TITLE:

Synthesis of Borylated Ibuprofen Derivative through Suzuki Cross-Coupling and Alkene Boracarboxylation Reactions

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SUMMARY:

The present protocol describes a detailed benchtop catalytic method that yields a unique borylated derivative of ibuprofen.

ABSTRACT:

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most common drugs used to manage and treat pain and inflammation. A new class of boron functionalized NSAID (*bora* NSAID) was accessed under mild conditions *via* copper-catalyzed regioselective boracarboxylation of vinyl arenes using carbon dioxide (balloon) and a diboron reductant at room temperature in 2016. This original method was performed primarily in a glovebox or with a Schlenk manifold under rigorous air and moisture free conditions, leading often to irreproducible reaction outcomes due to trace impurities. Here, a simpler and more convenient benchtop method for synthesizing a representative *bora*-NSAID, *bora*-ibuprofen, is disclosed. A Suzuki-Miyaura cross-coupling reaction between 4-bromo-isobutylbenzene and vinylboronic acid pinacol ester, provides access to 4-isobutylstyrene. The styrene is subsequently boracarboxylated regioselectively to provide *bora* ibuprofen, an α-aryl-β-boryl-propionic acid, in good yield on multi-gram scale. This procedure allows for the broader utilization of copper-catalyzed boracarboxylation in synthetic laboratories, enabling research to ensue on *bora*-NSAIDs and other unique boron-functionalized drug-like molecules.

INTRODUCTION:

Organoboron compounds have been employed strategically in chemical synthesis for more than 50 years.[1–6] Reactions such as hydroboration-oxidation,[7–10] halogenation,[11, 12] amination,[13, 14] and Suzuki-Miyaura cross-coupling[15–17] have led to significant multidisciplinary innovations in chemistry and related-disciplines. The Suzuki-Miyaura reactions, for example, account for 40% of all carbon-carbon bond forming reactions in the pursuit of pharmaceutical drug candidates.[18]The Suzuki-Miyaura cross-coupling reaction allows direct access to vinyl arenes in one step from the halogenated arene precursor.[19] This greener catalytic strategy is valuable relative to traditional poorly atom economical Wittig syntheses from aldehydes that produce stoichiometric triphenylphosphine oxide byproduct

A regioselective hetero(element)carboxylation of vinyl arenes was envisaged to allow for direct access to novel hetero(element)-containing non-steroidal anti-inflammatory drugs (NSAIDs) utilizing CO_2 directly in the synthesis. However, hetero(element)carboxylation reactions were exceedingly rare, and limited to alkynyl and allenyl substrates prior to 2016.[20–22] Extension of the boracarboxylation reaction to vinyl arenes would provide boron-functionalized NSAIDs, and boron-based pharmaceutical candidates (Figure 1) have been gaining popularity marked by recent decisions by the FDA to approve the chemotherapeutic bortezomib, antifungal tavaborole, and anti-inflammatory crisaborole. The Lewis acidity of boron is interesting from a drug design standpoint due to the capability to readily bind Lewis bases such as diols, hydroxyl groups on carbohydrates, or nitrogen-bases in RNA and DNA since these Lewis bases play important roles in physiological and pathological processes.[23]

This catalytic approach to boracarboxylation relies upon borylcupration of the alkene by a Cu-boryl intermediate, followed by CO_2 insertion into the resulting Cu-alkyl intermediate. Sadeghi and coworkers reported the borylcupration of styrene derivatives through use of (NHC)Cu-boryl,[24] and carboxylation of Cu-alkyl species has also been observed.[25] In 2016, the Popp lab developed a new synthetic approach to achieve mild difunctionalization, of vinyl arenes using a (NHC)Cu-boryl catalyst and only a single atmosphere of gaseous CO_2.[26] Using this method, the α-aryl propionic acid pharmacophore is accessed in a single step, and a novel unexplored class of boron-modified NSAID can be prepared in excellent yields. In 2019, catalytic additives improved catalyst efficiency and broadening of substrate scope, including the preparation of an additional two novel borylated NSAIDs (Figure 1).[27]

