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Synthesis of Novel Multifunctional *bora*-Ibuprofen Derivatives

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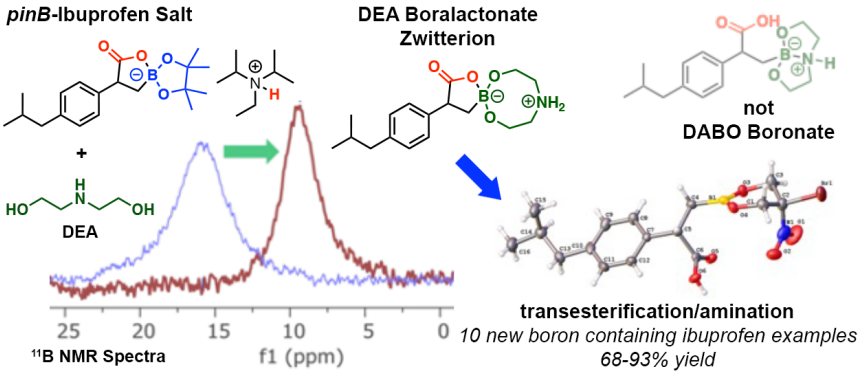
Abstract: A unique class of β-boron-functionalized non-steroidal anti-inflammatory compound (*pinB*-NSAID) was previously synthesized via copper-catalyzed 1,2-difunctionalization of the respective vinyl arene with CO_2 and B_2pin_2 reagents. Here, pinacolylboron-functionalized ibuprofen (*pinB*-ibuprofen) was used as a model substrate to develop conditions for pinacol deprotection and subsequent boron functionalization. Initial pinacol-boronic ester deprotection was achieved by transesterification with diethanolamine (DEA) from the boralactonate organic salt. The resulting DEA boronate adopts a spirocyclic boralactonate structure rather than a diazaborocane – DABO boronate – structure. Subsequent acid-mediated hydrolysis of DEA and transesterification/transamination provided a diverse scope of new boron containing ibuprofen derivatives.

Keywords: organoboron compounds, boracarboxylation, NSAIDs, synthesis, transesterification



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1. Introduction

Boronic acid and ester containing molecules have garnered significant attention in synthetic and medicinal chemistry due to the unique chemical properties of the boron center.[1] Neutral, trivalent boron compounds feature an empty *p*-orbital that makes the compounds Lewis acidic, enabling reactions with nucleophiles/Lewis bases such as organometallic reagents, alcohols/alkoxides, amines, hydroxy acids, halides, etc..[1] This reactivity has made organoboron compounds important synthons in catalysis as staring materials and intermediates in transition-metal-catalyzed cross coupling reactions (e.g., Suzuki-Miyaura [2] and Chan-Lam [3]) and C-X bond forming reactions [4]. Under physiological conditions, boronic acid derivatives convert from trivalent sp^2 hybridized form to tetravalent sp^3 hybridized form upon capture by Lewis bases, enabling enzyme inhibition. In 2003, the United States Federal Drug Administration (FDA) approved the first boron containing therapeutic agent, Bortezomib, that acts as a proteasome inhibitor to treat multiple myeloma and cell lymphoma.[5] In subsequent years, several other boron containing drugs featuring either a boronic acid bioisostere replacing a carboxylic acid/aldehyde

(e.g., Bortezomib and Ixazomib) or an oxaborole motif (e.g., Tavaborole and Crisaborole) were approved by the FDA to treat various conditions (Figure 1a**)** [5-7].

The identification and preparation of new boron therapeutic agents, especially ones featuring unique pharmacologically important motifs, has been a highly active area of investigation [5-13]. In 2016, Popp and co-workers reported a redox neutral copper catalyzed boracarboxylation method to add carboxylic acid and boron ester (pinacolylboron – pinB) groups to vinyl styrene regioselectively [14]. This unique catalytic entry point to the pharmacologically important α-aryl propionic acid pharmacophore allowed for the first synthesis of boron containing non-steroidal anti-inflammatory drug (*pinB*-NSAID) congeners of ibuprofen and naproxen (Figure 1b). Subsequently, the synthesis of *pinB*-fenoprofen and *pinB*-flurbiprofen, using the same copper catalyst system with inclusion of triphenyl phosphine (PPh_3) as a catalytic additive, was reported [12-13]. Herein, we report a mild, high yielding method to remove pinacol from *pinB*-ibuprofen (**1**), allowing for structural and electronic diversification of the boron center through transesterification/transamination reactions and providing new opportunities for screening the medicinal potential of boron containing NSAIDs [10-11].

