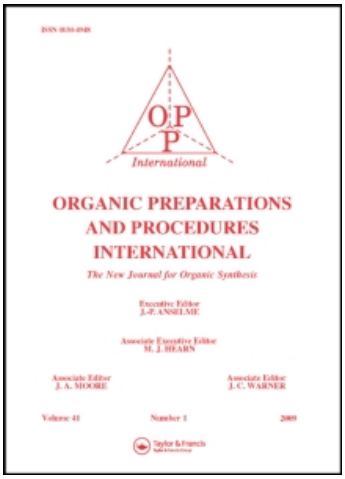

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PRACTICAL PROCEDURE FOR THE PREPARATION OF FUNCTIONALIZED (*E*)-1-ALKENYLBORONIC ACIDS INCLUDING THE UNPRECEDENTED 1-ALKOXYCARBONYL DERIVATIVES

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PRACTICAL PROCEDURE FOR THE PREPARATION OF FUNCTIONALIZED (*E*)-1-ALKENYLBORONIC ACIDS INCLUDING THE UNPRECEDENTED 1-ALKOXYCARBONYL DERIVATIVES

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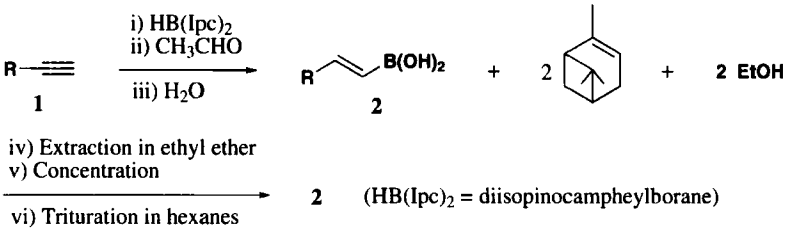
In recent years, boronic acids have gained significant importance in organic synthesis. The synthetic applications of these compounds include the Suzuki-Miyaura cross-coupling reaction,[1] the rhodium-catalyzed addition onto aldehydes[2] and alkenes,[3] the copper diacetate-promoted cross-coupling reactions involving amines, alcohols,[4] and thiols,[5] as well as the borono-Mannich reaction.[6] Both aryl- and alkenylboronic acids can participate in these reactions; however, the challenge posed by the isolation of alkenylboronic acids has significantly hampered their use. Indeed, most alkenylboronic acids are unstable under conventional purification conditions and their corresponding esters, although stable, are not suitable for some synthetic applications.[4-6] As part of our ongoing program on the applications of unsaturated boronic acids in organic synthesis,[7] we became interested in developing a convenient and general procedure for the preparation and isolation of free alkenylboronic acids that could complement our solid-phase capture approach.[8]

Typically, (*E*)-1-alkenylboronic acids are accessed through hydroboration of the corresponding terminal alkynes. However, the most common methods used for this purpose suffer from chemo- and regioselectivity problems. For example, catecholborane,[9] which constitutes the reagent of choice to effect these transformations, does not tolerate acetal or ether functionalities at the propargylic carbon.[10,11] Moreover, hydrolysis of the boronate following catecholboration yields an equimolar amount of acidic catechol, which must be removed by recrystallization in water. In our hands, this isolation method proved difficult and not always reliable. Dibromoborane-methyl sulfide complex[12] or the haloborane/silane combination,[13] on the other hand, conveniently give access to (*E*)-1-alkenylboronic acids bearing simple alkyl or aryl substituents. However, these reagents do not tolerate most other functionalities. In sharp contrast, dicyclohexylborane constitutes a mild alkyne hydroboration reagent, but the reaction is limited mainly

to the preparation of boronates. Typically, hydroboration using dicyclohexylborane is followed by a selective oxidation with trimethylamine *N*-oxide, and treatment with a diol gives a boronic ester accompanied by cyclohexanol as by-product, which must be removed by distillation.[10] Likewise, diisopinocampheylborane has proven to be a mild and chemoselective hydroboration reagent,[14] albeit this method has also been used mainly for the preparation of boronic esters[15] by *in-situ* transesterification of the diethylboronic ester intermediate with appropriate diols. Here again, a distillation is required to separate the pinene by-product generated during the oxidative dealkylation work-up[15] with acetaldehyde.[11,16] It is noteworthy that some alkenylboronic acids were shown to undergo partial *E/Z* isomerization when distilled.[17] Herein, we report that the diisopinocampheylboration method yields several useful (*E*)-1-alkenylboronic acids in high purity through a simple and practical distillation-free procedure involving hydrolysis of the labile diethylboronic ester intermediate, followed by partition and trituration with the appropriate solvent mixture. Of particular interest is the isolation of the hitherto unknown and potentially useful 1-alkoxycarbonyl 1-alkenylboronic acids.

