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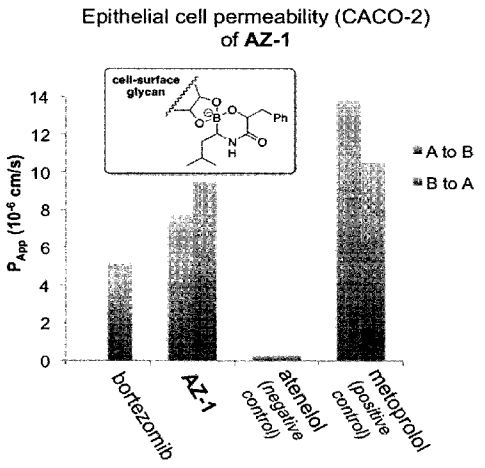
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(54) Title: A-BORYL ISOCYANIDES, BOROPEPTIDES AND BORON HETEROCYCLES

Figure 8



AZ-1 = 11ad

(57) Abstract: This application pertains to α-boryl isocyanates, wherein the boronate moiety is in the form of an N-methyliminodiacetic acid (MIDA) boronate of the Formula (2) and the utility of said compounds in the synthesis of the borylamide motif (B-C-N_{amide}) in the scaffold of biologically-active boropeptides, such as bortezomib, in the enablement of heterocycle synthesis, and in multi-component reactions (MCRs), such as the Ugi and Passerini processes.

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α-BORYL ISOCYANIDES, BOROPEPTIDES AND BORON HETEROCYCLES

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application No. 61/807,400 filed on April 2, 2013, which is incorporated herein by reference.

FIELD OF THE INVENTION

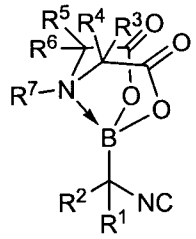
The invention relates to novel α-boryl isocyanides, their synthesis, as well as their use in the preparation of boron-containing compounds.

BACKGROUND OF THE INVENTION

Boronic acids and their derivatives are useful as synthetic building blocks, [1] chemosensors,[2] and biologically active targets of synthesis. Both the biological activity and chemical reactivity of boronic acids stem from boron's Lewis acidity. While useful in a broad range of applications, boron's propensity to undergo reactions with Lewis bases becomes problematic for functional group compatibility during synthesis.[1] Reagents that streamline installation of a carbon-boron bond in stereochemically complex, heteroatom-rich environments, are expected to find application not only as starting materials but also as valuable endpoints of synthesis.

SUMMARY OF INVENTION

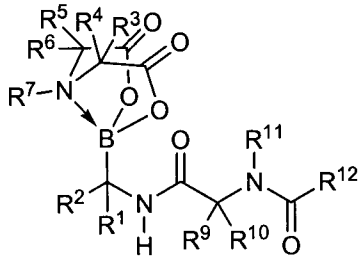
In an aspect, there is provided a compound of Formula (2):



Formula (2)

wherein R^1, R^2, R^3, R^4, R^5, R^6 and R^7 and are each independently H or an organic group.

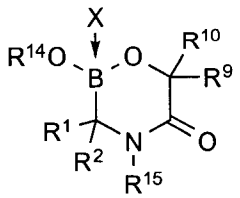
In a further aspect, there is provided a compound of Formula (9):



Formula (9)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^9, R^{10}, R^{11} and R^{12} are each independently H or an organic group.

In a further aspect, there is provided a compound of Formula (11):



Formula (11)

wherein R^1, R^2, R^9, R^{10}, R^{14}, and R^{15} are each independently H or an organic group and X is any Lewis basic ligand.

There is also described herein, processes for the synthesis of the above compounds.

BRIEF DESCRIPTION OF FIGURES

These and other features of the preferred embodiments of the invention will become more apparent in the following detailed description in which reference is made to the appended drawings wherein:

Figure 1 shows the *in vitro* cytosolic chymotrypsin-like 20S proteasome inhibition by boropeptide derivative 7a-A.

Figure 2 shows the *in vitro* cytosolic chymotrypsin-like 20S proteasome inhibition by boropeptide derivative 7a-B.

Figure 3 shows the *in vitro* cytosolic chymotrypsin-like 20S proteasome inhibition by boromorpholinone *anti*-11ad.

Figure 4 shows the *in vitro* cytosolic caspase-like 20S proteasome inhibition by boromorpholinone *anti*-11ad.

Figure 5 shows the *in vitro* cytosolic trypsin-like 20S proteasome inhibition by boromorpholinone *anti*-11ad.

Figure 6 shows the *in vitro* cytosolic chymotrypsin-like 20S proteasome inhibition by boromorpholinones *syn*-11ad and *anti*-11ad.

Figure 7 shows the computational analysis of possible hydrolytic degradation of *anti*-11ad. Data reflects enthalpic energy differences between reaction partners.

Figure 8 shows the cellular permeability of *anti*-11ad compared to bortezomib with positive (metoprolol) and negative (atenolol) controls.

Figure 9 shows a computational model of *anti*-11ad in complex with a chymotrypsin-like member of proteasome 20S.

Figure 10 shows the structures of several MIDA-boronate containing compounds which act as potent protease inhibitors.

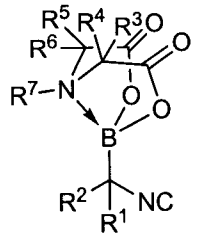
DETAILED DESCRIPTION

In the following description, numerous specific details are set forth to provide a thorough understanding of the invention. However, it is understood that the invention may be practiced without these specific details.

The borylamide motif (B–C–N_{amide}) is commonly found in the structures of biologically active boropeptides.[3] Recent efforts have been focused on the amphoteric aziridine aldehyde- and isocyanide-driven macrocyclizations of linear peptides and peptidomimetics.[4] This methodology is enabled by the development of functionally dense, heteroatom-rich environments where a kinetic barrier prevents two otherwise reactive functional groups from prematurely reacting with each other.[5] In the present invention, we expand the scope of this methodology to include amphoteric boron-containing building blocks for use in multi-component preparation of boropeptides and their derivatives.

As part of our efforts to develop amphoteric boron-transfer reagents, we considered an isocyanide/boron combination. Isocyanides are 1,1-amphoteric molecules that enable heterocycle synthesis[6] and participate in multi-component reactions (MCRs) such as Ugi and Passerini processes.[7] Herein, we outline the preparation and utility of bench-stable α-boryl isocyanides. We demonstrate the application of these novel derivatives in heterocycle synthesis as well as in MCRs to generate biologically active boropeptides. As part of our study, we demonstrate a two-step synthesis of both diastereomers of bortezomib, an FDA approved, boron-containing proteasome inhibitor used to treat multiple myeloma.[8] Furthermore, our documented discovery of a novel class of boron-containing heterocycles, with biological activity comparable to bortezomib, will be useful in efforts to prepare libraries of biologically active boropeptide derivatives using readily available starting materials.[3b, d, f, g, l, n, o, p]

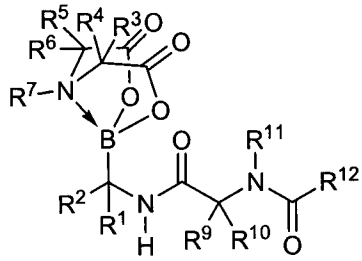
In an aspect, there is provided a compound of Formula (2):



Formula (2)

wherein R^1, R^2, R^3, R^4, R^5, R^6 and R^7 and are each independently H or an organic group.

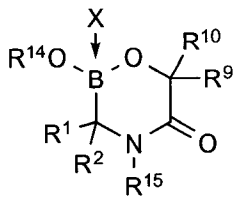
In a further aspect, there is provided a compound of Formula (9):



Formula (9)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^9, R^{10}, R^{11} and R^{12} are each independently H or an organic group.

In a further aspect, there is provided a compound of Formula (11):



Formula (11)

wherein R^1, R^2, R^9, R^{10}, R^{14}, and R^{15} are each independently H or an organic group and X is any Lewis basic ligand.

In some embodiments, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are each independently selected from the group consisting of H, an alkyl group, a heteroalkyl group, a cycloalkyl group, an alkenyl group, a heteroalkenyl group, an alkynyl group, a heteroalkynyl group, an aryl group, a heteroaryl group, a heterocyclic group, and an acyl group. Preferably, the organic group is substituted with one or more halide, hydroxyl, alkoxyl, acyloxyl or acyl groups.

In some embodiments, R^3, R^4, R^5, R^6 are H and R^7 is CH_3.

In some embodiments, R^1 and R^2 are independently selected from the group consisting of H, isobutyl, cyclohexyl and phenyl. In some embodiments, R^1 and R^2 are independently selected from the group consisting of H, isobutyl, cyclohexyl and phenyl. In some embodiments, R^1 and R^2 are independently selected from the group consisting of H, isobutyl, cyclohexyl and phenyl.

In some embodiments, R^9 and R^{10} are independently selected from the group consisting of H, benzyl and isopropyl. In other embodiments, R^9 and R^{10} are independently selected from the group consisting of H, benzyl, isopropyl, 4-F-phenyl, phenyl, 3-pyridinyl, 4-Me-phenyl, 2-Br-phenyl, isopropyl, and 3-pyridinyl.

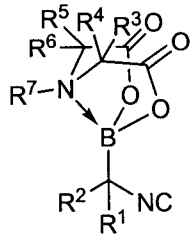
In some embodiments, R^{11} is H.

In some embodiments, R^{12} is independently selected from the group consisting of H, an alkyl group, a heteroalkyl group, a cycloalkyl group, an alkenyl group, a heteroalkenyl group, an alkynyl group, a heteroalkynyl group, an aryl group, a heteroaryl group, a heterocyclic group, and an acyl group.

In some embodiments, R^{12} is an amino acid or peptide, preferably selected from the group consisting of G, F, V, GG, FA, PLF and PGLF. In some embodiments, the amino acid or peptide comprises a protecting group.

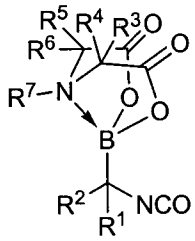
In some embodiments, R^{14} is H and X is tetrahydrofuran.

In a further aspect, there is provided a process for preparing the compound of Formula (2):



Formula (2)

comprising reducing the compound of Formula (1):

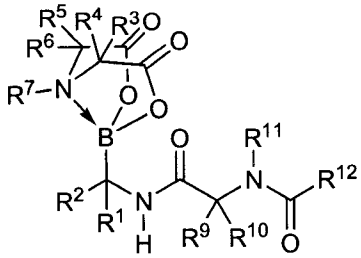


Formula (1)

wherein R^1, R^2, R^3, R^4, R^5, R^6 and R^7 and are each independently H or an organic group.

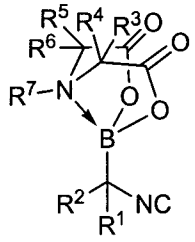
In some embodiments, reducing the compound of Formula (1) is performed with at least one condition and/or reagent selected from $HSiCl_3$, Et_3N, CH_2Cl_2, and 0-23°C.

In a further aspect, there is provided a process for preparing the compound of Formula (9):



Formula (9)

comprising subjecting to a Ugi 4-component reaction, the compound of Formula (2):



Formula (2)

R^{12} – COOH;

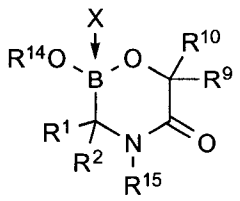
$R^{11}NH_2$; and

R^9R^{10}-CO;

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^9, R^{10}, R^{11} and R^{12} are each independently H or an organic group..

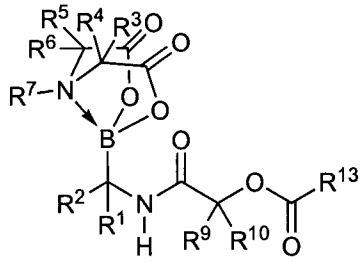
In some embodiments, the Ugi 4-component reaction is performed with at least one condition and/or reagent selected from TFE, 23°C and time.

In a further aspect, there is provided a process for preparing the compound of Formula (11):



Formula (11)

comprising ester hydrolysis and deprotection of the compound of Formula (10):



Formula (10)

wherein R^1, R^2, R^9, R^{10}, R^{14}, and R^{15} are each independently H or an organic group and X is any Lewis basic ligand.

In some embodiments, the ester hydrolysis and deprotection of the compound of Formula (10) is performed with at least one condition and/or reagent selected from NaOH, THF/H_2O, 23°C and time (10 min.).

In some embodiments, the process further comprises performing a Passerini 3-component reaction with the compound of Formula (2), R^9R^{10}-CO, and an organic acid R^{13}-COOH (preferably Ph-CH_2-COOH), to obtain the compound of Formula (10).

In some embodiments, the Passerini 3-component reaction is performed with at least one condition and/or reagent selected from CH_2Cl_2 and 23°C.

In some embodiments, the preparation of the compound of formula (11) in which R^{15} is an alkyl group is performed by subjecting the corresponding compound of formula 11 in which R^{15} is H with at least one condition and/or reagent selected from NaH, $R^{15}I$, THF, crushed 4Å molecular sieves, 23°C and time (12 h) in a deprotonation/alkylation reaction.

The term "group" means a linked collection of atoms or a single atom within a molecular entity, where a molecular entity is any constitutionally or isotopically distinct atom, molecule, ion, ion pair, radical, radical ion, complex, conformer etc., identifiable as a separately distinguishable entity. The description of a group as being "formed by" a particular chemical transformation does not imply that this chemical transformation is involved in making the molecular entity that includes the group.

The term "organic group" means a group containing at least one carbon atom.

The term "alkyl group" means a group formed by removing a hydrogen from a carbon of an alkane, where an alkane is an acyclic or cyclic compound consisting entirely of hydrogen atoms and saturated carbon atoms. An alkyl group may include one or more substituent groups.

The term "heteroalkyl group" means a group formed by removing a hydrogen from a carbon of a heteroalkane, where a heteroalkane is an acyclic or cyclic compound consisting entirely of hydrogen atoms, saturated carbon atoms, and one or more heteroatoms. A heteroalkyl group may include one or more substituent groups.

The term "alkenyl group" means a group formed by removing a hydrogen from a carbon of an alkene, where an alkene is an acyclic or cyclic compound consisting entirely of hydrogen atoms and carbon atoms, and including at least one carbon-carbon double bond. An alkenyl group may include one or more substituent groups.

The term "heteroalkenyl group" means a group formed by removing a hydrogen from a carbon of a heteroalkene, where a heteroalkene is an acyclic or cyclic compound consisting entirely of hydrogen atoms, carbon atoms and one or more heteroatoms, and including at least one carbon-carbon double bond. A heteroalkenyl group may include one or more substituent groups.

The term "alkynyl group" means a group formed by removing a hydrogen from a carbon of an alkyne, where an alkyne is an acyclic or cyclic compound consisting entirely of hydrogen atoms and carbon atoms, and including at least one carbon-carbon triple bond. An alkynyl group may include one or more substituent groups.

The term "heteroalkynyl group" means a group formed by removing a hydrogen from a carbon of a heteroalkyne, where a heteroalkyne is an acyclic or cyclic compound consisting entirely of hydrogen atoms, carbon atoms and one or more heteroatoms, and including at least one carbon-carbon triple bond. A heteroalkynyl group may include one or more substituent groups.

The term "aryl group" means a group formed by removing a hydrogen from a ring carbon atom of an aromatic hydrocarbon. An aryl group may by monocyclic or polycyclic and may include one or more substituent groups.

The term "heteroaryl group" means a group formed by replacing one or more methine (-C=) and/or vinylene (-CH=CH-) groups in an aryl group with a trivalent or divalent heteroatom, respectively. A heteroaryl group may by monocyclic or polycyclic and may include one or more substituent groups.

The term "substituent group" means a group that replaces one or more hydrogen atoms in a molecular entity.

The term "heterocyclic group" means a group formed by removing a hydrogen from a cyclic compound that has atoms of at least two different elements as members of its ring(s).

The term "acyl group" means a group formed by removing one or more hydroxyl groups from an oxoacid, i.e. RCO-.

The term "halogen group" means F-, Cl-, Br- or I-.

The term "hydroxyl group" means the group containing an oxygen atom connected by a covalent bond to a hydrogen atom, i.e. OH-.

The term "alkoxy group" means an alkyl group singularly bonded to oxygen, i.e. R-O.

The term "acyloxyl group" means a group formed by removal of hydrogen from oxygen in an organic acid, e.g. RCOO−.

The term "organohalide" means an organic compound that includes at least one halogen group.

One would understand that chemical reactions, in some cases, may require and would include protecting certain peptide or amino acid side chains with a protecting group in manner known to a person skilled in the art.

The advantages of the present invention are further illustrated by the following examples. The examples and their particular details set forth herein are presented for illustration only and should not be construed as a limitation on the claims of the present invention.

EXAMPLES

MATERIALS AND METHODS

General: Anhydrous solvents were obtained by distillation under nitrogen prior to use. Dichloromethane was purified using an MBraun Solvent Purification System. All other solvents were of reagent grade quality. All reagents, catalysts and ligands were purchased from Combi-Blocks Inc., Sigma-Aldrich, Strem-Chemical Company, VWR International, or Aapptec and used as received unless otherwise noted.

Nuclear Magnetic Resonance Spectroscopy: NMR spectra were recorded at 25°C on Bruker Advance III 400, Varian Mercury 400 or Agilent DD2-500 instrument. The DD2-500 MHz spectrometer used an Agilent HC 5-mm XSens cryogenically-cooled probe. A ^{1}H pulse width of 45° was used, acquiring a spectral window of 7000 Hz (14 ppm) using 32k points. The ^{1}H 90° pulse width was 11.75 µs. A ^{13}C pulse width of 30° was used acquiring a spectral window of 28750 Hz (230 ppm) using 64k points. The ^{13}C 90° pulse width was 21.4 µs. All pulse sequences used were provided by Agilent. ^{13}C NMR spectra were registered with broad-band decoupling. Recorded shifts for protons are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvents (DMSO-d_6: 2.54 or MeCN-d_3: δ 1.94, centre line). Chemical shifts for carbon resonances are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (DMSO-d_6: 40.45 or MeCN-d_3: δ 1.32, centre line). Carbons exhibiting significant line broadening brought about by boron substituents were not reported (quadrupolar relaxation).^{11}B NMR was recorded at 25°C on a Bruker Advance III 400 MHz spectrometer or on an Agilent DD2 600 MHz spectrometer with an Agilent OneNMR probe and referenced to an external standard of $BF_3 \cdot Et_2O$. Data are represented as follows: chemical shift δ in ppm, multiplicity (s singlet, d doublet, t triplet, q quartet, m multiplet, br broad), coupling constant J in Hz and integration.

Chromatography: Flash column chromatography was carried out using Silicycle 230-400 mesh silica gel. Thin-layer chromatography (TLC) was performed on Macherey Nagel pre-coated glass backed TLC plates (SIL G/UV254, 0.25 mm) and visualized using a UV lamp (254 nm) or $KMnO_4$ or Curcumin stain in case of no UV activity.

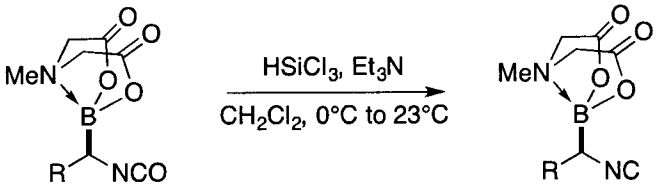
Infrared Spectroscopy: Infrared (IR) spectra were recorded on a Perkin-Elmer Spectrum 100 instrument equipped with a single-reflection diamond/ZnSe ATR accessory.

Mass Spectroscopy: 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.

It should be noted that intermediates used directly in subsequent reactions without purification are characterized by crude ^{1}H NMR only.

RESULTS

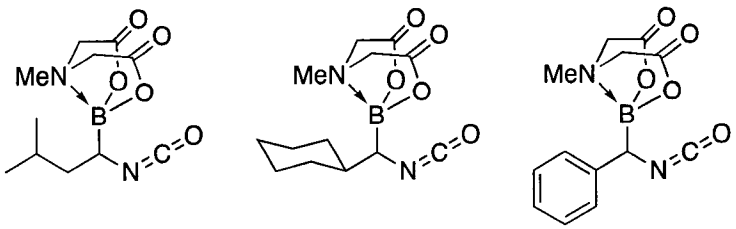
General procedure for the synthesis of α-boryl isocyanides 2a-c



1 2

α-Boryl isocyanates used in this paper for the synthesis of α-boryl isocyanides were prepared according to the literature method[13] in which the preparation and characterization of phenyl-, isobutyl-, and cyclohexyl- substituted α-boryl isocyanates were reported.

List of known α-boryl isocyanates:

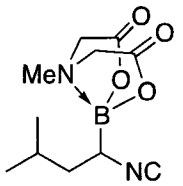


(isobutyl-) (cyclohexyl-) (phenyl-)

To a flame-dried flask flushed with Ar was added freshly distilled DCM (10 mL) which was cooled to 0°C. Trichlorosilane (4.86 mmol, 0.5 mL, 1.3 equiv.) was added followed

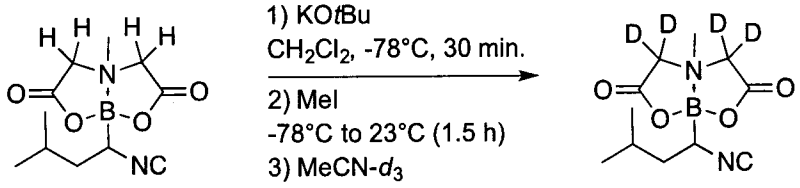
by dropwise addition of triethylamine (11.22 mmol, 0.82 mL, 3.0 equiv.). α-Boryl isocyanate (3.74 mmol, 1.1 g, 1.0 equiv.) was added and the resulting suspension was stirred vigorously at 0°C for 30 minutes. The resulting solution was allowed to warm to rt. Stirring was continued until starting material was completely consumed as indicated by TLC or crude ^{1}H NMR. The reaction solution was cooled to 0°C and saturated aq. $NaHCO_3$ (10 mL) was added slowly. The resulting suspension was stirred at 0°C until bubbling ceased at which point it was allowed to warm to rt. The layers were separated and the aqueous layer was washed with EtOAc. The combined organic layers were washed with saturated aq. $NaHCO_3/H_2O$ (50/50) and saturated aq. $NaHCO_3$/brine (50/50), dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on neutralized silica (slurry prepared in hexanes/Et_3N 95:5, eluent; EtOAc/Et_3N 95:5 → EtOAc/MeCN/Et_3N 70:25:5) to yield the desired product.

Isobutyl(MIDA boryl)methyl isocyanide (2a)



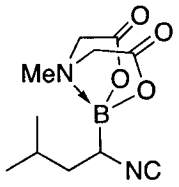
White solid; 75% yield; TLC (EtOAc) R_f = 0.36; m.p. 194-196°C; ^{1}H NMR (400 MHz, MeCN-d_3) δ 4.37 (d, J = 17.3 Hz, 1H), 4.34 (d, J = 17.3 Hz, 1H), 4.08 (d, J = 17.3 Hz, 1H), 4.04 (d, J = 17.3 Hz, 1H), 3.37 (dd, J = 12.0, 3.1 Hz, 1H), 3.06 (s, 3H), 1.82 – 1.72 (m, 1H), 1.56 (ddd, J = 14.0, 12.0, 3.1 Hz, 1H), 1.19 (dd, J = 12.0 Hz, 3.1 1H), 0.94 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.79, 168.75, 156.14, 63.09, 63.05, 46.58, 38.89, 25.20, 23.68, 20.85 ppm; ^{11}B NMR (128 MHz, DMSO-d_6) δ 14.4 ppm; HRMS (DART-TOF) $[M+NH_4]^+$ calcd. For $C_{11}H_{17}BN_2O_4$ 270.16196, found 270.16180; IR (thin film, cm^{-1}) 3961, 2277, 2130, 1746, 1665, 1470, 1337, 1287, 1248, 1220, 1194, 1159, 1100, 1078, 1049, 1023, 992, 962, 929, 897, 867, 818, 731, 692.

Tetradeuteration of *α*-boryl isocyanide 2a



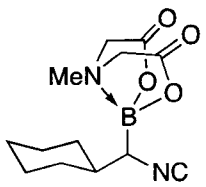
To a flame-dried flask under Ar was added *α*-boryl isocyanide **2a** (0.040 mmol, 10 mg, 1.0 equiv.) and CH_2Cl_2 (0.1 mL). The resulting suspension was cooled to -78°C and KO*t*Bu (0.044 mmol, 5.2 mg, 1.1 equiv.) was added. The resulting suspension was stirred for 30 minutes at -78°C and MeI (0.04 mmol, 5.7 mg, 2.49 µL, 1.0 equiv.) was added. The resulting suspension was stirred at -78°C for 30 minutes and was allowed to warm to 23°C followed by 1.5 h of stirring. The solvent was removed under reduced pressure and MeCN-d_3 (0.5 mL) was added. ^{1}H NMR and mass spectra were taken directly from the resulting solution.