Previous boracarboxylation reactions of alkenes could only be achieved under stringent air and moisture free conditions with use of an isolated N-heterocyclic-carbene ligated copper(I) precatalyst (NHC-Cu; NHC = 1,3-bis(cyclohexyl)-1,3-dihydro-2*H*-imidazol-2-ylidene, ICy). A benchtop method wherein borylated Ibuprofen can be synthesized using simple reagents would be more desirable to the synthetic community, prompting us to develop reaction conditions that allowed for boracarboxylation of vinyl arenes, particularly 4-isobutylstyrene, to proceed from the *in-situ* generation of NHC-Cu precatalyst, and without the need of a glovebox. Recently, a boracarboxylation protocol was reported using imidazolium salts and copper(I)-chloride to generate in-situ active NHC-ligated copper(I) catalyst.[28] Using this method, α-methyl styrene was boracarboxylated to afford 71% isolated yield of the desired

product, albeit with use of a glovebox. Inspired by this result, a modified procedure to boracarboxylate tert-butylstyrene without using a nitrogen-filled glovebox was devised. The desired boracarboxylated tert-butyl styrene product was afforded in 90% yield on a 1.5-gram scale. Gratifyingly, this method could be applied to 4-isobutylstyrene to afford *bora*-Ibuprofen NSAID derivative in moderate yield. The α-aryl propionic acid pharmacophore is the core motif amongst NSAIDs, therefore synthetic strategies that allow direct access to this motif are highly desirable chemical transformations. Herein, a synthetic pathway to access a novel *bora*-Ibuprofen NSAID derivative from an abundant, inexpensive 1-bromo-4-isobutylbenzene starting material (~$2.50/1 g) in moderate yield in two steps, without the need for a glovebox, is presented.

PROTOCOL:

1. Synthesis of 4-isobutylstyrene through Suzuki Cross Coupling of 1-bromo-4-isobutylbenzene with vinylboronic acid pinacol ester

1.1. Add 144 mg of palladium(0) tetrakistriphenylphosphine (5 mol%, see **Table of Materials**), 1.04 g of anhydrous potassium carbonate (2 equiv), and a magnetic stir bar (0.5 x 0.125 in.) to a 40 mL scintillation vial then seal with a pressure relief cap. Completely encapsulate the vial seal with electrical tape.

1.1.1. Purge the reaction mixture with argon for 2 min. After the 2 min, add 1.07 g of 1-bromo-4-isobutylbenzene (1 equiv, see **Table of Materials**), then add 13 mL of anhydrous THF obtained from a solvent purification system (or still pot) with continuous argon flow, then commence magnetic stirring.

Note: Argon gas can be replaced with dry nitrogen gas.

1.1.2. Add 1.5 mL of argon-sparged deionized water to the solution, followed by 0.72 mL of vinylboronic acid pinacol ester (1.5 equiv, see **Table of Materials**), then purge the reaction mixture with argon for an additional 5 min.

1.1.3. Once the purge has finished, heated at 85 ^{o}C for 24 h on an IKA stirring hot plate.

1.1.4. After 24 h, remove a small aliquot from the reaction and dilute it with 2 mL of dichloromethane, then perform TLC (UV visualization) using hexane to ensure reaction completion (R_f = 0.9 reactant, R_f = 0.91 product).

1.2. Upon confirmation of 1-bromo-4-isobutylbenzene consumption, add the reaction mixture to a 125 mL separatory funnel and then add 30 mL of deionized water.

1.2.1. Extract 3x with 5 mL dichloromethane, adding the organic extracts to a 125 mL Erlenmeyer flask, then discard the aqueous layer.

1.2.2. Transfer the organic extracts into a 125 mL separatory funnel, wash with 30 mL of brine, an aqueous saturated sodium chloride solution and discard the brine.

1.2.3. Transfer the organic layer to a 125 mL Erlenmeyer flask, then add 5 g of sodium sulfate and swirl the flask for at least 20 s.

1.2.4. Vacuum filter, using a Buchner funnel, the solution into a 125 mL filter flask.

1.2.5. Transfer the organic layer to a 100 mL round-bottom flask, then concentrate the reaction in vacuum for 15-30 minutes, pending vacuum strength, to provide a pale-yellow viscous oil.