Various alkynes (**1**) were subjected to hydroboration with diisopinocampheylborane, followed by oxidative dealkylation using acetaldehyde to afford diethyl boronic esters, which are treated *in situ* with water followed by extraction of the reaction mixture using diethylether (*Scheme 1*). We found that most alkenylboronic acids (**2**) had limited solubility in ethyl ether and

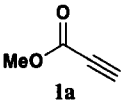
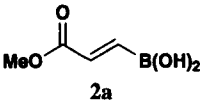
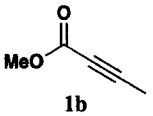
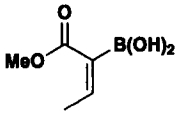
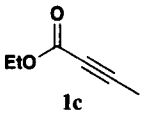
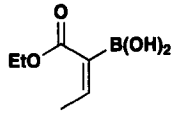
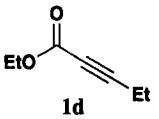
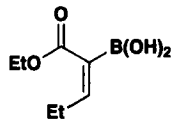
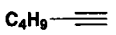
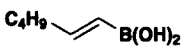
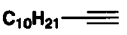
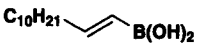
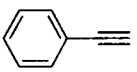
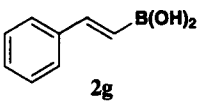
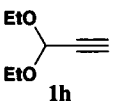
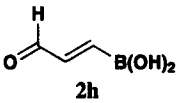
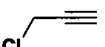
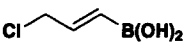
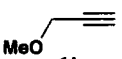
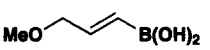


Scheme 1

could be easily purified by concentration of the ethereal solution, followed by trituration of the precipitate with hexanes or cold dichloromethane. The latter operation eliminated all residual pinene and afforded the corresponding boronic acids (**2a-j**) in good to excellent yield and in high purity according to NMR analysis (*Table*).

All products were obtained as air-stable white solids, and ^{1}H NMR analysis of the isolated boronic acids indicated the presence of a single regioisomer. Interestingly, we observed a complete reversal of regioselectivity between *entries 1* and *2*, indicating a competition between steric and electronic factors in the hydroboration of these alkynes. The preparation and stability of the 1-alkoxycarbonyl 1-alkenylboronic acids **2b-2d**, seemingly unprecedented according to compound databases, is particularly significant because the corresponding saturated derivatives are known to rearrange spontaneously through a 1,3-carbon-to-oxygen migration of boron.[18] The mild distillation-free procedure allows the isolation of these novel 2-boronoacrylate derivatives,

Table. Preparation of (*E*)-1-Alkenylboronic Acids

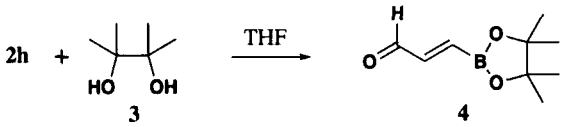
Entry	Alkyne	Product[a]	Yield (%)[b]
1	 **1a**	 **2a**	70
2	 **1b**	 **2b**	49
3	 **1c**	 **2c**	64
4	 **1d**	 **2d**	62
5	 **1e**	 **2e**	51
6	 **1f**	 **2f**	61
7	 **1g**	 **2g**	80
8	 **1h**	 **2h**	84
9	 **1i**	 **2i**	51
10	 **1j**	 **2j**	84

a) Obtained as a mixture of boronic acid/boronic anhydride, which is inconsequential for most synthetic applications. b) Yield of isolated, pure product.

which are potentially useful substrates in organic synthesis. This simple procedure also allowed the preparation of other highly functionalized alkenylboronic acids such as **2h-2j**. It is note-

worthy that 3-boronoacrolein (**2h**) was obtained directly as the free aldehyde, following *in situ* hydrolysis of the diethyl acetal.

This approach also greatly facilitates access to pure alkenylboronates following simple protection with any desired diol (*Scheme 2*). For example, boronoacrolein pinacolate **4**, which has found great applications in hetero-Diels-Alder reactions,[7] is easily obtained in pure form by condensation of boronic acid **2h** with pinacol (**3**) without the need for any distillation or chromatographic purification. It is worth noting that **4** could only be prepared in 31% yield after two difficult distillations by previous methods,[11] further highlighting the efficiency of our procedure.



Scheme 2

In conclusion, we have developed a convenient distillation-free isolation procedure to facilitate the preparation of free (*E*)-1-alkenylboronic acids in high purity. The new protocol gives direct access to various functionalized (*E*)-1-alkenylboronic acids, including 3-boronoacrolein (**4**), through an efficient work-up procedure featuring an extraction in ethyl ether followed by a high yielding trituration in hexanes. The preparation and surprising stability of the unprecedented 1-alkoxycarbonyl 1-alkenylboronic acids **2b-2d** is particularly significant. The synthetic utility of these new 2-boronoacrylates and other 1-alkenylboronic acid derivatives is presently under investigation in our laboratories and will be reported in due course.

