Efficient Preparation of α-Aminoboronic Acid Derivatives via Boroalkyl Group Migration

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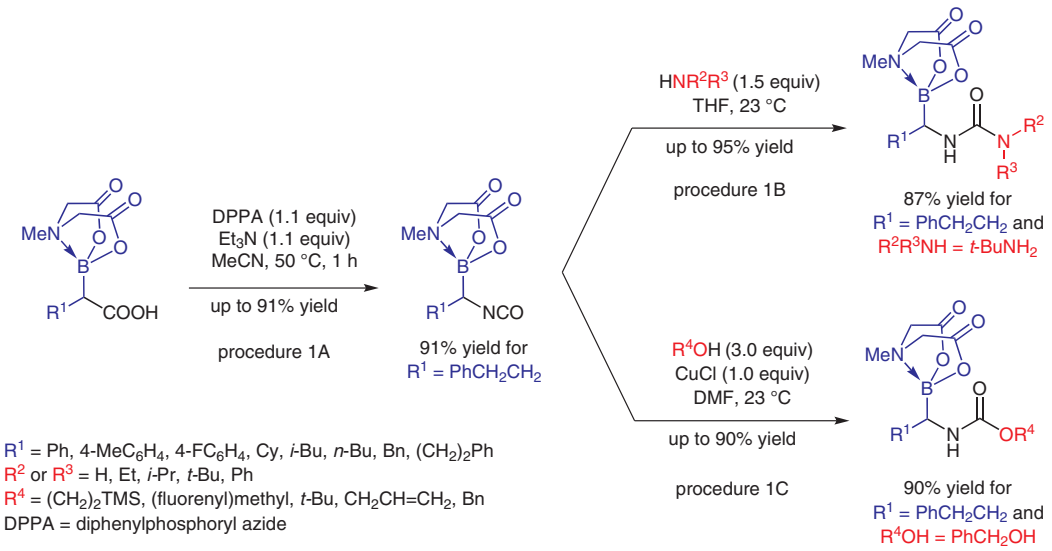
Abstract: A reaction demonstrating migration of boron-substituted carbon is presented. It is shown that α-boroalkyl groups of transient boroalkyl acyl azide intermediates migrate readily from carbon to nitrogen. This transformation allows access to a novel class of stable molecules, α-boryl isocyanates, from easily preparable α-borylcarboxylic acid precursors. The protocol enables the synthesis of a diverse range of α-aminoboronic acid derivatives, including α,α-disubstituted analogues.

Key words: boron, isocyanates, Curtius rearrangement, boroalkyl shift



Scheme 1 Preparation and application of α-boryl isocyanates in the synthesis of α-aminoboronic acid derivatives

Introduction

Organoboronic acids have found widespread application both as synthetic building blocks[2] and as biologically active targets of chemical synthesis.[3] A subset of these compounds containing a *gem*-aminoboronic acid motif have been recognized for their utility as both probes[3e,4] and inhibitors of enzyme function.[3g] The utility of these molecules is exemplified by the recent FDA-approval of bortezomib, a boropeptide currently used as a front-line therapeutic in the treatment of multiple myeloma.[5] The biological activity of boron-containing peptide derivatives results from boron's tendency to undergo interactions with Lewis basic species including those at an enzyme's active site. While desirable in biological settings, the Lewis acidity of organoboron compounds complicates their synthesis by limiting the reaction conditions under which they are stable. Thus, late-stage boron installation is common during synthesis but chemoselectivity issues still impose restrictions on compatible functional groups.[2]

Our group's approach to the preparation of organoboronic acid derivatives involves installation of boron at an early stage of the synthesis, followed by manipulation of adjacent functionalities and transposition of the boron fragment. This has allowed access to novel amphoteric building blocks containing a nucleophilic C–B bond directly adjacent to various electrophilic groups.[6] Among these compounds are the α-boryl aldehydes.[6a] These reagents contain a C–B bond directly adjacent to an aldehyde, which can be functionalized leaving the boronate

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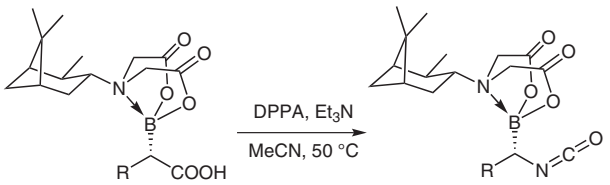
moiety intact for access to a variety of α-borylated functionalities. In this report, we highlight the synthesis of stable, isolable α-boryl isocyanates via 1,2-migration of a boroalkyl fragment to establish the *gem*-aminoboron motif (Scheme 1). These unique boron building blocks are useful precursors to aminoboronic acids and their derivatives including boryl ureas, carbamates, isocyanides, and peptides, and are readily available from commercially available materials.

Scope and Limitations

Recent commercial availability of α-boryl aldehydes has fueled extensive investigations of their synthetic utility. The aldehyde participates in a diverse range of functionalizations including mild oxidative conversion to the corresponding α-boryl carboxylic acids **1**. These configurationally stable molecules are easily converted to the corresponding isocyanates **2** under mild conditions (50 °C, 1 h) via Curtius rearrangement using a slight excess of both diphenylphosphoryl azide (DPPA) and Et_3N (Table 1).[7] This protocol tolerates all commercially available boryl aldehydes including a variety of aromatic and alkyl substituted compounds. The presence of the isocyanate functional group is confirmed by IR (isocyanate stretch at ~2200 cm^{-1}) and NMR (^{13}C signal at ~120 ppm) spectroscopy.

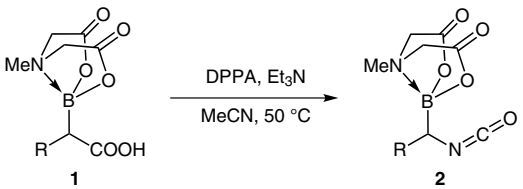
The carbon-to-nitrogen migration of the boryl fragment occurs with complete retention of stereochemistry for the phenylethyl-substituted acid **3b** as determined by an investigation of enantiomerically pure substrates prepared using the chiral PIDA (pinene-derived iminodiacetic acid) ligand (Scheme 2).[6e] However, the phenyl substrate **3a** exhibits slight erosion of stereochemistry, which we attribute to the increased susceptibility of the α-proton to base under the reaction conditions.

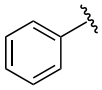
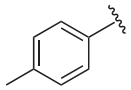
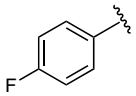
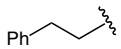
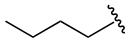
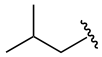
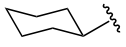


Scheme 2 Stereochemical investigation of the Curtius rearrangement. Diastereomeric ratios (dr) were determined by ^1H NMR analysis of the crude reaction mixtures.

Under acidic hydrolysis conditions, α-boryl isocyanate **2d** undergoes quantitative conversion into the corresponding ammonium chloride salt (Scheme 3). Of note is the concomitant hydrolysis of the MIDA (methyliminodiacetic acid) group to give the corresponding free boronic acid. Boryl ammonium salt **5** is difficult to separate from the free MIDA component and could not be applied in downstream transformations. Isocyanate **2a** behaves similarly

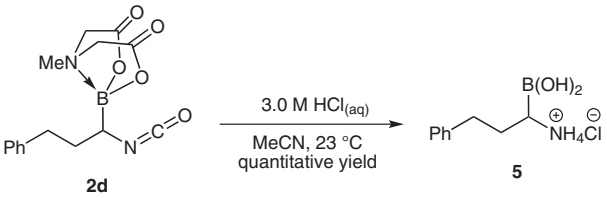
Table 1 Preparation of α-Boryl Isocyanates via Curtius Rearrangement[a]



Entry[b]	1	R	Product	Yield (%)[c]
1	**1a**		**2a**	71
2	**1b**		**2b**	57
3	**1c**		**2c**	62
4	**1d**		**2d**	91
5	**1e**		**2e**	84
6	**1f**		**2f**	86
7	**1g**		**2g**	71
8	**1h**		**2h**	73

[a] Reactions were carried our using 1.0 equiv of α-boryl carboxylic acid **1**, 1.1 equiv of DPPA, and 1.1 equiv of Et_3N in anhydrous MeCN at 50 °C for 1 h.
[b] Carboxylic acids were prepared by oxidation of commercially available α-boryl aldehydes.
[c] Yield of isolated product after silica gel chromatography.

