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Journal of Organometallic Chemistry 680 (2003) 263–270
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

Design of chiral boronate-substituted acrylanilides. Self-activation and boron-transmitted 1,8-stereoinduction in [4+2] cycloaddition

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Received 4 March 2003; accepted 17 April 2003

On the occasion of Professor Frederick Hawthorne's 75th birthday

Abstract

The [4+2] cycloaddition of *ortho*-boronoanilide dienophile **4** with cyclopentadiene was found to proceed faster than both its *para* isomer **8** and the unsubstituted derivative **6**, thereby confirming that self-activation by internal coordination is operative in the case of **4**. Chiral boronic esters derivatives **9**–**13** provided a small level of remote 1,8-stereoinduction transmitted through a putative tetrahedral stereogenic boronate complex. These results show that dialkoxyboronic esters can operate as weak, internal Lewis acids and activate carbonyl-containing functionalities in cycloaddition reactions.

Keywords: Lewis acids; Diels–Alder reactions; Boronate esters; Substituent effects; Chiral auxiliaries; Stereoselective synthesis; Remote stereoinduction

1. Introduction

Borate esters have long been used to activate and even influence the regioselectivity of phenoxy-derivatized quinones as dienophiles in [4+2] cycloadditions [1]. For example, through transesterification of the phenolic substituent in juglone, a modified dienophile is formed as a borate ester that can coordinate one of the quinone carbonyls and act as an internal Lewis acid to activate the dienophile component (Fig. 1). We envisaged that a similar concept could be extended to the useful class of acrylate dienophiles. We were particularly interested in investigating the potential role of a chiral boronic ester as an internal activator and as a source or a transmitter of remote stereoinduction [2,3] in a model Diels–Alder reaction using modified acrylamide dienophiles of type I (Fig. 1). Dialkoxyboronic esters are *a priori* very weak Lewis acids [4,5]. The possibility of employing chiral diols as boronate substituents, however, constitutes a potentially significant advantage in the use of boronic esters as Lewis acids for cycloadditions and other reactions. This article describes the design, synthesis and evaluation of several chiral boronate-substituted acrylamide dienophiles [6].

2. Results and discussion

2.1. Synthesis of a boronate-substituted acrylanilide dienophile

The ideal boronate-substituted acrylamide would be stable, and conjugated in such a way as to be easily hydrolyzed from the resulting cycloadducts to provide enantioenriched product. Due to the superior stability of aromatic boronates and the facilitated cleavage of anilides over the corresponding saturated amides, we decided to first consider borono-anilides of type I (Fig. 1). Thus, the pinacolboronate-substituted dienophile **4** required for studying the carbonyl activating effect of

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doi:10.1016/S0022-328X(03)00400-5

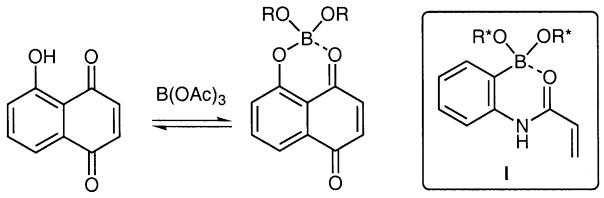


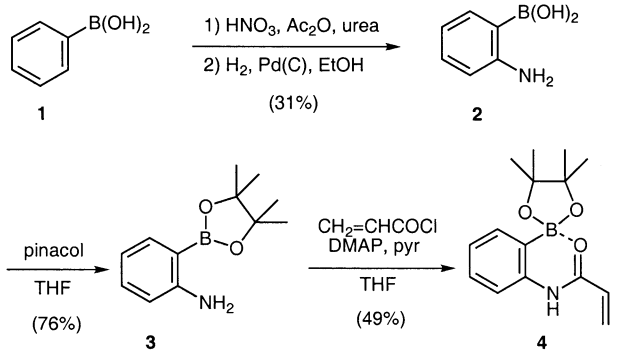
Fig. 1. Internal activation via boronic ester coordination.

the boronic ester was easily prepared in four steps from phenylboronic acid (Scheme 1).

Nitration of phenylboronic acid [7] followed by hydrogenation of the isolated *ortho* isomer [8] yielded aminoboronic acid **2**. Esterification of the boronic acid with pinacol furnished boronate **3**, which was reacted with acryloyl chloride to provide acrylanilide **4**. The corresponding dienophile **6** lacking the boronate group was also made as a reference compound [9] for a qualitative comparison of relative reaction rates in a model Diels–Alder reaction with cyclopentadiene.

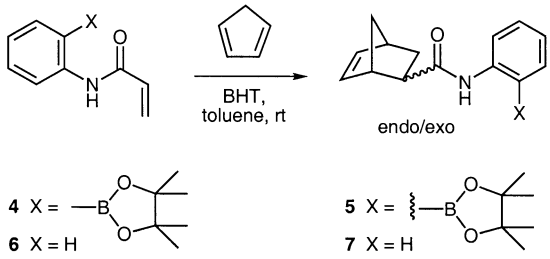
2.2. Comparative kinetic studies

To probe the effect of the boronate substituent, the [4+2] cycloaddition of dienophiles **4** and **6** with cyclopentadiene was studied by measuring ratios of starting materials to cycloadducts by ^{1}H-NMR analysis on crude reaction mixtures. Although dienophile **4** is more sterically hindered, the data show that it does react noticeably faster than **6** and with increased *endo*/*exo* selectivity in the resulting adducts **5** (Table 1). These results are consistent with a small self-activation effect by internal coordination between the boronic ester and the carbonyl group in dienophile **4**. To rule out the possibility that the activation may be due to the electron-withdrawing effect of the boronate group on the reactivity of the acrylamide dienophile, a competitive kinetic experiment was performed whereby **4** and the corresponding *para*-substituted isomer **8** were allowed to react simultaneously with excess cyclopentadiene (Scheme 2). The proportion of components in the reaction mixture showed the faster consumption and