1.3. Subject the crude reaction mixture to column chromatography using 50 g of SilicaFlash P60 silica gel (see **Table of Materials**) and pure hexane as the eluent to obtain pure 4-isobutylstyrene (**1**).

NOTE: For the present study, the yield was 89% (average of 3 reactions).

NOTE: 4-isobutylstyrene is subjected to polymerization at room temperature under light, so once isolated, the product must be stored in the dark at or below -20 ^{o}C until needed. If necessary, a small amount of butylated hydroxytoluene (BHT) can be added to inhibit polymerization. BHT does not impact the efficiency of copper-catalyzed boracarboxylation.

2. Glovebox large-scale synthesis of *bora*-Ibuprofen

NOTE: This reaction was prepared inside a nitrogen-filled glove box. All chemicals are dried or purified before moving into the box. The 4-isobutylstyrene was freeze-pump-thawed prior to use. All vials and glassware are dried and heated in an oven (180 ^{o}C) for at least 24 h prior to use. The copper pre-catalyst (ICyCuCl) was prepared according to the literature.[29]

2.1. Add 160 mg of ICyCuCl (5 mol%), 131 mg of triphenylphosphine (5 mol%), 1.92 g of sodium tert-butoxide (2 equiv), 20 mL of anhydrous, degassed THF, and a 0.5 x 0.125 in. magnetic stir bar to a 20 mL scintillation vial, then seal with an air-tight septum, and stir the resulting solution for 20 min.

2.1.1. After 20 min, the catalyst solution was transferred to a 60 mL syringe, and the needle was plugged into a septum.

2.1.2. Add 2.79 g of bis(pinacolato)diboron (1.1 equiv), 1.87 mL of 4-isobutylstyrene (1 equiv), 140 mL of THF, and a 2 x 0.3125 in. magnetic stir bar to a 500 mL round-bottom flask, seal with a septum, then tape around the septum until the seal is encapsulated.

2.2. Remove the 500 mL round-bottom flask containing the styrene solution and the 60 mL syringe containing the catalyst solution from the glovebox and move to a fume hood.

NOTE: After preparation, the 500 mL round-bottom flask and catalyst solution syringe must be removed immediately from the glovebox. The styrene substrate is subjected to polymerization in THF, and the catalyst solution decomposes upon standing for a long period of time or upon exposure to air.

2.2.1. While purging the 500 mL round-bottom flask with dry carbon dioxide, add the catalyst solution over 30 s, then stir the reaction at ambient temperature for 3 h.

2.2.2. After 3 h, again purge the round-bottom flask with dry carbon dioxide (bone dry) for 15 min, then stir at ambient temperature for 33 h.

2.3. Upon reaction completion, concentrate the reaction mixture in vacuum then acidify with 30 mL of aqueous HCl (1.0 M).

2.3.1. Add 50 mL of diethyl ether to the round-bottom flask containing the acidified reaction solution, swirl the solution for at least 10 s, transfer the solution to a 500 mL separatory funnel, separate organic and aqueous layers adding the aqueous layer to a 1000 mL Erlenmeyer flask.

2.3.2. Extract the organic layer 8x with 50 mL saturated $NaHCO_3$, and transfer aqueous extracts to a 1000 mL Erlenmeyer flask.

2.3.3. Acidify combined aqueous layers in 1000 mL Erlenmeyer flask with 12 M HCl (to pH ≤ 1.0 by litmus paper), transfer solution to clean 1000 mL separatory funnel.

2.3.4. Extract aqueous solution 8x with 50 mL of dichloromethane, and transfer the organic extracts to a clean 1000 mL Erlenmeyer flask.

2.3.5. Add 50 g of sodium sulfate to the organic extraction solution, and swirl the flask for at least 20 s.

2.3.6. Filter the organic extraction solution through a Buchner funnel, and collect in a clean 1000 mL filtration flask.

2.3.7. Concentrate the solution in vacuum

2.4. Dissolve the residue in 10 mL of HPLC-grade heptane, then store it in a freezer (-20 ^{o}C) overnight to afford pure recrystallized *bora*-Ibuprofen.