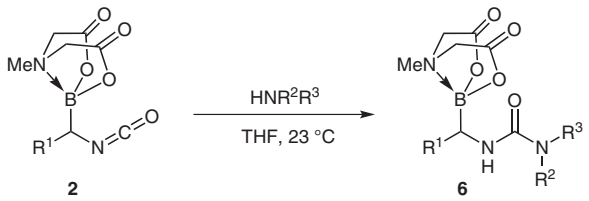
under the reaction conditions; however, identification of the product by crude ^1H NMR spectroscopy is made difficult by the lack of coupling partners for the α-proton.



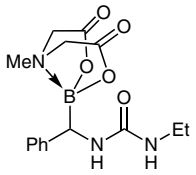
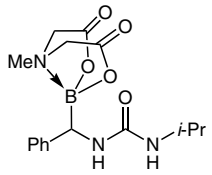
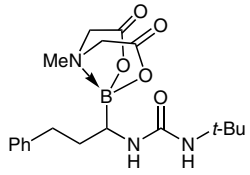
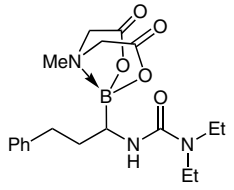
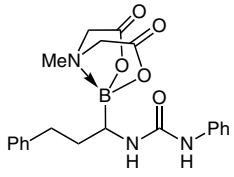
Scheme 3 Acidic hydrolysis of α-boryl isocyanates

Nucleophilic attack at the isocyanate carbon by either amines or alcohol yields the corresponding ureas and carbamates, respectively. Amine addition to the isocyanate occurs smoothly at room temperature in THF with complete selectivity for the isocyanate carbonyl over the MIDA ester (Table 2). A variety of amine nucleophiles are tolerated including primary, secondary, aliphatic, and aromatic. The use of aniline results in decreased yields

Table 2 Preparation of α-Boryl Ureas[a]

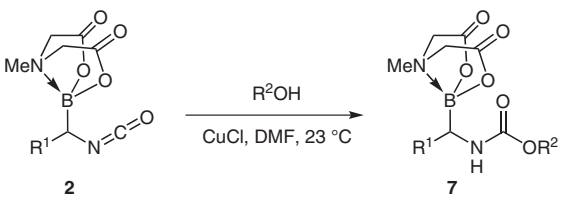


2 **6**

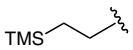
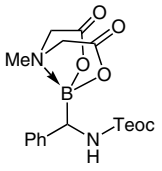
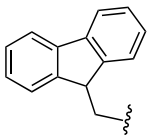
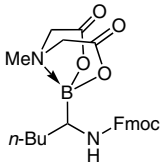
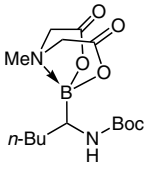
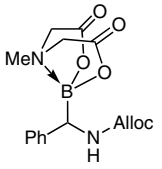
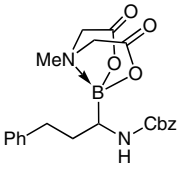
Entry	R^1	R^2	R^3	Product	Yield (%)[b]
1	Ph	H	Et	 **6a**	93
2	Ph	H	*i*-Pr	 **6b**	95
3	$PhCH_2CH_2$	H	*t*-Bu	 **6c**	87
4	$PhCH_2CH_2$	Et	Et	 **6d**	77
5	$PhCH_2CH_2$	H	Ph	 **6e**	30

[a] Reactions were carried out using 1.0 equiv of α-boryl isocyanate and 1.5 equiv of amine in anhydrous THF at 23 °C for 1–12 h.
[b] Yield of isolated product after silica gel chromatography.

Table 3 Preparation of α-Boryl Carbamates[a]

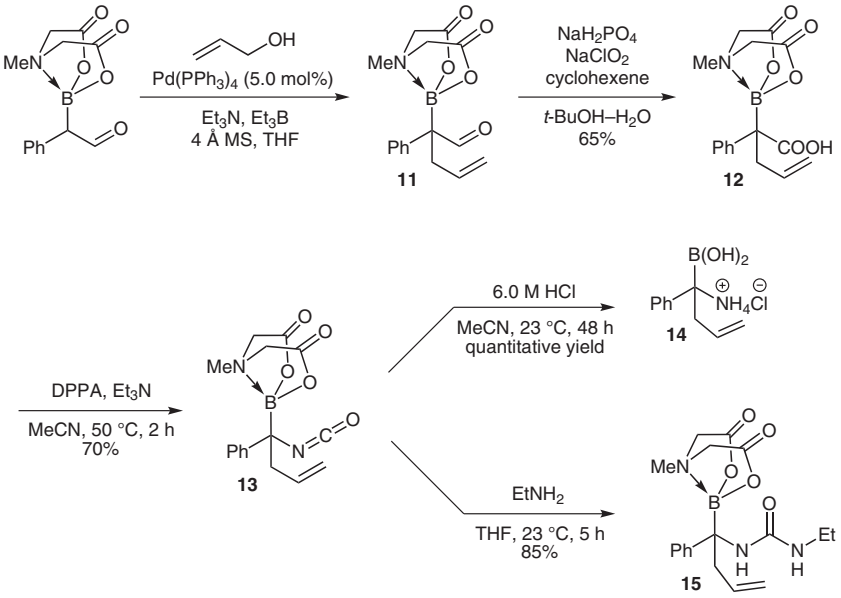


2 **7**

Entry	R^1	R^2	Product	Yield (%)[b]
1	Ph		 **7a**	75
2	*n*-Bu		 **7b**	80
3[c]	*n*-Bu		 **7c**	60
4	Ph		 **7d**	67
5	$PhCH_2CH_2$		 **7e**	90

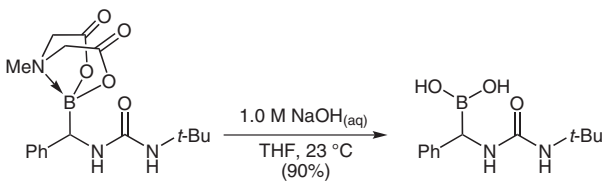
[a] Reactions were carried out using 1.0 equiv of α-boryl isocyanate, 3.0 equiv of alcohol, and 1.0 equiv of CuCl in anhydrous DMF at 23 °C for 3 h.
[b] Yield of isolated product after silica gel chromatography.
[c] Reaction was carried out using 10.0 equiv of *t*-BuOH at 70 °C for 24 h.

due to its decreased nucleophilicity relative to aliphatic amines. Alcohol addition requires a more polar solvent (DMF) and an equimolar amount of CuCl (Table 3).[8] A variety of alcohols are tolerated including those required to prepare typical carbamate protecting groups for amines [Teoc (trimethylsilylethoxycarbonyl), Fmoc (fluorenylmethyloxycarbonyl), Boc (*tert*-butyloxycarbonyl), Alloc (allyloxycarbonyl), and Cbz (carboxybenzyl)]. Both aromatic **2a** and aliphatic **2d**, **2f** side chains of the isocyanate are tolerated. Quaternary centers adjacent to the isocya-



Scheme 4 Preparation of α-aminoboronic acid derivatives with a quaternary carbon center

nate are also amenable to this protocol as exemplified by the allyl-substituted isocyanate **13** (Scheme 4).[9] The free boronic acid of boryl urea **6c** can be obtained in high yield by treatment with 1.0 M aqueous NaOH (Scheme 5).

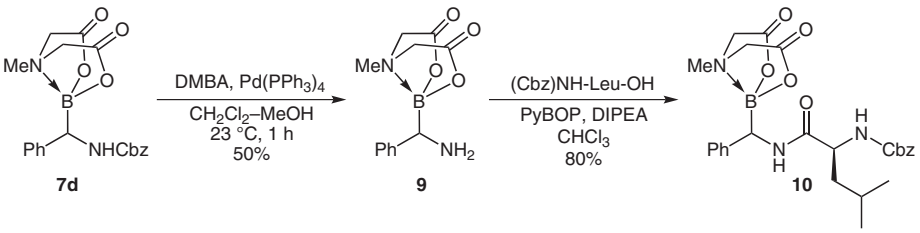


Scheme 5 Preparation of unprotected α-boryl urea via alkaline hydrolysis of the MIDA group

Deprotection of the Cbz-protected amine of boryl carbamate **7d** can be achieved via Pd(0) catalysis. The resulting primary amine is stable under coupling conditions and affords the corresponding borodipeptide in a 1:1 mixture of diastereomers when coupled with *N*(Cbz)-leucine using PyBOP as a coupling agent (Scheme 6). An important limitation to this protocol is that attempted deallylation of alkyl-substituted boryl carbamates results in decomposition. The desired free amines could not be isolated.