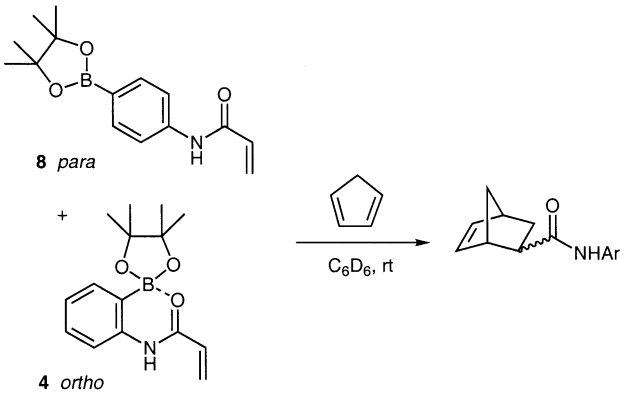
Scheme 1.

Table 1
Relative speed and *endo*/*exo* ratios from Diels–Alder reactions of **4** and **6** [a]



Time (h)	6		4	
	s.m.:adduct	*endo*:*exo*	s.m.:adduct	*endo*:*exo*
1	No reaction	2.7:1	3.8:1	
6	1:0.4	2.5:1	1.2:1	3.8:1
48	1:5	2.8:1	1:13	4.3:1

[a] Ratios of starting materials (s.m.) and cycloadducts were measured by ^{1}H-NMR spectroscopy on the crude reaction mixtures.



	para s.m.	:	*ortho* s.m.	:	*para* adducts	:	*ortho* adducts (%)[a]
Start point:	55	:	45	:	0	:	0
After 17 d:	43	:	11	:	10	:	36

[a] Relative percentages of components as measured by signal integration on proton NMR spectra of the crude reaction mixtures. (s.m. = starting material)

Scheme 2.

conversion to cycloadducts of **4** compared to **6**. This result further confirms that self-activation by internal coordination is operative in the case of *ortho*-substituted dienophile **4**.

2.3. Investigation of remote stereochemical induction in the cycloadducts

We then turned our attention towards evaluating the appealing possibility that internal coordination could serve at communicating stereochemistry in a long-range fashion. There are very few examples of remote stereoinduction beyond a 1,7 relative relationship between the

inducing center and the reactive one [2]. In the present case, 1,8-stereoinduction (as measured between the closest carbon atoms in the dienophilic component and the chiral boronate substituent in the absence of coordination) could be transmitted via internal carbonyl coordination to the boron atom. In this way, the resulting tetrahedral boronate, rendered stereogenic at boron, would involve a temporary situation of 1,4-stereoinduction. We imagined that known diol boronate auxiliaries such as pinanediol, 1,2-dicyclohexyl-1,2-ethanediol [10], 1,4-dimethoxy-1,1,4,4-tetraphenyl-2,3-butanediol [11], and Hoffmann's camphor-based diol [12] could be tested. Thus, the chiral dienophiles **9**, **11**, and **12** (Fig. 2) were assembled from the corresponding free boronic acids and enantiopure diols in a manner analogous to **4**.

Attempts to evaluate Hoffmann's diol in this chemistry were not successful. The corresponding acrylanilide **13** was prepared in very low yield and, surprisingly, did not readily undergo Diels–Alder reaction with cyclopentadiene.

The novel methylated analogue of **9**, pinanediol boronate **10**, was synthesized starting with the palladium-catalyzed borylation of aryl bromide **14** [13], followed by transesterification of the resulting boronic ester **15** with pinanediol to give **16** (Scheme 3). The latter intermediate was hydrogenated and reacted with acryloyl chloride to provide acrylamide dienophile **10** in moderate yield.

Unfortunately, the level of 1,8-stereoinduction observed in these compounds was quite low, and the highest value of 28% diastereomeric excess originated from the *exo* cycloadduct of dienophile **11** (Table 2). The selectivities observed in the *endo* cycloadducts were uniformly poor. The higher selectivity of the *exo* addition pathway in the approach of cyclopentadiene

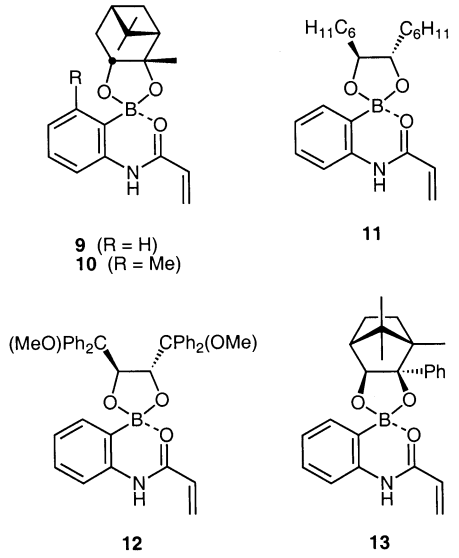
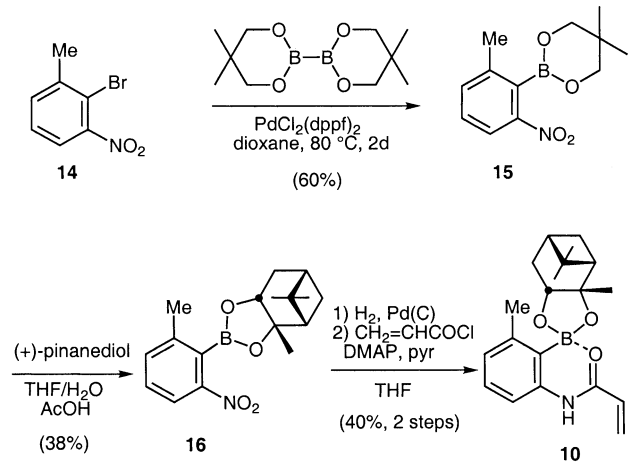


Fig. 2. Chiral 2-boronoacrylanilides.