Isobutyl(d_4-MIDA boryl)methyl isocyanide (2a-d_4)



White solid; TLC (EtOAc) R_f = 0.36; ^{1}H NMR (400 MHz, MeCN-d_3) δ 3.06 (s, 3H), 1.82 – 1.72 (m, 1H), 1.56 (ddd, J = 14.0, 12.0, 3.1 Hz, 1H), 1.19 (dd, J = 12.0 Hz, 3.1 1H), 0.94 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H) ppm; HRMS (DART-TOF) $[M+NH_4]^+$ calcd. For $C_{11}H_{13}D_4BN_2O_4$ 257.16107, found 257.16056.

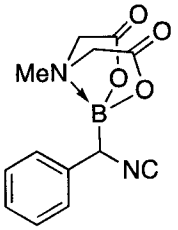
Cyclohexyl(MIDA boryl)methyl isocyanide (2a)



Off-White solid; 35% yield; TLC (EtOAc) R_f = 0.32; m.p. 205-208°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.31(3) (d, J = 17.2 Hz, 1H), 4.31(1) (d, J = 17.4 Hz, 1H), 4.05 (d, J

= 17.2 Hz, 1H), 4.00 (d, *J* = 17.4 Hz, 1H), 3.32 (d, *J* = 2.7 Hz, 1H), 3.01 (s, 3H), 1.75 - 1.71 (m, 3H), 1.62 - 1.49 (m, 4H), 1.34 - 1.19 (m, 4H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 182.96, 169.04, 168.75, 62.53, 62.50, 46.46, 37.61, 31.47, 27.94, 26.31, 25.99, 25.98 ppm; ^{11}B NMR (128 MHz, DMSO-d_6) δ 11.75 ppm; HRMS (DART-TOF) $[M+NH_4]^+$ calcd. For $C_{13}H_{19}BN_2O_4$ 296.17761, found 296.17844; IR (thin film, cm^{-1}) 2927, 2854, 2273, 2136, 1749, 1451, 1338, 1289, 1244, 1194, 1156, 1105, 1078, 1038, 992, 972, 955, 894, 868.44, 839, 772, 734, 697, 675.

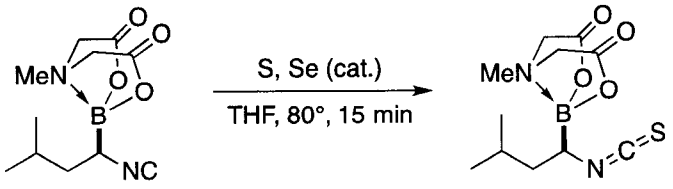
Phenyl(MIDA boryl)methyl isocyanide (2c)



Off-White solid; 31% yield; TLC (EtOAc) R_f = 0.28; ^1H NMR (500 MHz, MeCN-d_3 + DMSO-d_6) δ 7.41 - 7.38 (m, 2H), 7.35 - 7.29 (m, 3H), 4.75 (s, 1H), 4.40 (d, *J* = 17.2, 1H), 4.38 (d, *J* = 17.2 Hz, 1H), 4.14 (d, *J* = 17.2 Hz, 1H), 4.09 (d, *J* = 17.2 Hz, 1H), 3.19 (s, 3H) ppm; ^{13}C NMR (125 MHz, MeCN-d_3 + DMSO-d_6) δ 168.1, 168.0, 136.4, 128.3, 127.0, 126.7, 63.0, 62.8, 46.4 ppm; ^{11}B NMR (128 MHz, MeCN-d_3 + DMSO-d_6) δ 9.7 ppm; HRMS (DART-TOF) $[M+NH_4]^+$ calcd. For $C_{13}H_{17}BN_3O_4$ 290.13121, found 290.13115; IR (thin film, cm^{-1}) 2951, 2875, 2138, 1747, 1666, 1495, 1452, 1370, 1337, 1279, 1244, 1154, 1102, 1050, 951, 895, 818, 759, 702.

<u>General procedures for the functionalization of *α*-boryl isocyanide 2a</u>

Preparation of *α*-boryl isothiocyanate 3a

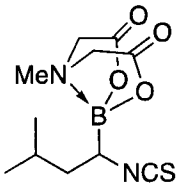


2a **3a**

Elemental sulfur (15 mg, 0.48 mmol, 1.2 equiv.) and selenium (2.0 mg, 0.020 mmol, 5.0 mol%) were suspended in THF (0.8 mL) and Et_3N (134 µL, 0.96 mmol, 2.4 equiv.) was added. The isocyanide (100 mg, 0.40 mmol, 1.0 equiv.) was added, the vial was sealed and the resulting suspension was stirred at 80°C for 15 min at which point TLC indicated that the reaction had gone to completion. The solution was allowed to cool to

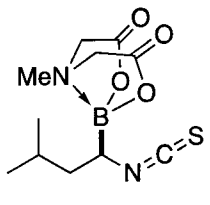
23°C, filtered (rinsing with EtOAc) and concentrated. The crude product was purified via flash column chromatography using hexanes/EtOAc (6:4 → 1:0) and was isolated as an off-white solid (88 mg, 77%).

1-(MIDA boryl)-1-isothiocyanato-3-methylbutane (3a)

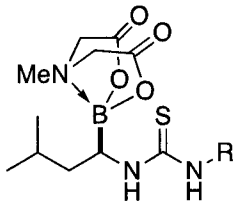


Off-white solid; 77% yield; TLC (EtOAc) R_f = 0.58, m.p. = 192 - 194°C (decomp.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.38 (d, J = 17.3 Hz, 1H), 4.10 (d, J = 17.1 Hz, 1H), 4.37 (d, J = 17.1 Hz, 1H), 4.02 (d, J = 17.3 Hz, 1H), 3.54 (dd, J = 11.8, 3.0 Hz, 1H), 3.02 (s, 3H), 1.79 - 1.69 (m, 1H), 1.64 (ddd, J = 14.3, 11.8, 3.5 Hz, 1H), 1.31 (ddd, J = 14.1, 10.1, 3.0 Hz, 1H), 0.96 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.3, 168.2, 126.3, 62.4, 62.4, 46.2, 39.5, 25.3, 23.2, 20.6 ppm; ^{11}B NMR (128 MHz, DMSO-d_6) δ 10.3 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd. for $C_{11}H_{17}BN_2O_4S$ 302.13458, found 302.13452; IR (thin film, cm^{-1}) 3013, 2959, 2871, 2148, 2091, 1746, 1633, 1450, 1337, 1284, 1246, 1217, 1195, 1158, 1094, 1075, 1042, 993, 956, 897, 867, 815, 725, 688.

Preparation of *α*-boryl thioureas 4aa, 4ab



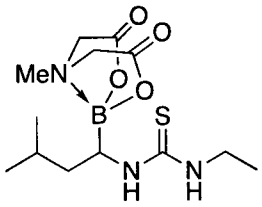
3a



4a

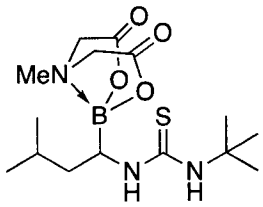
To a solution of *α*-boryl isothiocyanate **3a** (45 mg, 0.158 mmol, 1.0 equiv.) in THF (0.5 mL) was added amine (0.32 mmol, 2.0 equiv.) and the resulting solution was stirred at 23°C until TLC or LRMS (ESI, positive) indicated that the reaction had gone to completion (9-24 h). The solvent was removed and the crude product was purified via flash column chromatography using a gradient of hexanes/EtOAc (1:0 → 0:1) as the eluent. Purified products were isolated as off-white solids.

1-(1-(MIDA boryl)-3-methylbutyl)-3-ethylthiourea (4aa)



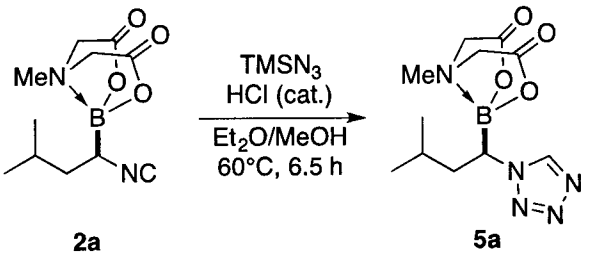
Off-white solid; 79% yield; TLC (EtOAc) R_f = 0.43; ^{1}H NMR (500 MHz, MeCN-d_3) δ 6.19 (br s, 1H), 5.76 (d, J = 9.6 Hz, 1H), 4.26 (br s, 1H), 3.95 (d, J = 17.2 Hz, 1H), 7.89 (d, J = 16.9 Hz, 1H), 3.85 (d, J = 17.1 Hz, 1H), 3.76 (d, J = 16.9 Hz, 1H), 3.39 (br s, 2H), 3.05 (s, 3H), 1.69 - 1.61 (m, 1H), 1.44 - 1.34 (m, 2H), 1.09 (t, J = 7.2 Hz, 1H), 0.97 (d, J = 6.5 Hz, 1H), 0.91 (d, J = 6.7 Hz, 1H) ppm; ^{13}C NMR (125 MHz, MeCN-d_3) δ 169.1, 168.9, 128.0, 63.3, 63.2, 47.1, 42.9, 39.6, 25.5, 24.2, 23.1, 14.7 ppm; ^{11}B NMR (192 MHz, MeCN-d_3) δ 11.5 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd. for $C_{13}H_{25}BN_3O_4S$ 330.16588, found 330.16600; IR (thin film, cm^{-1}) 3303, 3084, 3951, 2893, 2863, 2841, 2240, 1770, 1752, 1540, 1484, 1482, 1450, 1337, 1331, 1259, 1187, 1152, 1098, 1076, 1048, 1005, 953, 880, 858, 820, 759, 735, 701.

1-(1-(MIDA boryl)-3-methylbutyl)-3-(*tert*-butyl)thiourea (4ab)



Off-white solid; 90% yield; TLC (EtOAc) R_f = 0.57; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.22 (s, 1H), 6.75 (d, J = 9.7 Hz, 1H), 4.23 (d, J = 17.2 Hz, 1H), 4.21 (d, J = 16.9 Hz, 1H), 4.09 - 4.06 (m, 1H), 4.02 (d, J = 17.2 Hz, 1H), 3.73 (d, J = 16.9 Hz, 1H), 2.94 (s, 3H), 1.68 - 1.61 (m, 1H), 1.33 - 1.28 (m, 1H), 1.26 - 1.21 (m, 1H), 0.93 (d, J = 6.5 Hz, 1H), 0.86 (d, J = 6.7 Hz, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 182.3, 169.1, 169.0, 62.6, 62.5, 52.5, 46.3, 42.6, 29.5, 24.6, 24.4, 23.6 ppm; ^{11}B NMR (192 MHz, DMSO-d_6) δ 10.15 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd. for $C_{15}H_{29}BN_3O_4S$ 358.19718, found 358.19713; IR (thin film, cm^{-1}) 3369, 2958, 2348, 763, 1745, 1525, 1459, 1391, 1341, 1297, 1240, 1202, 1163, 1103, 1076, 1023, 1004, 956, 898, 869, 822, 780, 739.

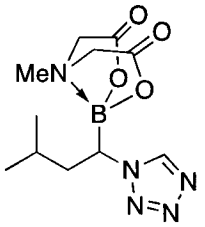
Preparation of *α*-boryl tetrazole 5a



2a **5a**

To a solution of *α*-boryl isocyanide **2a** (50 mg, 0.20 mmol 1.0 equiv.) in TFE (0.5 mL) was added HCl (400 µL, 4.0 µmol, 2.0 mol%) and $TMSN_3$ (40 µL, 0.30 mmol, 1.5 equiv.). The vial was sealed and heated to 60°C with stirring for 2.5 h at which point TLC indicated that the reaction had gone to completion. The solvent was removed and the crude product was purified via flash column chromatography using EtOAc/MeCN 1.0 → 8:2 as an eluent. The purified product was isolated as an off-white solid (46 mg, 78%).

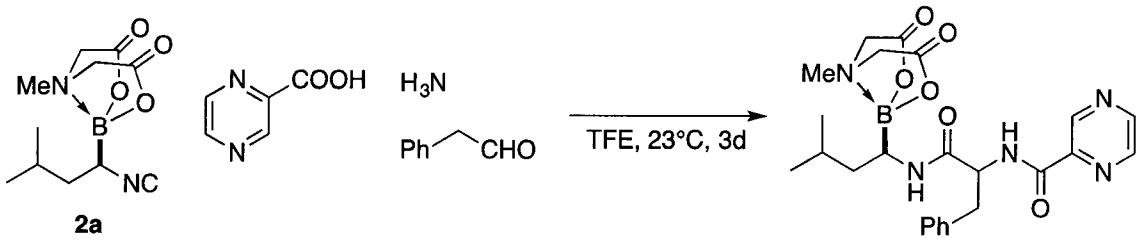
1-(1-(MIDA boryl)-3-methylbutyl)-1*H*-tetrazole (5a)



Off-white solid; 78% yield; TLC (EtOAC) R_f = 0.31, m.p. = 85°C (decomp.); ^{1}H NMR (500 MHz, MeCN-d_3) δ 8.85 (s, 1H), 4.56 (dd, J = 12.6, 3.0 Hz, 1H), 4.06 (d, J = 17.2 Hz, 1H), 3.99 (d, J = 17.3 Hz, 2H), 3.96 (d, J = 17.2 Hz, 1H), 3.55 (d, J = 17.3 Hz, 1H), 2.84 (s, 4H), 2.01 (ddd, J = 14.8, 12.6, 3.5 Hz, 3H), 1.64 (ddd, J = 14.8, 10.3, 3.0 Hz, 1H), 0.91 (d, J = 6.5 Hz, 3H), 0.82 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (125 MHz, MeCN-d_3) δ 168.3, 168.3, 144.2, 63.8, 63.6, 47.1, 40.7, 25.5, 23.4, 20.8 ppm; ^{11}B NMR (192 MHz, MeCN-d_3) δ 10.7 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd. for $C_{11}H_{19}BN_5O_4$, 296.15301 found 296.15299; IR (thin film, cm^{-1}) 2959, 2866, 2339, 2152, 1761, 1467, 1424, 1338, 1285, 1216, 1157, 1096, 1073, 1019, 959, 897, 866, 820, 739, 722, 684.

Ugi 4-component reactions utilizing α-boryl isocyanide 2a

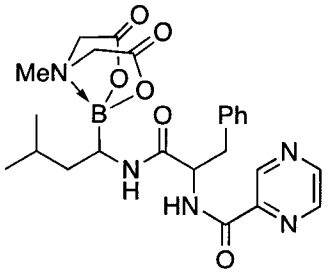
Preparation of MIDA-bortezomib



2a **7a**

To a solution of the carboxylic acid (25 mg, 0.20 mmol, 1.0 equiv.) was added ammonia (28.3 µL, 0.30 mmol, 1.5 equiv., 7.0 N solution in MeOH) and the resulting mixture was stirred at 23°C for 10 minutes. The aldehyde (23.1 µL, 0.20 mmol, 1.0 equiv.) and α-boryl isocyanide **2a** (50 mg, 0.20 mmol, 1.0 equiv.) were added and the resulting mixture was stirred at 23°C for 3 days at which point TLC indicated that the reaction had gone to completion. The reaction mixture was concentrated and the crude product was purified via flash column chromatography on silica gel (neutralized with hexanes/Et_3N (95:5)) using EtOAc/MeCN/Et_3N (20:0:1 → 16:4:1 → 10:10:1 → 4:16:1). To afford the desired product as an off-white solid in a 1:1 diastereomeric ratio (54 mg, 55%).

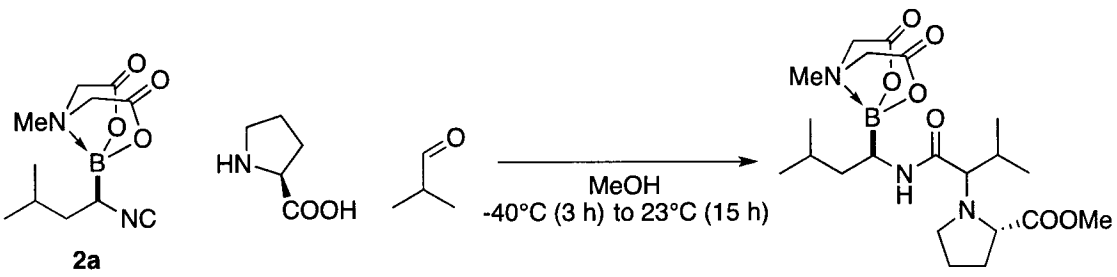
N-(1-((1-(MIDA boryl)-3-methylbutyl)amino)-1-oxo-3-phenylpropan-2-yl)pyrazine-2-carboxamide (7a)



Off-white solid; 55% yield; TLC (EtOAc/MeCN (1:1)) R_f = 0.49 (A), 0.43 (B) ; dr: 1:1; ^1H NMR (500 MHz, MeCN-d_3) δ A: 9.17 (dd, *J* = 1.5, 0.3 Hz, 1H), 8.76 (dd, *J* = 2.5, 0.3 Hz, 1H), 8.57 (dd, *J* = 2.5, 1.5 Hz, 1H), 8.24 (d, *J* = 7.6 Hz, 1H), 7.32 - 7.29 (m, 5H), 6.26 (d, *J* = 10.1 Hz, 1H), 4.68 (ddd, *J* = 8.9, 7.6, 5.9 Hz, 1H), 3.90 (d, *J* = 17.0 Hz, 1H), 3.81 (d, *J* = 17.1 Hz, 2H), 3.71 - 3.66 (m, 1H), 3.47 (d, *J* = 17.0 Hz, 1H), 3.22 (dd, *J* = 14.0, 5.9 Hz, 1H), 3.08 (dd, *J* = 14.0, 8.9 Hz, 1H), 2.85 (s, 3H), 1.55 - 1.48 (m, 1H), 1.42 - 1.36 (m, 1H), 1.27 - 1.21 (m, 1H), 0.86 (d, *J* = 6.5 Hz, 3H), 0.83 (d, *J* = 6.7 Hz,

3H), B: 9.17 (dd, J = 1.5, 0.4 Hz, 1H), 8.76 (dd, J = 2.5, 0.4 Hz, 1H), 8.56 (dd, J = 2.5, 1.5 Hz, 1H), 8.15 (d, J = 7.4 Hz, 1H), 7.31 - 7.29 (m, 4H), 7.23 - 7.20 (m, 1H), 6.40 (d, J = 10.1 Hz, 1H), 4.64 (ddd, J = 8.9, 7.4, 5.9 Hz, 1H), 4.03 (d, J = 16.7 Hz, 1H), 3.93 (d, J = 17.2 Hz, 1H), 3.89 (d, J = 16.7 Hz, 1H), 3.82 (d, J = 17.2 Hz, 1H), 3.66 (ddd, J = 11.5, 10.0, 3.1 Hz, 1H), 3.21 (dd, J = 14.0, 5.9 Hz, 1H), 3.05 (dd, J = 14.0, 9.0 Hz, 1H), 2.86 (s, 3H), 1.41 - 1.35 (m, 2H), 1.27 - 1.21 (m, 1H), 0.85 (d, J = 4.1 Hz, 3H), 0.84 (d, J = 4.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, MeCN-d_3) δ A: 171.3, 169.0, 168.7, 164.4, 148.9, 145.0, 144.7, 144.1, 138.3, 130.2, 129.6, 127.9, 63.7, 63.2, 56.6, 46.8, 41.4, 38.2, 25.1, 24.1, 21.5; B: 171.5, 169.1, 168.9, 164.1, 148.8, 145.0, 144.7, 144.2, 138.2, 130.3, 129.4, 127.7, 63.7, 63.1, 56.1, 46.6, 41.5, 38.3, 25.1, 24.2, 21.5 ppm; ^{11}B NMR (192 MHz, MeCN-d_3) δ 11.5 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd. for $C_{24}H_{31}BN_5O_6$ 496.23674, found 496.23765; IR (thin film, cm^{-1}) 3352, 3954, 3869, 1762, 1709, 1577, 1516, 1497, 1467, 1454, 1402, 1336, 1288, 1246, 1223, 1195, 1154, 1103, 1081, 1030, 994, 959, 896, 817, 866, 749, 725, 700.

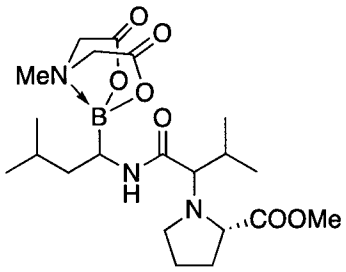
Proline-Ugi reaction with α-boryl isocyanide 2a



2a **8a**

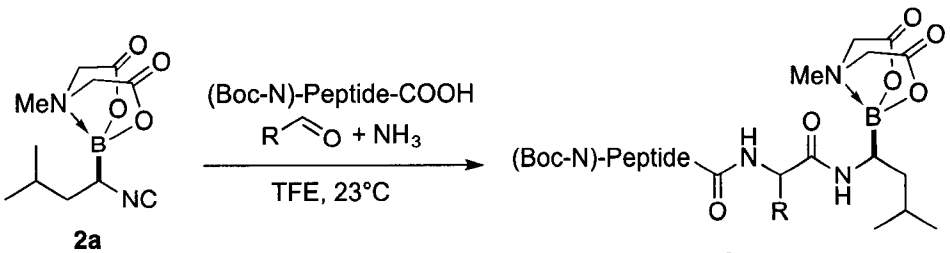
A solution of L-Proline (23 mg, 0.20 mmol, 1.0 equiv.) in MeOH (2 mL) was cooled to -40°C with stirring. α-Boryl isocyanide **2a** (50 mg, 0.20 mmol, 1.0 equiv.) and isobutyraldehyde (18 µL, 0.20 mmol) were added sequentially. The resulting mixture was stirred for 4 hours at -40°C followed by 15 hours at 23°C until the reaction was complete as indicated by TLC. The solvent was removed and the crude was suspended in EtOAc and washed with 5% aqueous $NaHCO_3$. The aqueous layer was washed twice with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4 filtered and concentrated. Purification of the product was achieved using preparative TLC with EtOAc/MeCN (1:1) as the eluent. The product was isolated as a light orange oil (an inseparable 43:26:17:13 mixture of 4 diastereomers) (6.2 mg, 7%).

Methyl (1-((1-(MIDA boryl)-3-methylbutyl)amino)-3-methyl-1-oxobutan-2-yl)-L-prolinate (8a)



Light orange oil; 7% yield; dr: 43:26:17:13; TLC (EtOAc) R_f = 0.34; ^{1}H NMR (500 MHz, MeCN-d_3) δ 7.71 (dd, J = 5.7, 3.3 Hz, 1H), 7.61 (dd, J = 5.7, 3.3 Hz, 1H), 6.18 (d, J = 9.5 Hz, 1H), 6.08 (d, J = 9.5 Hz, 1H), 4.19 - 4.17 (m, 2H), 4.08 - 4.01 (m, 2H), 3.96 - 3.83 (m, 16H), 3.71 (s, 3H), 3.67 (s, 3H), 3.65 (s, 3H), 3.62 (s, 3H), 3.53 (dd, J = 8.9, 5.4 Hz, 2H), 3.45 (dd, J = 8.9, 5.0 Hz, 2H), 3.15 - 3.10 (m, 2H), 3.05 (s, 3H), 3.04 (s, 3H), 3.01 (s, 3H), 2.96 (s, 3H), 2.82 - 2.75 (m, 2H), 2.05 - 1.98 (m, 4H), 1.89 - 1.84 (m, 4H), 1.75 - 1.03 (m, 32H), 0.97 - 0.78 (m, 48H) ppm; ^{13}C NMR (125 MHz, MeCN-d_3) δ 176.0, 175.6, 172.3, 171.1, 169.3, 168.9, 168.8, 168.8, 132.3, 129.7, 118.4, 70.2, 68.7, 63.5, 63.4, 63.3, 63.2, 63.1, 62.4, 62.4, 52.1, 52.1, 48.8, 47.7, 46.9, 46.8, 46.7, 42.2, 41.5, 31.2, 30.7, 30.4, 29.7, 29.2, 29.0, 29.0, 25.6, 25.5, 25.5, 24.6, 24.5, 24.1, 24.0, 23.7, 21.5, 21.4, 21.4, 20.3, 20.3, 20.2, 20.2, 15.1, 14.3, 11.3, 9.1 ppm; ^{11}B NMR (192 MHz, MeCN-d_3) δ 11.1 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd. for $C_{21}H_{37}BN_3O_7$ 454.27245, found 454.27440; IR (thin film, cm^{-1}) 3339, 2954, 2868, 1748, 1646, 1520, 1463, 1337, 1288, 1198, 1162, 1103, 1081, 1030, 994, 956, 896, 868, 709.