In short, amphoteric α-boryl isocyanates have proven to be useful tools in the streamlined preparation of various *gem*-aminoboronic acids and their derivatives. These bench-stable building blocks are readily available in two steps form commercially available materials via oxidation and subsequent Curtius rearrangement. α-Boryl amines and ammonium salts can be obtained in one step as well as ureas and carbamates via nucleophilic attack. These transformations occur readily under mild conditions to yield stable, isolable products with potential downstream functionalizations and biological applications.

Anhydrous CH_2Cl_2, MeCN, and $CHCl_3$ were purchased and used as received. Anhydrous THF was distilled from sodium benzophenone ketyl under argon. All other solvents were of reagent grade quality. Flash column chromatography was carried out using Silicycle 230–400 mesh silica gel. TLC was performed on Macherey-Nagel precoated glass backed TLC plates (SIL G/UV254, 0.25 mm) and visualized using a UV lamp (254 nm) or $KMnO_4$ stain in case of no UV activity. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Mercury 400 MHz spectrometer. ^{1}H NMR spectra chemical shifts (δ) are reported in parts per million (ppm) referenced to TMS (0 ppm) or residual protium in the NMR solvent. Note: Carbons exhibiting significant line broadening brought about by boron substituents were not reported (quadrupolar relaxation). ^{11}B NMR was recorded using Varian VNMRS 400 MHz spectrometer or Bruker



Scheme 6 Preparation and coupling of α-boryl amine

Avance III 400 MHz spectrometer and referenced to an external standard of $Et_2O{\cdot}BF_3$. IR spectra were recorded on a PerkinElmer Spectrum 100 instrument equipped with a single-reflection diamond/ZnSe ATR accessory. High-resolution mass spectra were obtained on a VG 70-250S (double focusing) mass spectrometer at 70 eV or on an ABI/Sciex Qstar mass spectrometer with ESI source, MS/MS and accurate mass capabilities or on Jeol AccuTOF-DART instrument.

α-Boryl Isocyanates 2a–h; Procedure 1A (Table 1)
To a solution (or suspension) of α-boryl carboxylic acid **1** (5.0 mmol) in anhydrous MeCN (30 mL) was added Et_3N (6.0 mmol, 1.2 equiv) and subsequently DPPA (6.0 mmol, 1.2 equiv). The resulting solution was stirred at r.t. under N_2 for 15 min, and then heated at 50 °C for 1 h until the reaction was complete as indicated by ^{1}H NMR analysis of the crude mixture. The mixture was cooled to r.t. and evaporated under reduced pressure to remove the solvent. The crude residue was purified by flash column chromatography on silica gel [hexanes–EtOAc (80:20) → hexanes–EtOAc (50:50) → EtOAc] to afford the respective pure product.

(MIDA boryl)(phenyl)methyl Isocyanate (2a)
The reaction was carried out on a 0.66 mmol scale; yield: 707 mg (2.46 mmol, 71%); white solid; mp 125 °C (dec.); R_f = 0.55 (EtOAc).

IR (film): 2244, 1752, 1453, 1341, 1297, 1252, 1100, 1039, 948, 904, 868, 770, 718, 701 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.39–7.24 (m, 5 H), 4.39 (d, J = 17.2 Hz, 1 H), 4.31 (d, J = 17.2 Hz, 1 H), 4.31 (s, 1 H), 4.16 (d, J = 17.2 Hz, 1 H), 4.07 (d, J = 17.2 Hz, 1 H), 3.09 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.4, 168.4, 140.7, 128.3, 126.8, 126.7, 122.9, 62.6, 62.3, 46.1.

^{11}B NMR (128 MHz, DMSO-d_6): δ = 10.5.

HRMS (DART-TOF): m/z [M + NH_4]$^+$ calcd for $C_{13}H_{17}BN_3O_5$: 306.12613; found: 306.12679.

(MIDA boryl)(*p*-tolyl)methyl Isocyanate (2b)
The reaction was carried out on a 3.05 mmol scale; yield: 114 mg (0.38 mmol, 57%); white solid; mp 149 °C (dec.); R_f = 0.72 (EtOAc).

IR (film): 2242, 1756, 1513, 1455, 1336, 1292, 1102, 1071, 1038, 949, 902, 886, 868, 810, 761, 736 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.18 (app br s, 4 H), 4.37 (d, J = 17.2 Hz, 1 H), 4.30 (d, J = 17.2 Hz, 1 H), 4.24 (s, 1 H), 4.15 (d, J = 17.2 Hz, 1 H), 4.05 (d, J = 17.2 Hz, 1 H), 3.06 (s, 3 H), 2.29 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.4, 168.4, 137.6, 135.9, 128.9, 126.7, 123.0, 62.6, 62.3, 46.1, 20.6.

^{11}B NMR (128 MHz, DMSO-d_6): δ = 10.3.

HRMS (DART-TOF): m/z [M + NH_4]$^+$ calcd for $C_{14}H_{19}BN_3O_5$: 320.14178; found: 320.14169.

(MIDA boryl)(4-fluorophenyl)methyl Isocyanate (2c)
The reaction was carried out on a 0.65 mmol scale; yield: 122 mg (0.40 mmol, 62%); white solid; mp 113 °C (dec.); R_f = 0.75 (EtOAc).

IR (film): 2246, 1756, 1603, 1508, 1465, 1336, 1279, 1218, 1158, 1100, 1071, 1035, 954, 897, 824, 739 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.34–7.29 (m, 2 H), 7.24–7.18 (m, 2 H), 4.39 (d, J = 17.2 Hz, 1 H), 4.35 (s, 1 H), 4.32 (d, J = 17.2 Hz, 1 H), 4.18 (d, J = 17.2 Hz, 1 H), 4.08 (d, J = 17.2 Hz, 1 H), 3.08 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.3(8), 168.3(6), 161.1 (d, $^1J_{CF}$ = 242.6 Hz), 136.8 (d, $^4J_{CF}$ = 3.0 Hz), 128.6 (d, $^3J_{CF}$ = 8.2 Hz), 122.9, 115.1 (d, $^2J_{CF}$ = 21.4 Hz), 62.7, 62.3, 46.2.

^{11}B NMR (128 MHz, DMSO-d_6): δ = 10.2.

HRMS (DART-TOF): m/z [M + NH_4]$^+$ calcd for $C_{13}H_{16}BFN_3O_5$: 324.11670; found: 324.11736.

1-(MIDA boryl)-3-phenylpropyl Isocyanate (2d)
The reaction was carried out on a 4.70 mmol scale; yield: 1.37 g (4.33 mmol, 92%); white solid; mp 133 °C (dec.); R_f = 0.80 (EtOAc).

IR (film): 2254, 1752, 1497, 1454, 1337, 1284, 1245, 1193, 1111, 1032, 990, 952, 897, 861, 820, 725, 700 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.32–7.28 (m, 2 H), 7.23–7.17 (m, 3 H), 4.34 (d, J = 17.2 Hz, 1 H), 4.27 (d, J = 17.2 Hz, 1 H), 4.11 (d, J = 17.2 Hz, 1 H), 4.04 (d, J = 17.2 Hz, 1 H), 3.04 (dd, J = 10.5, 3.2 Hz, 1 H), 2.97 (s, 3 H), 2.87–2.80 (m, 1 H), 2.67–2.56 (m, 1 H), 1.94–1.85 (m, 1 H), 1.83–1.73 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.6, 168.4, 141.2, 128.4, 128.3, 125.8, 121.5, 62.5, 62.3, 45.9, 34.3, 32.8.

^{11}B NMR (128 MHz, DMSO-d_6): δ = 10.7.

HRMS (DART-TOF): m/z [M + H]$^+$ calcd for $C_{15}H_{18}BN_2O_5$: 317.13088; found: 317.13060.

