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IBUPROFEN AND NAPROXEN *VIA* ORGANOBORANES[1]

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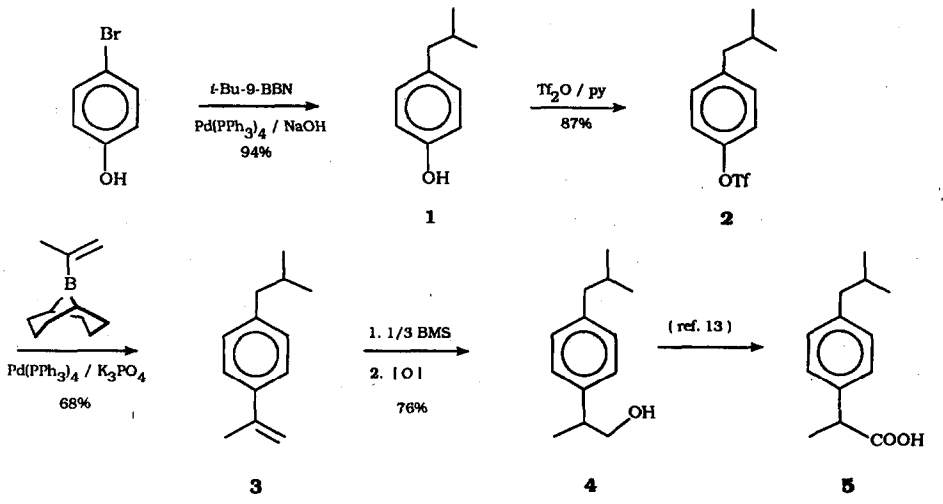
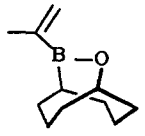
Abstract. *The sequential Pd-catalyzed couplings of aryl bromides and triflates with the appropriate organoboranes provide the key steps in new synthetic routes to both ibuprofen and naproxen in racemic form.*

Non-steroidal antiinflammatory agents such as ibuprofen (**5**) and naproxen (**11**) are members of a family of 2-arylpropanoic acids which, through cyclooxygenase inhibition by the S enantiomer, prevent the generation of prostaglandins and thromboxane A_2 *via* the arachidonic acid cascade. Electrophilic reactions are traditionally employed to attach the aliphatic appendages to the aromatic nucleus with additional steps often required to complete the carbon skeleton.[4] More recent organometallic-based syntheses have provided these pharmaceuticals in both racemic and optically active form.[4] In this Letter, we highlight the versatility of organoboranes by demonstrating that these intermediates,[5] through the Suzuki coupling,[6] can be generally employed to construct all of the key carbon-carbon bonds in these systems. For this purpose, 9-BBN derivatives were chosen because they are easily prepared in pure form as stable compounds and the 9-BBN ring system does not interfere with the coupling process.[6,7] Our all-boron approach to racemic ibuprofen is outlined in Scheme 1.

Scheme 1.



Organoboranes which contain 1°-alkyl groups, even those with β-branching, require no special palladium catalyst[5e,6c] to undergo clean cross coupling with aromatic (or vinylic) bromides.[6c,7e] Thus, employing $Pd(PPh_3)_4$ (1.8%), the coupling of excess *B*-*i*-Bu-9-BBN[8] with *p*-bromophenol (1.4:1) produces **1** cleanly (16 h, THF, 2.5 equiv 6.0 M NaOH) in excellent isolated yield (94%).[9] Because the hydroboration of isobutylene with borane-dimethyl sulfide (BMS) gives $B(i\text{-}Bu)_3$ without regioisomers,[8] we also examined the process with this borane which, even with a 1.2:1 stoichiometry, gives a lower yield of **1** (66%) with a minor amount (*ca.* 5%) of phenol detected as a reaction by-product. The straightforward conversion of **1** to its triflate, **2**, (Tf_2O, Py, CH_2Cl_2, 0 °C, 0.5 h) proved very efficient (87%). The cross coupling of **2** to *B*-isopropenyl-9-BBN[10] (**6**) under similar conditions[6a] gives the desired α-methylstyrene, **3** in 68% yield completing the construction of the ibuprofen carbon skeleton.[11] A similar result (73%) was also obtained for **3** from **2** employing the ring-oxidized borinate ester, 10-isopropenyl-9-oxa-10-borabicyclo[3.3.2]decane (**7**).[12]



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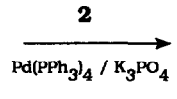

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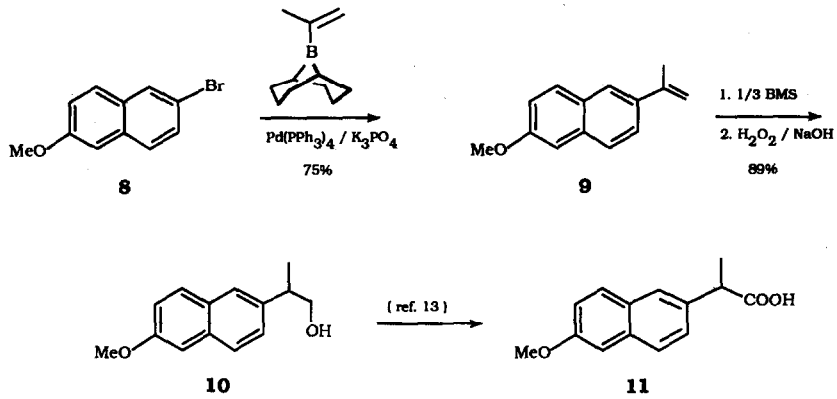
With only a modest increase in yield, the major advantage in employing **7** rather than **6** is that these borinate esters are much easier to handle because of their resistance to undergo further oxidation upon exposure to atmospheric oxygen.[15]