EXPERIMENTAL SECTION

All reactions were run under an argon atmosphere. Dried tetrahydrofuran was obtained by distillation over sodium/benzophenone ketyl. Commercially available alkynes were bulb-to-bulb distilled prior to use in the hydroboration reactions. NMR spectra were recorded on Bruker AM 300, Bruker AM 200, Varian i300, Varian i400, or Varian i500 MHz instruments. For ^{1}H NMR spectra, the uncertainty on the coupling constant is estimated to be 0.4-0.8 Hz. Due to their very low intensity, ^{13}C signals arising from the carbon bearing the boronic acid group were usually missing and were therefore not listed. Elemental analyses were not obtained as it is well known that boronic acids obtained from mixed aqueous organic solutions exist as variable mixtures of free acid and the corresponding boroxines.[19] Electrospray mass spectrometry was performed using Hewlett-Packard 1100 and ZabSpecETOF systems. Electron impact mass spectrometry was performed using a Kratos MS-50 instrument. Fourier-transform infrared spectroscopy was performed on a Nicolet 750 magna instrument. Melting points were determined using a Gallenkamp apparatus.

General Procedure for the Preparation of Boronic Acids (2a-j).- (*R*)-(+)-α-Pinene (91% ee, 3.18 mL, 20.0 mmol) was slowly added to a solution of borane-dimethyl sulfide complex (1 mL, 10.0 mmol) in THF (2 mL) at 0°C. The solution was warmed up to room temperature and stirred

for two hours. The resulting thick white suspension was cooled to –40°C and the alkyne (10.0 mmol) was added dropwise. The mixture was allowed to warm up to room temperature and stirred for 2 to 24 hours. The resulting solution was cooled to 0°C and freshly distilled acetaldehyde (8 mL) was slowly added. The mixture was then refluxed for 16 hours at 45°C, then water (15 mL) was added at 0°C. The biphasic mixture was vigorously stirred for 3 hours and the top organic layer was decanted. The aqueous layer was extracted with 3 times with 30 mL of ether and/or one time with 30 mL of ethyl acetate, then the organic layers were combined and concentrated on a rotary evaporator. The resulting suspension was triturated in cold hexanes then filtered and rinsed with cold hexane or cold dichloromethane to yield the boronic acid **2** as a white solid. A second crop could be obtained by concentration of the filtrate and trituration in cold hexane. If the product was still colored, it could be washed with cold dichloromethane.

(*E*)-2-(Methoxycarbonyl)ethyl-1-enylboronic Acid (2a), white solid, mp 121-128°C. ^{1}H NMR (500 MHz, CD_3OD + 5% D_2O): δ 6.78 (d, J = 17.9 Hz, 1H), 6.48 (d, J = 18.1 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD + 5% D_2O): δ 168.6, 136.3, 52.4; FTIR (microscope) 3427, 3321, 2953, 1706 cm^{-1}; HRMS (EI, *m/z*): Calcd for $C_4H_7BO_4$: 130.0437. Found: 130.0438.

(*Z*)-1-(Methoxycarbonyl)prop-1-enylboronic Acid (2b), white solid, mp 89-93°C. ^{1}H NMR (400 MHz, CD_3OD + 5% D_2O): δ 6.90-6.70 (m, 1H), 3.72 (s, 3H), 1.92 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD + 5% D_2O): δ 173.0, 151.5, 131.3, 51.9, 17.4; FTIR (microscope) 3369, 3223, 2956, 1661 cm^{-1}; HRMS (EI, *m/z*): Calcd for $C_5H_9BO_4$: 144.0594 found 144.0595.

(*Z*)-1-(Ethoxycarbonyl)prop-1-enylboronic Acid (2c), white solid, mp 90-94°C. ^{1}H NMR (400 MHz, CD_3OD + 5% D_2O): δ 6.90-6.70 (m, 1H), 4.19 (q, J = 7.1 Hz, 2H), 1.92 (d, J = 7.0 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD + 5% D_2O): δ 172.8, 151.1, 61.7, 17.4, 14.6; FTIR (microscope): 3294, 3004, 2986, 1670 cm^{-1}; HRMS (EI, *m/z*): Calcd for $C_6H_{11}BO_4$: 158.0750. Found: 158.0752.