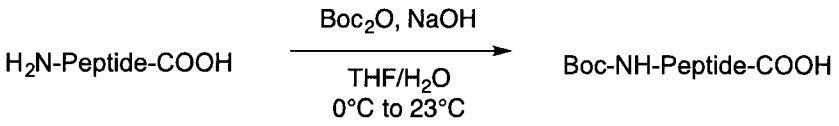
General preparation of protected boropeptides 9a-h



2a **9**

Commercially available N-Boc protected amino acids were used as supplied. Fully protected resin-bound tri- and tetra-peptides H-Pro-Leu-Phe-OH and H-Pro-Gly-Leu-Phe-OH were synthesized via standard Fmoc solid-phase peptide chemistry using an automated peptide synthesizer. Fmoc removal was achieved by treatment with 20% piperidine in NMP for 5 and 10 minutes with consecutive DMF and NMP washes after

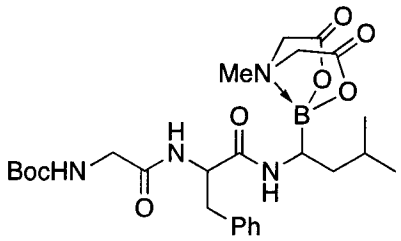
each addition. For all Fmoc amino acid coupling, the resin was treated once with 4.5 eq. of Fmoc amino acids, 4.5 eq. of HCTU and 9 eq. of DIPEA in NMP for 60 minutes. Once the peptide was synthesized, following Fmoc removal, the resin was treated with 1:3, HFIP:DCM, twice for one hour each, to afford cleavage from the solid support. The solvent was then removed, followed by trituration with tert-butyl methyl ether to give the linear peptide.The peptide products were then Boc-protected along with commercially available H-Phe-Ala-OH and H-Gly-Gly-OH according to the following method:



A solution of the peptide (1.0 equiv.) in THF (0.75M) and $NaOH_{(aq.)}$ (1.0 M, 2.0 equiv.) was cooled to 0°C and Boc_2O was added slowly. The resulting mixture was stirred at 0°C for 30 minutes and was then allowed to warm to 23°C. Once TLC indicated that the reaction had gone to completion, the solution was cooled to 0°C and acidified to pH ~ 2 with 1.0 M $HCl_{(aq.)}$. Et_2O was added and the layers were separated. The aqueous layer was washed twice with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered and concentrated to yield the crude products as white solids. The products were identified with LRMS (ESI, positive) and crude ^1H NMR and used in the Ugi 4-component reaction without further purification.

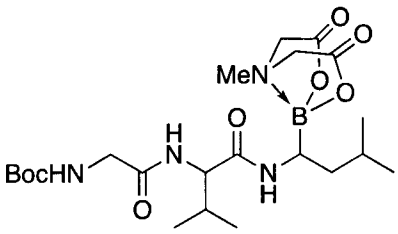
To a solution of the crude N-Boc protected peptide (1.0 equiv.) in TFE (0.50 M) was added ammonia (1.5 equiv., 7.0 N solution in MeOH) and the resulting mixture was stirred at 23°C for 10 minutes. The aldehyde (1.0 equiv.) and *α*-boryl isocyanide **2a** (1.0 equiv.) were added and the resulting mixture was stirred at 23°C until TLC indicated that the reaction had gone to completion (6-12 d). The reaction mixture was concentrated and a small sample (5-15 mg) was taken for crude ^1H NMR using 750 µL of a stock solution of 3,4,5-triiodobenzoic acid (48.1 mM in DMSO-d_6) as the solvent. The yield was calculated by comparative integration of the Boc *tert*-butyl signal and the aromatic protons of the internal standard. The crude product was purified via reverse-phase preparative high-performance liquid chromatography on an Agilent ZORBAX SB-C18 column (5 µM mesh, 9.4 x 250 mm) using a H_2O-MeCN (with added 0.1% formic acid) gradient to afford the desired products. Diastereomers are classified by their order of elution in reverse-phase chromatography (A eluting first being the most polar, B eluting second being less polar than A, and so on for C and D if applicable.)

(N-Boc)-Gly-DL-Phe-DL-(MIDA boro)-Leu (9a)



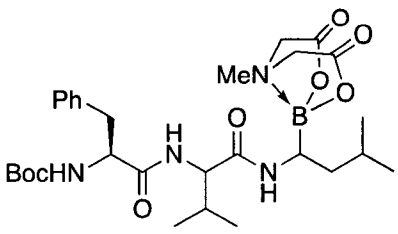
White solid; 66% (NMR), 11% (isolated) yield ; dr: 81:19 (A:B); ^{1}H NMR (500 MHz, MeCN-d_3) δ A: 7.33 - 7.29 (m, 2H), 7.26 - 7.23 (m, 3H), 6.78 (d, J = 7.5 Hz, 1H), 6.16 (d, J = 10.2 Hz, 1H), 5.59 (s, 1H), 4.41 (q, J = 7.7 Hz, 1H), 3.90 (d, J = 17.2 Hz, 1H), 3.82 (d, J = 16.8 Hz, 1H), 3.80 (d, J = 17.2 Hz, 1H), 3.69 - 3.63 (m, 1H), 3.54 (d, J = 17.2 Hz, 1H), 3.63 (d, J = 17.2 Hz, 1H), 3.61 (d, J = 17.3 Hz, 1H), 3.53 (d, J = 17.2 Hz, 1H), 3.06 (dd, J = 14.0, 5.6 Hz, 1H), 2.97 (dd, J = 13.9, 8.4 Hz, 1H), 2.83 (s, 3H), 1.54 - 1.46, (m, 1H), 1.40 (s, 9H), 1.28 - 1.22 (m, 1H), 0.89 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H); B: 7.30 - 7.27 (m, 2H), 7.26 - 7.22 (m, 3H), 6.81 (d, J = 7.3 Hz, 1H), 6.25 (d, J = 10.1 Hz, 1H), 5.54 (s, 1H), 4.36 (ddd, J = 8.8, 7.3, 6.3 Hz, 1H), 4.02 (d, J = 16.7 Hz, 1H), 3.92 (d, J = 17.2 Hz, 1H), 3.86 (d, J = 16.7 Hz, 1H), 3.82 (d, J = 17.2 Hz, 1H), 3.60 (ddd, J = 11.6, 9.5, 2.7 Hz, 1H), 3.55 (dd, J = 6.1, 5.1 Hz, 2H), 3.04 (dd, J = 13.9, 6.2 Hz, 1H), 2.87 (d, J = 8.9 Hz, 1H), 2.85 (s, 3H), 1.41 (s, 9H), 1.39 - 1.37 (m, 1H), 1.35 - 1.29 (m, 1H), 1.22 - 1.17 (m, 1H), 0.81 (d, J = 3.3 Hz, 3H), 0.80 (d, J = 3.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, MeCN-d_3) δ A: 171.3, 171.3, 169.2, 169.2, 169.1, 138.3, 130.2, 129.6, 127.8, 80.2, 63.7, 63.2, 56.4, 46.8, 44.6, 41.4, 37.7, 28.6, 25.0, 24.2, 21.5; B: 171.7, 171.0, 169.2, 169.0, 138.4, 130.2, 129.4, 127.6, 63.8, 63.1, 56.2, 46.6, 44.4, 41.4, 38.0, 28.6, 28.5, 24.9, 24.2, 21.5 ppm; ^{11}B NMR (192 MHz, MeCN-d_3) δ A: 11.5; B: 11.3 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd. for $C_{26}H_{40}BN_4O_8$ 547.2933, found 547.2922.

(N-Boc)-Gly-DL-Val-DL-(MIDA boro)-Leu (9b)



White solid; 79% (NMR), 40% (isolated) yield; dr: 83:17 (A:B); ^{1}H NMR (500 MHz, MeCN-d_3) δ 6.71 (d, J = 7.0 Hz, 1H), 6.69 (d, J = 7.0 Hz, 1H), 6.27 (d, J = 10.0 Hz, 1H), 6.16 (d, J = 10.1 Hz, 1H), 5.69 (s, 1H), 5.63 (s, 1H), 4.00 - 3.81 (m, 8H), 3.79 - 3.74 (m, 2H), 3.69 - 3.64 (m, 2H), 3.61 (dd, J = 16.9, 5.4 Hz, 4H), 2.93 (s, 3H), 2.85 (s, 3H), 1.62 - 1.48 (m, 4H), 1.43 (s, 9H), 1.42 (s, 9H), 1.30 - 1.24 (m, 2H), 0.96 - 0.92 (m, 2H), 0.93 (d, J = 6.9 Hz, 3H), 0.92 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 6.7 Hz, 6H), 0.88 (d, J = 6.9 Hz, 6H), 0.88 (d, J = 6.6 Hz, 6H) ppm; ^{13}C NMR (125 MHz, MeCN-d_3) δ 170.9, 170.7, 170.4, 170.0, 168.5, 168.2, 168.1, 167.9, 156.3, 156.1, 79.2, 62.9, 62.8, 62.4, 62.1, 60.0, 59.2, 46.0, 45.6, 43.7, 43.5, 40.6, 40.4, 29.4, 27.6, 27.6, 27.6, 24.5, 24.3, 23.1, 23.1, 20.5, 20.4, 19.0, 18.8, 18.2, 17.4, 17.0 ppm; ^{11}B NMR (192 MHz, MeCN-d_3) δ 11.5 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd. for $C_{22}H_{40}BN_4O_8$ 499.2933, found 499.2937.

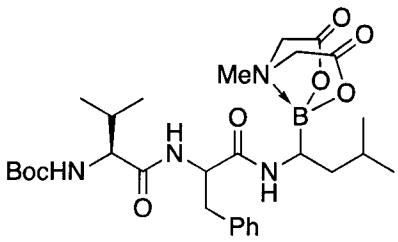
(N-Boc)-L-Phe-DL-Val-DL-(MIDA boro)-Leu (9c)



White solid; 74% (NMR), 22% (isolated) yield; dr: 32:48:13:7 (A:B:C:D) ^{1}H NMR (500 MHz, MeCN-d_3) δ 7.35 - 7.20 (m, 20H), 6.94 (br s, 2H), 6.90 (d, J = 7.8 Hz, 1H), 6.81 (d, J = 6.5 Hz, 1H), 6.34 (d, J = 11.2 Hz, 1H), 6.30 (d, J = 10.1 Hz, 2H), 6.19 (d, J = 9.8

Hz, 1H), 5.67 (d, J = 8.7 Hz, 1H), 5.61 - 5.54 (m, 3H), 4.32 - 4.25 (m, 4H), 4.06 - 3.98 (m, 4H), 3.97 - 3.80 (m, 16H), 3.74 - 3.64 (m, 4H), 3.18 - 3.04 (m, 4H), 2.95 (s, 3H), 2.94 (s, 3H), 2.83 (s, 3H), 2.82 (s, 3H), 1.61 - 1.51 (m, 4H), 1.47 - 1.41 (m, 8H), 1.38 (2, 9H). 1.34 (s, 9H), 1.33 (s, 9H), 1.30 (s, 9H), 1.28 - 1.25 (m, 4H), 0.94 - 0.80 (m, 52H) ppm; ^{13}C NMR (125 MHz, MeCN-d_3) δ 172.5, 172.1(7), 172.0(9), 172.0(2), 170.9, 170.4(1), 170.3(9), 170.3(7), 168.2, 168.1(1), 168.0(8), 168.0(6), 168.0(5), 168.0(3), 168.0(0), 167.9, 137.9, 137.8(3), 137.7(9), 137.6, 129.3(2), 129.3(1), 129.2(9), 129.2(4), 128.4(6), 128.4(3), 128.3(7), 128.3(2), 126.6(1), 126.5(8), 126.5(6), 126.5(2), 79.4(0), 79.3(7), 79.1(2), 79.0(6), 62.8(2), 62.7(7), 62.7(3), 62.6, 62.4(3), 62.4(0), 62.1(4), 62.0(9), 59.6, 59.5, 59.2(9), 59.2(8), 55.8(9), 55.8(5), 55.6(0), 55.5(8), 45.9(2), 45.8(6), 45.7, 45.6 40.7, 40.6(4), 40.6(2), 40.6, 37.9, 37.4, 36.9, 36.2, 30.1, 29.8, 29.6(1), 29.5(7), 27.7, 27.5(8), 27.5(6), 27.5(2), 24.4(8), 24.4, 24.3(3), 24.3(0), 23.2(1), 23.2(1), 23.1(6), 23.1(3), 20.5(1), 20.5(0), 20.4(5), 20.4(5), 19.0(4), 19.0(1), 18.9, 18.8, 17.6, 17.5(2), 17.5(1), 17.4, 16.8(4), 16.8(2), 16.7(7), 16.7(6), ppm; ^{11}B NMR (192 MHz, MeCN-d_3) δ 11.5 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd. for $C_{29}H_{46}BN_4O_8$ 589.3403, found 589.3381.

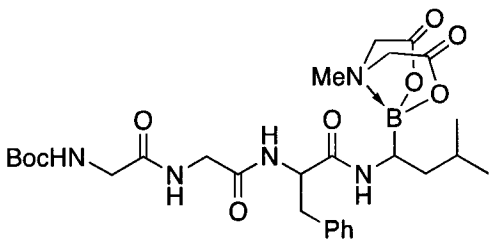
(N-Boc)-LVal-DL-Phe-DL-(MIDA boro)-Leu (9d)



White solid; 57% (NMR), 17% (isolated) yield; dr: 42:34:16:8 (A:B:C:D) ^{1}H NMR (500 MHz, MeCN-d_3) δ A+B: 7.32 - 7.22 (m, 10H), 6.94 (d, J = 6.0 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 6.42 (d, J = 10.3 Hz, 1H), 6.27 (d, J = 10.2 Hz, 1H), 5.46 (br s, 2H), 4.55 (br s, 2H), 3.90 - 3.73 (m, 8H), 3.69 - 3.66 (m, 2H), 3.64 - 3.59 (m, 2H), 3.25 (d, J = 17.3 Hz, 2H), 3.11 - 3.02 (m, 2H), 2.97 - 2.91 (m, 1H), 2.85 (dd, J = 13.8, 8.7 Hz, 1H), 2.75 (s, 3H), 2.73 (s, 3H), 1.82 (dq, J = 13.6, 6.8 Hz, 1H), 1.54 - 1.47 (m, 2H), 1.40 (s, 9H), 1.39 (s, 9H), 1.27 - 1.20 (m, 2H), 0.93 - 0.89 (m, 1H), 0.88 - 0.83 (m, 15H), 0.76 (d, J = 6.8 Hz, 3H), 0.74 (d, J = 6.6 Hz, 3H), 0.63 (d, J = 6.7 Hz, 3H); C+D: 7.31 - 7.25 (m,

8H), 7.23 - 7.19 (m, 2H), 6.83 (d, *J* = 7.1 Hz, 1H), 6.81 (d, *J* = 7.2 Hz, 1H), 6.33 (d, *J* = 10.2 Hz, 1H), 6.25 (d, *J* = 10.2 Hz, 1H), 5.41 (d, *J* = 8.2 Hz, 1H), 5.37 (d, *J* = 9.3 Hz, 1H), 4.42 - 4.34 (m, 2H), 4.07 (d, *J* = 16.1 Hz, 2H), 3.93 (d, *J* = 17.2 Hz, 1H), 3.92 (d, *J* = 17.2 Hz, 1H), 3.87 (d, *J* = 16.6 Hz, 1H), 3.87 (d, *J* = 16.6 Hz, 1H), 3.82 (d, *J* = 17.2 Hz, 1H), 3.80 (d, *J* = 17.2 Hz, 1H), 3.78 - 3.75 (m, 1H), 3.65 - 3.57 (m, 2H), 3.05 (dd, *J* = 13.6, 6.0 Hz, 1H), 3.02 (dd, *J* = 14.2, 6.0 Hz, 1H), 2.86 (d, *J* = 9.3 Hz, 1H), 2.84 (s, 3H), 2.83 (s, 3H), 2.82 - 2.80 (m, 1H), 1.87 - 1.83 (m, 1H), 1.39 (s, 18H), 1.35 - 1.27 (m, 4H), 1.24 - 1.17 (m, 2H), 0.95 - 0.88 (m, 2H), 0.86 - 0.79 (m, 15H), 0.76 (d, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 6.8 Hz, 3H), 0.68 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (125 MHz, MeCN-d_3) δ A+B: 173.1, 173.1, 172.0, 171.9, 169.2, 169.2, 168.9, 168.9, 138.3, 138.2, 130.2, 130.2, 129.4, 129.4, 127.6, 127.6, 79.8, 79.8, 63.8, 63.7, 63.1, 63.0, 60.7, 60.4, 56.4, 56.2, 46.6, 46.5, 41.4, 41.4, 38.3, 38.1, 31.7, 31.7, 28.6, 28.6, 25.0, 24.9, 24.2, 24.2, 21.5, 21.5, 19.6, 19.5, 17.9, 17.8; C+D: 173.1, 173.1, 172.0, 171.9, 169.2, 169.2, 168.9, 168.9, 138.3, 138.2, 130.2, 130.2, 129.4, 129.4, 127.6, 127.6, 79.8, 79.8, 63.8, 63.7, 63.1, 63.0, 60.7, 60.4, 56.4, 56.2, 46.6, 46.5, 41.4, 41.4, 38.3, 38.1, 31.7, 31.7, 28.6, 28.6, 25.0, 24.9, 24.2, 24.2, 21.5, 21.5, 19.6, 19.5, 17.9, 17.8 ppm; ^{11}B NMR (192 MHz, MeCN-d_3) δ 11.4 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd. for $C_{29}H_{46}BN_4O_8$ 589.3403, found 589.3381.

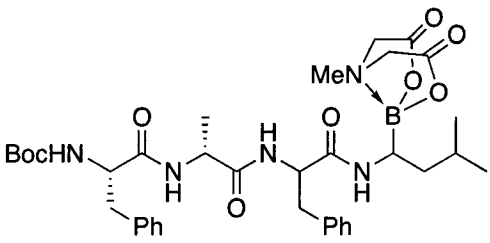
(N-Boc)-Gle-Gly-DL-Phe-DL-(MIDA boro)-Leu (9e)



White solid; 92% (NMR), 13% (isolated) yield; dr: 59:41 (A:B); ^{1}H NMR (500 MHz, A: MeCN-d_3; B: DMSO-d_6) δ A: 7.31 - 7.27 (m, 3H), 7.25 - 7.21 (m, 2H), 7.07 (br s, 1H), 6.99 (d, *J* = 6.7 Hz, 1H), 6.28 (d, *J* = 10.1 Hz, 1H), 5.74 (br s, 1H), 4.36 (ddd, *J* = 9.4, 7.4, 5.1 Hz, 1H), 3.90 (d, *J* = 17.2 Hz, 1H), 3.83 (d, *J* = 16.7 Hz, 1H), 3.81 (d, *J* = 17.2 Hz, 1H), 3.71 - 3.68 (m, 2H), 3.66 - 3.63 (m, 3H), 3.59 (d, *J* = 16.7 Hz, 1H), 3.16 (dd, *J* = 14.1, 5.1 Hz, 1H), 2.91 (dd, *J* = 14.0, 9.4 Hz, 1H), 2.84 (s, 3H), 1.56 - 1.45 (m, 2H), 1.43 (s, 9H), 1.28 - 1.23 (m, 1H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H); B:

8.10 (d, *J* = 7.6 Hz, 1H), 7.91 (t, *J* = 5.7 Hz, 1H), 7.56 (d, *J* = 10.3 Hz, 1H), 7.30 - 7.24 (m, 4H), 7.19 - 7.16 (m, 1H), 6.97 (t, *J* = 6.1 Hz, 1H), 4.45 - 4.40 (m, 1H), 4.23 (d, *J* = 17.3 Hz, 1H), 4.07 (d, *J* = 16.6 Hz, 1H), 3.97 (d, *J* = 16.6 Hz, 1H), 3.94 (d, *J* = 17.3 Hz, 1H), 3.71 (dd, *J* = 16.8, 5.4 Hz, 1H), 3.56 - 3.52 (m, 3H), 3.49 - 3.44 (m, 1H), 2.91 (dd, *J* = 13.8, 5.7 Hz, 1H), 2.76 (s, 3H), 2.75 - 2.73 (m, 1H), 1.38 (s, 9H), 1.35 - 1.30 (m, 2H), 1.10 (ddd, *J* = 13.3, 10.2, 2.9 Hz, 1H), 0.77 (d, *J* = 6.3 Hz, 3H), 0.76 (d, *J* = 6.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, A: MeCN-d_3; B: DMSO-d_6) δ A: 171.5, 171.2, 170.8, 169.2, 169.1, 157.5, 138.8, 130.1, 129.5, 127.6, 80.3, 63.7, 63.2, 56.9, 46.8, 44.9, 43.4, 41.3, 37.6, 28.6, 25.1, 24.3, 21.6 ppm; B: ^{13}C NMR data unavailable due to limited amount of purified material obtained; ^{11}B NMR (192 MHz, MeCN-d_3) δ 11.5 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd. for $C_{28}H_{43}BN_5O_9$ 604.3148, found 604.3138.

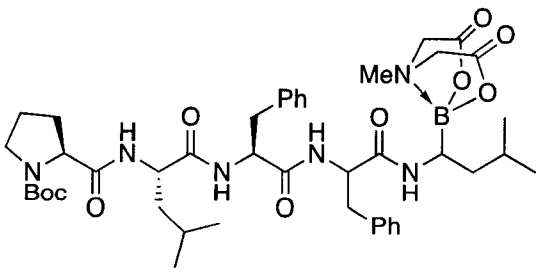
(N-Boc)-L-Phe-L-Ala-DL-Phe-DL-(MIDA boro)-Leu (9f)



White solid; 91% (NMR), 27% yield; dr: 25:31:23:22 (A:B:C:D). ^{1}H NMR (500 MHz, MeCN-d_3) δ A+B: 7.32 - 7.18 (m, 20H), 7.04 (br s, 3H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.37 (d, *J* = 10.2 Hz, 2H), 5.58 (d, *J* = 7.9 Hz, 1H), 5.54 (d, *J* = 7.5 Hz, 1H), 4.47 (td, *J* = 8.2, 6.0 Hz, 1H), 4.42 - 4.38 (m, 1H), 4.24 (ddd, J = 10.0, 8.0, 4.5 Hz, 1H), 4.25 - 4.19 (m, 1H), 4.16 - 4.09 (m, 2H), 3.90 (d, *J* = 17.1 Hz, 1H), 3.88 (d, *J* = 17.2 Hz, 1H), 3.83 (d, *J* = 16.8 Hz, 1H), 3.82 (d, *J* = 17.3 Hz, 1H), 3.80 (d, *J* = 17.1 Hz, 1H), 3.69 - 3.63 (m, 2H), 3.54 (d, *J* = 16.7 Hz, 1H), 3.44 (d, *J* = 16.7 Hz, 1H), 3.19 (dd, *J* = 14.1, 5.2 Hz, 1H), 3.13 (dd, *J* = 14.1, 4.6 Hz, 2H), 3.07 – 3.00 (m, 1H), 2.94 (d, *J* = 8.7 Hz, 1H), 2.91 (d, *J* = 7.1 Hz, 1H), 2.87 (dd, *J* = 9.6, 4.4 Hz, 1H), 2.82 (s, 3H), 2.79 (s, 3H), 2.77 - 2.74 (m, 2H), 1.56 - 1.49 (m, 2H), 1.47 - 1.41 (m, 2H), 1.33 (s, 18H), 1.29 - 1.22 (m, 2H), 1.19 (d, *J* = 7.2 Hz, 3H), 1.12 (d, *J* = 7.1 Hz, 3H), 0.88 - 0.85 (m, 12H); C+D: 7.32 - 7.19 (m, 20H), 7.01 - 6.95 (m, 4H), 6.35 (d, *J* = 10.1 Hz, 1H), 6.30 (d, *J* = 10.1 Hz, 1H), 5.56 (d, *J* = 8.1 Hz, 1H), 5.52 (d, *J* = 7.4 Hz, 1H), 4.39 (ddd, *J* = 8.9, 7.6, 6.2 Hz,

1H), 4.37 - 4.32 (m, 1H), 4.28 - 4.20 (m, 2H), 4.13 (dq, *J* = 13.8, 6.9 Hz, 2H), 4.05 (d, *J* = 16.7 Hz, 1H), 3.97 (d, *J* = 16.8 Hz, 1H), 3.93 (d, *J* = 17.2 Hz, 1H), 3.92 (d, *J* = 17.2 Hz, 1H), 3.88 (d, *J* = 16.6 Hz, 1H), 3.86 (d, *J* = 16.7 Hz, 1H), 3.83 (d, *J* = 17.2 Hz, 1H), 3.82 (d, *J* = 17.1 Hz, 1H), 3.64 - 3.59 (m, 2H), 3.11 - 3.04 (m, 4H), 2.87 (s, 3H), 2.86 (s, 3H), 2.85 - 2.81 (m, 2H), 2.80 - 2.72 (m, 2H), 1.33 (s, 9H), 1.32 (s, 9H), 1.23 - 1.19 (m, 2H), 0.92 - 0.84 (m, 4H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.13 (d, *J* = 7.1 Hz, 3H), 0.82 - 0.78 (m, 12H) ppm; ^{13}C NMR (125 MHz, MeCN-d_3) δ A+B: 173.6, 173.3, 173.1, 172.7, 171.3(4), 171.3(0), 169.1, 169.0(1), 169.0(0), 168.9, 138.8(1), 138.7(9), 138.7, 138.5, 130.3(3), 130.3(1), 130.2(9), 130.2, 129.5, 129.4(4), 129.3(7), 129.3, 127.7, 127.62, 127.62, 127.5, 80.3, 80.2, 63.6, 63.2, 56.9(4), 56.9(0), 56.5, 56.45, 55.9(9), 55.9(7), 50.6, 50.36, 46.7(1), 46.6(8), 41.6, 41.4, 38.2, 38.1, 37.9, 37.8, 28.6, 28.5, 25.1, 25.0, 24.3(0), 24.2(9), 21.7, 21.67, 17.7, 17.6; C+D: 181.5, 1765, 172.6, 171.7, 170.7, 170.6, 168.3, 168.1(4), 168.1(2), 168.0(5), 137.6, 137.4(9), 137.4(8), 137.4(7), 129.3(2), 129.3(0), 129.2(7), 129.2, 128.3(6), 128.3(5), 128.3(3), 128.2(9), 126.6(1), 126.5(7), 126.5(4), 126.5(3), 79.3, 79.2, 62.8, 62.7, 62.2(1), 62.1(7), 55.8(4), 55.7(6), 55.3, 55.1, 49.3(3), 49.2(7), 45.7, 45.67, 40.4, 40.3, 37.5, 37.3, 37.1, 36.9, 27.5(7), 27.5(6), 23.9, 23.8, 23.3, 23.2, 20.6, 20.5, 17.0(2), 17.0(1) ppm; ^{11}B NMR (192 MHz, MeCN-d_3) δ A: 11.4; B: 11.6 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd. for $C_{36}H_{51}BN_5O_9$ 708.3774, found 708.3764.