Scheme 3.

Table 2
Level of remote 1,8-stereoinduction in the Diels–Alder reaction between **9**–**12** and cyclopentadiene [a]

Dienophile	Yield	*endo*:*exo* [b]	De (*endo*) (%)	De (*exo*) (%)
9	94	2.0:1	8	6
10	56	1.5:1	5	9
11	46	1.4:1	5	18
11 [c]	72	3.7:1	0	28
12	(100) [d]	1.7:1	6	22
12 [e]	(73) [d]	1.9:1	9	18
12 [f]	(85) [d]	2.4:1	(−6) [g]	22

[a] Dienophile and cyclopentadiene refluxed in toluene (0.1 M) overnight with BHT except as noted.
[b] Ratios of cycloadducts were measured from representative signals by ^{1}H-NMR spectroscopy on the crude reaction mixtures.
[c] Reaction performed at room temperature in CH_2Cl_2 for 3 days.
[d] Yields in brackets are percent conversions determined from ^{1}H-NMR spectroscopy of the crude mixture.
[e] Reaction performed at room temperature.
[f] Reaction performed at room temperature in CH_2Cl_2.
[g] Preference is for the opposite isomer compared to the reaction in toluene.

to the S-*cis* acrylamide is consistent with the higher steric demand of the methylene unit compared to the flat diene moiety. An inspection of the X-ray crystal structure of dienophile **9**, displayed as an ORTEP diagram in Fig. 3, [14] may provide some insight towards explaining these results. Although the ^{11}B-NMR data did not show evidence for strong coordination (perhaps it is a dynamic process in solution), in the solid state structure the boronic ester is firmly coordinated to the acrylanilide carbonyl to form a tetrahedral boronate [15]. In this structure, the ester substituents appear to be too distant from the dienophile to allow effective transmission of stereochemistry. Specifically in the case of **9**, which provided diastereoselectivities below 10%, Fig. 3 shows that the bulkiest part of the pinanedioxy group, the gem-dimethyl bridge, is oriented

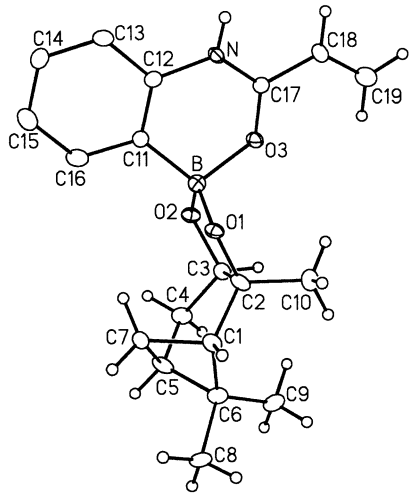


Fig. 3. X-ray structure of acrylanilide **9** [14].

away from the reaction center. This arrangement leaves only the C3 hydrogen and the C2 methyl as discriminating groups for effecting diastereofacial selectivity. Interestingly, this observation suggested that the replacement of hydrogen for a bulkier group at C16 of the aromatic ring (*ortho* to the boronic ester) could induce a preference for a different boronate configuration. Such an arrangement could place the bulk of the pinane group *syn* to the acrylamide moiety, or at least tip over the gem-dimethyl bridge closer to the reaction center to potentially allow a more effective transfer of chirality. In order to help in understanding the steric effect of the boronate ester on the diastereoselectivity of the Diels–Alder reaction, qualitative molecular modeling analysis of **9** and **10** was carried out based on the crystal structure of **9** [16]. The resulting models showed that while the added methyl group in **10** does indeed tip the pinane-unit closer to the reaction centre, the effect is very small and the chiral auxiliary remains quite remote from the acrylamide (Fig. 4). Unfortunately, the experimental results from the Diels–Alder reaction of **10** clearly confirmed that this additional methyl group is not sufficient to allow for high selectivities with these substrates. Molecular modeling analysis of **11** and **12**, however, supported the experimental results showing that these two chiral boronates were the most efficient ones at providing steric discrimination between the two faces of the dienophile component, with diastereomeric excesses that were notably higher than those obtained with boronates **9** and **10**. The qualitative models of boronates **11** and **12** show that the chiral auxiliaries are significantly closer to the acrylamide unit than the pinanediol moiety in boronates **9** and **10** (Fig. 4). However, as with the other two chiral boronates, the auxiliaries are still too far removed from the reaction centre to induce high levels of selectivity.

3. Conclusion

This work shows that non-activated dialkoxyboronic esters can operate as weak, internal Lewis acids and activate carbonyl-containing functionalities towards cycloaddition reactions. This moderate activation was clearly shown to be a result of the internal coordination of the carbonyl and the boron. This coordination was also shown to exist in the solid state by X-ray crystallography. We further showed that chiral boronates can induce selectivity in these cycloadditions in an example of 1,8-stereoinduction transmitted through a putative tetrahedral stereogenic boronate complex. Even if the observed diastereoselectivities were quite low, the fact that an auxiliary which is so remote from the reaction centre can have an effect at all is quite remarkable. Although the current system would need to be redesigned in order to find general applicability, these results validate this concept of internal activation and may pave the way to significant advances in the future.

