	98
13[d]	ICyCuCl	1.0		82	< 1	7	95
14[d]	**ICyCuCl**	**1.1**	**2.0**	**91**	**< 1**	**6**	**98**
15[d]	ICyCuCl	1.1	1.5	81	1	2	98
16[d]	ICyCuCl[e]	1.1	2.0	61	2	5	98
17	CuCl	1.5	3.0	0	1	2	92



[a]Styrene (0.25 mmol) in THF (4 mL). Reactions quenched with 1 M HCl_{aq}. [b]Catalyst system: CuCl (12 mol %) and phosphine ligand (13 mol %) or (NHC)CuCl (12 mol %). [c]Yield and conversion were determined by ^1H NMR spectroscopy using mesitylene as the internal standard. [d]36 h. [e]6 mol %.

Scheme 1. Scope of Vinyl Arene in Boracarboxylation Reactions



[a]Standard conditions: 0.25 mmol scale with respect to vinyl arene, 1.1 equiv of B_2pin_2, 2.0 equiv of NaOtBu, 1 atm of CO_2, rt, 36 h in 4 mL of THF. Reactions quenched with 1 M HCl_{aq}. Isolated yields corrected for trace B_2pin_2 impurity are given. [b]40 °C. [c]50 °C.

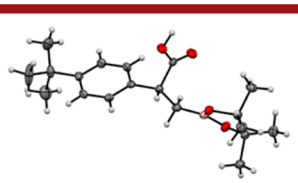


Figure 2. X-ray crystallographic structure of **2b** (thermal ellipsoids at 50% probability).

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m-methoxystyrene (**1h**), which is slightly electron-deficient, did not produce the boracarboxylated product at room temperature but rather required an elevated reaction temperature to achieve yields comparable to *p*/*o*-methoxystyrene and *p*-phenoxystyrene (**1g**, **1i**, **1n**, respectively). Incorporation of both a donating *o*-methoxy and a withdrawing *m*-methoxy substituent or an electron-rich *N*−bound tertiary amide gave modest yields of **2o** and **2p**. Reactions of slightly less electron-rich substrates *p*-fluorostyrene and fused aromatic system 2-vinylnaphthalene gave **2j** and **2q** in 63% and 69% yields, respectively. Other fluorinated congeners (**1k**−**l**) underwent boracarboxylation in very low yield. Styrenes bearing moderately and strongly electron-withdrawing substituents (e.g., chloro, bromo, cyano, and trifluoromethyl (**2r**)) did not give boracarboxylation products, even at elevated temperatures. Because electron-poor styrenes insert Cu-boryl species more readily than their electron-rich counterparts,[21] we suggest that the sensitivity of yield toward vinyl arene electronic character indicates that carboxylation is kinetically challenging, consistent with a less nucleophilic copper-alkyl intermediate.[22]

Our boracarboxylation strategy could have significant applications in drug development because of the synthetic versatility of the new carbon−boron functionality as well as the growing number of examples of boron-containing compounds that are potent therapeutics.[23] Members of the nonsteroidal anti-inflammatory drug (NSAID) family can be prepared from the corresponding vinyl arene precursor by generation of a benzylic carbanion using Fe-catalyzed hydromagnesiation[24] or Cu-catalyzed protoboration followed by base-induced C−B bond cleavage.[25] We demonstrate here a similar ability to prepare novel boron-containing examples of racemic Ibuprofen (**2s**) and Naproxen (**2t**) in high yield (Figure 3).

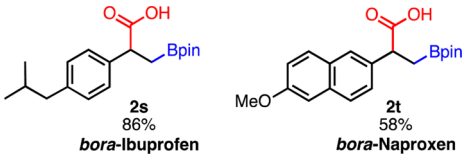
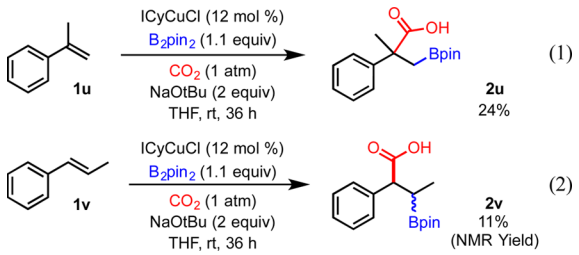


Figure 3. *Bora*-functionalized NSAID derivatives.