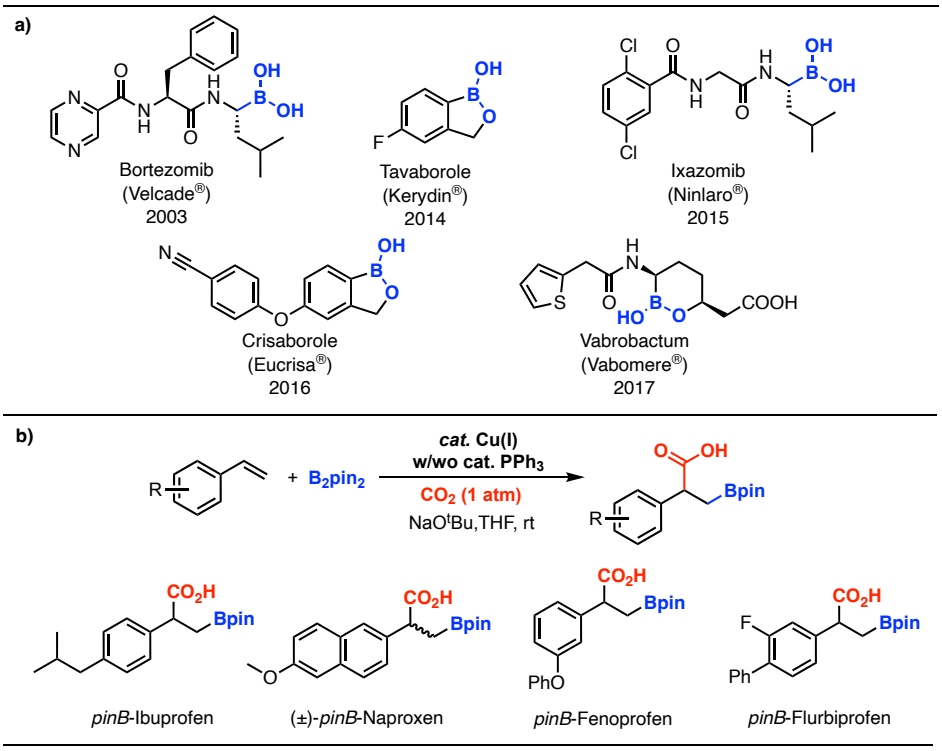


Figure 1. a) United States Federal Drug Administration approved boron containing therapeutic drugs. b) Boron containing *α*-aryl propionic acid derivatives (*pinB*-NSAIDs) prepared via copper(I) catalysis.

2. Results and Discussion

Numerous methods have been reported to hydrolyze/transesterify diols in organoboron esters [1]. We began evaluating classical methods to hydrolyze *pinB*-ibuprofen (**1**^{pin}) that generally use reagents that were expected to be incompatible with the carboxylic acid functional group (Figure 2a). Not surprisingly, transborylation with boron trichloride [17,18] and reductive cleavage with lithium aluminum hydride [19,20] led to intractable product mixtures. Oxidative cleavage with sodium periodate [21] cleaved the $_{sp3}$C–B bond to give the deborylation-hydroxylation product [14]. Hydrolysis with potassium hydrogen fluoride [22-25] led to isolation of a difluoroboralactonate salt that has proven remarkably stable [14,26].

Boronic ester hydrolysis via transesterification with an exogenous boronic acid has been achieved previously (Figure 2b). Biphasic transesterification with excess phenyl boronic acid and pinB-ibuprofen (**1**) led to difficulties in product isolation [27] while attempts to use solid-phase polystyrene-based boronic acid were also unsuccessful [28]. Klein and co-workers reported a monophasic transesterification method using excess methyl boronic acid after which the resultant methyl pinacol ester was removed via evaporation at slightly elevated temperature 40 °C [29]. Again, inefficient transesterification was observed leading to problematic isolation of boron-containing products.

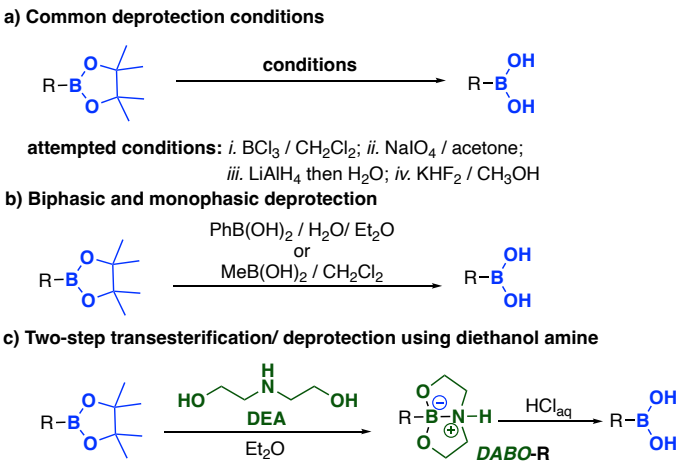


Figure 2. Pinacolylboronic ester deprotection methods.

Deprotection of cyclic boronic esters has been achieved by transesterification with a variety of diethanolamine derivatives, providing sp^3-hybridized zwitterionic diethanolamine boronate ester (dioxazaborocane – *DABO* boronate [30,31], Figure 2c) after which mild acid hydrolysis of DEA from *DABO* boronate provided the boronic acid cleanly [32-36]. Santos and coworkers demonstrated the two-step method with 2°-alkylpinacolyl boronate ester deprotection, yielding 2°-alkylboronic acids with a variety of functional groups (e.g., ester, cyano, amide) [35]. Gratifyingly, when $\mathbf{1}^{\mathbf{pin}}$ was mixed with DEA in diethyl ether, a suspension formed, and after extended stirring, a small amount of fine white precipitate appeared on the walls of the flask, albeit in amounts that prevented isolation. The white precipitate was presumed to be *DABO*-ibuprofen ($\mathbf{1}^{\mathbf{DABO}}$).