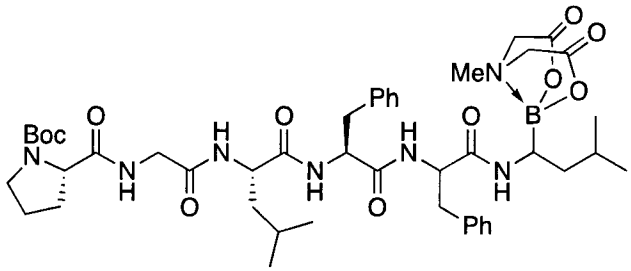
(N-Boc)-D-Pro-L-Leu-L-Phe-DL-Phe-DL-(MIDA boro)-Leu (9g)



White solid; 63% (NMR), 30% (isolated) yield; dr: 29:19:27:25; ^{1}H NMR (500 MHz, MeCN-d_3) δ A: 7.36 - 7.17 (m, 10H), 7.12 (br s, 1H), 7.11 (br s, 1H), 7.02 (br s, 1H), 6.32 (d, *J* = 10.2 Hz, 1H), 4.34 - 4.25 (m, 2H), 4.12 (dd, J = 8.4, 4.5 Hz, 1H), 4.07 - 4.01 (m, 1H), 3.96 - 3.75 (m, 4H), 3.72 - 3.60 (m, 2H), 3.52 - 3.47 (m, 1H), 3.42 - 3.33 (m, 2H), 3.23 (dd, *J* = 13.2, 3.5 Hz, 1H), 2.93 (s, 1H), 2.84 (s, 3H). 1.62 - 1.48 (m, 4H), 1.44 (s, 9H), 1.40 - 1.34 (m, 4H), 1.31 - 1.23 (m, 2H), 0.86 - 0.83 (m, 9H), 0.83 (d, *J* =

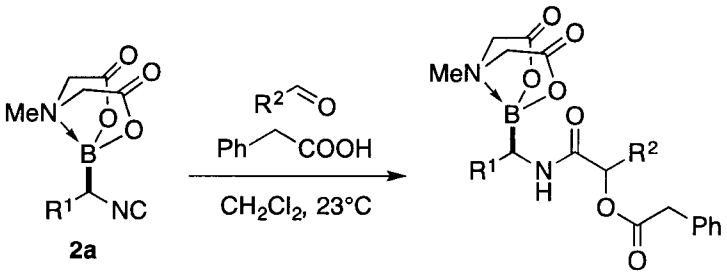
6.3 Hz, 1H) ppm; B, C, D: qualitative analysis only due to substantial peak overlap; ^{13}C NMR data unavailable due to limited amount of purified material obtained; ^{11}B NMR (192 MHz, MeCN-d_3) δ A: 11.2; B, C, D: 11.1 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd. for $C_{44}H_{64}BN_6O_{10}$ 847.4771, found 847.4757.

(N-Boc)-L-Pro-Gly-L-Leu-L-Phe-DL-Phe-DL-(MIDA boro)-Leu (9h)



White solid; 76% (NMR), 19% (isolated) yield; dr: 27:73 (A+B:C+D); ^1H NMR (500 MHz, MeCN-d_3) qualitative analysis only; ^{13}C NMR data unavailable due to limited amount of purified material obtained; ^{11}B NMR (192 MHz, MeCN-d_3) δ 11.4 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd. for $C_{46}H_{67}BN_7O_{11}$ 904.4986, found 904.5017.

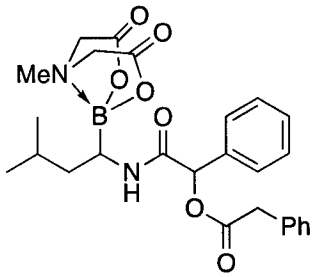
Passerini 3-component reactions using α-boryl isocyanides 2a-c



To a vial charged with α-boryl isocyanide (1.0 equiv.), phenyl acetic acid (1.0 equiv.) and aldehyde (1.0 equiv.) was added CH_2Cl_2 (0.5 mL) and the vial was sealed. The resulting suspension was stirred magnetically at 23°C until the reaction was complete as indicated by TLC. The crude product mixture was pipetted directly onto silica gel and the product diastereomers were eluted using a hexanes/EtOAc gradient (1:0 → 0:1). In some cases, EtOAc/MeCN (8:2) was required for complete elution of the

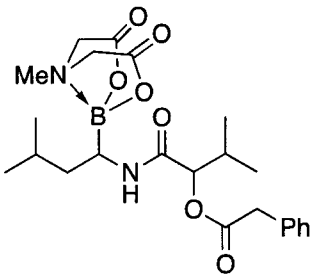
product. In most cases, TLC indicated complete separation of product diastereomers after column; however, ^{1}H NMR indicated trace amounts of either diastereomer in each sample. Diastereomeric ratios were determined using ^{1}H NMR proton integrations of the N-Me signal. It should be noted that reactions utilizing nicotinaldehyde were carried out in the dark until TLC indicated full consumption of starting material. Diastereomers are classified by their order of elution from silica gel (A eluting first being the least polar, B eluting second being more polar than A) Diastereomeric ratios were determined by comparative ^{1}H NMR integrations of the N-CH_3 signals.

2-((1-(MIDA boryl)-3-methylbutyl)amino)-2-oxo-1-phenylethyl 2-phenylacetate (10aa)



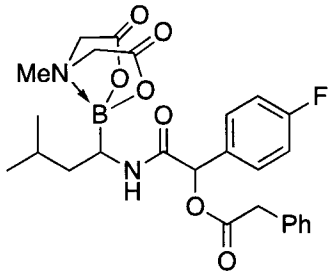
White solid; 56% yield; TLC (EtOAc) R_f = 0.69 (A), 0.49 (B); dr = 51:49 (A:B); mp = 58 - 64°C; ^{1}H NMR (500 MHz, MeCN-d_3) δ A: 7.48 - 7.46 (m, 2H), 7.42 - 7.27 (m, 5H), 6.36 (d, J = 10.1 Hz, 1H), 5.73 (s, 1H), 3.91 (d, J = 17.2 Hz, 1H), 3.84 (d, J = 16.6 Hz, 1H), 3.79 (d, J = 17.2 Hz, 1H), 3.78 (s, 2H), 3.62 (d, J = 16.6 Hz, 1H), 3.63 - 3.58 (m, 2H), 2.77 (s, 3H), 1.36 - 1.30 (m, 1H), 1.20 - 1.15 (m, 1H), 1.12 - 1.04 (m, 1H), 0.90 - 0.88 (m, 1H), 0.69 (d, J = 6.6 Hz, 1H), 0.66 (d, J = 6.4 Hz, 1H); B: 7.46 - 7.29 (m, 10H), 6.33 (d, J = 10.2 Hz, 1H), 5.80 (s, 1H), 3.89 (d, J = 17.2 Hz, 1H), 3.79 (d, J = 17.2 Hz, 1H), 3.79 (d, J = 2.9 Hz, 1H), 3.76 (d, J = 16.8 Hz, 1H), 3.69 – 3.60 (m, 1H), 3.00 (d, J = 16.8 Hz, 1H), 2.71 (s, 3H), 1.54 - 1.43 (m, 2H), 1.29 - 1.24 (m, 1H), 0.87 (d, J = 6.6 Hz, 3H), 0.77 (d, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, MeCN-d_3) δ A: 172.3, 169.1, 169.1, 168.7, 136.3, 135.2, 130.4, 129.8, 129.5, 129.4, 128.2, 128.0, 77.3, 63.6, 62.8, 46.4, 41.4, 41.2, 24.9, 24.0, 21.2; B: 171.8, 169.0, 168.9, 168.6, 137.0, 135.2, 130.5, 129.8, 129.6, 129.5, 128.1, 128.0, 77.3, 63.5, 62.8, 46.5, 41.3, 41.3, 24.9, 24.1, 21.3 ppm; ^{11}B NMR (192 MHz, MeCN-d_3) δ 11.4 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd. for $C_{26}H_{32}BN_2O_7$ 495.23026, found 495.23094; IR (thin film, cm^{-1}) 3337, 2955, 1745, 1668, 1528, 1497, 1455, 1289, 1243, 1148, 1103, 1080, 1028, 950, 896, 866, 696.

1-((1-(MIDA boryl)-3-methylbutyl)amino)-3-methyl-1-oxobutan-2-yl 2-phenylacetate (10ab)



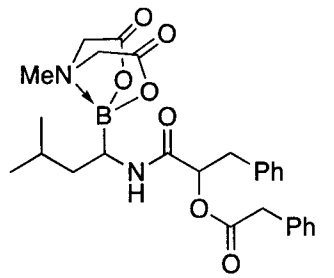
White solid; 68% yield; TLC (EtOAc) R_f = 0.39, 0.53; dr 41:59 (A:B); mp = 51-55°C; ^{1}H NMR (500 MHz, MeCN-d_3) δ A: 7.36 - 7.36 (m, 3H), 7.31 - 7.27 (m, 2H), 5.95 (d, J = 10.1 Hz, 1H), 4.76 (d, J = 4.5 Hz, 1H), 3.95 (d, J = 17.0 Hz, 1H), 3.95 (d, J = 17.5 Hz, 1H), 3.84 (d, J = 17.5 Hz, 1H), 3.81 (d, J = 17.0 Hz, 1H), 3.72 - 3.68 (m, 1H), 3.71 - 3.68 (m, 2H), 2.91 (s, 3H), 2.18 - 2.11 (m, 1H), 1.54 - 1.59 (m, 1H), 1.48 - 1.42 (m, 1H), 1.28 - 1.22 (m, 1H), 0.90 (d, J = 4.5 Hz, 3H), 0.89 (d, J = 6.5 Hz, 3H), 0.87 (d, J = 6.5 Hz, 3H), 0.84 (d, J = 4.5 Hz, 3H); B: δ 7.36 - 7.36 (m, 3H), 7.31 - 7.27 (m, 2H), 6.18 (d, J = 10.1 Hz, 1H), 4.59 (d, J = 4.8 Hz, 1H), 3.93 (d, J = 17.0 Hz, 1H), 3.88 (d, J = 16.5 Hz, 1H), 3.82 (d, J = 16.5 Hz, 1H), 3.73 - 3.71, (m, 2H), 3.66 - 3.63 (m, 1H), 3.58 (d, J = 17.0 Hz, 1H), 2.83 (s, 3H), 2.09 - 2.04 (m, 1H), 1.54 - 1.59 (m, 1H), 1.42 - 1.36 (m, 1H), 1.28 - 1.22 (m, 1H), 0.93 (d, J = 6.5 Hz, 3H), 0.86 (d, J = 4.5 Hz, 3H), 0.85 (d, J = 4.5 Hz, 3H), 0.84 (d, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, MeCN-d_3) δ 172.7, 172.5, 169.8, 169.7, 169.2, 169.0, 168.9, 168.8, 135.4, 135.3, 130.6, 130.3, 129.5, 129.5, 129.5, 128.0, 128.0, 79.9, 79.8, 79.8, 63.6, 63.6, 63.1, 62.9, 46.8, 46.5, 41.5, 41.5, 41.3, 41.0, 31.2, 31.2, 25.3, 25.2, 24.1, 24.1, 21.3, 21.2, 19.3, 19.2, 17.3, 17.3 ppm; ^{11}B NMR (192 MHz, MeCN-d_3) δ 11.4 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd. for $C_{23}H_{34}BN_2O_7$ 461.24591, found 461.24647; IR (thin film, cm^{-1}) 3349, 2959, 2866, 1748, 1661, 1526, 1467, 1455, 1338, 1291, 1244, 1161, 1103, 1081, 1031, 958, 896, 866, 764, 711.

2-((1-(MIDA boryl)-3-methylbutyl)amino)-1-(4-fluorophenyl)-2-oxoethyl 2-phenylacetate (10ac)



White solid; 60% yield; TLC (EtOAc) R_f = 0.63 (A), 0.53 (B); dr = 66:44 (A:B); mp = 81-84°C; ^{1}H NMR (500 MHz, MeCN-d_3) δ A: 7.50 (ddd, J = 8.7, 5.4, 2.6 Hz, 2H), 7.41 - 7.26 (m, 5H), 7.11 (ddd, J = 8.7, 5.4, 2.6 Hz, 3H), 6.42 (d, J = 10.1 Hz, 1H), 5.72 (s, 1H), 3.94 - 3.82 (m, 2H), 3.77 - 3.67 (m, 2H), 3.62 - 3.60 (m, 2H), 2.80 (s, 3H), 1.37 - 1.31 (m, 1H), 1.18 (ddd, J = 14.0, 10.6, 3.1 Hz, 1H), 1.08 - 1.00 (m, 1H), 0.89 (dd, J = 8.5, 6.5 Hz, 1H), 0.69 (d, J = 6.5 Hz, 2H), 0.65 (d, J = 6.5 Hz, 3H); B: 7.47 - 7.43 (m, 2H), 7.36 - 7.27 (m, 5H), 7.13 - 7.08 (m, 2H), 6.37 (d, J = 10.4 Hz, 1H), 5.79 (s, 1H), 3.90 (d, J = 17.0 Hz, 1H), 3.82 (d, J = 17.0 Hz, 1H), 3.77 (s, 2H), 3.79 (d, J = 17.0 Hz, 1H), 3.63 (ddd, J = 12.1, 10.4, 3.1 Hz, 1H), 3.13 (d, J = 17.0 Hz, 1H), 2.73 (s, 3H), 1.53 - 1.47 (m, 1H), 1.46 - 1.39 (m, 1H), 1.28 - 1.23 (m, 1H), 0.84 (d, J = 6.5 Hz, 3H), 0.74 (d, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, MeCN-d_3) δ A: 173.3, 172.4, 169.1, 169.1, 168.8, 135.2, 130.4, 130.4, 129.5, 129.4, 128.1, 127.8, 116.3, 76.6, 63.6, 62.8, 46.4, 41.3, 41.1, 24.9, 23.9, 21.1; B: 288.7, 285.9, 285.8, 285.6, 247.4, 247.1, 247.1, 246.4, 245.0, 235.3, 233.4, 233.2, 193.5, 180.4, 179.8, 163.5, 158.2, 158.1, 141.9, 141.0, 138.3 ppm; ^{11}B NMR (192 MHz, MeCN-d_3) δ 11.4 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd. for $C_{26}H_{31}BFN_2O_7$ 513.22083, found 513.22208; IR (thin film, cm^{-1}) 3338, 2954, 1746, 1665, 1606, 1510, 1455, 1292, 1223, 1149, 1103, 1030, 956, 896, 867, 844, 808, 724.

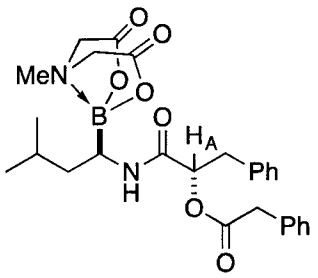
1-((1-(MIDA boryl)-3-methylbutyl)amino)-1-oxo-3-phenylpropan-2-yl 2-phenylacetate (10ad)



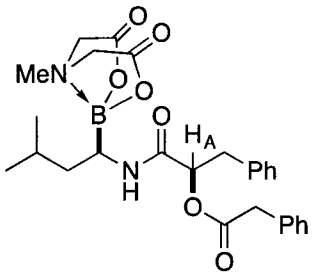
White solid; 81% yield; TLC (EtOAc) R_f = 0.60 (*syn*), 0.34 (*anti*); dr = 57:43 (*syn:anti*); ^{1}H NMR (400 MHz, MeCN-d_3) δ *anti*: 7.35 - 7.17 (m, 10H), 6.15 (d, J = 10.3 Hz, 1H), 5.07 (dd, J = 7.3, 5.2 Hz, 1H), 3.89 (d, J = 17.2 Hz, 1H), 3.78 (d, J = 17.2 Hz, 1H), 3.77 (d, J = 16.7 Hz, 1H), 3.64 (d, J = 1.8 Hz, 2H), 3.63 - 3.58 (m, 1H), 3.38 (d, J = 16.7 Hz, 1H), 3.04 - 3.02 (m, 2H), 2.72 (s, 3H), 1.34 - 1.27 (m, 2H), 1.23 - 1.16 (m, 1H), 0.82 (d, J = 6.4 Hz, 6H); *syn*: 7.34 - 7.19 (m, 8H), 7.15 - 7.12 (m, 2H), 5.97 (d, J = 10.0 Hz, 1H), 5.16 (dd, J = 7.4, 4.9 Hz, 1H), 3.93 (d, J = 17.1 Hz, 1H), 3.88 (d, J = 16.9 Hz, 1H), 3.81 (d, J = 17.1 Hz, 1H), 3.67 (d, J = 2.7 Hz, 2H), 3.42 (d, J = 16.9 Hz, 1H), 3.64 - 3.61 (m, 1H), 3.13 – 2.99 (m, 3H), 2.83 (s, 3H), 1.36 - 1.31 (m, 1H), 1.24 - 1.16 (m, 2H), 0.80 (d, J = 4.4 Hz, 3H), 0.79 (d, J = 4.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, MeCN-d_3) δ *anti*: 171.1, 168.5, 168.1, 167.7, 136.6, 134.1, 129.7, 129.3, 128.7, 128.3, 127.1, 126.8, 75.0, 62.6, 61.8, 45.5, 40.7, 40.3, 37.1, 24.1, 23.1, 20.4; *syn*: 170.9, 168.3, 168.0, 167.9, 136.5, 134.0, 129.6, 129.5, 128.6, 128.3, 127.0, 126.7, 75.2, 62.5, 62.1, 45.8, 40.6, 40.1, 37.1, 23.7, 23.2, 20.4 ppm; ^{11}B NMR (192 MHz, MeCN-d_3) δ 11.2 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd. for $C_{27}H_{34}BN_2O_7$ 509.24591, found 509.24676; IR (thin film, cm^{-1}) 2954, 1746, 1668, 1523, 1497, 1455, 1291, 1243, 1159, 1103, 1029, 956, 897, 866, 697.

The relative stereochemistry of P3CR product **10ad** was determined by computationally modeling the structure of each diastereomer. Using *GaussView 5.0.9* as a computational engine,[New Ref 3] the structure of **10ad** built (both the *syn* and *anti* diastereomers of each) and the optimization + frequencies calculation was carried out using the following parameters: Theory: DFT, Basis Set: B3LYP, 6-31G(d), additional keyword: "scrf=(solvent=acetonitrile) geom=connectivity". Using the optimized structures from these calculations, the NMR calculation was carried out using the giao method and the following computational parameters: Theory: DFT, Basis Set: RMPW1PW91, 6-311G(2d,p), additional keyword: "scrf=(solvent=acetonitrile) guess=input geom=connectivity". The isotropic Eigenvalues for the chemical shifts of the protons of interest were recorded in Table 1 along with their scaled values and the corresponding experimental values. The computational isotropic Eigenvalues were subject to scaling factors developed by Tantillo, et *al.* (slope: -1.0823, intercept 31.8486).

Table 1: Computational vs. experimental ^{1}H NMR chemical shifts of **10ad**



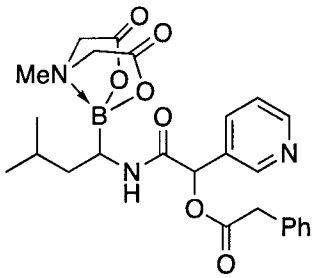
anti



syn

MPW1PW91, 6-311G(2d, p) NMR				**Experimental NMR**		
N-H	**H_A**	**N-Me**	**Stereochem**	**N-H**	**H_A**	**N-Me**
4.257	4.727	3.128	*syn* (D1)	5.975	5.154	2.831
4.775	4.410	3.059	*anti* (D2)	6.155	5.067	2.719

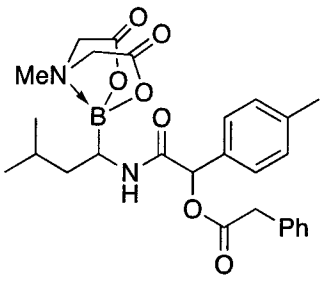
2-((1-(MIDA boryl)-3-methylbutyl)amino)-2-oxo-1-(pyridin-3-yl)ethyl 2-phenylacetate (10ae)



Off-white solid; 79% yield; TLC (EtOAc) R_f = 0.17 (A), 0.05 (B); dr = 44:56 (A:B); mp = 167 - 169°C (A), 61-65°C (B); ^{1}H NMR (500 MHz, MeCN-d_3) δ A: 8.66 (d, J = 2.2 Hz, 1H), 8.56 (dd, J = 4.8, 1.7 Hz, 1H), 7.84 (ddd, J = 8.1, 2.2, 1.7 Hz, 1H), 7.37 - 7.27 (m, 6H), 6.57 (d, J = 10.1 Hz, 1H), 5.77 (s, 1H), 3.95 (d, J = 17.2 Hz, 1H), 3.91 (d, J = 16.7 Hz, 1H), 3.82 (d, J = 17.2 Hz, 1H), 3.77 (d, J = 16.7 Hz, 1H), 3.77 (d, J = 10.7 Hz, 2H), 3.61 (ddd, J = 12.7, 10.1, 3.1 Hz, 1H), 2.83 (s, 3H), 1.38 - 1.32 (m, 1H), 1.21 - 1.15 (m, 1H), 1.05 - 0.96 (m, 1H), 0.68 (d, J = 6.5 Hz, 1H), 0.63 (d, J = 6.5 Hz, 3H); B: 8.61 (d, J = 1.5 Hz, 1H), 8.55 (dd, J = 3.8, 0.9 Hz, 1H), 7.77 (ddd, J = 6.4, 2.0, 1.5 Hz), 7.37 - 7.27 (m, 6H), 6.45 (d, J = 10.1 Hz, 1H), 5.85 (s, 1H), 3.92 (d, J = 17.2 Hz, 1H), 3.87 (d, J = 16.9 Hz, 1H), 3.81 (d, J = 17.2 Hz, 1H), 3.79 (d, J = 5.7 Hz, 1H), 3.65 (ddd, J = 12.5, 10.1, 2.9 Hz, 2H), 3.33 (d, J = 16.9 Hz, 1H), 2.79 (s, 3H), 1.54 - 1.48 (m, 1H),

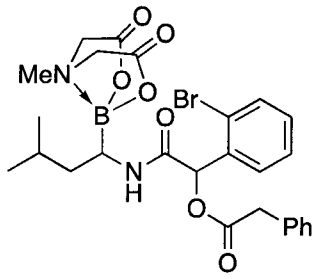
1.37 - 1.32 (m, 1H), 1.22 - 1.16 (m, 1H), 0.82 (d, J = 6.6 Hz, 1H), 0.71 (d, J = 6.4 Hz, 1H) ppm; ^{13}C NMR (125 MHz, MeCN-d_3) δ A: 172.4, 169.1, 168.8, 168.6, 151.0, 149.6, 135.8, 135.1, 132.2, 130.4, 129.5, 128.1, 124.4, 75.2, 63.6, 62.8, 46.4, 41.3, 41.0, 25.0, 23.9, 21.1; B: 171.7, 168.9, 168.7, 168.5, 150.9, 149.2, 135.5, 135.0, 132.8, 130.5, 129.5, 128.1, 124.5, 75.3, 63.5, 63.0, 46.6, 41.3, 41.1, 25.0, 24.0, 21.2 ppm; ^{11}B NMR (192 MHz, MeCN-d_3) δ 11.4 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd. for $C_{25}H_{31}BN_3O_7$ 496.22550, found 496.22657; IR (thin film, cm^{-1}) 3376, 2952, 1744, 1679, 1540, 1456, 1427, 1298, 1251, 1148, 1103, 1021, 996, 874, 767, 718.