Subsequent screening of other activated and unactivated olefins afforded mixed results. Our boracarboxylation method did not yield product for α-olefins and cyclic olefins, such as 1-octene and norbornene, or some β-substituted vinyl arenes, such as *trans*-stilbene and indene, even at elevated temperature. The reaction of sterically hindered α-methylstyrene produced only the tertiary α-carboxylic acid-β-boryl regioisomer (**2u**) in 24% yield (eq 1). Indeed, this same regioselectivity for Cu-boryl insertion was observed for asymmetric protoboration of 1,1-disubstituted vinyl arenes.[26] Boracarboxylation of *trans*-β-methylstyrene (**1v**) gave a low yield (11%) of an inseparable mixture of apparent diastereomeric products (eq 2).



Finally, the synthetic versatility of these novel boracarboxylated products was explored (Figure 4A). Oxidation of **2a** with hydrogen peroxide gave tropic acid (**5a**) in 57% yield. Silver-catalyzed fluorination with Selectfluor afforded the corresponding alkyl fluoride (**6a**) in 62% yield.[9a] Significantly, the two-step boracarboxylation/fluorination of olefins represents a new difunctionalization method that could have medicinal chemistry applications.[27] Treatment of **2a** with KHF_2, to remove the pinacol group, provided the novel difluoroboralactone anion (**7a**) in 78% yield.[28] This reaction was subsequently used to establish a 12:1 diastereomeric ratio from the boracarboxylation of **1v** (Figure 4B).[29] It is known that borylcupration occurs with *syn*-selectivity,[13,21] meaning the diastereoselectivity of the complete reaction will be determined by the mechanism of CO_2 insertion. The predominant *trans*-difluoroboralactone (*trans*-**7v**) could arise from stereoretentive insertion of CO_2 into a Cu-alkyl bond, while the corresponding *cis*-difluoroboralactone (*cis*-**7v**) could arise from a stereoinvertive, S_E2 carboxylation mechanism (Scheme S1). Given the observed 12:1 dr, it appears that a stereoretentive CO_2 insertion mechanism dominates.

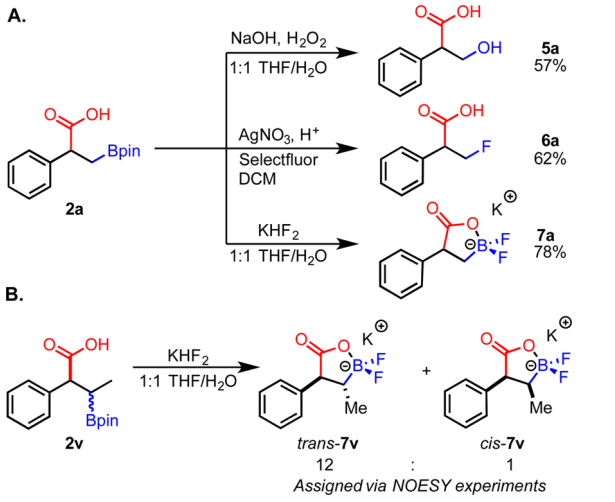


Figure 4. Derivatization of boracarboxylation products.

In conclusion, we have developed a mild method for the boracarboxylation of vinyl arenes affording moderate to excellent yields of a single constitutional isomer. The approach provides access to three new classes of compound: *bora*-NSAID derivatives, fluorocarboxylated olefins, and difluoroboralactones, which have high potential for pharmaceutical synthesis and medicinal chemistry applications. Expansion of the substrate scope that includes achieving asymmetric boracarboxylation, investigations of the reaction mechanism, development of new transformations of the boracarboxylated products, and evaluation of their therapeutic potential will be the subject of future work.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03326.

Crystallographic data for **2b** (CCDC 1510575) (CIF)
Experimental procedures and characterization data for new compounds (PDF)

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AUTHOR INFORMATION

Corresponding Author

*E-mail: Brian.Popp@mail.wvu.edu.

ORCID

Brian V. Popp: 0000-0001-6367-1168

Notes

The authors declare no competing financial interest.

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(19) Preliminary screening of MOtBu bases with the PCy_3/CuCl catalyst system showed that NaOtBu was optimal, so only this base was screened for the ICyCuCl catalyst system.

(20) A small B_2pin_2 impurity remains in boracarboxylated products that are purified by extraction, generally <10%. Reported yields are corrected to account for the mass of this impurity.

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(28) Preliminary screening of Suzuki coupling conditions indicate that difluoroboralactone **7a** is a competent substrate for sp^3−sp^2 coupling.

(29) See the Supporting Information for ^{1}H NMR experiments used to assign the identity of *trans*- and *cis*-difluoroboralactone products.

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