4. Experimental

4.1. General

Tetrahydrofuran was distilled from sodium/benzophenone ketyl. Toluene and CH_2Cl_2 were distilled over CaH_2. 2-Nitrophenylboronic acid and 4-aminophenylboronic acid hydrochloride pinacol ester were purchased from Combi-Blocks Inc. and used as received. 1,4-Dimethoxy-1,1,4,4-tetraphenyl-2,3-butanediol was prepared according to the literature procedure [11]. All other chemicals were purchased from either the Aldrich Chemical Company or Caledon Chemicals and used as received. Thin layer chromatography data was performed on Merck Silica Gel 60 F_{254} plates and were visualized with UV light and 1% $KMnO_{4(aq)}$. NMR spectra were recorded on Bruker AM 300, Bruker AM 200, Varian INOVA-300, INOVA-400 or INOVA-500 instruments. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards. Boron NMR spectra are referenced to external $BF_3 \cdot OEt_2$. ^1H-NMR data are presented as follows: chemical shift in ppm downfield from Me_4Si (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; ap t, apparent triplet; dd, doublet of doublets; dt, doublet of triplets; AB, AB quartet; m, multiplet. High resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using either electron impact (EI) ionization techniques. Infrared spectra were recorded by University of Alberta Spectral Services and combustion analyses were performed by the University of Alberta Micro-Analytical Lab.

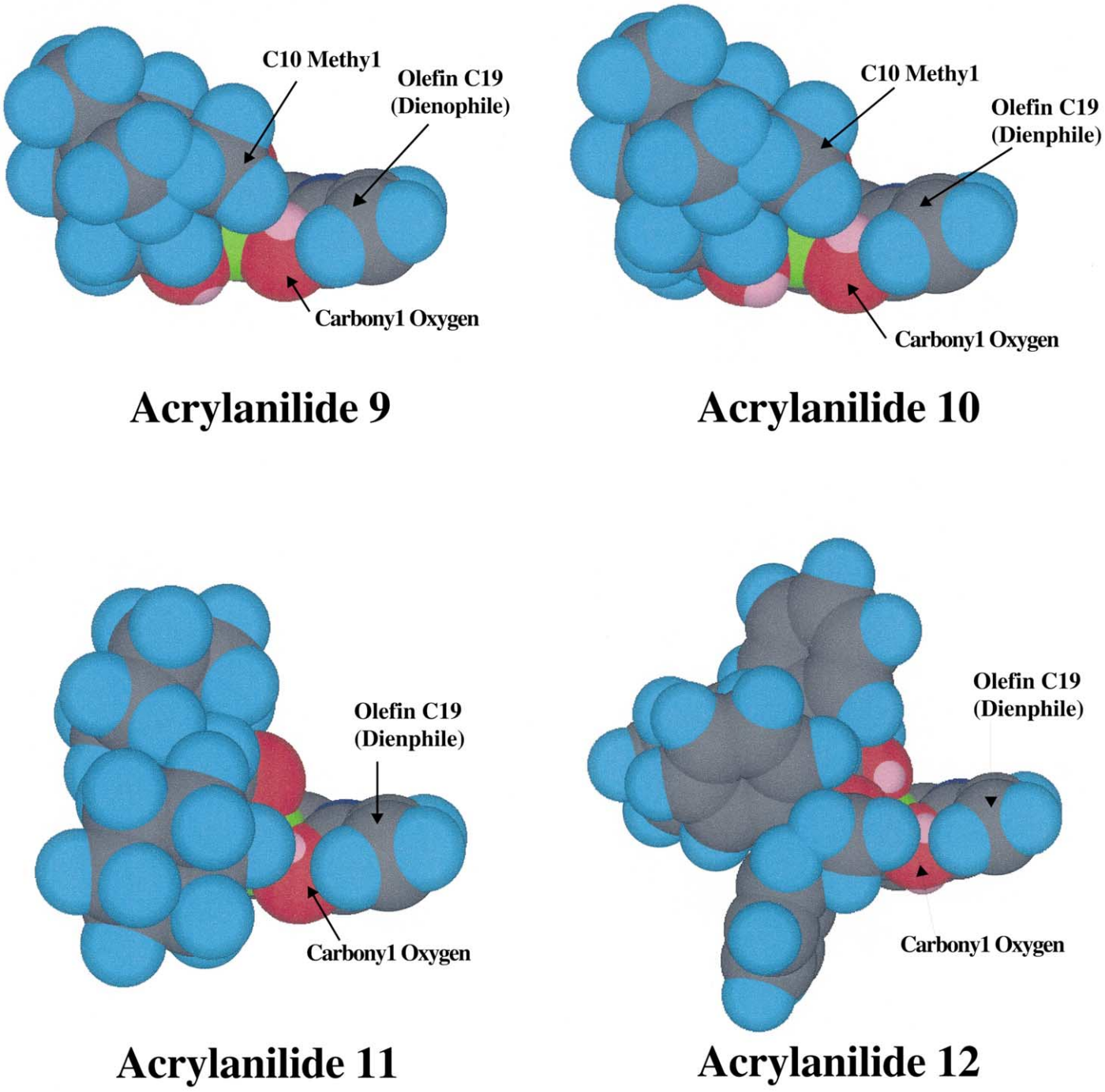


Fig. 4. Molecular models of acrylanilides **9**–**12** with atom numbering as per Fig. 3 [16].