NOTE: The present study, the yield of *bora*-Ibuprofen was 62% (average of 2 reactions).

3. Benchtop large-scale synthesis of *bora*-Ibuprofen

NOTE: This reaction procedure described below was carried out without using a nitrogen-filled

glovebox. All chemicals were used as received or synthesized without further purification (drying, distilling, etc.). All vials and glassware were dried and heated in an oven (180 °C) for at least 24 h prior to use and cooled under argon to room temperature immediately before reaction setup.

3.1. Add 334 mg of ICyH•Cl (13 mol%), 2.92 g of sodium tert-butoxide (3 equiv), and a 0.5 x 0.125 in. magnetic stir bar to a 20 mL scintillation vial, then seal with an air-tight septum and immediately purge with argon for 5 min.

3.1.1. Add 20 mL of anhydrous, degassed THF *via* syringe to the 20 mL scintillation vial containing the ligand and base mixture, purge the resulting solution for 5 min with argon, then stir for an additional 30 min.

3.1.2. Add 119 mg of CuCl (12 mol%) and a 0.5 x 0.125 in. magnetic stir bar to a 20 mL scintillation vial, then seal with an air-tight septum and immediately purge with argon for 5 min. After stirring the ligand solution (from step 3.1.1) for 30 min, add it to the CuCl scintillation vial under a positive argon flow, then stir the resulting solution for 1 h.

NOTE: When weighing out CuCl, take care to place it directly in the center of the bottom of the scintillation vial, as it tends to get stuck around the inside corner edges of the vial, resulting in poor dissolution in the ligand solution.

3.2. Add 5.08 g of bis(pinacolato)diboron (2 equiv) and a 2 x 0.3125 in. magnetic stir bar to a 500 mL round-bottom flask and seal with a septum, then encapsulate the septum seal with black electrical tape. Once sealed, add 140 mL of THF, and 1.78 mL of 4-isobutylstyrene (1 equiv) to the flask, then purge with argon for 5 min.

3.2.1. Purge the 500 mL round-bottom flask with dry carbon dioxide immediately following the argon purge. Then add the catalyst solution (from step 3.1.2) for 30 s, continue purging with dry carbon dioxide for 15 min, then stir the reaction at ambient temperature for 16 h.

3.3. Concentrate the reaction mixture for 15-30 minutes in vacuum upon reaction completion, then acidify with 30 mL of aqueous HCl (1.0 M).

3.3.1. Add 50 mL of diethyl ether to the round-bottom flask containing the acidified reaction solution, swirl the solution for at least 10 s, transfer the solution to a 500 mL separatory funnel, separate organic and aqueous layers, and add the aqueous layer to a 1000 mL Erlenmeyer flask.

3.3.2. Extract the organic layer 8x with 50 mL of saturated $NaHCO_3$, and transfer aqueous extracts to a 1000 mL Erlenmeyer flask.

3.3.3. Acidify combined aqueous layers in 1000 mL of Erlenmeyer flask with 12 M HCl (to pH ≤ 1.0 by litmus paper), transfer solution to clean 1000 mL separatory funnel.

3.3.4. Extract aqueous solution 8x with 50 mL dichloromethane, and transfer the organic extracts to a clean 1000 mL Erlenmeyer flask.

3.3.5. Add 50 g of sodium sulfate to the organic extraction solution, and swirl the flask for at least 20 s.

3.3.6. Filter the organic extraction solution through a Buchner funnel, and collect in a clean 1000 mL filtration flask.

3.3.7. Transfer the filtrate to a roundbottom flask

3.3.8. Concentrate the filtrate in vacuo.

3.4. Dissolve the residue in 10 mL of HPLC-grade heptane, then store it in a freezer (-20 °C) overnight to afford pure recrystallized *bora*-Ibuprofen.

NOTE: For the present study, the yield of *bora*-Ibuprofen was 59%.