2-((1-(MIDA boryl)-3-methylbutyl)amino)-2-oxo-1-(p-tolyl)ethyl 2-phenylacetate (10af)



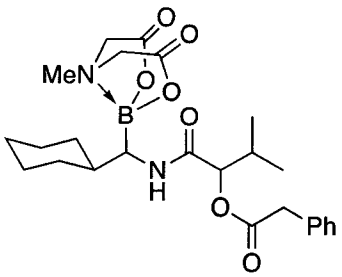
White solid; 50% yield; TLC (EtOAc) R_f = 0.72 (A), 0.53 (B); dr = 53:47 (A:B); ^{1}H NMR (500 MHz, MeCN-d_3) δ A: 7.41 - 7.27 (m, 8H), 7.19 - 7.17 (m, 1H), 6.28 (d, J = 7.2 Hz, 1H), 5.68 (s, 1H), 3.98 - 3.87 (m, 2H), 3.85 - 3.70 (m, 2H), 3.63 - 3.57 (m, 2H), 2.77 (s, 3H), 2.33 (s, 3H), 1.56 - 1.45 (m, 1H), 1.34 - 1.28 (m, 1h), 1.20 - 1.13 (m, 1H), 1.12 - 1.06 (m, 1H), 0.70 (d, J = 6.5 Hz, 3H), 0.68 (d, J = 6.2 Hz, 3H); B: 7.42 - 7.27 (m, 7H), 6.29 - 6.27 (m, 2H), 6.28 (d, J = 10.1 Hz, 1H), 5.75 (s, 1H), 3.88 (d, J = 17.0 Hz, 1H), 3.77 (d, J = 17.0 Hz, 2H), 3.75 (d, J = 2.8 Hz, 2H), 3.73 (d, J = 16.9 Hz, 2H), 2.96 (d, J = 16.9 Hz, 1H), 3.65 - 3.60 (m, 1H), 2.68 (s, 3H), 2.33 (s, 3H), 1.52 - 1.45 (m, 2H), 1.27 - 1.22 (m, 1H), 0.86 (d, J = 6.5 Hz, 3H), 0.77 (d, J = 6.4 Hz, 3H) ppm; ^{13}C NMR (125 MHz, MeCN-d_3) δ A: 172.3, 171.0, 169.2, 163.2, 139.8, 135.3, 133.4, 130.4, 130.0, 129.6, 128.2, 123.2, 77.3, 63.6, 62.8, 46.4, 41.4, 41.2, 24.9, 21.2, 21.2, 10.6; B: 171.8, 169.1, 169.0, 168.6, 139.9, 135.2, 134.0, 130.5, 130.2, 129.5, 128.1, 128.0, 77.1, 63.5, 62.8, 46.5, 41.4, 41.3, 24.9, 24.1, 21.4, 21.2 ppm; ^{11}B NMR (192 MHz, MeCN-d_3) δ 11.4 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd. for $C_{27}H_{34}BN_2O_7$ 509.24591, found 509.24678.

2-(((MIDA boryl)-3-methylbutyl)amino)-1-(2-bromophenyl)-2-oxoethyl 2-phenylacetate (10ag)



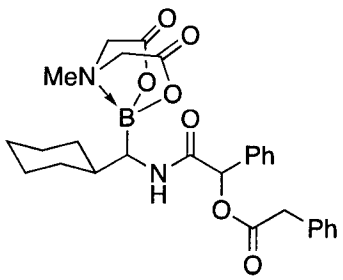
White solid; 93% yield; TLC (EtOAc) R_f = 0.67 (A), 0.50 (B); dr = 55:47; ^{1}H NMR (500 MHz, MeCN-d_3) δ A: 7.64 (dd, J = 8.0, 1.3 Hz, 1H), 7.44 - 7.27 (m, 8H), 6.41 (d, J = 10.0 Hz, 1H), 6.11 (s, 1H), 3.94 (d, J = 17.2 Hz, 1H), 3.93 (d, J = 16.7 Hz, 1H), 3.83 (d, J = 17.2 Hz, 1H), 3.78 (d, J = 16.7 Hz, 1H), 3.75 (d, J = 2.0 Hz, 2H), 3.72 - 3.67 (m, 1H), 2.86 (s, 3H), 1.40 - 1.35 (m, 1H), 1.32 - 1.26 (m, 1H), 0.92 - 0.87 (m, 1H), 0.80 (d, J = 6.2 Hz, 3H), 0.77 (d, J = 6.3 Hz, 3H); B: 7.62 - 7.60 (m, 1H), 7.37 - 7.33 (m, 4H), 7.31 - 7.24 (m, 4H), 6.36 (d, J = 9.9 Hz, 1H), 6.27 (s, 1H), 3.93 (d, J = 17.1 Hz, 1H), 3.91 (d, J = 16.9 Hz, 1H), 3.83 (d, J = 17.1 Hz, 1H), 3.77 (d, J = 1.4 Hz, 2H), 3.71 - 3.66 (m, 1H), 3.52 (d, J = 16.9 Hz, 1H), 2.82 (s, 3H), 1.56 - 1.50 (m, 2H), 1.31 - 1.26 (m, 1H), 0.89 (d, J = 6.5 Hz, 3H), 0.79 (d, J = 6.4 Hz, 3H) ppm; ^{13}C NMR (125 MHz, MeCN-d_3) δ A: 171.9, 168.9, 168.6, 167.7, 135.6, 134.9, 133.8, 131.6, 130.2, 130.0, 129.4, 128.7, 127.9, 124.7, 75.9, 63.4, 62.8, 46.4, 41.1, 41.0, 25.0, 23.8, 21.1; B: 171.4, 168.9, 168.8, 167.9, 136.8, 134.9, 134.0, 131.5, 130.5, 129.8, 129.6, 128.9, 128.1, 124.4, 76.0, 63.5, 63.1, 46.7, 41.3, 41.3, 25.2, 24.1, 21.4 ppm; ^{11}B NMR (192 MHz, MeCN-d_3) δ 11.4 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd. for $C_{26}H_{31}BBrN_2O_7$ 573.14077, found 573.14104; IR (thin film, cm^{-1}) 2955, 2261, 1747, 1668, 1523, 1470, 1290, 1242, 1194, 1103, 1030, 948, 896, 867, 753, 723.

1-(((MIDA boryl)-(cyclohexyl)methyl)amino)-3-methyl-1-oxobutan-2-yl 2-phenylacetate (10bb)



White solid; 46% yield; TLC (EtOAc) R_f = 0.55 (A), 0.38 (B); dr = 56:44 (A:B); ^{1}H NMR (500 MHz, MeCN-d_3) δ A: 7.39 - 7.34 (m, 3H), 1.33 - 7.29 (m, 2H), 6.26 (d, = 10.4 Hz, 1H), 4.67 (d, J = 5.0 Hz, 1H), 3.92 (d, J = 17.2 Hz, 1H), 3.87 (d, J = 16.7 Hz, 1H), 3.82 (d, J = 17.1 Hz, 1H), 3.82 (d, J = 16.7 Hz, 1H), 3.72 (s, 2H), 3.63 - 3.60 (m, 1H), 2.79 (s, 3H), 2.14 - 2.09 (m, 1H), 1.87 - 1.80 (m, 1H), 1.75 - 1.66 (m, 4H), 1.64 - 1.52 (m, 4H), 1.29 - 1.22 (m, 2H), 0.98 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H); B: 7.38 - 7.26 (m, 5H), 5.93 (d, J = 10.5 Hz, 1H), 4.81 (d, J = 4.1 Hz, 1H), 3.96 (d, J = 17.0 Hz, 1H), 3.94 (d, J = 17.1 Hz, 1H), 3.84 (d, J = 17.0 Hz, 1H), 3.75 (d, J = 14.2 Hz, 2H), 3.62 - 3.58 (m, 1H), 3.60 (d, J = 17.1 Hz, 1H), 2.82 (s, 3H), 2.19 - 2.14 (m, 1H), 1.75 - 1.64 (m, 4H), 1.61 - 1.50 (m, 4H), 1.28 - 1.19 (m, 2H), 1.08 - 1.05 (m, 1H), 0.88 (d, J = 6.9 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (125 MHz, MeCN-d_3) δ A: 172.8, 170.2, 169.1, 169.0, 135.4, 130.3, 129.5, 128.0, 79.9, 63.2, 62.6, 46.6, 41.5, 41.4, 32.3, 31.3, 29.3, 27.4, 27.4, 27.1, 19.3, 17.5; B: 172.3, 169.3, 168.8, 135.1, 130.6, 129.5, 128.0, 79.9, 63.0, 62.8, 46.7, 41.6, 41.1, 32.3, 31.2, 29.1, 27.4, 27.3, 27.1, 19.3, 17.2 ppm; ^{11}B NMR (192 MHz, MeCN-d_3) δ 11.3 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd. for $C_{25}H_{36}BN_2O_7$ 487.26156, found 587.26119; IR (thin film, cm^{-1}) 2926, 2853, 2266, 1748, 1667, 1525, 1451, 1339, 1294, 1239, 1159, 1109, 1025, 969, 894, 857, 764, 711.

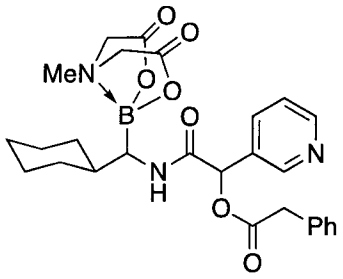
2-(((MIDA boryl)-(cyclohexyl)methyl)amino)-2-oxo-1-phenylethyl 2-phenylacetate (10ba)



Off-white solid; 52% yield; TLC (EtOAc) R_f = 0.58 (A), 0.35 (B); dr = 56:44 (A:B); ^{1}H NMR (500 MHz, MeCN-d_3 (A) DMSO-d_6+MeCNd_3 (B)) δ A: δ 7.51 - 7.50 (m, 2H), 7.41 - 7.25 (m, 10H), 6.38 (d, J = 10.5 Hz, 1H), 5.81 (s, 1H), 3.88 (d, J = 17.1 Hz, 1H), 3.83 (d, J = 16.6 Hz, 1H), 3.77 (d, J = 17.1 Hz, 1H), 3.64 (d, J = 16.7 Hz, 1H), 3.61 (s, 2H), 3.51 (dd, J = 10.6, 3.0 Hz, 1H), 2.70 (s, 3H), 1.84 - 1.56 (m, 4H), 1.51 - 1.24 (m, 4H), 1.17 - 1.08 (m, 1H), 0.81 - 0.74 (m, 1H), 0.65 - 0.57 (m, 1H); B: 7.55 - 7.53 (m, 1H), 7.45 - 7.43 (m, 2H), 7.33 - 7.23 (m, 8H), 5.95 (s, 1H), 3.96 (d, J = 17.2 Hz, 1H), 3.78 (d, J = 17.2 Hz, 1H), 3.77 (d, J = 16.8 Hz, 1H), 3.71 (d, J = 16.8 Hz, 1H), 3.42 - 3.37

(m, 1H), 2.71 (s, 2H), 2.69 - 2.66 (m, 1H), 2.33 (s, 3H), 1.70 - 1.40 (m, 6H), 1.22 - 0.96 (m, 4H) ppm; ^{13}C NMR (125 MHz, MeCN-d_3 (A) DMSO-d_6+MeCNd_3 (B)) δ A: 172.3, 169.6, 169.0, 168.9, 136.6, 135.2, 130.4, 129.5, 129.5, 128.0, 127.8, 118.3, 77.2, 63.1, 62.6, 46.4, 41.4, 41.3, 31.8, 29.2, 28.9, 27.3, 26.9; B: 172.1, 171.2, 169.5, 168.8, 137.1, 135.0, 130.3, 129.2, 129.2, 129.0, 128.0, 127.7, 76.4, 62.7, 62.2, 45.8, 41.1, 41.1, 31.7, 29.1, 27.2, 27.1, 26.8 ppm; ^{11}B NMR (192 MHz, MeCN-d_3) δ 10.4 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd. for $C_{28}H_{34}BN_2O_7$ 521.24591, found 521.24771; IR (thin film, cm^{-1}) 3337, 2923, 2853, 1750, 1678, 1653, 1536, 1497, 1449, 1344, 1298, 1258, 1156, 1116, 1030, 965, 895, 860, 710, 694.

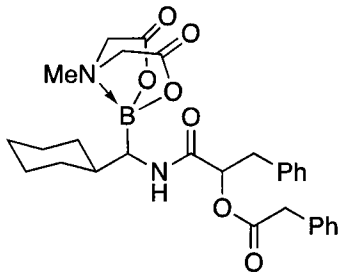
2-(((MIDA boryl)-(cyclohexyl)methyl)amino)-2-oxo-1-(pyridin-3-yl)ethyl 2-phenylacetate (10be)



Off-white solid; 42% yield; TLC (EtOAc) R_f = 0.08 (A), 0.03 (B); dr = 40:60 (A:B); ^{1}H NMR (500 MHz, MeCN-d_3) δ A: 8.75 (d, J = 2.2 Hz, 1H), 8.61 (dd, J = 5.0, 1.6 Hz, 1H), 8.00 (dddd, J = 8.0, 2.2, 1.6, 0.5 Hz, 1H), 7.48 (ddd, J = 8.0, 5.0, 0.5 Hz, 1H), 7.37 - 7.25 (m, 5H), 6.61 (d, J = 10.5 Hz, 1H), 5.91 (s, 1H), 3.91 (d, J = 17.1 Hz, 1H), 3.88 (d, J = 16.7 Hz, 1H), 3.80 (d, J = 17.1 Hz, 1H), 3.77 (s, 2H), 3.75 (d, J = 16.7 Hz, 1H), 3.54 (dd, J = 10.5, 3.1 Hz, 1H), 2.75 (s, 3H), 1.66 - 1.58 (m, 2H), 1.53 - 1.42 (m, 3H), 1.31 - 1.27 (m, 1H), 1.16 - 1.08 (m, 2H), 0,96 - 0.72 (m, 2H), 0.56 - 0.48 (m, 1H); B: 8.61 (s, 1H), 8.55 (d, J = 3.9 Hz, 1H), 7.76 - 7.74 (m, 1H), 7.73 - 7.28 (m, 6H), 6.42 (d, J = 10.6 Hz, 1H), 5.90 (s, 1H), 3.91 (d, J = 17.0 Hz, 1H), 3.85 (d, J = 17.1 Hz, 1H), 3.81 (d, J = 10.7 Hz, 2H), 3.77 (d, J = 17.1 Hz, 1H), 3.55 (dd, J = 10.6, 3.2 Hz, 1H), 3.35 (d, J = 17.0 Hz, 1H), 2.67 (s, 3H), 1.75 - 1.66 (m, 2H), 1.60 - 1.54 (m, 3H), 1.42 - 1.39 (m, 1H), 1.25 - 1.15 (m, 2H), 1.01 - 0.92 (m, 2H), 0.88 - 0.80 (m, 1H) ppm; ^{13}C NMR (125 MHz, MeCN-d_3) δ A: 172.2, 169.0, 168.9, 168.8, 149.5, 147.9, 137.4, 135.0, 130.4, 129.6, 129.4, 128.1, 125.1, 74.8, 63.1, 62.6, 46.5, 41.3, 41.2, 32.0, 29.0, 27.2, 27.2, 26.9; B: 171.4, 169.1, 168.8, 168.5, 150.9, 149.3, 135.4, 134.9, 130.5, 130.4, 129.6, 128.1, 124.5, 75.2, 63.0, 62.7, 46.5, 41.4, 41.3, 32.0, 29.1, 27.3, 27.3, 27.0 ppm; ^{11}B NMR (192 MHz, MeCN-d_3) δ 11.2 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd.

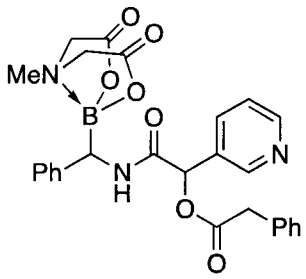
for $C_{27}H_{33}BN_3O_7$ 522.24115, found 522.24275; IR (thin film, cm^{-1}) 3027, 1747, 1673, 1496, 1453, 1427, 1337, 1286, 1242, 1126, 1028, 949, 894, 789, 759, 702.

1-(((MIDA boryl)-(cyclohexyl)methyl)amino)-1-oxo-3-phenylpropan-2-yl 2-phenylacetate (10bd)



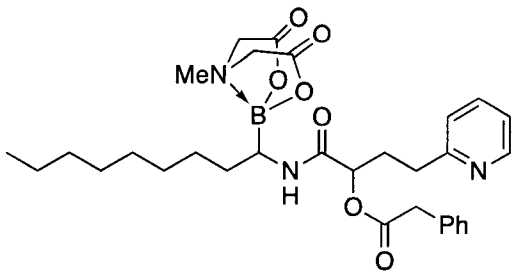
White solid; 57% yield; TLC (EtOAc) R_f = 0.62 (A), 0.32 (B); dr = 54:46 (A:B); ^{1}H NMR (500 MHz, MeCN-d_3) δ A: 7.30 - 7.20 (m, 10H), 6.26 (d, J = 10.5 Hz, 1H), 5.15 (dd, J = 7.8, 5.0 Hz, 1H), 3.87 (d, J = 17.1 Hz, 1H), 3.77 (d, J = 17.1 Hz, 1H), 3.76 (d, J = 16.8 Hz, 1H), 3.64 (s, 2H), 3.52 (dd, J = 10.5, 3.2 Hz, 1H), 3.39 (d, J = 16.8 Hz, 1H), 3.08 - 3.05 (m, 2H), 2.65 (s, 3H), 1.85 - 1.77 (m, 1H), 1.71 - 1.42 (m, 5H), 1.25 - 1.12 (m, 2H), 1.02 - 0.92 (m, 1H), 0.90 - 0.78 (m, 2H); B: 7.36 - 7.19 (m, 8H), 7.10 - 7.08 (m, 2H), 5.96 (d, J = 10.6 Hz, 1H), 5.23 (dd, J = 6.9, 4.9 Hz, 1H), 3.90 (d, J = 17.0 Hz, 1H), 3.86 (d, J = 17.0 Hz, 1H), 3.80 (d, J = 17.0 Hz, 1H), 3.71 (d, J = 16.0 Hz, 1H), 3.67 (d, J = 16.0 Hz, 1H), 3.50 (dd, J = 10.6, 3.0 Hz, 1H), 3.43 (d, J = 17.0 Hz, 1H), 3.09 (dd, J = 14.2, 4.9 Hz, 1H), 3.04 (dd, J = 14.2, 6.9 Hz, 1H), 2.74 (s, 3H), 1.69 - 1.64 (m, 1H), 1.59 - 1.50 (m, 3H), 1.50 - 1.42 (m, 1H), 1.32 - 1.27 (m, 1H), 1.20 - 1.11 (m, 2H), 0.95 - 0.87 (m, 1H), 0.76 - 0.62 (m, 2H) ppm; ^{13}C NMR (125 MHz, MeCN-d_3) δ A: 172.1, 169.9, 169.0, 168.9, 137.6, 135.0, 130.7, 130.3, 129.6, 129.3, 128.0, 127.8, 76.0, 63.1, 62.5, 46.5, 41.6, 41.3, 38.2, 32.0, 29.1, 27.4, 27.3, 26.8; B: 171.7, 169.2, 169.1, 168.8, 137.3, 134.9, 130.8, 130.5, 129.6, 129.2, 128.0, 127.7, 76.1, 63.0, 62.7, 46.7, 41.6, 40.9, 38.0, 31.6, 28.9, 27.3, 27.3, 26.7 ppm; ^{11}B NMR (192 MHz, MeCN-d_3) δ 11.2 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd. for $C_{29}H_{36}BN_2O_7$ 535.26156, found 535.26276; IR (thin film, cm^{-1}) 2925, 2852, 2266, 1748, 1612, 1531, 1497, 1453, 1338, 1293, 1239, 1157, 1111, 1027, 967, 894, 858, 698.

2-(((MIDA boryl)-(phenyl)methyl)amino)-2-oxo-1-(pyridin-3-yl)ethyl 2-phenylacetate (10ca)



Off-white solid; 48% yield; TLC (EtOAc) R_f = 0.10 (A), 0.03 (B); dr = 40:60 (A:B); ^{1}H NMR (500 MHz, DMSO-d_6 (A), MeCN-d_3 (B)) δ A: 8.69 (d, J = 9.1 Hz, 1H), 8.63 (d, J = 2.0 Hz, 1H), 8.52 (dd, J = 4.8, 1.7 Hz, 1H), 7.77 (dt, J = 8.5, 2.0 Hz, 1H), 7.37 - 7.23 (m, 7H), 7.14 - 7.11 (m, 2H), 7.07 - 7.03 (m, 2H), 6.14 (s, 1H), 4.63 (d, J = 9.1 Hz, 1H), 4.30 (d, J = 17.0 Hz, 1H), 4.24 (d, J = 17.0 Hz, 1H), 4.18 (d, J = 17.0 Hz, 1H), 3.95 (d, J = 17.0 Hz, 1H), 3.80 (s, 2H), 2.94 (s, 3H); B: 8.57 (d, J = 2.5 Hz, 1H), 8.53 (d, J = 4.0 Hz, 1H), 7.70 (dt, J = 7.9, 2.0 Hz, 1H), 7.37 (m, 11H), 7.21 - 7.16 (m, 1H), 5.96 (s, 1H), 4.63 (d, J = 9.7 Hz, 1H), 3.95 (d, J = 17.1 Hz, 1H), 3.93 (d, J = 17.1 Hz, 1H), 3.86 (d, J = 17.1 Hz, 1H), 3.77 (d, J = 3.2 Hz, 2H), 3.49 (d, J = 17.1 Hz, 1H), 2.70 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6 (A), MeCN-d_3 (B)) δ A: 170.9, 168.8, 168.3, 167.1, 149.6, 148.3, 142.4, 134.8, 134.0, 129.3, 129.3, 128.3, 128.2, 127.4, 126.9, 125.4, 123.4, 73.1, 62.3, 62.0, 45.5, 40.7: B; 171.5, 168.9, 168.4, 168.2, 151.0, 149.5, 143.1, 135.7, 134.9, 130.5, 129.6, 129.1, 129.0, 128.4, 128.1, 127.2, 124.5, 74.8, 63.4, 63.2, 46.6, 41.3 ppm; ^{11}B NMR (192 MHz, MeCN-d_3) δ 10.9 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd. for $C_{27}H_{27}BN_3O_7$ 516.19420, found 516.19663; IR (thin film, cm^{-1}) 2927, 2853, 1749, 1654, 1536, 1449, 1341, 1295, 1116, 1025, 968, 894, 859, 774, 710.

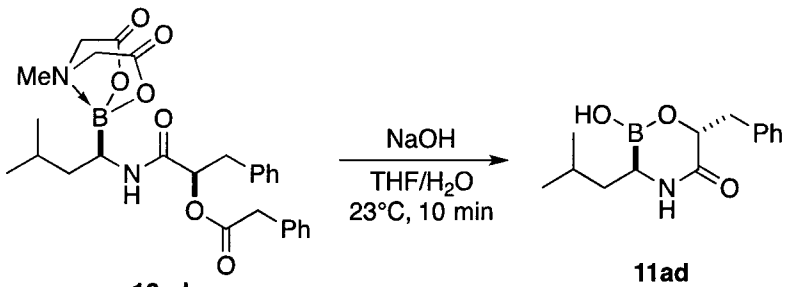
MIDA (1-(2-(2-phenylacetoxy)-4-(pyridin-2-yl)butanamido)nonyl)boronate 10cp



Off-white solid; 39% yield; TLC (EtOAc/MeCN (8:2)) R_f = A: 0.43, B: 0.22; ^{1}H NMR (500 MHz, MeCN-d_6) δ Diastereomer A: 8.40 (dd, J = 4.8, 1.7 Hz, 1H), 8.36 (dd, J = 2.4, 0.8 Hz, 1H), 7.52 – 7.47 (m, 1H), 7.40 - 7.37 (m, 2H), 7.35 - 7.30 (m, 3H), 7.24

(ddd, J = 7.8, 4.8, 0.9 Hz, 1H), 6.36 (d, J = 10.1 Hz, 1H), 4.74 (dd, J = 8.3, 4.7 Hz, 1H), 3.96 (d, J = 17.2 Hz, 1H), 3.92 (d, J = 16.7 Hz, 1H), 3.83 (d, J = 17.2 Hz, 1H), 3.82 (d, J = 16.7 Hz, 1H), 3.72 (s, 2H), 3.56 (td, J = 10.7, 3.2 Hz, 1H), 2.84 (s, 3H), 2.76 - 2.62 (m, 2H), 2.09 - 2.01 (m, 2H), 1.59 - 1.52 (m, 1H), 1.36 - 1.15 (m, 12H), 0.95 - 0.86 (m, 4); Diastereomer B: 8.42 (d, J = 4.6 Hz, 1H), 7.49 (ddd, J = 7.7, 2.3, 1.6 Hz, 1H), 7.41 - 7.36 (m, 3H), 7.35 - 7.30 (m, 2H), 7.25 (ddd, J = 7.8, 4.8, 0.9 Hz, 1H), 6.17 (d, J = 10.1 Hz, 1H), 4.85 (dd, J = 7.0, 5.6 Hz, 1H), 3.99 - 3.59 (m, 8H), 2.88 (m 3H), 2.67 - 2.56 (m, 2H), 2.10 - 2.05 (m, 2H), 1.61 - 1.54 (m, 1H), 1.47 - 1.40 (m, 1H), 1.35 - 1.18 (m, 11H), 0.90 - 0.86 (m, 4H) ppm; ^{13}C NMR (125 MHz, MeCN-d_3) δ Diastereomer A: 171.5, 169.4, 168.1, 168.0, 149.8, 147.4, 136.4, 135.9, 134.3, 129.4, 128.6, 127.1, 123.4, 73.8, 62.5, 61.9, 45.5, 40.5, 32.9, 31.6, 31.0, 29.3, 29.0, 29.0, 28.1, 26.3, 22.4, 13.4; Diastereomer B: 172.3, 170.3, 169.0, 169.0, 150.8, 148.5, 136.7, 135.2, 130.6, 130.4, 129.6, 128.1, 124.4, 75.0, 63.5, 63.1, 46.8, 41.4, 33.9, 32.6, 31.9, 30.3, 30.0, 30.0, 28.9, 27.2, 23.4, 14.4 ppm; ^{11}B NMR (192 MHz, MeCN-d_3) δ Diastereomer A: 11.2; Diastereomer B: 11.3 ppm.