4.2. Preparation of aminoarylboronic acids

4.2.1. 2-Aminophenylboronic acid, pinacol ester (*3*)

A solution of 2-aminoboronic acid **2** (1.68 g, 12.3 mmol) and pinacol (1.50 g, 12.6 mmol) in THF (120 ml) was stirred under N_2 overnight. The solvent was removed and the residue was purified by flash chromatography (20% EtOAc–toluene, 160 g SiO_2) to give the product as a white solid (76%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.68 (dd, $J = 7.4$, 1.4 Hz, 1H), 7.26 (m, 1H), 6.72 (m, 1H), 6.63 (d, $J = 8.2$ Hz, 1H), 4.76 (br s, 2H), 1.39 (s, 12H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 153.3, 136.3, 132.6, 116.5, 114.6, 110.2 (broad), 83.3, 24.6; IR (microscope): 3488, 3384, 2977,

1606, 1354 cm^{-1}; HRMS (EI, *m/z*): Calc. for $C_{12}H_{18}^{11}BNO_2$ 219.14307, found 219.14317.

4.2.2. 2-Aminophenylboronic acid, (+)-pinanediol ester

As per **3**, with 2-aminoboronic acid **2** (585 mg, 4.27 mmol) and (+)-pinanediol (811 mg, 4.76 mmol) in THF (50 ml). Flash chromatography (20% EtOAc–toluene, 40 g silica) gave the product as a white solid (1.03 g, 3.81 mmol, 89%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.63 (d, $J = 7.4$ Hz, 1H), 7.22 (t, $J = 8.2$ Hz, 1H), 6.68 (t, $J = 7.3$, 1H), 6.60 (d, $J = 8.1$ Hz, 1H), 4.69 (br s, 2H), 4.44 (dd, $J = 8.6$, 1.1 Hz, 1H), 2.40 (m, 1H), 2.22 (m, 1H), 2.14 (m, 1H), 1.99 (m, 1H), 1.94 (m, 1H), 1.48 (s, 3H), 1.31 (s, 3H), 0.89 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 153.5, 136.7, 132.5, 116.7, 114.6, 110.4, 85.8, 77.7, 51.3, 39.4, 38.0, 35.5, 28.7, 27.0, 26.4, 23.9; IR (CH_2Cl_2 cast): 3487, 3388, 1605 cm^{-1}; HRMS (EI, *m/z*): Calc. for $C_{16}H_{22}^{11}BNO_2$ 271.17435, found 271.17466.

4.2.3. 2-Aminophenylboronic acid, (−)-1,2-dicyclohexyl-1,2-ethanediol ester

As per **3**, with 2-aminoboronic acid **2** (152 mg, 1.11 mmol), (−)-1,2-dicyclohexyl-1,2-ethanediol (282 mg, 1.25 mmol) and THF (10 ml). Flash chromatography (10% Et_2O–hexane, 27 g silica, pre-absorption) gave the product as a colourless oil (340 mg, 1.04 mmol, 93%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.65 (dd, $J = 7.5$, 1.6 Hz, 1H), 7.23 (m, 1H), 6.88 (dt, $J = 7.2$, 0.8 Hz, 1H), 6.61 (d, $J = 8.2$ Hz, 1H), 4.65 (br s, 2H), 4.00 (d, $J = 5.3$ Hz, 2H), 2.0–1.6 (m, 9H), 1.42 (m, 2H), 1.3–0.8 (m, 11H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 153.6, 136.9, 132.7, 116.9, 114.8, 83.6, 43.0, 28.5, 27.5, 26.4, 26.0, 25.8; IR (CH_2Cl_2 cast): 3488, 3389, 1609, 754 cm^{-1}; HRMS (EI, *m/z*): Calc. for $C_{20}H_{30}^{11}BNO_2$ 327.23697, found 327.23704.

4.2.4. 2-Aminophenylboronic acid, (2*R*,3*R*)-1,4-dimethoxy-1,1,4,4-tetraphenyl-2,3-butanediol ester

2-Aminoboronic acid **2** (133 mg, 0.970 mmol) and (2*R*,3*R*)-1,4-dimethoxy-1,1,4,4-tetraphenyl-2,3-butanediol (438 mg, 0.964 mmol) were refluxed in THF (5 ml) in the presence of 4 Å molecular sieves under Ar for 2 days. The mixture was then filtered through silica and concentrated to give the crude product. Flash chromatography (10% acetone–hexanes, 25 g SiO_2) gave the product as a colourless oil (408 mg, 0.735 mmol, 76%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.40–7.20 (m, 21H), 7.07 (dt, $J = 8.2$, 1.5 Hz, 1H), 6.47 (t, $J = 7.2$ Hz, 1H), 6.39 (d, $J = 8.1$ Hz, 1H), 5.45 (s, 2H), 4.15 (br s, 2H), 2.98 (s, 6H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 152.8, 141.5, 141.1, 136.6, 132.3, 129.5, 128.3, 127.8, 127.5, 127.4, 127.2, 116.5, 114.4, 83.5, 78.0, 52.0; ^{11}B-NMR (64 MHz, $CDCl_3$): δ 30.6; IR (CH_2Cl_2 cast): 3490, 3392, 3056, 2832, 1617, 1605, 1353, 757, 701 cm^{-1}; HRMS (EI, *m/z*): Calc. for $C_{36}H_{34}^{11}BNO_4$ 555.25812, found 555.23687.