1-(MIDA boryl)-2-phenylethyl Isocyanate (2e)
The reaction was carried out on a 0.85 mmol scale; yield: 214 mg (0.71 mmol, 84%); white solid; mp 130 °C (dec.); R_f = 0.56 (EtOAc).

IR (film): 3065, 3027, 2953, 2904, 2257, 2170, 1773, 1741, 1709, 1590, 1511, 1489, 14551448, 1426, 1343, 1327, 1294, 1252, 1237, 1200, 1183, 1161, 1117, 1072, 1041, 1010, 991, 960, 944, 904, 873, 822, 781, 754, 739, 724, 695 cm^{-1}.

^{1}H NMR (400 MHz, CD_3CN): δ = 7.38–7.32 (m, 4 H), 7.29–7.25 (m, 1 H), 4.06 (d, J = 17.2 Hz, 1 H), 4.05 (d, J = 17.0 Hz, 1 H), 3.95 (d, J = 17.0 Hz, 1 H), 3.91 (d, J = 17.2 Hz, 1 H), 3.37 (dd, J = 12.0, 2.8 Hz, 1 H), 3.11 (dd, J = 14.2, 2.8 Hz, 1 H), 3.02 (s, 3 H), 2.77 (dd, J = 14.2, 12.0 Hz, 1 H).

^{13}C NMR (100 MHz, CD_3CN): δ = 169.1, 168.7, 140.6, 130.2, 129.5, 127.7, 118.4, 63.7, 63.4, 47.0, 39.4.

^{11}B NMR (128 MHz, CD_3CN): δ = 10.6.

HRMS (DART-TOF): m/z [M + NH_4]$^+$ calcd for $C_{14}H_{19}BN_3O_5$: 320.14178; found: 320.14186.

1-(MIDA boryl)pentyl Isocyanate (2f)
The reaction was carried out on a 3.69 mmol scale; yield: 859 mg (3.20 mmol, 86%); white solid; mp 163–164 °C; R_f = 0.60 (EtOAc).

IR (film): 2959, 2261, 1742, 1465, 1339, 1294, 1230, 1160, 1141, 1099, 1069, 1045, 1026, 990, 954, 900, 861, 726 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.34 (d, J = 17.2 Hz, 1 H), 4.26 (d, J = 17.2 Hz, 1 H), 4.09 (d, J = 17.2 Hz, 1 H), 4.04 (d, J = 17.2 Hz, 1 H), 3.03 (dd, J = 10.0, 3.2 Hz, 1 H), 2.98 (s, 3 H), 1.68–1.56 (m, 1 H), 1.56–1.42 (m, 2 H), 1.40–1.25 (m, 3 H), 0.90 (t, J = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.7, 168.5, 121.5, 62.4, 62.2, 45.9, 31.8, 28.8, 21.7, 13.9.

^{11}B NMR (128 MHz, DMSO-d_6): δ = 10.6.

HRMS (DART-TOF): m/z [M + NH_4]$^+$ calcd for $C_{11}H_{21}BN_3O_5$: 285.15743; found: 286.15789.

3-Methyl-1-(MIDA boryl)butyl Isocyanate (2g)
The reaction was carried out on a 0.66 mmol scale; yield: 127 mg (0.47 mmol, 71%); white solid; mp 160–161 °C; R_f = 0.55 (EtOAc).

IR (film): 3016, 2961, 2873, 2266, 2139, 1742, 1705, 1517, 1469, 1451, 1338, 1289, 1249, 1197, 1161, 1102, 1081, 1070, 1045, 1018, 992, 956, 915, 898, 866, 816, 776, 725, 687 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.34 (d, J = 17.2 Hz, 1 H), 4.25 (d, J = 17.2 Hz, 1 H), 4.09 (d, J = 17.2 Hz, 1 H), 4.04 (d, J = 17.2

Hz, 1 H), 3.09 (dd, *J* = 11.8, 2.9 Hz, 1 H), 2.99 (s, 3 H), 1.79–1.69 (m, 1 H), 1.53 (ddd, *J* = 14.0, 11.8, 3.8 Hz, 1 H), 1.28 (ddd, *J* = 14.0, 10.3, 2.9 Hz, 1 H), 0.95 (d, *J* = 6.6 Hz, 3 H), 0.90 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.7, 168.4, 121.4, 62.5, 62.3, 45.9, 41.0, 24.8, 23.4, 20.6.

^{11}B NMR (128 MHz, DMSO-d_6): δ = 10.7.

HRMS (DART-TOF): *m*/*z* [M + NH_4]$^+$ calcd for $C_{11}H_{21}BN_3O_5$: 286.15743; found: 286.15807.

Cyclohexyl(MIDA boryl)methyl Isocyanate (2h)
The reaction was carried out on a 0.66 mmol scale; white solid; yield: 137 mg (464 mmol, 69%); mp 175–176 °C; R_f = 0.39 (EtOAc).

IR (film): 2925, 2852, 2261, 1749, 1449, 1338, 1292, 1233, 1109, 1030, 969, 894, 862, 818, 729 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.29 (d, *J* = 17.2 Hz, 1 H), 4.25 (d, *J* = 17.1 Hz, 1 H), 4.05 (d, *J* = 17.2 Hz, 1 H), 4.03 (d, *J* = 17.1 Hz, 1 H), 2.96 (s, 3 H), 1.76–1.73 (m, 3 H), 1.64–1.56 (m, 4 H), 1.30–1.17 (m, 3 H), 1.29–1.00 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.6(3), 168.6(0), 121.0, 62.0, 61.8, 45.9, 39.9, 31.4, 27.8, 26.1, 25.7(5), 25.7(2).

^{11}B NMR (128 MHz, DMSO-d_6): δ = 10.6.

HRMS (DART-TOF): *m*/*z* [M + NH_4]$^+$ calcd for $C_{13}H_{23}BN_3O_5$: 312.17308; found: 312.17444.

α-Aminoboronic Acid; (1-Amino-3-phenylpropyl)boronic Acid (5) (Scheme 3)
In a vial equipped with a stirring bar and a screw-cap lid was dissolved the α-boryl isocyanate **2d** (50 mg, 0.158 mmol, 1.0 equiv) in MeCN (2 mL). Aq 3.0 M HCl (0.53 mL, 10 equiv) was added dropwise and the reaction mixture was stirred at r.t. for 12 h until the reaction was complete as judged by TLC (eluent: EtOAc). The resulting solution was evaporated to remove the solvent under reduced pressure. The residue was azeotroped with MeCN three times to obtain the desired product as a white powder; yield: 34 mg (0.158 mmol, ~100%); white solid (a 1:1 mixture with MIDA).

^{1}H NMR (400 MHz, CD_3OD): δ = 7.31–7.17 (m, 5 H), 4.11 (s, 4 H) (MIDA α-CH_2), 3.05 (s, 3 H) (MIDA CH_3), 2.91 (br s, 1 H), 2.72 (t, *J* = 7.9 Hz, 2 H), 2.03–1.97 (m, 2 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 168.7 (MIDA C=O), 142.1, 129.7, 129.6, 127.5, 57.4 (MIDA α-CH_2), 43.4 (MIDA CH_3), 33.7, 32.6.

^{11}B NMR (128 MHz, CD_3OD): δ = 28.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{15}BNO_2$: 180.1196; found: 180.1199.

α-Boryl Ureas 6a–e; Procedure 1B (Table 2)
In a vial equipped with a stirring bar and a screw-cap lid was dissolved the appropriate α-boryl isocyanate **2** (0.30 mmol, 1.0 equiv) in THF (2 mL). The respective amine (0.36 mmol, 1.2 equiv) was added and the reaction mixture was stirred at r.t. for 1–5 h until the reaction was complete as judged by TLC (eluent: EtOAc). The resulting cloudy mixture was concentrated under reduced pressure to remove the solvent to obtain the desired product as a white solid. The crude product was subjected to purification by flash column chromatography on silica gel.

1-Ethyl-3-[(MIDA boryl)(phenyl)methyl]urea (6a)
The reaction was carried out on a 0.17 mmol scale; yield: 54 mg (162 mmol, 93%); white solid; mp 150–153 °C; R_f = 0.20 (EtOAc).