REPRESENTATIVE RESULTS:

4-Isobutylstyrene was characterized by ^{1}H and ^{13}C NMR spectroscopy. *bora*-Ibuprofen was characterized by ^{1}H, ^{13}C, and ^{11}B NMR spectroscopy to confirm the product structure and assess purity. Key data for these compounds are described in this section.

Spectral data are in good agreement with the structure of 4-isobutylstyrene **1** (Figure 2). The ^{1}H NMR spectrum obtained in $CDCl_3$ (**Figure 3**) shows the characteristic AMX splitting pattern seen for monosubstituted styrene derivatives. These resonances are observed as a doublet at 5.17 (d, J = 10.9 Hz, 1H), a doublet at 5.69 (d, J = 17.6 Hz, 1H), and a doublet of doublets at 6.62 – 6.78 (dd, J = 10.9, 17.6 Hz 1H). A second characteristic feature is the iso-butyl methine proton, appearing as a nonet at 2.37–2.52 (m, 2H) with corresponding methyl groups at 0.89 (d, J = 6.6 Hz, 6H).[30] The nine resonances observed in the ^{13}C NMR spectrum agree with literature values (**Figure 4**).[30]

Synthesis of 4-isobutylstyrene *via* this protocol reliably provides direct access to the product in 89% yield (average of 3 reactions, 5 mmol scale); however, deviation from any of the key reaction conditions such as temperature and time significantly impact the efficiency of the reaction. It is important that the reaction be heated at no less than 85 °C. Reaction completion should be verified by TLC at or after 24 hours.

Spectral data are in good agreement with the structure of boracarboxylated product **2** (Figure 5). As with the previous substrate the ^{1}H NMR spectrum obtained in $CDCl_3$ (Figure 6) shows an ABX splitting pattern, but this pattern occurs due to diastereotopic methylene protons, arising from the newly generated benzylic stereogenic center. The AB resonances are observed as a pair of doublets of doublets at 1.53 (dd, *J* = 16.0, 9.1 Hz, 1H) and 1.29 (dd, *J* = 16.0, 7.6 Hz, 1H) while the X resonance is observed at 3.82 (dd, *J* = 9.1, 7.6 Hz, 1H). The latter resonance is

deshielded, which is consistent with a methine proton alpha to two sp^2 carbons. Another set of significant resonances are at 1.12 (s, 6H) and 1.11 (s, 6H), corresponding to magnetically inequivalent methyl groups on the two sides of the pinacolato boron moiety.[26]

The ^{13}C NMR spectrum of boracarboxylated product **2** (**Figure 7**) shows a very broad signal at 16 ppm, which is characteristic of a quadrupolar-broadened carbon bound to the boron. Another significant resonance is at 180.8 ppm corresponding to the carbonyl carbon of the free carboxylic acid group.

The ^{11}B NMR spectrum (**Figure 8**) shows a single broad resonance at 33.4 ppm that is characteristic of a trivalent boronic ester.

The synthesis of *bora*-Ibuprofen via this protocol reliably provides direct access to the product in 62% yield (average of 2 reactions, 2.05 g isolated), however, this reaction is far more sensitive than the previous Suzuki cross-coupling reaction. Any deviation that occurs from the reported protocol will result in significantly diminished yields. Particular attention needs to be paid to the air sensitive nature of this reaction. Using the benchtop protocol, the large-scale synthesis of *bora*-Ibuprofen provides the desired product in 59% yield (1.95 g isolated) which is comparable to the glovebox method.

FIGURE LEGENDS:

Figure 1. Medicinal relevance of organoboron compound. a) Carboxylic acid group containing non-steroidal anti inflammatory drugs. b) FDA approved Boron containing pharmaceuticals. c) boron containing NSAID analouges (*bora*-NSAIDs)
Figure 2. Synthesis of 4-Isobutylstyrene (**1**) via Suzuki Cross Coupling reaction
Figure 3. ^{1}H NMR spectrum of 4-Isobutyl styrene (**1**)
Figure 4. ^{13}C NMR spectrum of 4-Isobutyl styrene (**1**)
Figure 5. Synthesis of *bora*-Ibuprofen (**2**) via glovebox and benchtop boracarboxylation methods.
Figure 6. ^{1}H NMR spectrum of *bora*-Ibuprofen (**2**)
Figure 7. ^{13}C NMR spectrum of *bora*-Ibuprofen (**2**)
Figure 8. ^{11}B NMR spectrum of *bora*-Ibuprofen (**2**)
Figure 9. Derivatization of *bora*-Ibuprofen