4.2.5. 2-Nitro-6-methylphenylboronic acid, neopentylglycol ester (*15*)

A slurry of bis(neopentyl glycolato)diboron (677 mg, 3.00 mmol), $PdCl_2(dppf)_2$, (56 mg, 0.069 mmol), dppf (39 mg, 0.071 mmol) and KOAc (758 mg, 7.72 mmol) in anhydrous dioxane (15 ml) under Ar was treated with 3-nitro-2-bromotoluene **14** (553 mg, 2.56 mmol) and heated at 80 °C for 2 days. The resulting dark mixture was then diluted with toluene (50 ml), washed with brine (50 ml), dried (Na_2SO_4) and evaporated to give the crude product. Krugelrhro distillation (250 °C, 0.1 torr) gave the product as a brown oil that solidified over time (385 mg, 1.54 mmol, 60%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.96 (dd, $J = 8.3$, 0.5 Hz, 1H), 7.43 (m, 1H), 7.33 (m, 1H), 3.81 (s, 4H), 2.49 (s, 3H), 1.13 (s, 6H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 151.7, 142.8, 136.1, 130.0, 120.7, 73.0, 32.3, 22.5, 21.5; ^{11}B-NMR (64 MHz, acetone-d_6): δ 28.1; IR (CH_2Cl_2 cast): 2941, 1519, 1352, 1282 cm^{-1}; HRMS (EI, *m/z*): Calc. for $C_{12}H_{16}^{11}BNO_4$ 249.11723, found 249.11772.

4.2.6. 2-Nitro-6-methylphenylboronic acid, (+)-pinanediol ester (*16*)

A solution of boronate **15** (48 mg, 0.19 mmol) and (+)-pinanediol (44 mg, 0.26 mmol) in THF (2.5 ml) and water (1 ml) was stirred at room temperature (r.t.) under Ar for 48 h. The mixture was then concentrated, diluted with water (5 ml) and extracted with ether (3 × 5 ml). The combined ether layers were washed with brine (5 ml), dried (Na_2SO_4) and evaporated to give the crude product as an oil (106 mg). Flash chromatography (25% EtOAc–hexanes, 5.6 g SiO_2) gave the product as brown crystals (23 mg, 0.072 mmol, 38%) that were contaminated with ~2% of the initial boronate.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.99 (m, 1H), 7.45 (m, 1H), 7.37 (m, 1H), 4.56 (dd, $J = 8.9$, 2.6 Hz, 1H), 2.50 (s, 3H), 2.45 (m, 1H), 2.28 (m, 1H), 2.14 (m, 1H), 1.98 (m, 2H), 1.70 (d, $J = 11.4$, 1H), 1.55 (s, 3H), 1.32 (s, 3H), 0.90 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 151.3, 143.0, 135.2, 129.6, 120.4, 86.8, 78.4, 51.4, 39.7, 38.6, 35.4, 28.3, 27.1, 26.4, 24.3, 22.0; ^{11}B-NMR (64 MHz, acetone-d_6): δ 29.7; IR (CH_2Cl_2 cast): 2928, 1617, 1349 cm^{-1}; HRMS (EI, *m/z*): Calc. for $C_{17}H_{22}^{11}BNO_4$ 315.16418, found 315.16508.

4.3. Preparation of *N*-acryloylaminoarylboronic esters

4.3.1. *N*-Acryloylaniline *6*

This compound was prepared as per the literature procedure [9]. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.58 (m, 2H), 7.31 (m, 2H), 7.18 (br s, 1H), 7.10 (m, 1H), 6.43 (d, $J = 17$ Hz, 1H), 6.25 (dd, $J = 17$, 10.2 Hz, 1H), 5.78 (d,

$J = 10$ Hz, 1H); ^{13}C ($CDC1_3$, 75 MHz): δ 164.0, 140.2, 132.8, 129.5, 126.9, 124.4, 120.3.

4.3.2. 2-N-Acryloylaminophenylboronic acid, pinacol ester (*4*)

A solution of aniline **3** (296 mg, 1.35 mmol), pyridine (0.22 ml, 2.7 mmol) and DMAP (42 mg, 0.34 mmol) in THF (5 ml) at 0 °C was treated dropwise with a solution of acryloyl chloride (152 mg, 1.68 mmol) in THF (2.5 ml). After 1 h the mixture was warmed to r.t. and left to stir for 4 h. The thick white slurry was then partitioned between brine (20 ml) and THF (20 ml). The layers were separated and the aqueous layer was extracted with THF (3×10 ml). The combined organic layers were dried (Na_2SO_4) and evaporated to give a light brown solid which was dried under vacuum overnight to give the product (181.3 mg, 49%).

^{1}H-NMR (acetone-d_6, 400 MHz): δ 10.34 (br s, 1H), 8.06 (m, 1H), 7.67 (d, $J = 8$ Hz, 1H), 7.37 (m, 1H), 7.10 (apparent t, $J = 8$ Hz, 1H), 6.38 (m, 2H), 5.82 (dd, $J = 7$, 5 Hz, 1H), 1.38 (s, 12H);^{13}C-NMR (acetone-d_6, 100 MHz): δ 164.1, 143.6, 136.0, 135.9, 132.2, 131.8, 131.7, 127.9, 127.8, 124.6, 124.5, 119.0, 84.1, 84.0, 25,6, 25.5; ^{13}C-NMR (benzene-d_6, 100 MHz): δ 163.2, 145.3, 136.4, 133.1, 132.8, 125.8, 123.4, 119.6, 83.9, 24.8. A very slight peak duplication effect, ca. 0.05 ppm, was observed for arene carbons in acetone. This duplication may be due to a slow competing effect from this coordinating solvent; ^{11}B-NMR (benzene-d_6, 64 MHz): δ 30.1; IR (CH_2Cl_2 cast): 3316, 3058, 2970, 1646, 731 cm^{-1}; HRMS (EI): Calc. for $C_{15}H^{11}_{20}BNO_3$ 273.15363, found 273.15376.