IR (film): 3374, 2967, 1748, 1634, 1547, 1494, 1451, 1338, 1282, 1244, 1107, 1075, 1028, 991, 950, 895, 878, 802, 703 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.25–7.09 (m, 5 H), 6.05 (d, *J* = 9.7 Hz, 1 H), 6.02 (t, *J* = 5.5 Hz, 1 H), 4.34 (d, *J* = 9.7 Hz, 1 H), 4.26 (d, *J* = 17.1 Hz, 1 H), 4.25 (d, *J* = 16.9 Hz, 1 H), 4.15 (d, *J* = 17.1 Hz, 1 H), 3.89 (d, *J* = 16.9 Hz, 1 H), 2.98 (s, 3 H), 2.97–2.91 (m, 2 H), 0.94 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.8, 168.5, 158.0, 144.6, 127.4, 126.9, 125.0, 62.3, 62.3, 45.7, 34.1, 15.5.

^{11}B NMR (128 MHz, DMSO-d_6): δ = 11.5.

HRMS (DART-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{21}BN_3O_5$: 334.15743; found: 334.15849.

1-Isopropyl-3-[(MIDA boryl)(phenyl)methyl]urea (6b)
The reaction was carried out on a 0.17 mmol scale; yield: 56 mg (0.16 mmol, 95%); white solid; mp 160–162 °C; R_f = 0.22 (EtOAc).

IR (film): 3405, 2965, 1747, 1639, 1539, 1495, 1451, 1338, 1282, 1239, 1152, 1099, 1028, 950, 896, 817, 704 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.25–7.21 (m, 2 H), 7.17–7.08 (m, 3 H), 6.00 (d, *J* = 9.6 Hz, 1 H), 5.95 (d, *J* = 7.6 Hz, 1 H), 4.33 (d, *J* = 9.6 Hz, 1 H), 4.26 (d, *J* = 17.0 Hz, 1 H), 4.25 (d, *J* = 17.1 Hz, 1 H), 4.16 (d, *J* = 17.1 Hz, 1 H), 3.88 (d, *J* = 17.0 Hz, 1 H), 3.60–3.52 (m, 1 H), 2.98 (s, 3 H), 0.99 (d, *J* = 6.5 Hz, 3 H), 0.96 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.8, 168.4, 157.5, 144.6, 127.4, 126.9, 125.0, 62.4, 62.3, 45.6, 40.9, 23.3, 23.2.

^{11}B NMR (128 MHz, DMSO-d_6): δ = 11.7.

HRMS (DART-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{23}BN_3O_5$: 348.17308; found: 348.17306.

1-(*tert*-Butyl)-3-[1-(MIDA boryl)-3-phenylpropyl]urea (6c)
The reaction was carried out on a 0.32 mmol scale; yield: 107 mg (0.27 mmol, 87%); white solid; mp 120–125 °C; R_f = 0.25 (EtOAc).

IR (film): 3381, 2963, 1762, 1747, 1644, 1549, 1497, 1453, 1337, 1285, 1216, 1110, 993, 952, 896, 862, 749, 699 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.28–7.23 (m, 2 H), 7.18–7.13 (m, 3 H), 5.32 (br s, 1 H), 4.24 (d, *J* = 17.1 Hz, 1 H), 4.20 (d, *J* = 16.7 Hz, 1 H), 4.04 (d, *J* = 17.1 Hz, 1 H), 3.75 (d, *J* = 16.7 Hz, 1 H), 3.26 (app d, *J* = 6.3 Hz, 1 H), 2.89 (s, 3 H), 2.64–2.55 (m, 1 H), 2.52–2.45 (m, 1 H), 1.76–1.67 (m, 1 H), 1.51–1.41 (m, 1 H), 1.22 (s, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.8, 168.7, 158.3, 143.1, 128.2, 128.2, 125.4, 62.2, 62.1, 49.1, 45.4, 35.1, 32.5, 29.3.

^{11}B NMR (128 MHz, DMSO-d_6): δ = 11.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{29}BN_3O_5$: 390.2200; found: 390.2202.

1,1-Diethyl-3-[1-(MIDA boryl)-3-phenylpropyl]urea (6d)
The reaction was carried out on a 0.32 mmol scale; yield: 95 mg (0.24 mmol, 77%); white solid; mp 150–152 °C; R_f = 0.40 (EtOAc–MeOH, 9:1).

IR (film): 3382, 2979, 2933, 1770, 1740, 1617, 1521, 1496, 1455, 1401, 1334, 1293, 1247, 1198, 1122, 1080, 1061, 1017, 1000, 955, 897, 856, 757, 702 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.27–7.23 (m, 2 H), 7.19–7.12 (m, 3 H), 5.07 (d, *J* = 9.1 Hz, 1 H), 4.24 (d, *J* = 17.2 Hz, 1 H), 4.17 (d, *J* = 16.8 Hz, 1 H), 4.01 (d, *J* = 17.2 Hz, 1 H), 3.70 (d, *J* = 16.8 Hz, 1 H), 3.50–3.44 (m, 1 H), 3.30–3.23 (m, 2 H), 3.20–3.11 (m, 2 H), 2.92 (s, 3 H), 2.64–2.56 (m, 1 H), 2.46–2.38 (m, 1 H), 1.74–1.68 (m, 2 H), 1.01 (t, *J* = 7.0 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 167.6, 157.6, 142.6, 128.6, 128.5, 125.9, 62.8, 62.2, 46.0, 41.6, 34.3, 33.4, 14.2.

^{11}B NMR (128 MHz, DMSO-d_6): δ = 12.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{29}BN_3O_5$: 390.2200; found: 390.2181.

1-[1-(MIDA boryl)-3-phenylpropyl]-3-phenylurea (6e)
The reaction was carried out on a 0.32 mmol scale; yield: 31 mg (75 μmol, 30%); white solid; mp 130–134 °C; R_f = 0.45 (EtOAc).

IR (film): 3382, 2943, 1762, 1745, 1646, 1597, 1540, 1497, 1440, 1292, 1230, 1119, 1075, 1046, 1029, 991, 952, 895, 861, 749, 694 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.55 (s, 1 H), 7.38 (d, *J* = 7.7 Hz, 2 H), 7.31–7.13 (m, 7 H), 6.87 (app t, *J* = 7.2 Hz, 1 H), 5.83 (d, *J* = 9.6 Hz, 1 H), 4.26 (d, *J* = 17.1 Hz, 1 H), 4.24 (d, *J* = 17.1 Hz, 1 H), 4.10 (d, *J* = 17.1 Hz, 1 H), 3.90 (d, *J* = 17.1 Hz, 1 H), 3.46–3.40 (m, 1 H), 2.91 (s, 3 H), 2.69–2.60 (m, 1 H), 2.60–2.51 (m, 1 H), 1.85–1.75 (m, 1 H), 1.61–1.51 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.9, 168.7, 155.6, 142.8, 140.7, 128.6, 128.2, 128.1, 125.5, 120.7, 117.2, 62.1(8), 62.1(7), 45.6, 34.9, 32.5.

^{11}B NMR (128 MHz, DMSO-d_6): δ = 11.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{25}BN_3O_5$: 410.1881; found: 410.1880.

α-Boryl Carbamates 7a–e; Procedure 1C (Table 3)
In a vial equipped with a stirring bar and a screw-cap lid was dissolved the appropriate α-boryl isocyanate **2** (0.30 mmol, 1.0 equiv) in anhydrous DMF (2 mL). Alcohol (0.90 mmol, 3.0 equiv) and CuCl (0.30 mmol, 1.0 equiv) were added subsequently and the reaction mixture was stirred at r.t. for 3 h until the reaction was complete as judged by TLC (eluent: EtOAc) or crude ^1H NMR analysis. The resulting green mixture was diluted with EtOAc (10 mL) and the CuCl suspension was filtered off. The filtrate was washed with H_2O (2 × 3 mL) and brine (3 mL). The organic layers were concentrated to remove the solvent. The crude residue was purified by flash column chromatography on silica gel [hexanes–EtOAc (50:50) → EtOAc → EtOAc–MeCN (90:10)] to afford the pure product.

Note: For the preparation of compound **7c**, 10.0 equiv of *t*-BuOH was used. The reaction was carried out at 70 °C for 24 h.