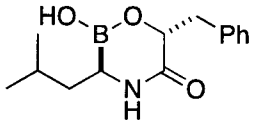
Preparation of 6-boromorpholin-3-one 11ad



syn-**10ad** **11ad**

To a small vial charged with P3CR product *syn*-**10ad** (50 mg, 0.10 mmol) was added THF (1.5 mL) and NaOH (1.0 M (aq.), 0.40 mL, 0.40 mmol) and the resulting mixture was magnetically stirred at 23°C for 10 minutes at which point TLC indicated that the reaction had gone to completion. To the reaction mixture was added 1.5 mL of pH 7 aqueous phosphate buffer and 1.5 mL Et_2O. The layers were separated and the aqueous layer was washed 3 times with THF/Et_2O (1:1). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. 2 mL 1,4-dioxane was added and the solution was concentrated via rotary evaporation without submersion into a water bath to remove only the THF and Et_2O. The 1,4-dioxane was lyophilized to afford the desired product as a white powder in 79% crude yield.

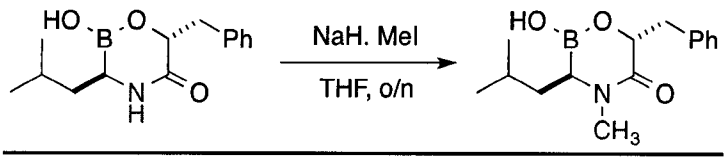
***anti*-2-benzyl-3-boro-6-hydroxy-5-isobutylmorpholin-3-one 11ad (complex with THF)**



White solid; 79% yield; TLC R_f data unavailable (decomposes on silica); ^{1}H NMR (400 MHz, MeCN-d_3) δ 7.35 - 7.17 (m, 5H), 6.14 (s, 1H), 4.67 (t, J = 5.0 Hz, 1H), 3.12 (dd, J = 13.7, 5.0 Hz, 1H), 3.04 (dd, J = 13.7, 5.0 Hz, 1H), 2.80 - 2.75 (m, 1H), 1.48 - 1.39 (m, 1H), 1.36 - 1.27 (m, 1H), 0.74 (d, J = 6.7 Hz, 3H), 0.72 (d, J = 6.7 Hz, 3H), 0.32 (ddd, J = 13.7, 10.4, 5.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.2, 136.6, 130.0, 128.2, 126.1, 74.5, 41.3, 40.4, 23.4, 23.1, 21.5 ppm (selected peaks reported. In DMSO, some dehydrated product exists (B-O-B dimer)); ^{11}B NMR (128 MHz, MeCN-d_3) δ 30.4 ppm; HRMS (DART-TOF) $[M+H]^+$ calcd. for $C_{14}H_{21}BNO_3$ 262.16145, found 262.16106; IR (thin film, cm^{-1}) 3220, 3064, 3031, 2954, 2926, 2868, 2348, 1704, 1654, 1618, 1534, 1497, 1454, 1411, 1384, 1367, 1299, 1260, 1195, 1142, 1091, 1031, 641, 868, 798, 746.

The P3CR product **10cp** was subjected to the standard procedure for preparation of 11ad above. LRMS (ESI) indicated the presence of the desired product with some hydrolyzed byproduct. The IC_{50} of the impure compound for inhibition of 20S proteases was determined using the procedure outlined for 11ad. An IC_{50} of ~ 1 µM was obtained for the CT-L enzymes and no observable inhibition occurred for the T-L or C-L enzymes.

N-Methylation of 11ad



To a solution of **11ad** (84 mg, 0.32 mmol, 1.0 equiv.) in anhydrous THF (6.5 mL) was added crushed 4Å molecular sieves (100 mg) and methyl iodide (80 µL, 1.29 mmol, 4.0 equiv.) and the resulting solution was stirred for 15 minutes under Ar. A 60% dispersion of NaH in mineral oil (51.5 mg, 1.29 mmol, 4.0 equiv.) was added and the resulting mixture was stirred overnight. The reaction was cooled to 0°C and quenched with 1M $HCl_{(aq.)}$ (5 mL). The layers were separated and the aqueous layer was washed

with Et_2O/THF (1:1) (3 x 6 mL). The combined organic layers were dried over Na_2SO_4 and filtered. 1,4-dioxane (2 mL) was added and the resulting solution was concentrated under reduced pressure in the absence of any temperature bath until only the dioxane remained. The solution was then lyophilized to yield 55 mg of orange residue. HRMS (DART-TOF) confirmed the presence of the desired product: $[M+H]^+$ calcd. for $C_{15}H_{23}BNO_3$ 276.17730, found 276.17710. Absence of the N-H signal in the crude ^1H NMR spectra further supports the presence of the desired product.

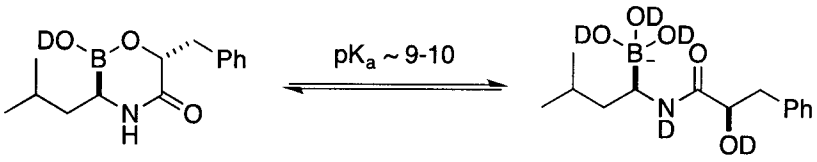
A2. Computational modeling of equilibrium energies for 11ad hydrolysis

Each compound shown in Figure 7 was modeled using the Gaussian '09 computational engine.[New Ref 3] Geometry optimizations were carried out using B3LYP 6-31G+(d). Single-point energy calculations were performed on the optimized structures using B3LYP 6-311G++(d,p). It should be noted that the water molecules were not modeled separately from the boron-containing structures but rather were included as hydrogen-bonding partners to give a more accurate estimate of enthalphic energy. The results are summarized in Figure 7.

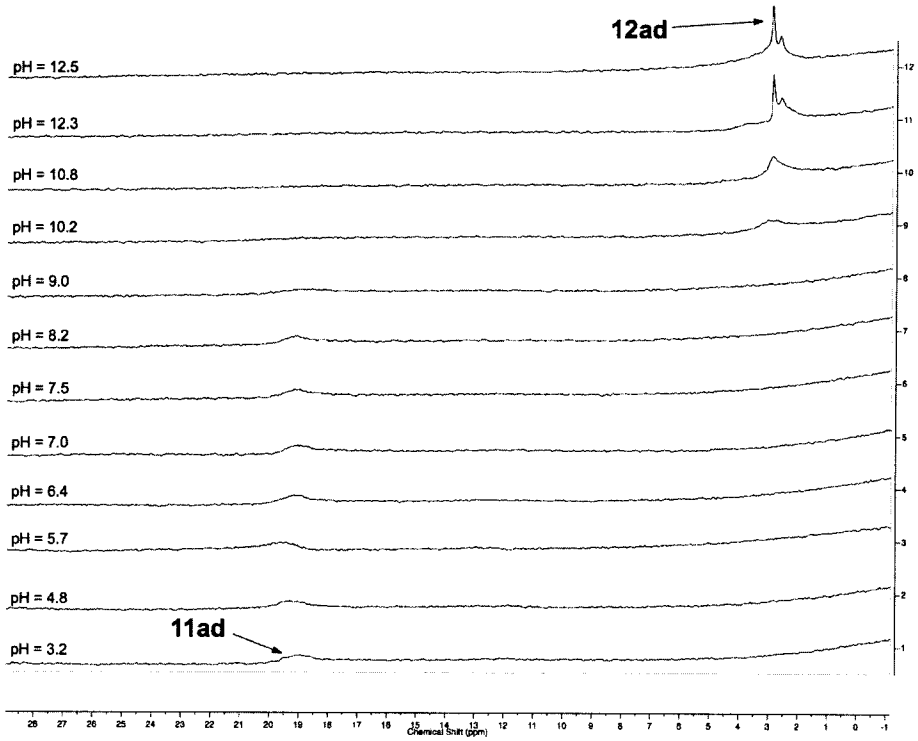
pK_a determination of 11ad

To a solution of **11ad** (25.4 mg, 0.097 mmol) in 4.1 mL of CD_3OD was added 1.2 mL of HEPES buffer (0.10 M in D_2O). The pH was adjusted to 3.2 by addition of 2.0 M $HClO_{4(aq.)}$. A 250 µL aliquot was taken for ^{11}B NMR. LRMS (ESI, positive) showed this sample contained a mass corresponding to the monodeuterated borocycle shown in Scheme 1. The pH was increased by ~ 1 pH unit by addition of 2.0 M $NaOH_{(aq.)}$ until a pH of ~ 12 was reached. At each pH, a 250 µL sample was taken for ^{11}B NMR. LRMS (ESI, positive) of the sample with pH 12.3 showed a mass corresponding to the pentadeuterated boronate shown in Scheme 1. The ^{11}B NMR spectra were taken with a sweep width of 51000 Hz, 131000 data points, 90° pulse width, 1.2 second recycle time, 10 Hz line broadening and a 2nd order polynomial fitting routine.

Scheme 1: pH vs. ^{11}B NMR spectra for boromorpholinone **11ad**



m/z = 263.2 $[M+1]^+$ m/z = 302.2 $[M]^-$



20S

proteasome inhibition assay of 7a and 11ad

7a:

Solutions of **7a** (each diastereomer) and bortezomib were prepared by serial dilution of 10 mM stocks in DMSO. To a feshly prepared sample of OCI-AML-2 human leukemia cells was added 5 mL of freshly prepared lysis buffer containing 50 mM pH 7.5 HEPES buffer, 150 mM NaCl, 1% Trition X-100 and 2 mM ATP. The cells were suspended by pipetting up and down several times and were vortexed every 5 minutes for 30 minutes at 0°C. Each well of a 96 well-plate was loaded with 87 µL of freshly prepared assay buffer (containing 50 mM pH 7 Tris-HCl buffer, 150 mM NaCl and 2 mM ATP), 10 µL of cell lysate solution and 1 µL of each stock solution of either **7a** or bortezomib (to final concentrations of 10 µM to 10 pM, in $1/10^{th}$ dilution increments). The resulting solutions were incubated at 37°C for 1h. To each well was added 2 µL of 3.75 mM N-Succinyl-Leu-Leu-Val-Tyr-7-amino-4-methylcoumarin in DMSO. The fluorescence

spectrum of each well was measured at 5 minute intervals over 30 minutes at 37°C (using a Spectromax spectrometer by Molecular Devices, excitation: 360 nm; emission 460 nm). The slope of the increase in fluorescence vs. time (converted to a percent of the slope for a blank sample) was plotted against the inhibitor concentration (Figures 1-2). The IC_{50} of each of each diastereomer of **7a** and bortezomib was calculated by applying a sigmoidal fit to each curve shown in Figures 1-2 and interpolating to 50% enzyme activity. In each assay, rates were measure in triplicate and averaged. Error bars represent 1 standard deviation. The IC_{50} values are tabulated in Table 2.

Table 2: Summary of IC_{50} values obtained for 20S proteasome inhibition assays of **7a**

Assay	**IC_{50} (nM)**		
	bortezomib	**7a** (diastereomer A)	**7a** (diastereomer B)
chymotrypsin-like	0.15	22	71

11ad:

Solutions of **11ad** and bortezomib were prepared by serial dilution of a 10 mM stock in DMSO. To a feshly prepared sample of OCI-AML-2 human leukemia cells was added 5 mL of freshly prepared lysis buffer containing 50 mM pH 7.5 HEPES buffer, 150 mM NaCl, 1% Trition X-100 and 2 mM ATP. The cells were suspended by pipetting up and down several times and were vortexed every 5 minutes for 30 minutes at 0°C. Each well of a 96 well-plate was loaded with 87 µL of freshly prepared assay buffer (containing 50 mM pH 7 Tris-HCl buffer, 150 mM NaCl and 2 mM ATP), 10 µL of cell lysate solution and 1 µL of each stock solution of either **11ad** or bortezomib (to final concentrations of 100 µM to 1 nM, in $1/10^{th}$ dilution increments). The resulting solutions were incubated at 37°C for 1h. To each well was added 2 µL of either 3.75 mM N-Succinyl-Leu-Leu-Val-Tyr-7-amino-4-methylcoumarin for the chymotrypsin-like assay, 3.75 mM t-butoxycarbonyl-Leu-Arg-Arg-7-amino-4-methylcoumarin for the trypsin-like assay or 3.75 mM benzyloxycarbonyl-Leu-Leu-Glu-7-amino-4-methylcoumarin for the caspase-like assay (all in DMSO). The fluorescence spectrum of each well was measured at 5 minute intervals over 30 minutes at 37°C (using a Spectromax spectrometer by Molecular Devices, excitation: 360 nm; emission 460 nm). The slope of the increase in fluorescence vs. time (converted to a percent of the slope for a blank sample) was plotted against the inhibitor concentration (Figures 3-5).

The IC_{50} of each of **11ad** and bortezomib was calculated by applying a sigmoidal fit to each curve shown in Figures 3-5 and interpolating to 50% enzyme activity. In each assay, rates were measure in triplicate and averaged. Error bars represent 1 standard deviation. Figure 6 shows a comparison of the *syn-* and *anti-* isomers of **11ad** in the chymotrypsin-like assay. It should be noted that IC_{50} values obtained in the assays of *syn-* and *anti-***11ad** cannot be compared to those obtained in the bortezomib comparison studies as different cell preparations were used. The IC_{50} values are tabulated in Table 3.

Table 3: Summary of IC_{50} values obtained for 20S proteasome inhibition assays

Assay	**IC_{50} (nM)**		
	bortezomib	*anti-***11ad**	*syn-***11ad**
chymotrypsin-like	0.44	19	N/A
caspase-like	3.9	84	N/A
trypsin-like	N/A	N/A	N/A
chymotrypsin-like[a]	N/A	2.9	52

[a] performed using a different cell line than the first 3; IC_{50} values differ.

Buffer-mediated hydrolysis of MIDA-bortezomib 7a (control experiment)

A 1 mM stock solution of 7a-A in DMSO was prepared. Each of 5 HPLC vials were loaded with 870 µL of freshly prepared assay buffer (containing 50 mM pH 7 Tris-HCl buffer, 150 mM NaCl and 2 mM ATP), 100 µL of cell lysis buffer (containing 50 mM pH 7.5 HEPES buffer, 150 mM NaCl, 1% Trition X-100 and 2 mM ATP) (no cells were added) and 15 µL of **7a-A** stock solution. One vial was immediately subjected to HPLC-MS analysis. The remaining 4 were incubated at 37°C. One vial was removed each 30 minutes and immediately subjected to HPLC-MS analysis. The final vial was left incubating overnight.

The first vial showed a large amount of **7a-A** (m/z = 496.2) and a trace of the free boronic acid (m/z = 385.7). The vial after 30 minutes of incubation showed an increased amount of the free boronic acid (m/z = 385.7) relative to **7a-A** (m/z = 496.2). The remaining vials gave similar results (no qualitative change in either species was observed). It should be noted that quantitative comparisons of peak data could not be obtained as multiple, poorly separated peaks were observed for each species presumably due to non-covalent bonding interactions with one or more of the buffer components.

Caco-2 assays of 11ad and 7a

Human, epithelial Caco-2 cells were grown as monolayers, fully polarized and differentiated. All compounds were tested under non-gradient pH conditions (pH 7.4/7.4) for 90 minutes as previously described.[23] LC/MS analysis were performed for all samples using a Waters Xevo QTof mass spectrometer and an ACQUITY UPLC system, to determine relative peak areas of parent compound. The percent of transported drug were calculated based on these peak areas, relative to the initial, dosing concentration.

Permeability was classified based on A-B P_{app} values (for absorptive transport) as:

Low (P_{app} < 2), **Medium** (P_{app} 2 – 10) or **High** (P_{app} >10) x 10^{-6} cm/sec.

Efflux ratios correspond to the B-A P_{app} coefficient divided by A-B P_{app} value. Efflux ratios were classified as:

Negative (ratio < 3), **Minor/Moderate** (ratio 3 – 10), or **High** (ratio > 10).

The results are summarized in Table 4.

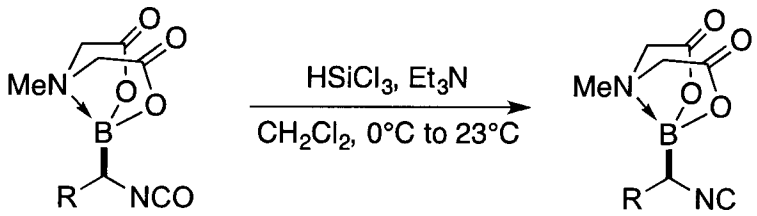
Table 4: Caco-2 cell permeability assay results for **7a-A** and *anti*-**11ad**

Compound	P_{app} (A to B)	P_{app} (B to A)	Permeability Classification	Efflux Ratio (BA/AB)	Efflux Classification	Post Assay Recovery (%)
bortezomib	0.0	5.2	Low	>10	High	28
7a-A	0.0	5.2	Low	>10	High	50
anti-**11ad**	7.7	9.5	Moderate	1.2	Negative	55
Digoxin (P-gp control)	0.1	11.2	Low	>10	High	73
Atenelol (negative control)	0.3	0.3	Low	1.1	N/A	93
Metoprolol (positive control)	13.8	10.5	High	0.8	Negative	70

At the outset, we were aware of the known propensity of tricoordinate boron to react with isocyanides.[9] Moreover, rapid decomposition upon exposure to air has limited synthetic applicability of boron-containing isocyanides.[10] To circumvent this undesired reactivity, we focused our search on fragments with tetracoordinate boron. In N-methyliminodiacetyl (MIDA) boronates, an intramolecular coordinative stabilization of boron's empty p-orbital effectively masks its Lewis acidity.[11] The tetracoordinate boronate fragment is tolerant to a diverse range of functional group transformations, allowing access to a variety of borylated derivatives. These include *α*-boryl aldehydes, [12] which contain a carbon-boron bond adjacent to an electrophilic aldehyde, and *α*-boryl isocyanates 1, a group of reagents that are now readily available from a protocol recently reported.[13]

The structural integrity of α-boryl isocyanates 1 in various functionalizations prompted us to attempt a trichlorosilane-mediated deoxygenation,[14] which gratifyingly afforded the corresponding isocyanides 2 as solid materials stable to column chromatography (Table 5). To explore the properties of these compounds we first investigated the possibility of α-proton removal given the documented utility of α-metalated isocyanides.[6a] During attempted α-deprotonation using weak bases (10 equiv. of Et_3N or 15 equiv. of $NaHCO_3$) there was no observable decrease in the ^1H NMR integration of the α-proton signal. Under strongly basic conditions (1 equiv. of potassium *tert*-butoxide) followed by exposure to deuterated solvents (MeCN-d_3) a similar lack of α-deprotonation was observed. Interestingly, tetradeuteration of the MIDA moiety was observed in both the ^1H NMR and HRMS spectra. These results showcase the dual nature of the MIDA moiety as a protective group for both the carbon-boron bond and the α-proton, which serves to enforce configurational stability of the carbon-boron bond.[15]

Table 5. Preparation of MIDA α-boryl isocyanides.[a]

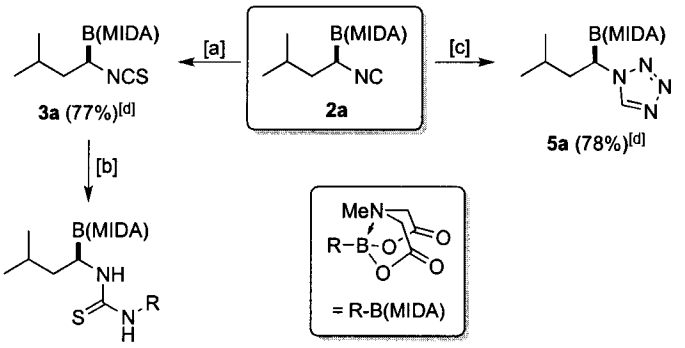


1 **2**

Starting Material	R	Product	Yield [%][b]
1a	isobutyl	**2a**	75
1b	cyclohexyl	**2b**	31
1c	phenyl	**2c**	30

[a] The reactions were carried out using α-boryl isocyanate (1.0 equiv.), trichlorosilane (1.6 equiv.) and triethylamine (3.6 equiv.) in anhydrous CH_2Cl_2 at 0°C for 30 minutes followed by 6 hours at 23°C. [b] Yields of isolated products after silica gel chromatography.

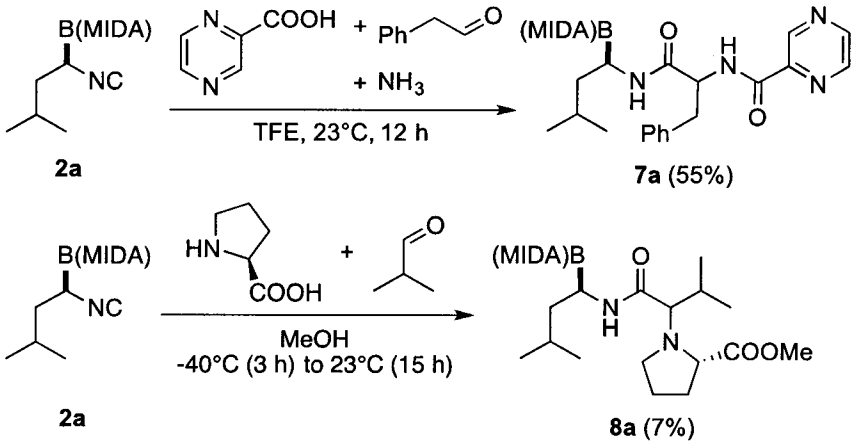
The protected nature of the α-proton led us to focus our efforts on a variety of isocyanide functionalizations (Scheme 2). Selenium-catalyzed sulfurization gave rise to α-boryl isothiocyanate 3a in moderate yield.[16] Reaction of isothiocyanate 3a with various amines afforded the corresponding thioureas 4aa – 4ab in quantitative yield.[17] Reaction of the isocyanide 2a with in situ-generated hydrazoic acid yielded the α-boryl tetrazole 5a in moderate yield.[18]



4aa, R = ethyl (79%)[d]
4ab, R = tert-butyl (90%)[d]

Scheme 2. Functionalization of MIDA α-boryl isocyanide **2a**.
[a] α-Boryl isocyanide **2a** (1.0 equiv.), sulfur (1.2 equiv.), selenium (5.0 mol %) and triethylamine (2.4 equiv.) in THF at 80°C for 15 min. [b] α-Boryl isothiocyanate **3a** (1.0 equiv.) and amine (2.0 equiv.) in THF at 23°C. [c] α-Boryl isocyanide **2a** (1.0 equiv.), HCl (2.0 mol%) and $TMSN_3$ (1.5 equiv.) in TFE/Et_2O at 60°C for 6.5 h. [d] Yields of isolated products after silica gel chromatography.