Further experimental screening showed that after addition of a slight excess of Hünig's base to $\mathbf{1}^{\mathbf{pin}}$ in diethyl ether, the initial suspension resolved to a clear solution over 30 minutes. NMR characterization of the pale-yellow oil remaining after removal of solvent indicated formation of a new, possibly tetravalent boron species as indicated by an upfield shift in the ^{11}B NMR resonance from 33.5 ppm ($\mathbf{1}^{\mathbf{pin}}$) to 15.8 ppm (Figure 3a, left overlay), mirroring the ^{11}B and ^{1}H shifts observed in IPr-copper(I) boralactonate complexes that we recently isolated and characterized [16]. Although definitive X-ray structural characterization of the molecule has been elusive, we cautiously assign it as the **[$\mathbf{1}^{\mathbf{pin}}$][DIPEA-H]** organic salt.

Redissolution of the salt in diethyl ether, and addition of excess DEA led to formation of significant amounts of an insoluble white precipitate. The precipitate was collected via simple filtration and found to be insoluble in most non-polar solvents including $CDCl_3$. NMR characterization in CD_3OD revealed no pinacol resonances and characteristic DEA resonances in the ^{1}H NMR spectrum while a further upfield shift of the boron resonance to 9.34 ppm was observed in the ^{11}B NMR spectrum (Figure 3a, right overlay). This shift

was consistent with other previously characterized DABO boronate esters; [35,37] however, there was some ambiguity since the shift could also be consistent with retention of the boralactonate structure (**1**^{DEA}). All attempts to grow X-ray quality crystals were unsuccessful, so we carried out extensive NMR characterization to elucidate the solution structure [38]. Detailed analysis of the ^{1}H NMR spectrum showed that the methylene ^{1}H resonances of the α-aryl propionic ester AMX spin system were upfield shifted, consistent with retention of the boralactonate ring [16], while the four magnetically inequivalent pairs of DEA protons were best described as an AA'XX' spin system (Figure S4) that is markedly different from the ABMX system observed for independently prepared DABO methyl boronate (Figure S5). Final structural confirmation was obtained by acquiring two-dimensional ^{1}H-^{15}N CIGAR-HMBC spectra [39] for the DEA boronate and DABO methyl boronate (Figure 3b and S6, respectively). The heteronuclear inverse correlation experiment was optimized to reveal vicinal (^{3}J), and to a lesser extent geminal (^{2}J) ^{1}H-^{15}N coupling. The DEA boronate CIGAR spectrum showed 2- and 3-bond correlations to the DEA AA'XX' spin system (Figure 3b). In contrast, the DABO methyl boronate CIGAR spectrum showed 3-bond correlations to the DEA AB spin system, as well as a 3-bond correlation, across the ^{11}B nucleus, to the methyl group. These NMR experiments collectively confirm DEA boronate adopts the spirocyclic boralactonate structure (**1**^{DEA}) rather than the DABO boronate structure (**1**^{DABO}).

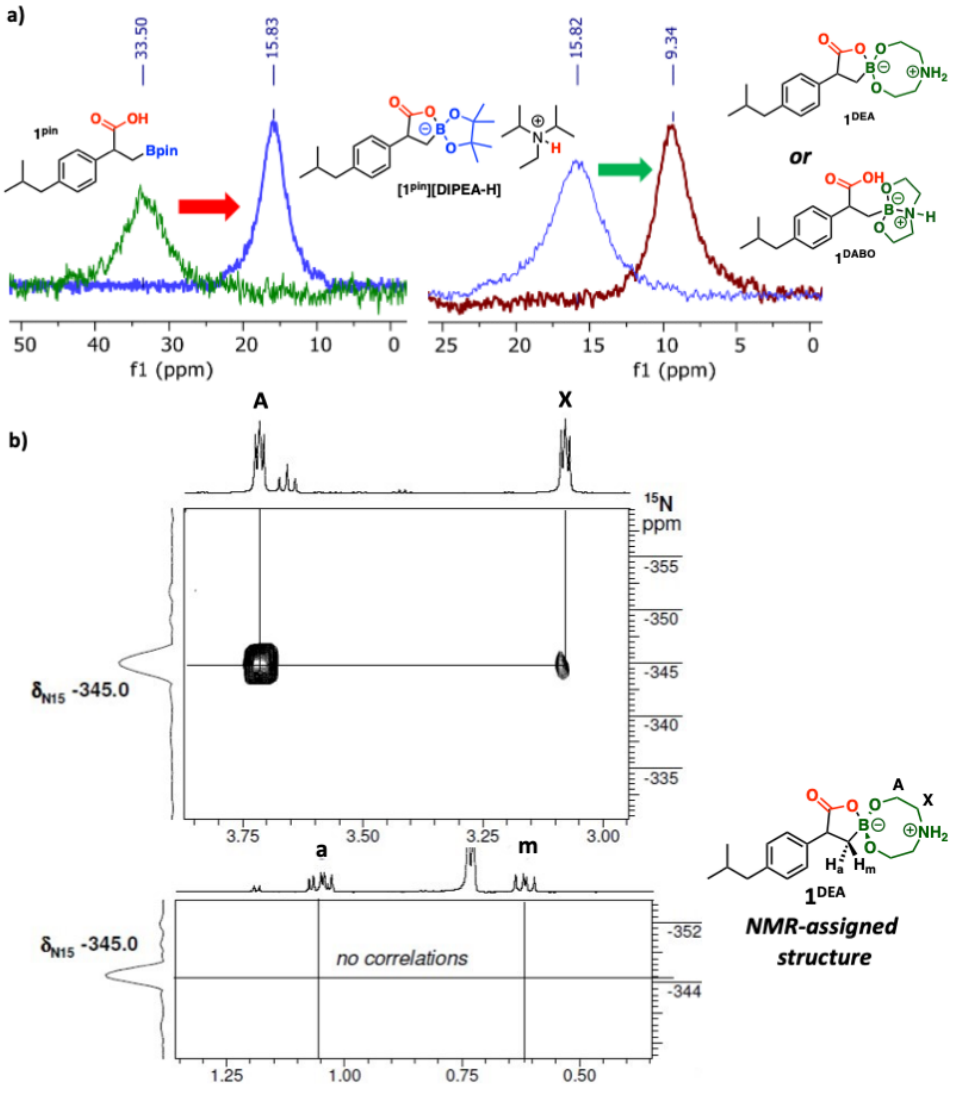
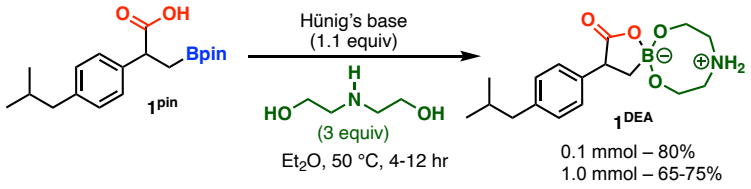