While the hydroboration/oxidation of **3** with $NaBH_4/BF_3$-EE is known to give **4**,[13] we chose to examine the use of the more convenient reagent, BMS, which smoothly hydroborates **3**, proceeding to the trialkylborane stage (^{11}B NMR δ 89.7 ppm) with a 1:3 stoichiometry. Even on a 2.5 mmol reaction scale, after oxidation, pure **4** is efficiently isolated by distillation (76%). The further basic Pd-catalyzed oxidation of **4** to **5** with molecular oxygen is an established process which gives excellent product yields (*i.e.* 92%).[13]

Pleased with the success of the new boron-based approach to ibuprofen, we applied this methodology to racemic naproxen (Scheme 2), coupling **6** with 2-bromo-6-methoxynaphthalene (**8**) to obtain the desired isopropenyl derivative **9** cleanly in 75% yield. As for **4**, **9** was efficiently (89%) converted to the corresponding primary alcohol **10** with the BMS hydroboration/oxidation sequence, thereby also completing the formal synthesis of (±)-naproxen (**11**). Through these studies, a new totally boron-based approach to important non-steroidal antiinflammatory agents in racemic form has been developed, a process which appears to be quite general for the preparation of 2-arylpropanoic acids.

Scheme 2.



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1. Dedicated to Professor Herbert C. Brown on the occasion of his 80th birthday.

2. Graduate student supported by the NSF EPSCoR Program of Puerto Rico.

3. Graduate student supported by the NIH-MBRS Program (RR08102).

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8. Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic Press: London, 1988 and references cited therein. A stoichiometric amount of *B*-*i*-Bu-9-BBN results in unreacted *p*-BrC_6H_4OH.

9. While the triflate derivative of *p*-bromophenol is known to undergo selective coupling with the bromide,[6a] we prefer using the phenol which eliminates the possibility of either competitive reactivity or dialkylation.

10. Prepared in 50% yield from the addition of isopropenylmagnesiun bromide in THF to *B*-methoxy-9-BBN at -78 °C followed by a pentane work-up (bp 39-43 °C, 0.2 Torr). ^{1}H NMR ($CDCl_3$) δ 1.65-1.76 (m, 2H), 1.8-2.0 (m, 15H), 5.75 (bs, 1H), 5.93 (dq, *J* = 4.0, 1.4 Hz, 1 H); ^{13}C NMR δ 21.5, 23.3, 29.4 (b), 33.7, 129.8, 149.5 (b); ^{11}B NMR δ 79 ppm. Several attempts were also made to prepare this vinylborane from isopropenyllithium (metal/halogen exchange), but these gave less satisfactory results. Our recent approach to Markovnikov vinylboranes leads to a ring-expansion product rather than to **6**.[14]

11. The preparation of **3** is representative of the cross coupling procedures followed: To a mixture of **2** (2.00 g, 7.1 mmol), $Pd(PPh_3)_4$ (0.2 g, 0.2 mmol), K_3PO_4 (2.97 g, 14.0 mmol), and THF (25 mL), was added **6** (1.9 g, 11.7 mmol) and the stirred mixture was heated at reflux temperature for 18 h. Oxidation was carried out with the successive addition of NaOH (5 mL, 3 M) and 30% H_2O_2 (5 mL), dropwise. After cooling to 25 °C, addition of pentane (75 mL), separation and extraction of the organic layer with water (20 X 20 mL) followed by elution through neutral alumina with pentane, gave, after concentration and distillation at 0.25 Torr, 0.83 g (68%) of **3**[13] (bp 72-3 °C). ^{1}H NMR ($CDCl_3$) δ 1.10 (d, *J* = 6.6 Hz, 6H), 2.05 (sept, *J* = 6.6 Hz, 1H), 2.33 (s, 3H), 2.65 (d, *J* = 7.2 Hz, 2H), 5.22 (d, *J* = 1.0 Hz, 1H), 5.55 (s, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR δ 21.8, 22.4, 30.2, 45.1, 111.5, 125.2, 128.9, 140.9, 143.0 ppm. MS *m/e* 174 (M^+, 15), 131 (100).

12. Prepared in 79% yield from the Me_3NO oxidation[15] of **6** in CH_2Cl_2 at 0 °C followed by distillation (bp 70-73 °C, 0.65 Torr). ^{1}H NMR ($CDCl_3$) δ 1.35-2.05 (m, 16H), 4.62 (bs, 1H), 5.68 (s, 2H); ^{13}C NMR δ 20.8, 22.1, 22.3, 26.3, 31.8, 73.4, 129.1, 147.5 (b); ^{11}B NMR δ 47.5 ppm.

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