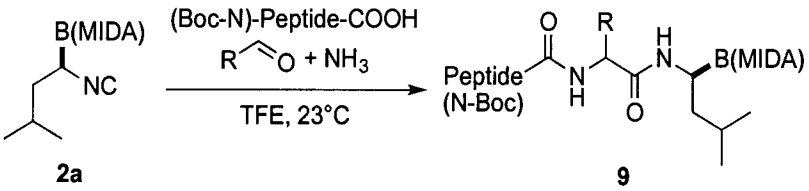
Successful retention of the carbon-boron bond during functionalization of the isocyanide moiety prompted us to investigate more challenging transformations. Isocyanide 2a participated in an Ugi 4-component reaction (U4CR) with 2-pyrazinyl carboxylic acid, phenylacetaldehyde and ammonia to afford the MIDA-bortezomib analogue 7a in 55% isolated yield (Scheme 3). We then attempted to generalize this reaction by employing amino acids as both the acid and amine component. When isocyanide 2a was reacted with L-proline and isobutyraldehyde the borodipeptide 8a was obtained in 7% isolated yield (Scheme 3).[19] In a number of other reactions, we have found that methanol solvolyzes the MIDA moiety yielding decomposition products. We attributed the low yield of 8a to the nucleophilicity of the solvent. The reaction was attempted using trifluoroethanol (TFE) as the solvent given its decreased nucleophilicity relative to methanol; however, the desired product was not obtained.[6a]



Scheme 3. U4CRs involving *α*-boryl isocyanide **2a**.

We therefore shifted our focus to U4CRs without solvent participation using N-protected amino acids and peptides as the carboxylic acid component and ammonia as the amine. The reactions proceeded at room temperature to give diastereomeric mixtures of the desired protected boropeptides 9 in moderate to excellent yields (Table 6). In most cases, diastereomers were separable by preparative reverse-phase high-performance liquid chromatography (HPLC). For larger peptides separation became more difficult due to considerable peak overlap.

Table 6. Preparation of protected boropeptides using *α*-boryl isocyanide **2a**.[a]



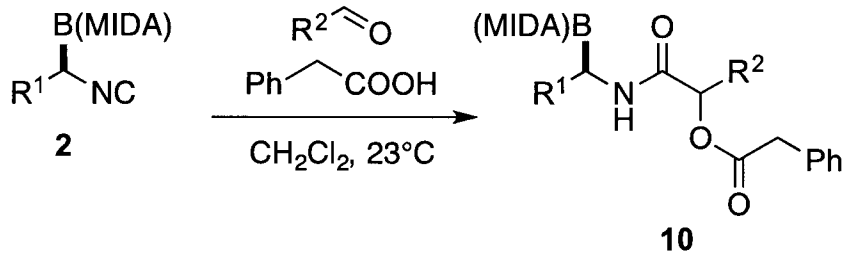
Entry	Peptide/AA[b]	R	Product	Time (d)	Yield (%)[c]
1	G	benzyl	**9a**	7	69
2	G	isopropyl	**9b**	6	79
3	F	Isopropyl	**9c**	10	74

4	V	benzyl	**9d**	6	57
5	GG	benzyl	**9e**	6	92
6	FA	benzyl	**9f**	6	91
7	PLF	benzyl	**9g**	7	63
8	PGLF	benzyl	**9h**	12	76

[a] The reactions were carried out using *α*-boryl isocyanide **2a** (1.0 equiv.), aldehyde (1.0 equiv.), ammonia (1.5 equiv., 7N solution in MeOH) and peptide (1.0 equiv.) in TFE at 23°C. [b] Boc protected at *N*-terminus; written from *N*- to *C*-terminus using standard 1-letter amino acid abbreviations. [c] Yield of diastereomeric products determined by comparison of ^{1}H NMR integration with 3,4,5-triiodobenzoic acid as an internal standard.

The successful participation of isocyanide 2a in U4CRs led us to explore its applicability in Passerini 3-component reactions (P3CRs).[6a] We found this reaction to proceed smoothly with a variety of aldehydes affording minimal by-products. Generally, the P3CR products 10 could be isolated in an acceptably pure form with simple aqueous workup. The two diastereomers could be separated by flash column chromatography on silica gel in the vast majority of cases. The reaction proceeded with moderate to excellent yields (Table 7). The rate of the reaction could be increased at elevated temperature and pressure (120°C, μwave, 2h); however, this necessitated the addition of 1 equiv. of Et_3N to eliminate aldol addition products. Dichloromethane was found to be an ideal solvent as protic solvents did not yield the desired product and the isocyanide was not soluble in diethyl ether or tetrahydrofuran.

Table 7. P3CRs involving *α*-boryl isocyanides.[a]

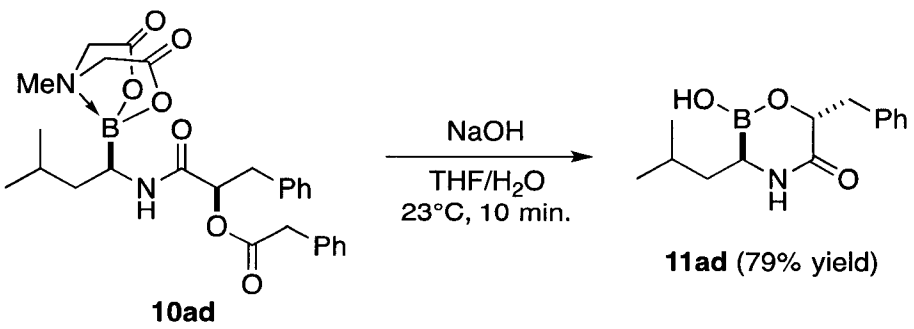


Entry	R^1	R^2	Product	Time (d)	Yield [%][b]
1	isobutyl	phenyl	**10aa**	7	81
2[c]	isobutyl	isopropyl	**10ab**	4	68
3	isobutyl	4-F-phenyl	**10ac**	4	60
4	isobutyl	benzyl	**10ad**	4	56
5	isobutyl	3-pyradinyl	**10ae**	2	79
6	isobutyl	4-Me-phenyl	**10af**	4	50
7	isobutyl	2-Br-phenyl	**10ag**	7	93
8	cyclohexyl	phenyl	**10ba**	7	53
9	cyclohexyl	isopropyl	**10bb**	7	46
10	cyclohexyl	benzyl	**10bd**	4	57

11	cyclohexyl	3-pyradinyl	**10be**	2	42
12	phenyl	benzyl	**10ca**	7	61

[a] The reactions were carried out using *α*-boryl isocyanide (1.0 equiv.), aldehyde (1.0 equiv.) and phenylacetic acid (1.0 equiv.) in CH_2Cl_2 at 23°C. [b] Yields of isolated products after silica gel chromatography. [c] The two diastereomeric products could not be separated via silica gel chromatography.

We then attempted to remove MIDA from the P3CR product *anti*-10ad under standard aqueous basic conditions to afford the corresponding free boronic acid.[10c] We found that under the deprotection conditions, hydrolysis of the ester also occurred followed by condensation of the resulting free hydroxyl with the newly formed boronic acid yielding disubstituted 6-boromorpholinone 11ad as an air-stable white solid (Scheme 4). The relative stereochemistry of borocycle 11ad was determined by computational modeling of the starting material. Computational predictions (MPW1PW91, 6-311G(2d, p)) of several ^1H NMR chemical shift differences between the two diastereomers of P3CR product 10ad correlated well with experimental observations allowing an inference of the relative stereochemistry.



10ad **11ad** (79% yield)

Scheme 4. Deprotection/Condensation of P3CR product **10ad**.

The unique structure of boromorpholinone 11ad led us to investigate its behaviour in aqueous solution. To determine the pKa of the boronate moiety, the ^{11}B NMR spectrum was taken at various pHs in buffered aqueous methanol.[20] A sharp

decrease in the signal at 19.3 ppm was observed at a pH of 9.0 accompanied by a sharp increase in a signal at 2.9 ppm. ESI mass spectra of these samples identified compound 11ad as the primary component in the lower pH samples while pentadeuterated boronate 12ad was identified in the samples at higher pH. From these data we approximated the pKa of the boronate moiety as 9.0. This is an important feature of the boromorpholinone scaffold as it implies that under biological conditions, the compound will remain in its ring-closed form allowing its application as an electrophilic pharmacophore for covalent inhibition.

Covalent electrophilic inhibitors are designed to react with nucleophilic groups at an enzyme's active site resulting in covalent bonding and inhibition. A commonly encountered problem with this approach is competing reactivity of the inhibitor with water (a weak but often reactive nucleophile). In many cases, water attacks the electrophilic site of the inhibitor before it can reach its enzyme target resulting in hydrolysis and a loss of activity. Having established that the pKa of 11ad is approximately 9.0, we can conclude that at pH < 8 (virtually all environments encountered in biological systems), the electrophilic center is impervious to attack by water. In other words, the BMN scaffold is hydrolytically stable below pH 8. This is an important feature of an electrophilic inhibitor as it suggests that the drug will be able to reach its target without hydrolytic deactivation.

We have further investigated the hydrolytic stability of 11ad using computational experiments. By applying literature protocols for computational modeling of the thermodynamic profiles of hydrolysis pathways,[22] we have established that the non-hydrolyzed form of 11ad is more stable than any of the potential products resulting from hydrolysis (Figure 7). This further enforces the assertion that the BMN core is hydrolytically stable under biological conditions. We have also demonstrated computationally that kinetically reasonable transition states exist for both ring-opening and ring-closing processes, which supports that the claim that the process will likely be governed by thermodynamics. The likelihood that the boromorpholinone scaffold is impervious to hydrolysis under biological conditions suggests that it has the potential to permeate cell membranes because the polarity of the compound is minimized in its non-hydrolyzed form.

The ability of a potential drug candidate to permeate epithelial cells is a crucial factor for oral bioavailability. There is a strong correlation between epithelial cell permeability

of a drug and its ability to be absorbed into the circulatory system following oral administration. Drugs exhibiting poor cell permeability are most often administered via intravenous (IV), subcutaneous (SC), or intramuscular (IM) injection. This limits their therapeutic applicability due to the inconvenience of imposing regular injections (and therefore regular clinic visits) on patients. For example, bortezomib, which despite its efficacy in the treatment of multiple myeloma must be administered by injection. Over the past several years, significant effort has been made toward the development of orally bioavailable bortezomib alternatives, several of which are now in various stages of clinical trials. We have demonstrated that 11ad exhibits greatly improved epithelial cell permeability over bortezomib in CACO-2 assays (Figure 8, 11ad denoted "AZ-1").

Given the known propensity of boropeptide analogues to inhibit members of the 20S proteasome[3n, q] we decided to investigate the interaction of 6-boromorpholinone 11ad with various classes of this protease family. We found that borocycle 11ad inhibited the chymotrypsin-like members of the 20S proteasome with an IC_{50} of 19 nM (compared to bortezomib in the same assay; IC_{50} = 0.4 nM) (Figure 3). A similar correlation was observed for the caspase-like and trypsin-like members of the 20S proteasome (Figure 4 and Figure 5). Both 11ad and bortezomib exhibited much weaker inhibition of the caspase-like enzymes (IC_{50}s of 2.0 μM and 3.2 nM respectively) and no inhibition of the trypsin-like members. The syn-diastereomer of 11ad was prepared from anti-10ad and exhibited inhibition of the chymotrypsin-like enzymes with an IC_{50} roughly 20 times greater than that of the anti-isomer (52 nM vs. 2.9 nM in the same assay) (Figure 6).

While the boromorpholinone inhibitors showed weaker inhibition than bortezomib, structural optimization has the potential to drastically improve these results. The pyrazine side chain in bortezomib does not exhibit a defined interaction with the active site binding pockets within the 20S proteasome causing a lack of selectivity and therefore a range of undesired side effects.[21] The multi-component nature of our boropeptide preparation methodology facilitates diversity-oriented synthesis by allowing addition of a second level of structural diversity in the same step as boron integration. This facilitates the preparation of diverse inhibitor libraries and therefore elucidation of a structure-activity relationship and optimization of a selective proteasome inhibitor. To facilitate these efforts, we have carried out computational modeling of 11ad in complex with the active site of chymotrypsin using the Glide software. This allows an understanding of the points of non-covalent bonding

interactions between the inhibitor and the enzyme and therefore optimization of binding efficiency. These experiments have shown that the ring-opened BMN structure exhibits several favorable points of interaction with its enzyme target that the unopened scaffold does not (Figure 9). This suggests that the BMN ring remains closed until it reaches its target, at which point it undergoes ring-opening to efficiently occupy the active site binding pocket. This is an important conclusion as it suggests that certain binding elements can be incorporated into a BMN-containing drug candidate and that these elements will not be exposed until the target is reached.

We have demonstrated that altering the isobutyl and benzyl substituents of 11ad drastically changes its behavior. We have also shown that derivatization of the N-H bond to N-alkyl substituents is possible. By adding sodium hydride and methyl iodide to a dry solution of 11ad in THF at 23°C, methylation of the nitrogen occurs after stirring overnight. The product of the reaction has been partially characterized by crude ^{1}H NMR and high-resolution mass spectrometry.

In addition to the established biological profile of the BMN scaffold, we have also discovered that their MIDA-protected precursors (and several closely related compounds) exhibit potent and selective inhibition of various serine and threonine hydrolases. Studies using mass spectrometry have indicated that MIDA bortezomib slowly hydrolyzes to the active free boronic acid after 30 minutes of incubation at 37°C in aqueous buffered solution. This is an example of prodrug behavior in which the active form of a drug is released after administration. The results are summarized in Figure 10 and demonstrate that MIDA removal and isolation of the resulting free boronic acids are not required for effective enzyme inhibition. This is an important result because a multitude of organoboronic acid derivatives are unstable toward isolation as free boronic acids. In these cases, synthetic chemists must resort to protecting group strategies to prevent decomposition during isolation and purification. The ability to employ protected compounds as enzyme inhibitors greatly expands the scope of organoboronic acids that can be employed in therapeutic settings.

In summary, we have demonstrated a straightforward deoxygenation of MIDA-protected α-boryl isocyanates to yield the corresponding α-boryl isocyanides as bench-stable solids. The isocyanide moiety participates in a number of functional group interconversions affording borylated tetrazoles, isothiocyanates and thioureas. Isocyanide 2a also participates in several U4CRs affording boropeptide derivatives

including MIDA-bortezomib. As a component in P3CRs, the boryl isocyanides gave rise to boryl acyloxyamide derivatives. One-pot deprotection and condensation of the P3CR product 10ad gave access to a new class of boron-containing heterocycles (6-boromorpholinones). These air-stable solids exhibited inhibition of chymotrypsin-like members of the 20S proteasome with IC_{50}s in the low nanomolar range. We have also shown that these compounds exhibit improved epithelial cell permeability and hydrolytic stability compared to other leading inhibitors in the same class. In addition to the boromorpholinone pharmacophore, we have also demonstrated that their MIDA boronate containing precursors and several similar compounds act as pro-drugs for their biologically active free-boronic acid counterparts. The step-economy and experimental simplicity with which these inhibitors can be obtained is likely to enable development of many new examples of boron-containing drug candidates.

Although preferred embodiments of the invention have been described herein, it will be understood by those skilled in the art that variations may be made thereto without departing from the spirit of the invention or the scope of the appended claims. All documents disclosed herein are incorporated by reference.

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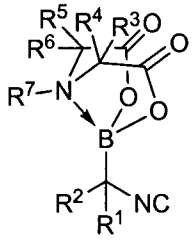
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CLAIMS:

1. A compound of Formula (2):



Formula (2)

wherein R^1, R^2, R^3, R^4, R^5, R^6 and R^7 and are each independently H or an organic group.

2. The compound of claim 1, wherein:

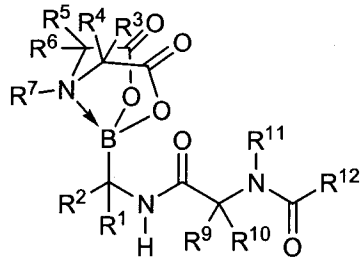
R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are each independently selected from the group consisting of H, an alkyl group, a heteroalkyl group, a cycloalkyl group, an alkenyl group, a heteroalkenyl group, an alkynyl group, a heteroalkynyl group, an aryl group, a heteroaryl group, a heterocyclic group, and an acyl group.

3. The compound of claim 1, wherein the organic group is substituted with one or more halide, hydroxyl, alkoxyl, acyloxyl or acyl groups.

4. The compound of claim 1 or 2, wherein R^3, R^4, R^5, R^6 are H and R^7 is CH_3.

5. The compound of any one of claims 1-4, wherein R^1 and R^2 are independently selected from the group consisting of H, isobutyl, cyclohexyl and phenyl.

6. A compound of Formula (9):



Formula (9)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^9, R^{10}, R^{11} and R^{12} are each independently H or an organic group.

7. The compound of claim 6, wherein:

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^9, R^{10} and R^{11} are each independently selected from the group consisting of H, an alkyl group, a heteroalkyl group, a cycloalkyl group, an alkenyl group, a heteroalkenyl group, an alkynyl group, a heteroalkynyl group, an aryl group, a heteroaryl group, a heterocyclic group, and an acyl group.

8. The compound of claim 7, wherein the organic group is substituted with one or more halide, hydroxyl, alkoxyl, acyloxyl or acyl groups.

9. The compound of claim 6 or 7, wherein R^3, R^4, R^5, R^6 are H and R^7 is CH_3.

10. The compound of any one of claims 6-9, wherein R^1 and R^2 are independently selected from the group consisting of H, isobutyl, cyclohexyl and phenyl.

11. The compound of any one of claims 6-10, wherein R^9 and R^{10} are independently selected from the group consisting of H, benzyl and isopropyl.

12. The compound of any one of claims 6-11, wherein R^{11} is H.

13. The compound of any one of claims 6-12, wherein R^{12} is independently selected from the group consisting of H, an alkyl group, a heteroalkyl group, a cycloalkyl group, an alkenyl group, a heteroalkenyl group, an alkynyl group, a

heteroalkynyl group, an aryl group, a heteroaryl group, a heterocyclic group, and an acyl group.

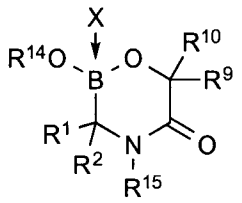
14. The compound of claim 13, wherein the organic group is substituted with one or more halide, hydroxyl, alkoxyl, acyloxyl or acyl groups.

15. The compound of any one of claims 6-12, wherein R^{12} is an amino acid or peptide.

16. The compound of claim 15, wherein R^{12} is selected from the group consisting of G, F, V, GG, FA, PLF and PGLF.

17. The compound of claim 15 or 16, wherein the amino acid or peptide comprises a protecting group.

18. A compound of Formula (11):



Formula (11)

wherein R^1, R^2, R^9, R^{10}, R^{14}, and R^{15} are each independently H or an organic group and X is any Lewis basic ligand.

19. The compound of claim 18, wherein:

R^1, R^2, R^9, R^{10}, R^{14}, and R^{15} are each independently selected from the group consisting of H, an alkyl group, a heteroalkyl group, a cycloalkyl group, an alkenyl group, a heteroalkenyl group, an alkynyl group, a heteroalkynyl group, an aryl group, a heteroaryl group, a heterocyclic group, and an acyl group and X is any Lewis basic ligand.

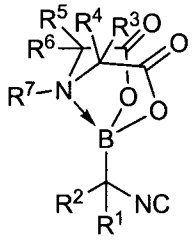
20. The compound of claim 19, wherein the organic group is substituted with one or more halide, hydroxyl, alkoxyl, acyloxyl or acyl groups.

21. The compound of any one of claims 18-20, wherein R^1 and R^2 are independently selected from the group consisting of H, isobutyl, cyclohexyl and phenyl.

22. The compound of any one of claims 18-21, wherein R^9 and R^{10} are independently selected from the group consisting of H, benzyl, isopropyl, 4-F-phenyl, phenyl, 3-pyradinyl, 4-Me-phenyl, 2-Br-phenyl, isopropyl and 3-pyradinyl.

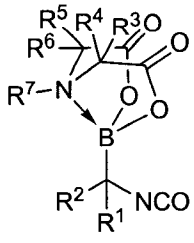
23. The compound of any one of claims 18-22, wherein R^{14} is selected from H or methyl.

24. A process for preparing the compound of Formula (2):



Formula (2)

comprising reducing the compound of Formula (1):

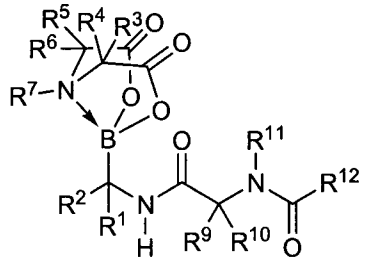


Formula (1)

wherein R^1, R^2, R^3, R^4, R^5, R^6 and R^7 and are each independently H or an organic group.

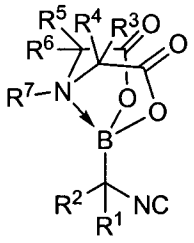
25. The process of claim 24, wherein reducing the compound of Formula (1) is performed with at least one condition and/or reagents selected from $HSiCl_3$, Et_3N, CH_2Cl_2, and 0-23°C.

26. A process for preparing the compound of Formula (9):



Formula (9)

comprising subjecting to a Ugi 4-component reaction, the compound of Formula (2):



Formula (2)

R^{12} – COOH;

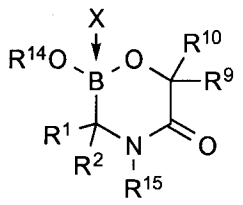
$R^{11}NH_2$; and

R^9R^{10}-CO;

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^9, R^{10}, R^{11} and R^{12} are each independently H or an organic group.

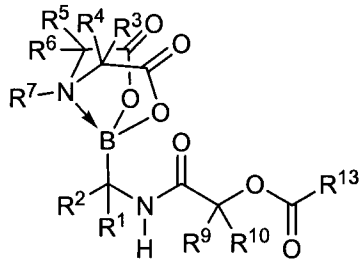
27. The process of claim 26, wherein the Ugi 4-component reaction is performed with at least one condition and/or reagent selected from TFE, 23°C and time.

28. A process for preparing the compound of Formula (11):



Formula (11)

comprising ester hydrolysis and deprotection of the compound of Formula (10):



Formula (10)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^9, R^{10}, and R^{13} and are each independently H or an organic group.

29. The process of claim 28, wherein the ester hydrolysis and deprotection of the compound of Formula (10) is performed with at least one condition and/or reagent selected NaOH, THF/H_2O, rt, and time (10 min.).

30. The process of claim 28 and 29, wherein the process further comprises performing a Passerini 3-component reaction with the compound of Formula

(2), R^9R^{10}-CO, and an organic acid R^{13}-COOH (preferably Ph-CH_2-COOH), to obtain the compound of Formula (10).

31. The process of claim 30, wherein the Passerini 3-component reaction is performed with at least one condition and/or reagent selected from CH_2Cl_2, and 23°C.