Figure 3. (a) Stepwise preparation of diethanolamine boronate ibuprofen (*DEAB*-ibuprofen, $\mathbf{1}^{DEA}$) via boralactonate organic salt **[1^{pin}][DIPEA-H]** as illustrated by ^{11}B NMR spectra in CDCl3 ($\mathbf{1}^{pin}$) and CD_3OD (**[1^{pin}][DIPEA-H]** and $\mathbf{1}^{DEA}$). (b) Two-dimensional ^{1}H-^{15}N CIGAR-HMBC NMR spectrum of $\mathbf{1}^{DEA}$ in CD_3OD.

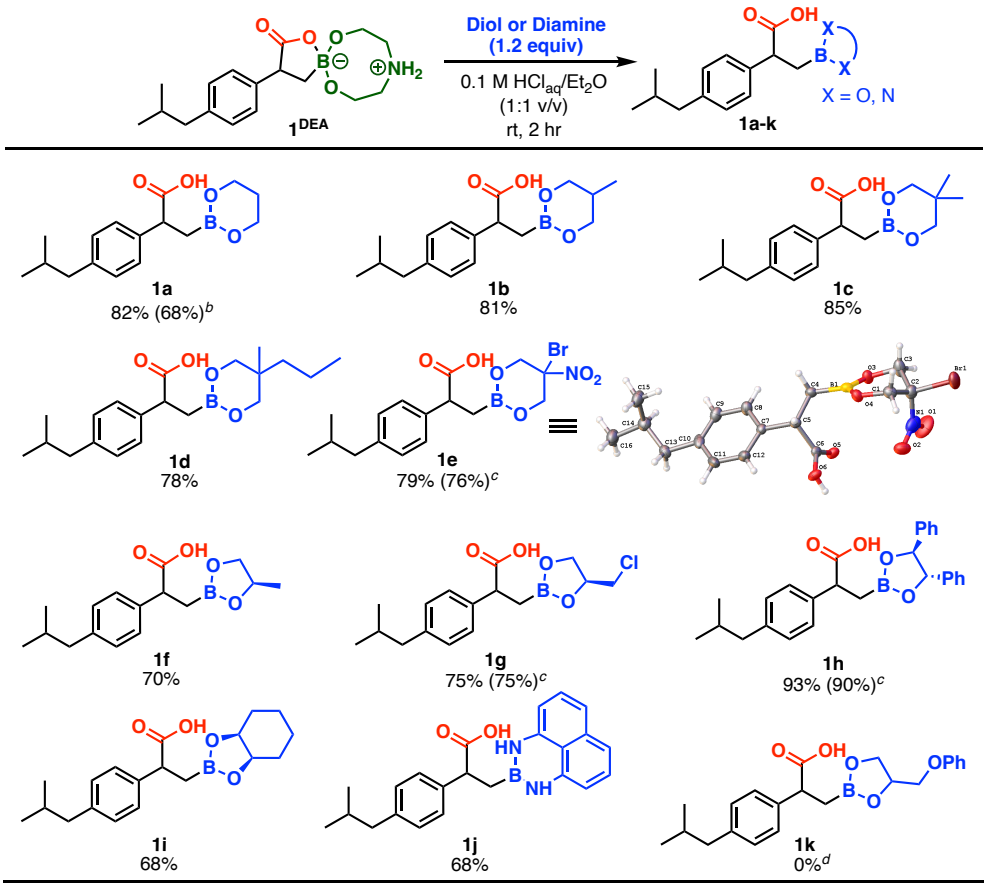
After further synthetic optimization, conditions were identified for the preparation of $\mathbf{1}^{DEA}$ by mixing $\mathbf{1}^{pin}$, Hünig's base, and excess DEA in Et_2O and then heating the mixture in a sealed vial for 4 hours (Scheme 1). Yields up to 80% were achieved at 0.1 mmol scale. Reactions at scales up to 1 mmol required longer reaction times (8-12 hours) and generally gave slightly lower yields (65-75%). The isolated compound was found to be reasonably air and moisture stable with no significant decomposition observed over 2-3 months when stored in the solid-state on the benchtop in a clear glass vial. Further, the compound was observed to be stable with no apparent decomposition when dissolved in CD_3OD for at least 4 weeks as judged by ^{1}H and ^{11}B NMR experiments.