4.3.3. 4-N-Acryloylaminophenylboronic acid, pinacol ester (*8*)

A slurry of 4-aminophenylboronic acid hydrochloride pinacol ester (524 mg, 2.05 mmol), Et_3N (0.85 ml, 6.1 mmol) and DMAP (45 mg, 0.37 mmol) in THF (7.5 ml) at 0 °C was treated dropwise with a solution of acryloyl chloride (1.9 ml, 2.3 mmol) in THF (2.5 ml). The resulting mixture was stirred at 0 °C for 2 h and then at r.t. overnight. The thick mixture was then diluted with brine (25 ml) and water was added to make the mixture homogenous. The layers were separated and the aqueous phase was extracted with THF (3×25 ml). The combined organic extracts were washed with brine (25 ml), dried ($MgSO_4$,) and evaporate. Flash chromatography (20% EtOAc–toluene, 51 g SiO_2) gave the pure product as a white solid (0.38 g, 1.4 mmol, 68%).

^{1}H-NMR (acetone-d_6, 300 MHz): δ 7.75 (AB, $J = 9$ Hz, 2H), 7.68 (AB, $J = 9$ Hz, 2H), 6.46 (dd, $J = 17$, 10 Hz, 1H), 6.34 (dd, $J = 16$, 3 Hz, 1H), 5.70 (dd, $J = 10$, 3 Hz, 1H), 1,31 (s, 12H); ^{13}C-NMR (acetone-d_6, 100 MHz): δ 164.1, 142.8, 136.3, 136.2 (broad), 132.7, 127.4, 119.2, 84.3, 25.2; ^{11}B-NMR (benzene-d_6, 64 MHz): δ 30.8; IR (CH_2Cl_2 cast): 3303, 3102, 2978, 1667, 1635, 1593, 1361, 860 cm^{-1}; HRMS (EI): Calc. for $C_{15}H^{11}_{20}BNO_3$ 273.15363, found 273.15381.

4.3.4. 2-N-Acryloylaminophenylboronic acid, (+)-pinanediol ester (*9*)

As per **4**, with the aniline (613 mg, 226 mmol), pyridine (0.37 ml, 4.5 mmol), and DMAP (29 mg, 0.24 mmol) in THF (25 ml), and acryloyl chloride (243 mg, 2.69 mmol) in THF (5 ml). Once the reaction was complete, the mixture was diluted with brine (25 ml) and the layers were separated. The aqueous layer was then extracted with THF (3×25 ml). The combined THF layers were then washed with 0.1 M H_2SO_4–brine (10 ml), saturated $NaHCO_3$, (2×20 ml) and brine (20 ml), dried (Na_2SO_4) and evaporated to give the crude product as a white solid (619 mg, 1.90 mmol, 84%).

^{1}H-NMR (300 MHz, C_6D_6): 9.73 (br s, 1H), 9.16 (d, $J = 8.4$ Hz, 1H), 8.06 (dd, $J = 7.4$, 1.2 Hz, 1H), 7.29 (dd, $J = 8.8$, 1.5 Hz, 1H), 6.93 (t, $J = 7.4$ Hz, 1H), 6.40 (dd, $J = 17.0$, 1.0 Hz, 1H), 6.17 (dd, $J = 17.0$, 10.3 Hz, 1H), 5.29 (dd, $J = 10.4$, 1.1 Hz, 1H), 4.09 (dd, $J = 8.5$, 1.6 Hz, 1H), 2.04 (m, 1H), 2.00 (m, 1H), 1.94 (m, 1H), 1.79 (m, 1H), 1.57 (m, 1H), 1.19 (s, 3H), 1.14 (m, 1H), 1.03 (s, 3H), 0.49 (s, 3H); ^{13}C-NMR (125 MHz, C_6D_6): δ 163.2, 145.4, 136.6, 133.4, 132.9, 125.9, 123.4, 119.8, 86.6, 78.2, 51.6, 39.7, 38.0, 35.5, 28.6, 26.9, 26.6, 23.8; ^{11}B-NMR (64 MHz, C_6D_6): δ 30.4; IR (CH_2Cl_2 cast): 3362, 3054, 2924, 1644, 1628, 1050, 735 cm^{-1}; HRMS (EI, *m/z*): Calc. for $C_{19}H^{11}_{24}BNO_3$ 325.18494, found 325.18508.

4.3.5. 2-N-Acryloylamino-6-methylphenylboronic acid, (+)-pinanediol ester (*10*)

Nitro compound **16** (36 mg, 0.11 mmol) was hydrogenated in a Parr bottle over 10% Pd/C (4 mg) in EtOH (2 ml) at r.t. under 45 psi H_2 for 4 h. The mixture was filtered through Celite® and the pad was washed with EtOH (5×1 ml). The combined alcohol filtrates were evaporated to give the crude aniline (31 mg, 94%) as a yellow oil. This oil was dissolved in THF (0.8 ml), cooled to 0 °C and treated successively with DMAP (8 mg, 0.07 mmol), pyridine (25 μl, 0.30 mmol) and acryloyl chloride (16 μl, 0.20 mmol). The thick mixture was then stirred at. r.t. for 90 min. It was then diluted with brine (2 ml) and extracted with THF (4×2 ml). The combined organic extracts were washed with brine (2 ml), dried (Na_2SO_4) and evaporated to give the crude product (35 mg). Flash chromatography (5% EtOAc–toluene, 16 g SiO_2) and Krugelrhro distillation (250 °C, 0.1 torr) gave the pure product (15 mg, 0.045 mmol, 40%).