(*Z*)-1-(Ethoxycarbonyl)but-1-enylboronic Acid (2d), white solid, mp 63-67°C. ^{1}H NMR (300 MHz, CD_3OD + 5% D_2O): δ 6.80-6.56 (m, 1H), 4.19 (q, J = 7.1 Hz, 2H), 2.34 (q, J = 7.4 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.02 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD + 5% D_2O): δ 172.6, 158.5, 157.2, 61.6, 25.5, 14.6, 13.6; FTIR (microscope): 3379, 3259, 2977, 1665, 1328 cm^{-1}; HRMS (EI, *m/z*): Calcd for $C_7H_{13}BO_4$: 172.0907. Found 172.0909.

(*E*)-Hex-1-enylboronic Acid (2e),[12,20] white solid, mp 104-110°C. ^{1}H NMR (300 MHz, CD_3OD + 5% D_2O): δ 6.57-6.40 (m, 1H), 5.34 (d, J = 17.8 Hz, 1H), 2.19-2.06 (m, 2H), 1.45-1.25 (m, 4H) 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD + 5% D_2O): δ 152.5, 124.1, 36.4, 31.9, 23.2, 14.3; FTIR (microscope): 3178, 2929, 1638 cm^{-1}; HRMS (EI, *m/z*): Calcd for $C_6H_{13}BO_2$: 128.1009. Found: 128.1011.

(*E*)-Dodec-1-enylboronic Acid (2f), white solid, mp 84-90°C. ^{1}H NMR (500 MHz, CD_3OD + 5% D_2O): δ 6.55-6.43 (m, 1H), 5.35 (dt, J = 17.9, 1.4 Hz, 1H), 2.17-2.08 (m, 2H), 1.44-1.36 (m, 2H), 1.34-1.24 (m, 14H) 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD + 5% D_2O): δ 152.5, 36.9, 36.7, 33.0, 30.7, 30.6, 30.4, 30.3, 29.7, 23.7, 14.4; FTIR (microscope): 3457, 3334,

2922, 2848 cm^{-1}; HRMS (EI, *m/z*): Calcd for $C_{12}H_{25}BO_2$: 212.1948. Found: 212.1950.

(*E*)-Styrylboronic Acid (2g),[9,21] white solid, mp 145-148°C. ^1H NMR (400 MHz, CD_3OD + 5% D_2O): δ 7.50-7.45 (m, 2H), 7.34-7.22 (m, 4H), 6.15 (d, *J* = 13.5 Hz, 1H); ^{13}C (100 MHz, CD_3OD + 5% D_2O): δ 148.3, 148.2, 139.1, 129.6, 127.9; FTIR (film cast): 3020, 1615, 1574, 1493, 1438; HRMS (EI, *m/z*): Calcd for $C_8H_9BO_2$: 148.0696. Found: 148.0699.

(*E*)-3-Boronoacrolein (2h), white solid, mp 128-131°C. ^1H NMR (400 MHz, CD_3OD + 5% D_2O): δ 9.52 (d, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 18.0 Hz, 1H), 6.64 (dd, *J* = 18.0, 7.7 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD + 5% D_2O): δ 197.6, 145.6, 105.1; FTIR (film cast): 3175, 2850, 1673 cm^{-1}; HRMS (EI, *m/z*): Calcd for $C_3H_5BO_3$: 100.0332. Found: 100.0334.

(*E*)-3-Chloroprop-1-enylboronic Acid (2i), white solid, mp 110-112°C. ^1H NMR (400 MHz, CD_3OD + 5% D_2O): δ 6.50 (dt, *J* = 17.6, 6.1 Hz, 1H), 5.69 (d, *J* = 17.4 Hz, 1H), 4.11 (dd, *J* = 6.1 Hz, 1.3 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD + 5% D_2O): δ 145.4, 126.9, 47.0; FTIR (film cast): 3213, 1640 cm^{-1}; HRMS (EI, *m/z*): Calcd for $C_3H_6BClO_2$: 120.0155. Found: 120.0147.

(*E*)-3-Methoxyprop-1-enylboronic Acid (2j), white solid, mp 124-127°C. ^1H NMR (400 MHz, CD_3OD + 5% D_2O): δ 6.54-6.40 (m, 1H), 5.68-5.56 (m, 1H), 3.98-3.96 (m, 3H); ^{13}C NMR (100 MHz, CD_3OD + 5% D_2O): δ 146.9, 75.3, 58.4; FTIR (film cast): 3184, 2998 cm^{-1}; HRMS (EI, *m/z*): Calcd for $C_{12}H_{21}B_3O_6$: 294.1617. Found: 294.1628 (only boronic anhydride detected).

(*E*)-3-Boronoacrolein Pinacolate (4)[7b].- Boronic acid **2h** (1 g, 10.0 mmol) was dissolved in THF (25 mL) at room temperature and dry pinacol (recrystallized from dichloromethane) (1.12 g, 10.0 mmol) was added. The solution was stirred for 30 minutes, then the solvent was evaporated under reduced pressure at 45°C to afford boronate **4** as a colorless oil, which was used directly in the next step without further purification.

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