Scheme 1. Synthesis of DEA boralactonate $\mathbf{1}^{DEA}$.



From the outset, our objective was to identify a synthetic method that would first enable pinacol deprotection from pinB-NSAIDs and other boracarboxylated products and then enable addition of new diols, amino alcohols, diamines, etc. to the boron center for

Scheme 2. Scope of Boron Containing Ibuprofen Derivatives



[a] Reactions performed on 0.1 mmol scale with respect to **1**^{DEA}. All reported yields are isolated yields. [b] 0.7 mmol scale. [c] 0.31 mmol scale. [d] Intractable mixture observed after reaction work-up.

catalytic and medicinal chemistry substrate library generation. Given the instability of reported DABO boronates to aqueous acid (cf., [35]), we reasoned that a biphasic reaction mixture would allow for initial generation of aqueous soluble boronic acid via DEA hydrolysis followed by formation of organic soluble desired boronic ester via esterification with an exogenous diol. Indeed, we have preliminary evidence to support rapid hydrolysis of DEA from **1**^{DEA} in 0.1 M HCl; however, unambiguous solution and solid-state characterization of the presumed ibuprofen-derived boronic acid has not yet been obtained and will be reported in due course elsewhere.

Using biphasic reaction medium composed of equivalent volumes of aqueous HCl and diethyl ether, we observed excellent formal transesterification reactivity in 2 hours at room temperature with a variety of diols (Scheme 2). Six-membered, 1,3-diol boronic ester derivatives (**1a-e**) were prepared in yields between 78-83%. Preparation of **1a** and **1e** was performed at 0.7 and 0.31 mmol scale, respectively, providing slightly reduced yields in both cases. A single crystal of **1e** was obtained by slow recrystallization from *n*-heptane at room temperature, revealing similar structural features to that which was reported previously for **1**^{pin} [15]. Five-membered, 1,2-diol boronic ester derivatives (**1f-i)** were also synthesized in moderate to excellent yields, and no reduction in yield was observed when the reactions were scaled 3-fold. In all cases, mixtures of the diastereomers (ie., benzylic α-aryl propionic acid racemate) were obtained and attempts at selective recrystallizaton have not been successful. Transamination with 1,8-diaminonaphthalene provided **1**^{Bdan} (**1j**) in 68% yield. Diols with acid sensitive groups such as ethers (e.g., 3-phenoxypropane-1,2-diol, **1k**) and monosaccharides were not tolerated under the reaction conditions, producing intractable mixtures of product.

3. Materials and Methods

3.1 General Methods

All commercially available compounds were used as received, and all were purchased from either Oakwood chemicals, Alfa Aesar, or Fisher chemicals. **1**^{pin} was prepared according to literature precedent [40]. DABO methyl boronate was prepared based on literature precedent and matched previous spectroscopic characterization [35,41]. ^{1}H, ^{13}C, and ^{11}B NMR spectra were recorded on JEOL 400 MHz and Varian INOVA 600 MHz NMR spectrometers, and all deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. Chemical shifts (δ) are given in parts per million and referenced relative to tetramethylsilane (0.0 ppm for $CDCl_3$) or to residual proteo solvent (1.94 or 3.31 ppm for CD_3CN and CD_3OD, respectively), CD_3CN or CD_3OD (1.30 or 49.30 ppm for ^{13}C), and internal (capillary) $BF_3 \bullet OEt_2$ (32.1 ppm). ^{11}B NMR spectra were recorded using quartz NMR tubes purchased from Wilmad. High-resolution mass spectra were recorded on a Thermofisher Scientific Q-Exactive Mass Spectrometer with samples dissolved in methanol (Fisher Optima grade).

*3.2 General procedure for preparing spirocyclic boralactonate salt **[1**^{pin}**][DIPEA-H]***

A 20 mL scintillation vial was charged with *pinB*-ibuprofen **1**^{pin} (1 equiv, 0.1 mmol, 33.1 mg) and *N,N*-diisopropylethylamine (1.1 equiv, 0.11 mmol, 19 μL). Diethyl ether (2 mL) was added to the vial, and the resulting suspension was stirred at ambient temperature for 1 hour. The resulting solution was concentrated under vacuum providing a yellow oil. The oil was dissolved in CD_3OD and analyzed by ^{1}H and ^{11}B NMR spectroscopy. The salt was used without further purification.

^{1}H NMR (400 MHz, CD_3OD) δ 7.18 – 7.11 (m, 2H), 7.08 – 7.00 (m, 2H), 3.85 – 3.59 (m, 1H), 3.58 – 3.50 (m, 2H), 3.04 (d, *J* 7.4, 2H), 2.43 (d, *J* 7.2, 2H), 1.83 (hept, *J* 6.8, 1H), 1.45 (s, 2H), 1.28 (m, 20 H), 1.22 – 1.07 (m, 1H), 0.89 (d, *J* 6.6, 6H), 0.75 – 0.62 (m, 1H). **^{11}B NMR** (128 MHz, CD_3OD) δ 15.8.