DISCUSSION:

4-Isobutylstyrene (**1**) was obtained efficiently via a Suzuki Cross Coupling reaction from inexpensive, commercially available 4-bromoIsobutylbenzene, and vinylboronic acid pinacol ester. This allows for access to the desired styrene in a greener, more atom economical manner than the conventional Wittig approach. Reaction monitoring via TLC was crucial to ensure full conversion of the 1-bromo-4-isobutylbenzene substrate, because reactions not proceeding to full conversion led to difficult flash chromatographic separation of the substrate and products.

Boracarboxylation of 4-isobutylstyrene with an NHC-copper(I) catalyst at ambient temperature

using a pincolato diboron reductant under an atmosphere of gaseous CO_2 provides *bora*-Ibuprofen (**2**) in high yield. It is important to note that the styrene must be rigorously freeze-pump-thawed[31] to ensure no dioxygen remains in the solution, presumably due to copper(I)-aerobic decomposition[32] that leads to diminished reactivity and unwanted side products such as formal hydroboration of the styrene. The catalyst must be added to the reaction mixture quickly due the air sensitive nature of the catalyst. A tell-tale sign that dioxygen has contaminated the reaction is the evolution of a sky-blue reaction color. Reactions that progress appropriately to high yield will appear cloudy white with a slight pink tint after addition of the catalyst solution then will turn to brown and ultimately light green after the reaction is exposed to CO_2 for 3 or more hours. The boracarboxylation reaction can tolerate gentle heating up to 45 ^oC but higher temperatures lead to diminished yields.[27]

The reaction cannot be stored for any amount of time and must be immediately purified. The resulting end color of a successful boracarboxylation reaction is either brown or light green. Reactions not immediately purified will turn sky blue, owing to copper oxidation with concomitant product decomposition. Product isolation is still possible but diminished yields will result. *bora*-Ibuprofen cannot be isolated by column chromatography of any type (eg., silica gel, Florisil) and must be isolated following the acid-base workup protocol described above. Once isolated *bora*-ibuprofen, as well as many other similar α-aryl-β-boryl proprionic acid derivatives studied thus far, is an air stable white solid. Trace amounts of diboron reductant often remain after the first acid-base workup. A second acid-base workup followed by a second recrystallization in heptane often satisfactorily removes trace impurities to provide analytically pure products.

The benchtop boracarboxylation method is more convenient and easier to execute that the glovebox method, while still producing similar reaction outcomes. Nevertheless, there are some known limitations associated with the benchtop method. The reaction must be performed under moisture and air-free conditions. In order to further understand moisture sensitivity, a boracarboxylation reaction was performed using the benchtop method with “wet” THF (a high purity 4 L bottle that was previously opened) for both the *in situ* catalyst preparation and reaction steps. In this case, only 2% NMR yield of the desired product was obtained. Next, a reaction was performed in which the catalyst solution was prepared using anyhydrous THF (solvent system dried) while the remaining THF used in the reaction was “wet”. A modest increase to 13% NMR yield of boracarboxylated product was observed. It is clear that trace, adventitious water impacts the reaction negatively, especially during pre-/active-catalyst formation. Using the benchtop protocol without an Ar purge (or N_2 purge) of the reaction solution prior to the introduction of CO_2 gas, an NMR yield of 46% (vs. 66% with Ar purge) was obtained. However, a second identical reaction setup provided an NMR yield of only 17%, suggesting that adventious oxygen/air impacts the reaction in various, irreproducible ways.

In the future, the Popp Group expect that *bora*-Ibuprofen, and other boracarboxylated compounds, will provide access to a host of other functionalized-ibuprofen derivatives (Figure 9), thus allowing for their study as potential therapeutic agents for pain management[33–37] or other pharmaceutical applications.

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DISCLOSURES:

The authors declare no competing financial interests.

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