2-(Trimethylsilyl)ethyl [(MIDA boryl)(phenyl)methyl]carbamate (7a)
The reaction was carried out on a 0.35 mmol scale; yield: 123 mg (0.26 mmol, 75%); white solid; mp 84–87 °C; R_f = 0.55 (EtOAc).

IR (film): 2958, 1760, 1696, 1496, 1337, 1284, 1246, 1136, 1102, 1074, 1031, 1003, 952, 896, 858, 834, 702 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.25–7.19 (m, 5 H), 7.13–7.09 (m, 1 H), 4.24 (d, *J* = 17.1 Hz, 1 H), 4.22 (d, *J* = 17.1 Hz, 2 H), 4.19 (s, 1 H), 3.97 (t, *J* = 7.3 Hz, 2 H), 3.85 (d, *J* = 17.1 Hz, 1 H), 2.99 (s, 3 H), 0.88 (t, *J* = 7.3 Hz, 2 H), –0.01 (s, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.9, 168.2, 156.6, 143.8, 127.4, 127.1, 125.2, 62.6, 62.5, 61.5, 45.9, 17.4, –1.5.

^{11}B NMR (128 MHz, DMSO-d_6): δ = 10.2.

HRMS (DART-TOF): *m*/*z* $[M + NH_4]^+$ calcd for $C_{18}H_{31}BN_3O_6Si$: 424.20752; found: 424.20952.

(9*H*-Fluoren-9-yl)methyl [1-(MIDA boryl)pentyl]carbamate (7b)
The reaction was carried out on a 0.96 mmol scale; yield: 358 mg (0.77 mmol, 80%); white solid; mp 72–73 °C; R_f = 0.70 (EtOAc).

IR (film): 2955, 1761, 1695, 1515, 1450, 1335, 1293, 1234, 1161, 1101, 1080, 1023, 990, 896, 856, 759, 739 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.88 (d, *J* = 7.4 Hz, 2 H), 7.72 (dd, *J* = 7.1, 3.9 Hz, 2 H), 7.41 (dd, *J* = 7.4, 7.1 Hz, 2 H), 7.31 (dd, *J* = 11.1, 7.1 Hz, 2 H), 6.73 (d, *J* = 9.4 Hz, 1 H), 4.29–4.15 (m, 5 H), 4.04 (d, *J* = 17.3 Hz, 1 H), 3.67 (d, *J* = 16.8 Hz, 1 H), 3.09 (ddd, *J* = 11.3, 9.4, 2.5 Hz, 1 H), 2.85 (s, 3 H), 1.54–1.41 (m, 1 H), 1.40–1.18 (m, 5 H), 0.83 (t, *J* = 5.8 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.7, 168.6, 156.8, 143.9(5), 143.9(1), 140.7(0), 140.6(8), 127.6, 127.0, 125.3, 125.2, 120.0(3), 120.0(1), 65.1, 62.2, 46.9, 45.5, 30.9, 28.4, 22.2, 14.0.

^{11}B NMR (128 MHz, DMSO-d_6): δ = 11.6.

HRMS (DART-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{30}BN_2O_6$: 465.21969; found: 465.22061.

***tert*-Butyl [1-(MIDA boryl)pentyl]carbamate (7c)**
The reaction was carried out on a 0.10 mmol scale; yield: 21 mg (60 μmol, 60%); white solid; mp 89–91 °C; R_f = 0.50 (EtOAc).

IR (film): 2959, 1763, 1688, 1503, 1457, 1365, 1336, 1296, 1243, 1165, 1101, 1079, 1023, 991, 947, 896, 863, 731 cm^{-1}.

^1H NMR (400 MHz, acetone-d_6): δ = 5.20 (d, *J* = 10.5 Hz, 1 H), 4.22 (d, *J* = 17.0 Hz, 1 H), 4.20 (d, *J* = 16.7 Hz, 1 H), 4.12 (d, *J* = 17.0 Hz, 1 H), 3.89 (d, *J* = 16.7 Hz, 1 H), 3.24 (ddd, *J* = 10.5, 9.8, 3.5 Hz, 1 H), 3.15 (s, 3 H), 1.65–1.56 (m, 1 H), 1.39 (s, 9 H), 1.47–1.23 (m, 5 H), 0.89 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, acetone-d_6): δ = 168.8, 168.7, 157.5, 78.5, 63.3, 63.2, 46.3, 32.6, 29.6, 28.7, 23.4, 14.6.

^{11}B NMR (128 MHz, DMSO-d_6): δ = 11.5.

HRMS (DART-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{28}BN_2O_6$: 343.20404; found: 343.20510.

Allyl [(MIDA boryl)(phenyl)methyl]carbamate (7d)
The reaction was carried out on a 0.69 mmol scale; yield: 160 mg, (0.46 mmol, 67%); white solid; mp 240 °C (dec.); R_f = 0.45 (EtOAc).

IR (film): 3423, 3372, 1753, 1700, 1524, 1496, 1452, 1342, 1299, 1239, 1146, 1101, 1072, 1046, 1022, 992, 945, 882, 817, 804, 746, 710 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.46 (d, *J* = 8.6 Hz, 1 H), 7.27–7.20 (m, 4 H), 7.14–7.10 (m, 1 H), 5.92–5.82 (m, 1 H), 5.26 (dd, *J* = 17.3, 1.5 Hz, 1 H), 5.13 (dd, *J* = 10.6, 1.5 Hz, 1 H), 4.46–4.37 (m, 2 H), 4.25 (d, *J* = 17.1 Hz, 1 H), 4.23 (d, *J* = 17.1 Hz, 2 H), 4.20 (s, 1 H), 3.87 (d, *J* = 17.1, 1 H), 3.00 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.9, 168.2, 156.2, 143.6, 133.8, 127.5, 127.1, 125.3, 116.6, 64.2, 62.7, 62.5, 45.9.

^{11}B NMR (128 MHz, DMSO-d_6): δ = 11.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{20}BN_2O_6$: 347.1414; found: 347.1418.

Benzyl [1-(MIDA boryl)-3-phenylpropyl]carbamate (7e)
The reaction was carried out on a 0.63 mmol scale; yield: 242 mg (0.57 mmol, 90%); white solid; mp 78–80 °C; R_f = 0.55 (EtOAc).

IR (film): 3328, 3030, 2947, 1761, 1694, 1517, 1497, 1454, 1335, 1291, 1234, 1124, 1076, 1017, 954, 896, 859, 741, 697 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.31 (m, 5 H), 7.27–7.23 (m, 2 H), 7.17–7.14 (m, 3 H), 5.10 (d, *J* = 12.2 Hz, 1 H), 5.06 (d, *J* = 12.2 Hz, 1 H), 4.68 (d, *J* = 10.3 Hz, 1 H), 3.76 (d, *J* = 16.5 Hz, 1 H), 3.72 (d, *J* = 16.1 Hz, 1 H), 3.67 (d, *J* = 16.5 Hz, 1 H), 3.52 (d, *J* = 16.1 Hz, 1 H), 3.33 (ddd, *J* = 10.3, 10.1, 3.3 Hz, 1 H), 2.91 (s, 3 H), 2.77–2.69 (m, 1 H), 2.62–2.54 (m, 1 H), 2.07–1.99 (m, 1 H), 1.80–1.70 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 167.7, 157.3, 142.2, 136.9, 128.7, 128.6, 128.5, 128.4, 128.2, 126.0, 67.0, 62.7, 62.3, 46.0, 33.9, 32.9.

^{11}B NMR (128 MHz, DMSO-d_6): δ = 12.6.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{26}BN_2O_6$: 425.1884; found: 425.1894.

α-Aminoboronic Acid Derivatives with a Quaternary Carbon Center (Scheme 4)

2-(MIDA boryl)-2-phenylpent-4-enoic Acid (12)

To a suspension of α,α-disubstituted α-boryl aldehyde **11** (250 mg, 0.79 mmol, 1 equiv) in *t*-BuOH (5 mL) was added cyclohexene (2.38 mmol, 0.24 mL, 3.0 equiv). A solution of $NaClO_2$ (80% purity, 0.107 g, 0.95 mmol, 1.2 equiv) and NaH_2PO_4 (0.131 g, 0.95 mmol, 1.2 equiv) in H_2O (5 mL) was added dropwise at r.t. The mixture was vigorously stirred at r.t. for 12 h. The reaction solution was then diluted with brine (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were concentrated to remove the solvent. The crude product was purified by flash column chromatography on silica gel [hexanes–EtOAc (50:50) → EtOAc → EtOAc–MeCN (90:10)] to afford the pure product as a white foam; yield: 162 mg (0.51 mmol, 65%); R_f = 0.37 (EtOAc).