*3.3 General procedure for synthesis of diethanolamine boronate ibuprofen **1**^{DEA}*

A 20 mL scintillation vial was charged with *pinB*-ibuprofen **1**^{pin} (1 equiv, 0.1 mmol, 33.1 mg), *N,N*-diisopropylethylamine (1.1 equiv, 0.11 mmol, 19 μL), and diethanolamine (3 equiv, 0.3 mmol, 31.5 mg). Diethyl ether (2 mL) was added to the vial, the vial was sealed with a Teflon cap, and the resulting suspension was stirred at 50℃ for 4 hours. After 4 hours, a white fine powder was vacuum filtered, washed with excess diethyl ether to remove impurities, and further dried in vacuo to provide the diethanolamine boronate ibuprofen diethanolamine adduct.

1^{DEA}**:** White solid, 80% **yield** (25.6 mg). **^{1}H NMR** (600 MHz, CD_3OD) δ 7.15 – 7.11 (m, 2H), 7.03 (d, *J* = 7.8 Hz, 2H), 3.81 – 3.76 (m, 4H), 3.65 (t, *J* = 9.5 Hz, 1H), 3.13 (t, *J* = 5.3 Hz, 4H), 2.42 (d, *J* = 7.2 Hz, 2H), 1.82 (hept, *J* = 6.7 Hz, 1H), 1.13 (dd, *J* = 13.7, 10.0 Hz, 1H), 0.88 (d, *J* = 6.7 Hz, 6H), 0.69 (dd, *J* = 13.7, 8.9 Hz, 1H). **^{13}C NMR** (101 MHz, CD_3OD) δ 186.7, 142.9, 140.2, 130.0, 128.9, 57.7, 51.8, 50.3, 46.1, 31.5, 22.7. **^{11}B NMR** (128 MHz, CD_3OD) δ 9.4. HRMS (ESI) m/z 320.2021 [$C_{17}H_{26}BNO_4^-$ $(M+H)^-$ requires 320.2028].

*3.4 General procedure for preparing bora-ibuprofen derivatives **1a-j***

A 20 mL scintillation vial was charged with *bora*-ibuprofen diethanolamine adduct ***1***^{DEA} (1 equiv, 0.1 mmol, 31.9 mg) and diol/diamine (1.1 equiv, 0.11 mmol). Diethyl ether (2 mL) and 0.1 M HCl (2 mL) were added to the vial, and the resulting suspension was stirred at ambient temperature for 2 hours. The biphasic solution was added to a 15 mL separatory funnel, and then extracted with diethyl ether (3 × 4 mL). The combined organic extracts were washed with saturated sodium chloride (4 mL) and dried with sodium sulfate. Organic solvent was removed under reduced pressure to obtain desired product. The

compound was further dried in vacuo and, if necessary, purified by recrystallization from *n*-heptane at room temperature.

1a: White solid, 82% **yield** (23.8 mg). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.19 (d, *J* = 7.7 Hz, 2H), 7.06 (d, *J* = 7.7 Hz, 2H), 3.95 – 3.86 (m, 4H), 3.76 (dd, *J* = 10.1, 6.0 Hz, 1H), 2.42 (d, *J* = 7.2 Hz, 2H), 1.88 – 1.77 (m, 2H), 1.49 (dd, *J* = 16.0, 10.2 Hz, 1H), 1.16 – 1.09 (m, 1H), 0.87 (dd, *J* = 6.6, 1.0 Hz, 7H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 180.1, 140.4, 138.1, 129.3, 127.5, 77.3, 77.2, 77.0, 76.7, 61.7, 46.3, 45.1, 30.2, 27.2, 22.4. **^{11}B NMR** (128 MHz, $CDCl_3$) δ 31.7. **HRMS (ESI) m/z** 289.1622 [$C_{16}H_{23}BO_4^-$ (M-H)$^-$ requires 289.1617].

1b: White solid, 81% **yield** (24.5 mg). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.24 – 7.18 (m, 2H), 7.09 – 7.04 (m, 2H), 3.88 (dddd, *J* = 11.0, 6.5, 4.4, 2.1 Hz, 2H), 3.77 (dd, *J* = 10.0, 6.2 Hz, 1H), 3.47 (dt, *J* = 11.0, 9.4 Hz, 2H), 2.43 (d, *J* = 7.2 Hz, 2H), 2.03 – 1.94 (m, 1H), 1.83 (hept, *J* = 6.7 Hz, 1H), 1.50 (dd, *J* = 15.9, 10.0 Hz, 1H), 1.18 – 1.09 (m, 1H), 0.88 (dd, *J* = 6.6, 1.0 Hz, 6H), 0.80 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.2, 181.1, 140.4, 138.1, 129.2, 127.6, 127.5, 83.4, 77.4, 77.2, 77.0, 76.7, 67.6, 46.4, 45.1, 31.2, 30.9, 30.2, 29.7, 24.6, 24.5, 22.4, 19.5, 12.6. **^{11}B NMR** (128 MHz, $CDCl_3$) δ 28.7. **HRMS (ESI) m/z** 303.1777 [$C_{17}H_{25}BO_4^-$ (M-H)$^-$ requires 303.1773].