^{1}H-NMR (500 MHz, acetone-d_6): δ 9.88 (br s, 1H), 7.81 (m, 1H), 7.24 (ap t, $J = 7.7$ Hz, 1H), 6.94 (d, $J = 7.5$ Hz, 1H), 6.34 (m, 2H), 5.78 (dd, $J = 8.4$, 3.4 Hz, 1H), 4.53 (dd, $J = 8.7$, 1.9 Hz, 1H), 2.52 (s, 3H), 2.46 (m, 1H), 2.22 (m, 1H), 2.12 (m, 1H), 2.1–1.9 (m, 2H), 1.52 (s, 3H), 1.44 (m, 1H), 1.31 (s, 3H), 1.30 (m, 1H), 0.93 (s,

3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 163.5, 146.2, 144.6, 132.6, 131.6, 126.2, 126.0, 117.6, 86.3, 77.6, 51.4, 39.6, 38.2, 35.5, 28.7, 27.0, 26.5, 24.0, 23.4; ^{11}B (64 MHz, acetone-d_6): δ 30.0; IR (CH_2Cl_2 cast): 2915, 1640, 1627 cm^{-1}; HRMS (EI, *m/z*): Calc. for $C_{20}H_{26}^{11}BNO_3$ 339.20056, found 339.20054.

*4.3.6. 2-N-Acryloylaminophenylboronic acid, (−)-1,2-dicyclohexyl-1,2-ethanediol ester(**11**)*

As per **4**, with the aniline (211 mg, 0.646 mmol), pyridine (0.10 ml, 1.2 mmol), and DMAP (catalytic amount) in THF (6 ml), and acryloyl chloride (73 mg, 0.80 mmol) in THF (1 ml). Work-up gave the product as an off white solid (188 mg, 0.510 mmol, 79%).

^{1}H-NMR (300 MHz, $CDCl_3$,): δ 9.56 (br s, 1H), 8.56 (d, $J = 7.8$ Hz, 1H), 7.79 (d, $J = 7.6$ Hz, 1H), 7.45 (ap t, $J = 7.7$ Hz, 1H), 7.10 (ap t, $J = 7.5$ Hz, 1H), 6.40 (d, $J =$ 16.5 Hz, 1H), 6.20 (dd, $J = 16.8$, 9.9 Hz, 1H), 5.72 (d, $J = 10.4$ Hz, 1H), 4.08 (d, $J = 4.2$ Hz, 2H), 2.0–1.0 (m, 22H + Hydrocarbon impurities); ^{13}C-NMR (75 MHz, CD_2Cl_2): δ 163.6, 135.7, 131.6, 131.0, 128.0, 124.5, 118.9, 84.4, 75.4, 43.5, 40.8, 30.1, 29.6, 28.6, 28.2, 26.9, 26.7, 26.5, 26.4; ^{11}B-NMR (64 MHz, C_6D_6): δ 29.6; IR (Microscope) 3278, 1647, 1575 cm^{-1}; HRMS (EI, *m/z*): Calc. for $C_{23}H_{32}^{11}BNO_3$ 381.24753, found 381.24790.

*4.3.7. 2-N-Acryloylaminophenylboronic acid, (2R,3R)-1,4-dimethoxy-1,1,4,4-tetraphenyl-2,3-butanediol ester (**12**)*

A solution of the aniline (346 mg, 0.624 mmol), pyridine (100 μl, 1.24 mmol), and DMAP (l5 mg, 0.12 mmol) in THF (3 ml) at 0 °C was treated slowly with acryloyl chloride (55 μl, 0.68 mmol). The resulting mixture was stirred as 0 °C for 1 h then at r.t. for 4 h before being worked-up as per **4**. Flash chromatography (20 g SiO_2, 5% EtOAc–toluene) gave the product as a colourless glass (209 mg, 0.343 mmol, 55%).

^{1}H-NMR (500 MHz, C_6D_6): δ 9.06 (d, $J = 8.3$ Hz, 1H), 8.70 (br s, 1H), 7.48 (m, 9H), 7.2–6.9 (m, 13H), 6.68 (dt, $J = 7.4$, 1.0 Hz, 1H), 6.31 (dd, $J = 16.8$, 1.6 Hz, 1H), 5.78 (s, 2H), 5.46 (dd, $J = 16.8$, 10.2 Hz, 1H), 5.17 (dd, $J = 10.3$, 1.7 Hz, 1H), 2.96 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 163.3, 143.6, 140.6, 140.2, 135.8, 132.5, 131.8, 129.6, 128.3, 128.0, 127.8, 127.6, 127.5, 126.5, 122.8, 119.1, 83.4, 78.5, 51.9; ^{11}B-NMR (64 MHz, $CDCl_3$): δ 30.5; IR (CH_2Cl_2 cast): 3377, 3057, 2938, 1693, 1611, 1348, 760, 701 cm^{-1}; HRMS (EI, *m/z*): Calc. for $C_{39}H_{36}^{11}BNO_5$ 609.26868, found 609.26921.

Acknowledgements

This work was funded by the Natural Sciences and Engineering Research Council (NSERC) of Canada. J.K. thanks NSERC and the Alberta Heritage Foundation for Medical Research (AHFMR) for graduate scholarships. The authors thank Mr. Juan Venegas for the preparation of some acrylamide substrates, Mr. Glen Bigam for help in NMR studies, and Dr. Bob McDonald for X-ray crystallographic analysis.

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