IR (film): 2926, 1765, 1743, 1467, 1447, 1344, 1291, 1243, 1195, 1162, 1096, 1066, 1022, 992, 962, 899, 874, 827, 734, 703 cm^{-1}.

^1H NMR (400 MHz, acetone-d_6): δ = 7.43–7.33 (m, 2 H), 7.33–7.23 (m, 2 H), 7.22–7.11 (m, 1 H), 5.88 (dddd, *J* = 17.1, 10.2, 8.0, 5.8 Hz, 1 H), 4.86 (ddt, *J* = 17.1, 2.6, 1.5 Hz, 1 H), 4.75 (ddt, *J* = 10.2, 2.6, 1.2 Hz, 1 H), 4.30 (d, *J* = 17.5 Hz, 1 H), 4.13 (d, *J* = 16.3 Hz, 1 H), 4.06 (d, *J* = 16.3 Hz, 1 H), 3.92 (d, *J* = 17.5 Hz, 1 H), 3.01 (ddt, *J* = 14.4, 5.8, 1.5 Hz, 1 H), 2.78 (dd, *J* = 14.4, 8.0 Hz, 1 H), 2.62 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.7, 168.9, 168.3, 140.4, 135.8, 129.0, 127.6, 126.7, 117.7, 65.1, 64.5, 48.6, 41.3.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 11.5.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{19}BNO_6$: 332.1306; found: 332.1304.

1-(MIDA boryl)-1-phenylbut-3-en-1-yl Isocyanate (13)

To a solution of **12** (75 mg, 0.227 mmol) in anhydrous MeCN (1 mL) was added Et_3N (38 μL, 0.273 mmol, 1.2 equiv) and subsequently DPPA (59 μL, 0.273 mmol, 1.2 equiv). The resulting solution was stirred at r.t. under N_2 for 15 min, and then heated at 50 °C for 2 h until the reaction was complete as indicated by the ^1H NMR analysis of the crude mixture. The reaction mixture was cooled to r.t. and evaporated under reduced pressure to remove the solvent. The crude residue was purified by flash column chromatography on silica gel [hexanes–EtOAc (80:20) → hexanes–EtOAc (50:50) → EtOAc] to afford the pure product; yield: 53 mg (0.16 mmol, 70%); white solid; mp 164–165 °C; R_f = 0.70 (EtOAc).

IR (film): 3009, 2964, 2250, 1773, 1746, 1494, 1448, 1347, 1303, 1253, 1197, 1162, 1127, 1082, 1061, 1033, 993, 976, 963, 926, 901, 874, 803, 759, 712 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.48 (m, 2 H), 7.38–7.34 (m, 2 H), 7.29–7.23 (m, 1 H), 5.43–5.33 (m, 1 H), 5.22 (d, *J* = 17.1 Hz, 1 H), 5.12 (d, *J* = 9.9 Hz, 1 H), 3.85 (d, *J* = 16.3 Hz, 1 H), 3.77 (d, *J* = 16.3 Hz, 1 H), 3.62 (d, *J* = 16.2 Hz, 1 H), 2.97 (d, *J* = 16.2 Hz, 1 H), 3.02 (ddt, *J* = 14.3, 5.2, 1.3 Hz, 1 H), 2.95 (dd, *J* = 14.3, 8.8 Hz, 1 H), 2.68 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 166.8, 140.7, 131.9, 129.1, 127.1, 126.0, 124.9, 121.0, 63.8, 63.3, 46.9, 45.8.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 10.8.

HRMS (DART-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{18}BN_2O_5$: 329.13088; found: 329.12999.

(1-Amino-1-phenylbut-3-en-1-yl)boronic Acid (14)

In a vial equipped with a stirring bar and a screw-cap lid was dissolved α-boryl isocyanate **13** (25 mg, 0.0762 mmol, 1.0 equiv) in MeCN (2 mL). Aq 6.0 M HCl (0.127 mL, 10 equiv) was added dropwise and the reaction mixture was stirred at r.t. for 48 h until the reaction was complete as judged by TLC (eluent: EtOAc). The resulting solution was evaporated to remove the solvent under reduced pressure. The residue was azeotroped with MeCN three times to obtain the desired product; yield: 17 mg (76 μmol, ~100%); white solid (1:1 mixture with MIDA).

^1H NMR (400 MHz, CD_3OD): δ = 7.48–7.43 (m, 4 H), 7.41–7.32 (m, 1 H), 5.88–5.76 (m, 1 H), 5.34 (d, *J* = 17.1 Hz, 1 H), 5.27 (d, *J* = 9.8 Hz, 1 H), 4.11 (s, 4 H, MIDA α-CH_2), 3.05 (s, 3 H, MIDA CH_3), 3.00–2.90 (m, 2 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 168.7 (MIDA C=O), 140.0, 133.1, 130.4, 129.6, 127.7, 121.6, 57.4 (MIDA α-CH_2), 43.4 (MIDA CH_3), 22.2.

^{11}B NMR (128 MHz, CD_3OD): δ = 28.5.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd For $C_{10}H_{15}BNO_2$: 192.1196; found: 192.1191.

1-Ethyl-3-[1-(MIDA boryl)-1-phenylbut-3-en-1-yl]urea (15)

In a vial equipped with a stirring bar and a screw-cap lid was dissolved the α-boryl isocyanate **13** (13.1 mg, 0.0399 mmol, 1.0 equiv) in anhydrous THF (1 mL). $EtNH_2$ (2.0 M in THF, 0.0479 mmol, 1.2 equiv) was added and the reaction mixture was stirred at r.t. for 5 h until the reaction was complete as judged by TLC (eluent: EtOAc). The resulting solution was concentrated to remove the solvent under reduced pressure. The crude product was subjected to purification by flash column chromatography on silica gel to obtain the pure product; yield: 13 mg (34 μmol, 85%); white solid; mp 112–115 °C; R_f = 0.33 (EtOAc).

IR (film): 3389, 2973, 1762, 1740, 1667, 1542, 1493, 1444, 1347, 1303, 1271, 1193, 1111, 1024, 1003, 953, 906, 864, 824, 766, 724, 704 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.26–7.19 (m, 4 H), 7.15–7.11 (m, 1 H), 6.21 (t, *J* = 3.5 Hz, 1 H), 5.82–5.71 (m, 1 H), 5.57 (br s, 1 H), 5.01 (dd, *J* = 18.4, 2.3 Hz, 1 H), 4.97 (dd, *J* = 10.1, 2.3 Hz, 1 H), 4.11 (d, *J* = 17.0 Hz, 1 H), 4.02 (d, *J* = 17.1 Hz, 1 H), 3.97 (d, *J* = 17.1 Hz, 1 H), 2.79 (d, *J* = 17.0 Hz, 1 H), 2.99 (qd, *J* = 7.1, 3.5 Hz, 2 H), 2.94 (dd, *J* = 13.9, 7.5 Hz, 1 H), 2.72 (dd, *J* = 13.9, 6.8 Hz, 1 H), 2.64 (s, 3 H), 1.00 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.2, 168.2, 157.9, 145.1, 135.6, 127.5, 126.2, 125.1, 117.1, 63.1, 62.9, 46.0, 43.2, 33.9, 15.7.

^{11}B NMR (128 MHz, DMSO-d_6): δ = 11.6.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{25}BN_3O_5$: 374.1887; found: 374.1882.

α-Ureido Boronic Acid; {1-[3-(*tert*-Butyl)ureido]-3-phenylpropyl}boronic Acid (Scheme 5)

In a vial equipped with a stirring bar and a screw-cap lid was dissolved the α-boryl urea **6c** (87 mg, 0.225 mmol, 1.0 equiv) in THF (3 mL). Aq 1.0 M NaOH (0.676 mL, 3.0 equiv) was added dropwise and the reaction mixture was stirred at r.t. for 15 min. The reaction was then quenched with sat. aq NH_4Cl (3 mL). Et_2O (3 mL) was added, the product extracted, and the layers were separated. The aqueous layer was further extracted with a mixed solvent E_2O–THF (1:1) (2 × 3 mL). The organic phases were combined and concentrated to dryness under reduced pressure to afford the desired free boronic acid product as a white powder; yield: 55.8 mg (0.20 mmol, 90%); mp 95 °C (dec.).