1c: White solid, 85% **yield** (27.1 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 – 7.18 (m, 2H), 7.08 – 7.03 (m, 2H), 3.79 (dd, *J* = 9.6, 6.6 Hz, 1H), 3.52 (s, 4H), 2.42 (s, 2H), 1.82 (hept, *J* = 6.7 Hz, 1H), 1.52 (dd, *J* = 16.0, 9.6 Hz, 1H), 1.19 (dd, *J* = 16.0, 6.7 Hz, 1H), 0.87 (d, *J* = 6.6 Hz, 6H), 0.83 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.5, 140.4, 138.0, 129.2, 127.5, 77.3, 77.0, 76.7, 72.0, 46.2, 45.0, 31.6, 30.1, 22.4, 22.3, 21.7. **^{11}B NMR** (128 MHz, $CDCl_3$) δ 30.2. **HRMS (ESI) m/z** 341.1895 [$C_{18}H_{27}BO_4$+Na (M+Na)$^+$ requires 341.1985].

1d: White solid, 78% **yield** (27.1 mg). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.23 – 7.19 (m, 2H), 7.08 – 7.03 (m, 2H), 3.78 (dd, *J* = 9.5, 6.7 Hz, 1H), 3.59 (ddd, *J* = 11.1, 4.4, 1.5 Hz, 2H), 3.51 (ddd, *J* = 11.3, 7.6, 1.5 Hz, 2H), 2.42 (d, *J* = 7.1 Hz, 2H), 1.82 (dp, *J* = 13.5, 6.8 Hz, 1H), 1.51 (dd, *J* = 16.0, 9.5 Hz, 1H), 1.20 (tdd, *J* = 11.0, 8.4, 5.4 Hz, 3H), 1.16 – 1.10 (m, 2H), 0.88 (d, *J* = 6.6 Hz, 7H), 0.85 (t, *J* = 7.1 Hz, 4H), 0.78 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 180.9, 140.5, 138.1, 129.3, 129.3, 127.6, 77.4, 77.1, 76.8, 70.9, 70.9, 46.4, 45.2, 37.1, 34.3, 30.2, 22.5, 18.9, 16.4, 14.9. **^{11}B NMR** (128 MHz, $CDCl_3$) δ 28.3. **HRMS (ESI) m/z** 345.2244 [$C_{20}H_{31}BO_4^-$ (M-H)$^-$ requires 345.2243].

1e: White solid, 79% **yield** (32.7 mg). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.25 (s, 1H), 7.13 (2 H, d, *J* 8.0), 7.06 (2 H, d, *J* 8.0), 4.84 (2 H, dd, *J* 13.2, 2.9), 4.31 (2 H, t, *J* 12.3), 3.76 (1 H, dd, *J* 10.5, 6.0), 2.42 (2 H, d, *J* 7.2), 1.82 (1 H, hept, *J* 6.7), 1.48 (1 H, dd, *J* 16.1, 10.4), 1.17 (1 H, dd, *J* 16.1, 6.0), 0.88 (6 H, d, *J* 6.6). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 180.6, 140.9, 137.4, 129.8, 129.5, 128.1, 127.5, 127.3, 83.4, 67.0, 46.3, 45.1, 30.2, 22.5, 19.0. **^{11}B NMR** (128 MHz, $CDCl_3$) δ 33.4. **HRMS (ESI) m/z** 412.0571 [$C_{16}H_{21}BBrNO_6^-$ (M-H)$^-$ requires 412.0573]. **Melting point:** 141-148°C

1f: White solid, 70% **yield** (20.4 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) 7.19 (2 H, d, *J* 7.9), 7.05 (2 H, dd, *J* 7.8, 5.2), 4.19 (1 H, t, *J* 8.3), 3.82 (1 H, dt, *J* 9.0, 6.8), 3.63 (1 H, q, *J* 7.5), 2.41 (2 H, dd, *J* 7.2, 2.9), 1.82 (1 H, dp, *J* 12.9, 6.3), 1.56 (1 H, ddd, *J* 32.5, 16.0, 9.4), 1.28 (1 H, dd, *J* 16.0, 7.6), 1.20 (2 H, t, *J* 6.6), 1.11 (4 H, d, *J* 5.0), 0.86 (6 H, dd, *J* 6.7, 4.4). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.6, 140.6, 137.5, 129.3, 129.2, 127.5, 127.4, 83.3, 73.2, 72.1, 46.3, 45.0, 30.1, 30.1, 24.6, 24.5, 22.4, 22.3, 22.3, 21.5, -0.04. **^{11}B NMR** (128 MHz, $CDCl_3$) δ 34.6. **HRMS (ESI) m/z** 289.1620 [$C_{16}H_{23}BO_4^-$ (M-H)$^-$ requires 289.1617].

1g: White solid, 75% **yield** (24.3 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 7.8 Hz, 2H), 7.08 (d, *J* = 7.8 Hz, 2H), 4.64 – 4.52 (m, 1H), 4.27 – 4.18 (m, 1H), 4.01 (ddd, *J* = 9.2, 7.5, 5.7 Hz, 1H), 3.85 (dd, *J* = 9.6, 6.6 Hz, 1H), 3.55 – 3.38 (m, 2H), 2.44 (d, *J* = 7.2 Hz, 2H), 1.84

(dp, *J* = 13.5, 6.8 Hz, 1H), 1.64 (ddd, *J* = 16.2, 9.8, 2.3 Hz, 1H), 1.39 – 1.23 (m, 1H), 0.89 (d, *J* = 6.6 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 180.4, 141.0, 137.5, 129.6, 127.6, 127.6, 68.7, 46.5, 46.5, 46.2, 45.2, 30.3, 22.6, 15.3. **^{11}B NMR** (128 MHz, $CDCl_3$) δ 33.0. **HRMS (ESI) m/z** 323.1230 [$C_{16}H_{22}BClO^-$ (M-H)$^-$ requires 323.1227].

1h: White solid, 93% yield (39.8 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) 7.30 (8 H, tdd, *J* 9.1, 4.8, 2.2), 7.24 – 7.05 (7 H, m), 5.07 (2 H, s), 4.11 – 3.97 (1 H, m), 2.50 (2 H, dd, *J* 7.2, 3.0), 2.00 – 1.76 (2 H, m), 1.61 (1 H, ddd, *J* 15.9, 14.2, 7.5), 1.01 – 0.87 (6 H, m).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.6, 140.8, 140.3, 137.5, 129.4, 128.7, 128.2, 128.1, 127.9, 127.7, 127.6, 126.9, 125.8, 125.7, 86.5, 79.1, 46.5, 45.1, 30.2, 22.4. **^{11}B NMR** (128 MHz, $CDCl_3$) δ 33.7. **HRMS (ESI) m/z** 427.2084 [$C_{27}H_{29}BO_4^-$ (M-H)$^-$ requires 427.2086]. **Melting point:** 149-152 ℃

1i: White solid, 78% **yield** (22.5 mg). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.24 – 7.20 (m, 2H), 7.10 – 7.05 (m, 2H), 4.31 – 4.25 (m, 2H), 3.86 (dd, *J* = 9.2, 7.3 Hz, 1H), 2.43 (d, *J* = 7.1 Hz, 2H), 1.83 (dp, *J* = 13.5, 6.7 Hz, 1H), 1.68 (ddd, *J* = 13.8, 9.2, 4.5 Hz, 2H), 1.61 (dd, *J* = 16.1, 9.2 Hz, 1H), 1.52 (s, 2H), 1.41 – 1.32 (m, 3H), 1.29 – 1.19 (m, 2H), 0.90 – 0.86 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 180.3, 140.7, 137.5, 129.3, 127.5, 77.3, 77.2, 77.0, 76.7, 75.2, 46.4, 45.0, 30.2, 28.3, 22.4, 19.0. **^{11}B NMR** (128 MHz, $CDCl_3$) δ 33.4. **HRMS (ESI) m/z** 329.1936 [$C_{19}H_{27}BO_4^-$ (M-H)$^-$ requires 329.1930]. **Melting point:** 136-140 ℃

1j: Orange oil, 68% **yield** (25.4 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) 7.28 – 7.24 (2 H, m), 7.22 – 7.18 (1 H, m), 7.17 – 7.09 (3 H, m), 7.03 (2 H, dd, *J* 8.3, 7.2), 6.96 (2 H, d, *J* 8.2), 6.47 (1 H, dd, *J* 7.2, 1.1), 6.14 (2 H, d, *J* 7.2), 5.47 (2 H, s), 3.76 (1 H, t, *J* 7.9), 2.45 (2 H, d, *J* 7.2), 1.83 (1 H, dq, *J* 13.4, 6.7), 1.59 (1 H, dd, *J* 15.3, 7.5), 1.48 – 1.40 (1 H, m), 0.89 (7 H, d, *J* 6.6). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.7, 141.4, 140.9, 140.3, 137.1, 136.3, 134.7, 129.8, 129.2, 128.4, 127.6, 127.6, 127.1, 119.7, 117.6, 117.3, 113.1, 106.1, 105.8, 64.7, 47.2, 45.1, 32.0, 30.3, 29.0, 22.8, 22.5, 14.3. **^{11}B NMR** (128 MHz, $CDCl_3$) δ 31.6. **HRMS (ESI) m/z** 371.1939 [$C_{23}H_{25}BN_2O_2^-$ (M-H)$^-$ requires 371.1936].

4. Conclusions

In this work, we have outlined a methodology to achieve pinacol deprotection from *pinB*-ibuprofen via transesterification with DEA. Characterization of the DEA adduct unexpectedly that it did not adopt the DABO boronate structure but rather the DEA boralactonate zwitterionic structure. The DEA adduct is bench stable and amenable to subsequent synthetic elaboration via DEA hydrolysis under acidic aqueous biphasic conditions, likely forming ibuprofen boronic acid species, which can be functionalized via esterification/amination by addition of diol or diamine to the biphasic reaction. Boron containing ibuprofen derivatives with 1,2-diol and 1,3-diol motifs and 1,2-diaminonaphthalene were synthesized in moderate to excellent yields. This work paves the way for broader library syntheses to commence with an aim toward utilizing these organoboron carboxylic acids in catalysis and medicinal chemistry. Given the importance of NSAIDs in pain management and other disease pathways [39-41] and recognizing their well-known side effects [42-44], boron containing NSAIDs may reveal new therapeutic opportunities [10-11].

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figure S1-S40: NMR spectra; Table S1: Selected crystallographic and refinement parameters.

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Data Availability Statement: X-ray crystallography data can be found through the CCDC (2225404, **1e**). All other data can be found in the **Supplementary Materials**.

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