IR (film): 3369, 2964, 2931, 1627, 1595, 1526, 1496, 1453, 1387, 1365, 1316, 1192, 1098, 811, 747, 697 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.19–7.15 (m, 2 H), 7.10–7.06 (m, 3 H), 6.49 (br s, 1 H), 6.16 (br s, 1 H), 2.57–2.50 (m, 2 H), 2.45–2.39 (m, 1 H), 1.80–1.69 (m, 1 H), 1.63–1.53 (m, 1 H), 1.21 (s, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.7, 143.4, 128.1, 127.9, 125.1, 50.0, 33.3, 30.4, 29.2.

^{11}B NMR (128 MHz, DMSO-d_6): δ = 16.7.

HRMS (DART-TOF): *m*/*z* $[(M - H_2O) + H]^+$ calcd for $C_{14}H_{22}BN_2O_2$: 261.17743; found: 261.17655.

Preparation and Coupling of α-Boryl Amine 9 (Scheme 6)

2-Amino(phenyl)methyl MIDA Boronate (9)

To a solution of carbamate **7d** (0.664 g, 1.92 mmol, 1.0 equiv) in CH_2Cl_2–MeOH (2:1, 60 mL, predegassed with N_2) was added 1,3-dimethylbarbituric acid (DMBA; 0.599 g, 3.84 mmol, 2.0 equiv) and subsequently $Pd(PPh_3)_4$ (44 mg, 0.0384 mmol, 0.02 equiv). The reaction mixture was stirred at r.t. under N_2 for 1 h until the reaction was complete as judged by TLC (eluent: EtOAc–MeCN–MeOH–H_2O, 70:10:10:5). The reaction mixture was concentrated to remove the solvent. The residue was diluted with EtOAc (100 mL) and quickly washed with sat. aq Na_2CO_3 (2 × 25 mL) and brine (25 mL). The organic phase was separated and concentrated to dryness to afford the crude product as a yellowish solid. The crude product was purified using a short pad of silica gel [hexanes–EtOAc (50:50) → EtOAc → EtOAc–MeCN–MeOH (70:10:10) → EtOAc–MeCN–MeOH–H_2O (70:10:10:5)] to afford the pure product **9** as a beige solid; yield: 252 mg (0.96 mmol, 50%); mp 90–91 °C; R_f = 0.15 (EtOAc–MeCN–MeOH–H_2O, 70:10:10:5).

IR (film): 1762, 1747, 1599, 1448, 1339, 1290, 1246, 1194, 1155, 1106, 1073, 1046, 1004, 949, 898, 862, 773, 703 cm^{-1}.

^1H NMR (400 MHz, CD_3CN): δ = 7.34–7.27 (m, 4 H), 7.20–7.15 (m, 1 H), 4.02 (d, *J* = 16.3 Hz, 1 H), 3.95 (d, *J* = 16.3 Hz, 1 H), 3.94 (d, *J* = 17.3 Hz, 1 H), 3.84 (d, *J* = 17.3 Hz, 1 H), 3.41 (s, 1 H), 3.19 (s, 3 H).

^{13}C NMR (100 MHz, CD_3CN): δ = 169.6, 169.1, 148.1, 129.0, 127.9, 126.6, 63.7, 63.5, 46.7.

^{11}B NMR (128 MHz, DMSO-d_6): δ = 11.5.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{16}BN_2O_4$: 263.1203; found: 263.1192.

Benzyl [(2*S*)-4-Methyl-1-({[MIDA boryl)(phenyl)methyl]amino}-1-oxopentan-2-yl)]carbamate (10)

To a solution of Cbz-Leu-OH (69 mg, 0.261 mmol, 1.2 equiv) and α-amino MIDA boronate **9** (57 mg, 0.217 mmol, 1.0 equiv) in anhydrous $CHCl_3$ (5 mL) was added PyBop (147 mg, 0.283 mmol, 1.3 equiv) and subsequently DIPEA (75 μL, 0.434 mmol, 2 equiv). The reaction mixture was stirred at r.t. under N_2 for 5 h. The reaction solution was washed with aq 10% citric acid (2 mL) and sat. aq $NaHCO_3$ (2 mL). The organic layer was concentrated and the residue was purified by flash column chromatography on silica gel [hexanes–EtOAc (50:50) → EtOAc → EtOAc–MeCN (90:10)] to afford the two diastereoisomers of the desired coupling products.

Diastereomer 1

Yield: 53 mg (0.10 mmol, 40%); white solid; mp 140–147 °C; R_f = 0.60(EtOAc).

IR (film): 3303, 2956, 1758, 1705, 1656, 1532, 1453, 1338, 1290, 1236, 1114, 1036, 950, 896, 736, 699 cm^{-1}.

^1H NMR (400 MHz, CD_3CN): δ = 7.41–7.33 (m, 5 H), 7.30–7.24 (m, 4 H), 7.20–7.16 (m, 1 H), 7.10 (d, *J* = 10.0 Hz, 1 H), 5.89 (d, *J* = 6.5 Hz, 1 H), 5.10 (d, *J* = 12.6 Hz, 1 H), 5.02 (d, *J* = 12.6 Hz, 1 H), 4.68 (d, *J* = 10.0 Hz, 1 H), 4.06 (d, *J* = 16.0 Hz, 1 H), 4.08–4.00 (m, 1 H), 3.96 (d, *J* = 17.1 Hz, 1 H), 3.93 (d, *J* = 16.0 Hz, 1 H), 3.89 (d, *J* = 17.1 Hz, 1 H), 2.86 (s, 3 H), 1.58–1.48 (m, 1 H), 1.46–1.30 (m, 2 H), 0.86 (d, *J* = 6.6 Hz, 3 H), 0.83 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, CD_3CN): δ = 173.5, 169.1, 168.7, 157.5, 143.7, 138.3, 129.6, 129.0, 128.7, 128.4, 127.0, 67.2, 63.86, 63.3, 54.8, 46.7, 41.1, 25.4, 23.324, 22.0.

^{11}B NMR (128 MHz, DMSO-d_6): δ = 11.1.

HRMS (ESI): *m*/*z* $[M+ H]^+$ calcd for $C_{26}H_{33}BN_3O_7$: 510.2412; found: 510.2404.

Diastereomer 2

Yield: 53 mg (0.10 mmol, 40%); white solid; mp 119–121 °C; R_f = 0.37 (EtOAc).

IR (film): 3328, 2959, 1760, 1706, 1668, 1518, 1454, 1337, 1287, 1251, 1111, 1038, 950, 895, 843, 739, 698 cm^{-1}.

^1H NMR (400 MHz, CD_3CN): δ = 7.39–7.32 (m, 5 H), 7.30–7.24 (m, 4 H), 7.21–7.17 (m, 1 H), 6.97 (d, *J* = 9.9 Hz, 1 H), 5.91 (d, *J* = 5.4 Hz, 1 H), 5.10 (d, *J* = 12.2 Hz, 1 H), 5.03 (d, *J* = 12.2 Hz, 1 H), 4.65 (d, *J* = 9.9 Hz, 1 H), 4.07–4.00 (m, 1 H), 4.00 (d, *J* = 17.0 Hz, 1 H), 3.99 (d, *J* = 17.1 Hz, 1 H), 3.93 (d, *J* = 17.0 Hz, 1 H), 3.83 (d, *J* = 17.1 Hz, 1 H), 2.97 (s, 3 H), 1.66–1.54 (m, 1 H), 1.46–1.42 (m, 2 H), 0.88 (d, *J* = 7.1 Hz, 3 H), 0.86 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, CD_3CN): δ = 173.2, 169.1, 168.5, 157.6, 143.6, 137.9, 129.6, 129.0(9), 129.0(6), 128.4, 127.17, 67.6, 63.7, 63.5, 55.3, 47.0, 41.1, 25.6, 23.3, 21.8.

^{11}B NMR (128 MHz, DMSO-d_6): δ = 11.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{33}BN_3O_7$: 510.2412; found: 510.2404.

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