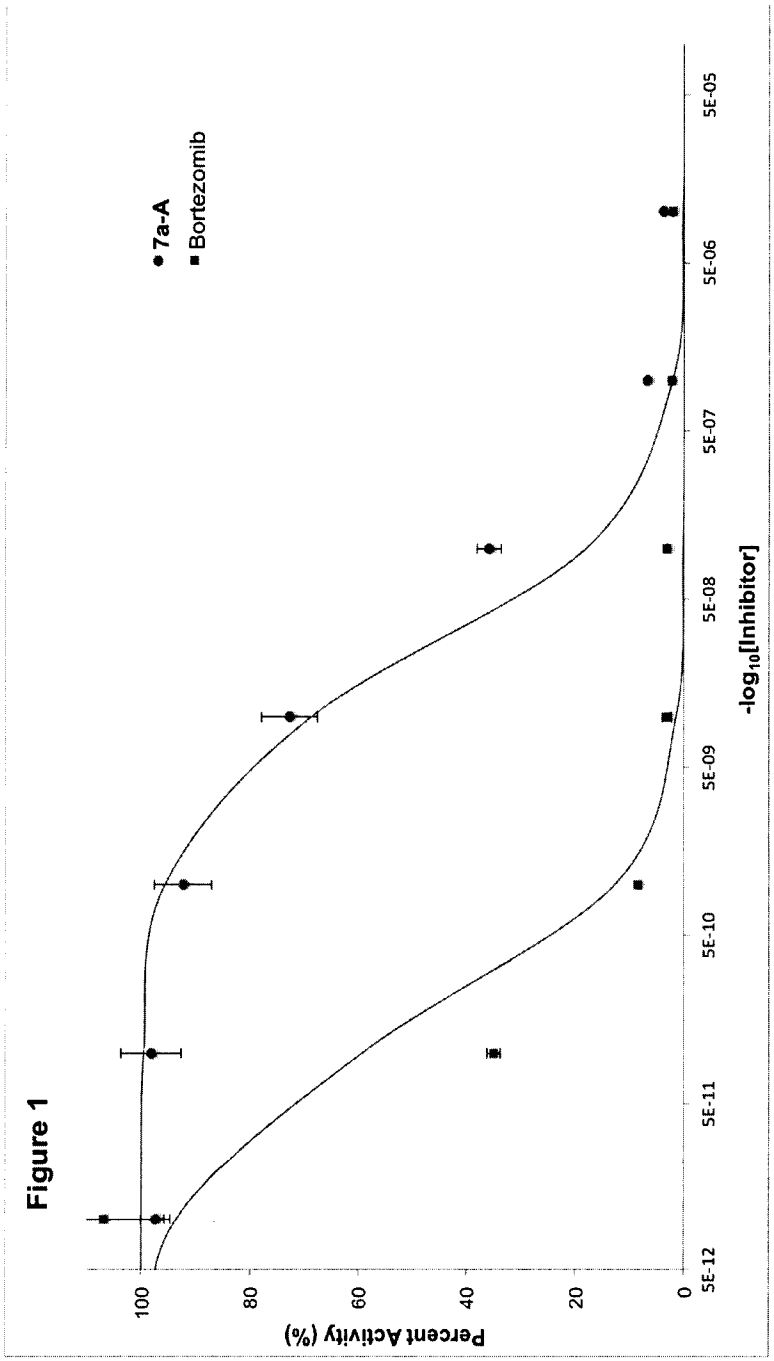

7a-A
Bortezomib
Percent Activity (%)
100
80
60
40
20
0
5E-12
5E-11
5E-10
5E-09
5E-08
5E-07
5E-06
5E-05
-log10[Inhibitor]

Figure 1

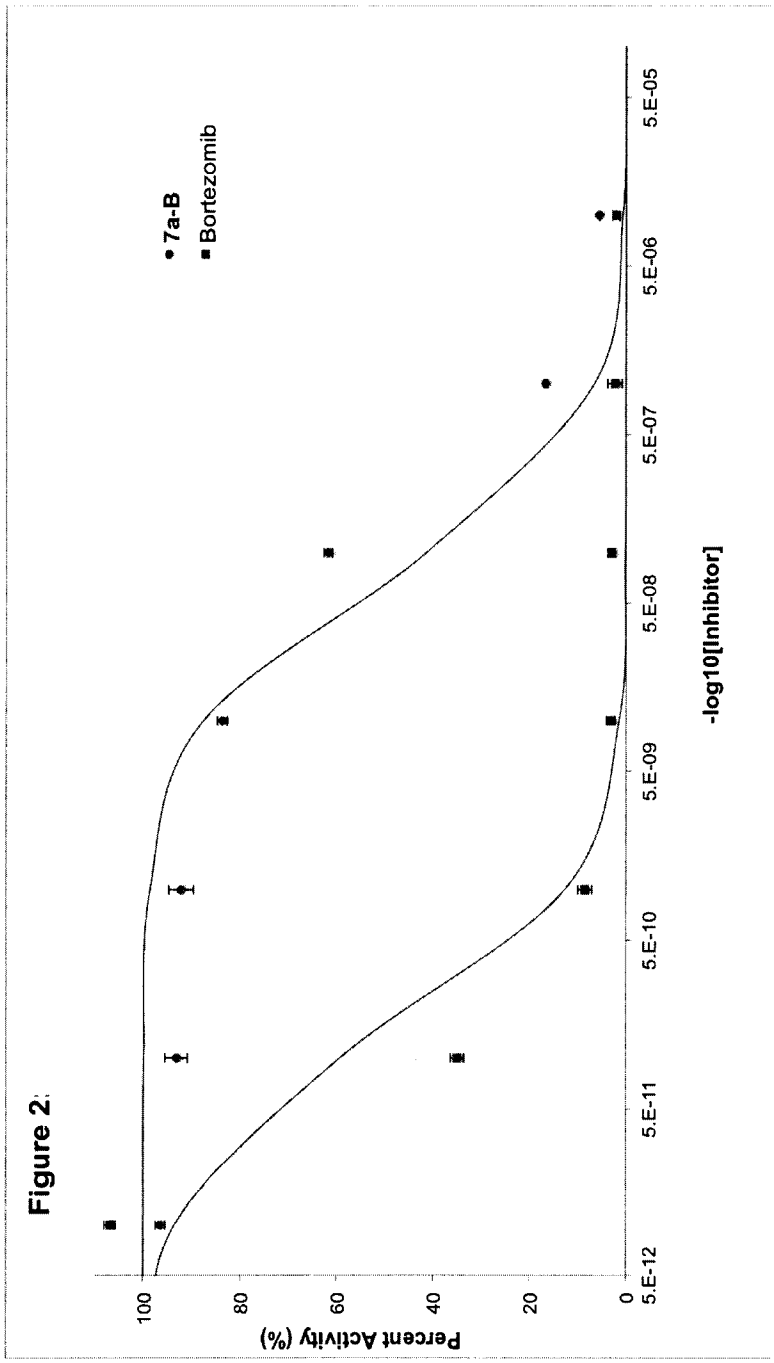

7a-B
Bortezomib
Percent Activity (%)
100
80
60
40
20
0
5.E-12
5.E-11
5.E-10
5.E-09
5.E-08
5.E-07
5.E-06
5.E-05
-log10[Inhibitor]

Figure 2:

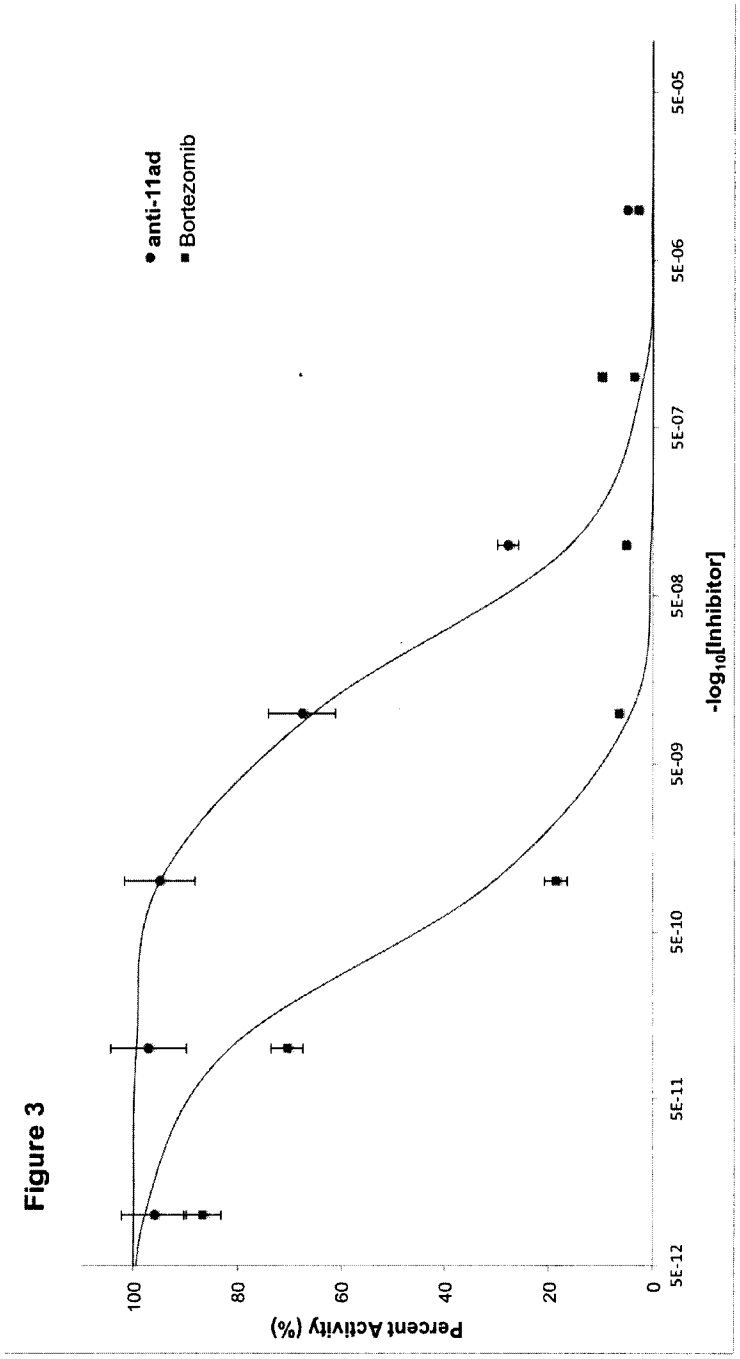

anti-11ad
Bortezomib
Percent Activity (%)
100
80
60
40
20
0
5E-12
5E-11
5E-10
5E-09
5E-08
5E-07
5E-06
5E-05
-log10[Inhibitor]

Figure 3

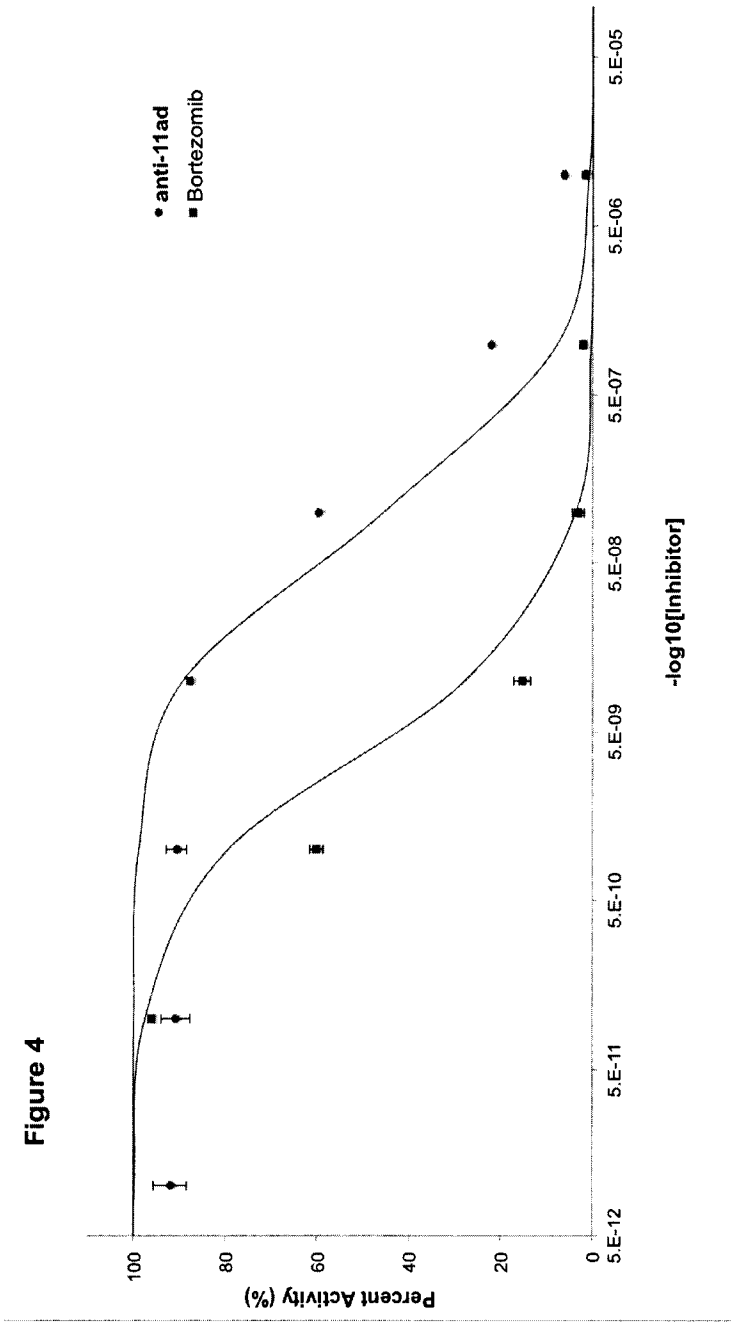

anti-11ad
Bortezomib
Percent Activity (%)
100
80
60
40
20
0
5.E-12
5.E-11
5.E-10
5.E-09
5.E-08
5.E-07
5.E-06
5.E-05
-log10[Inhibitor]

Figure 4

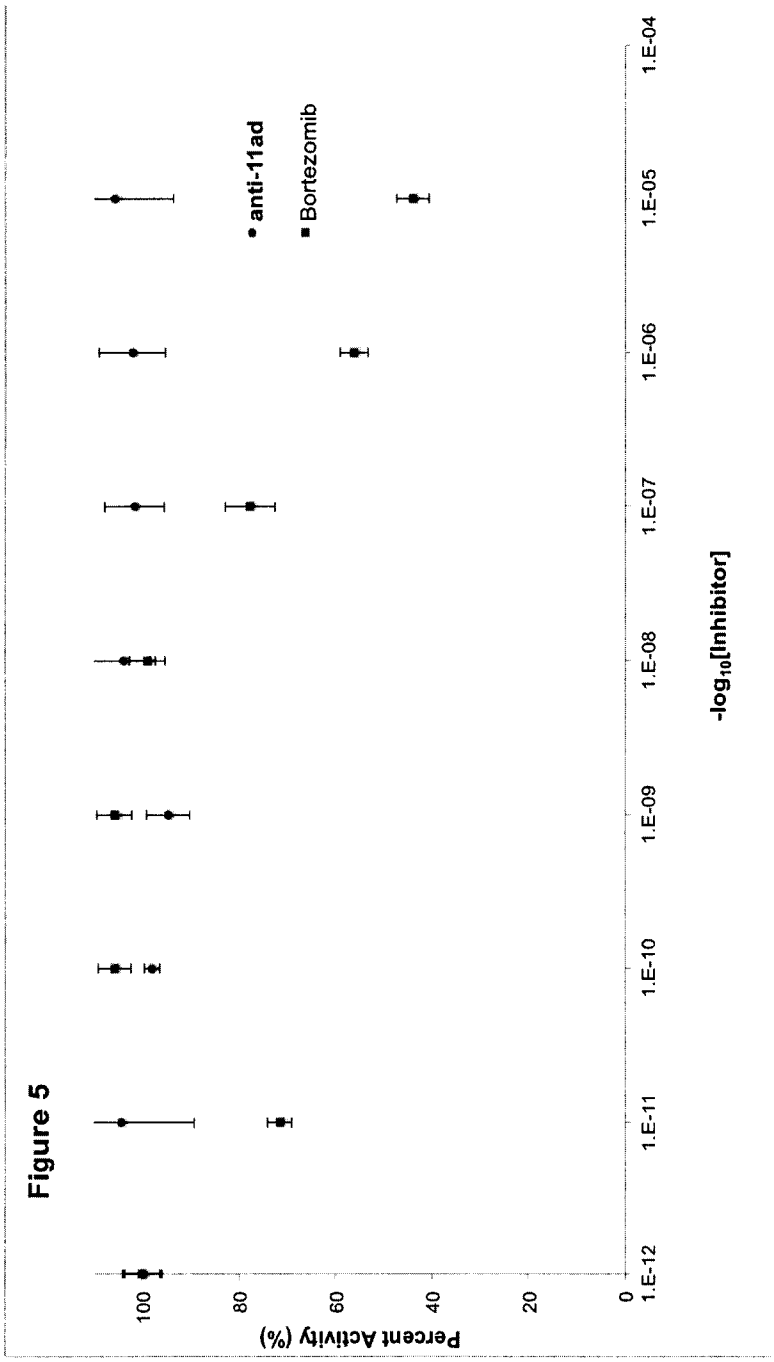

Percent Activity (%)
100
80
60
40
20
0
1.E-12
1.E-11
1.E-10
1.E-09
1.E-08
1.E-07
1.E-06
1.E-05
1.E-04
-log10[Inhibitor]
anti-11ad
Bortezomib

Figure 5

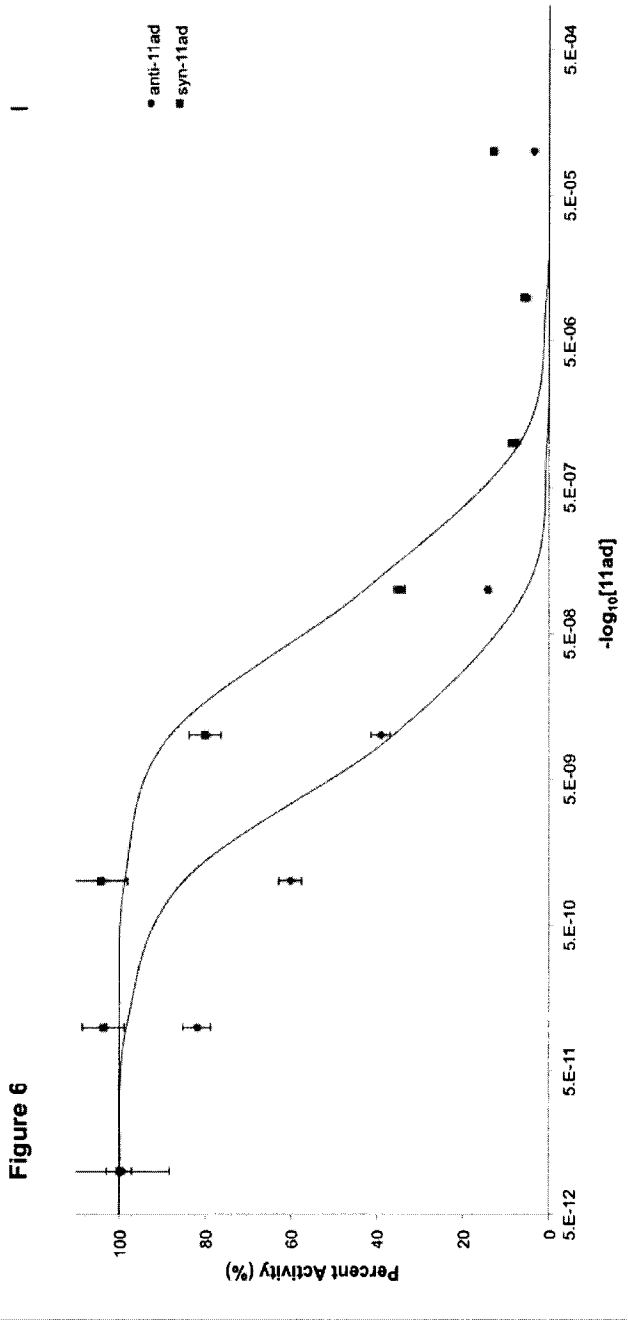

anti-11ad
syn-11ad
Percent Activity (%)
100
80
60
40
20
0
5.E-12
5.E-11
5.E-10
5.E-09
5.E-08
5.E-07
5.E-06
5.E-05
5.E-04
-log10[11ad]

Figure 6

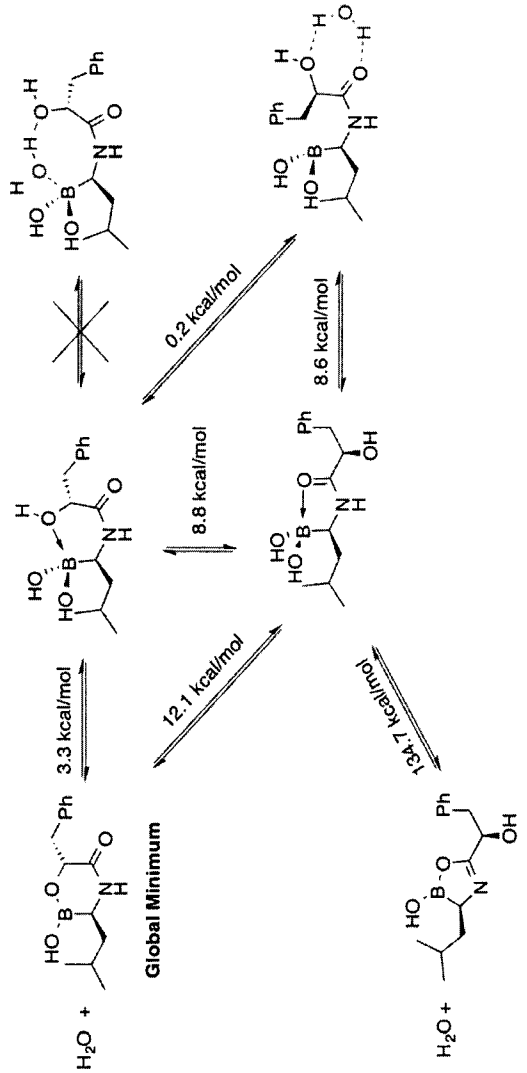

0.2 kcal/mol
8.6 kcal/mol
8.8 kcal/mol
12.1 kcal/mol
3.3 kcal/mol
134.7 kcal/mol
Global Minimum
H2O +
H2O +

Figure 7

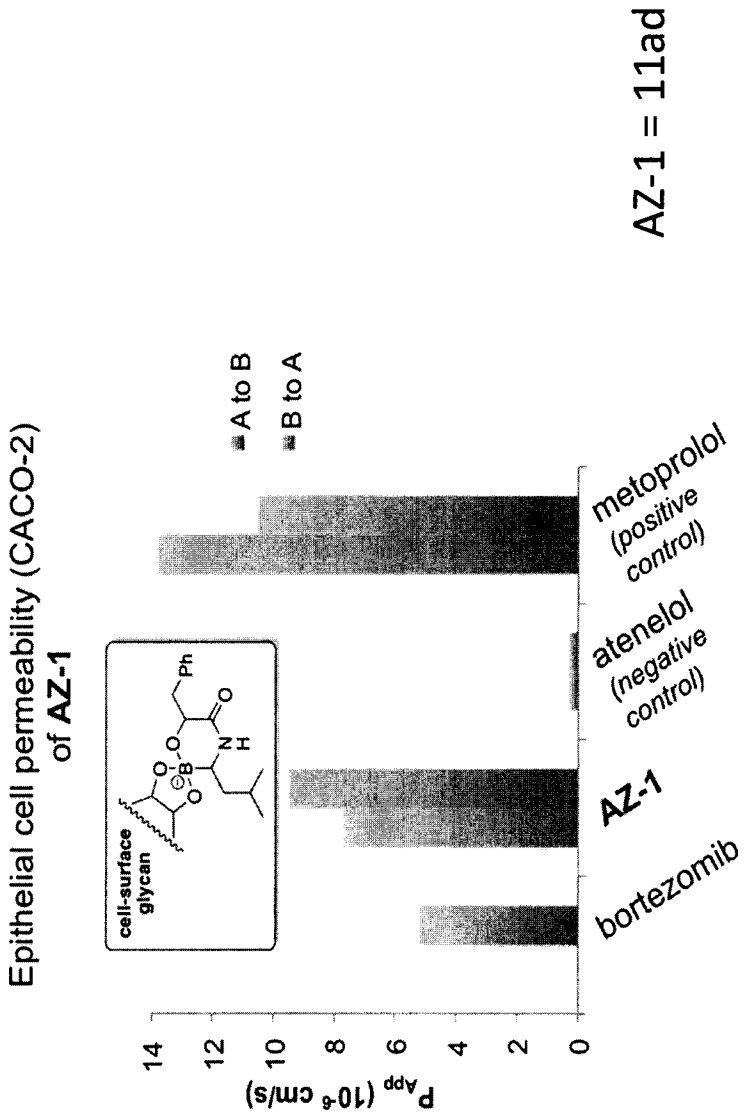
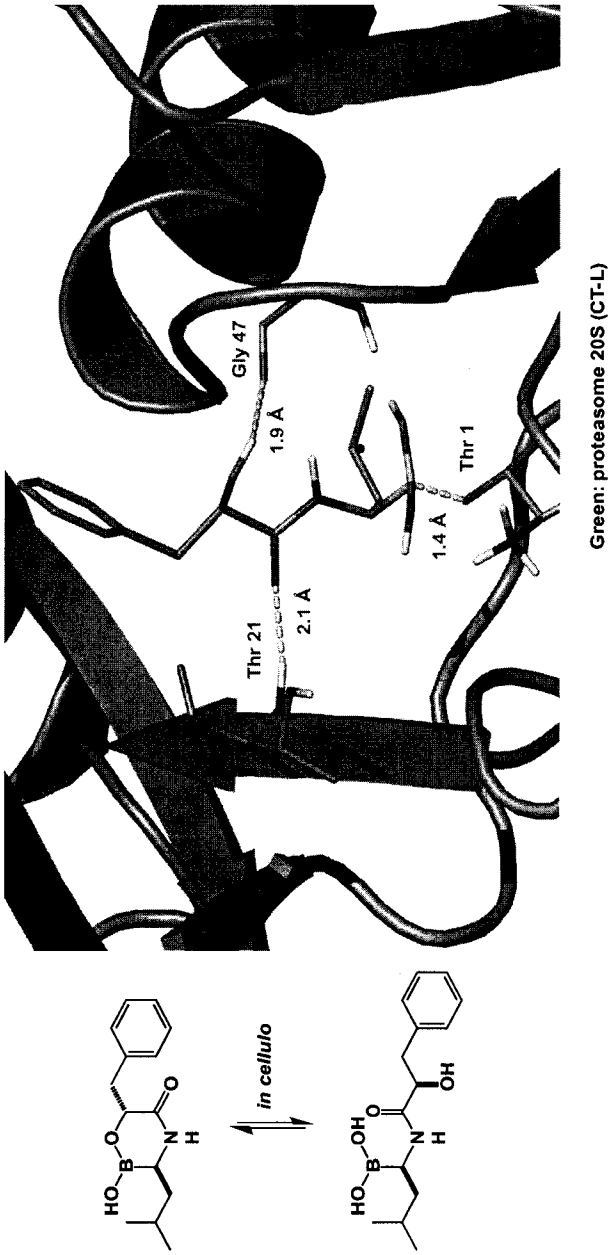
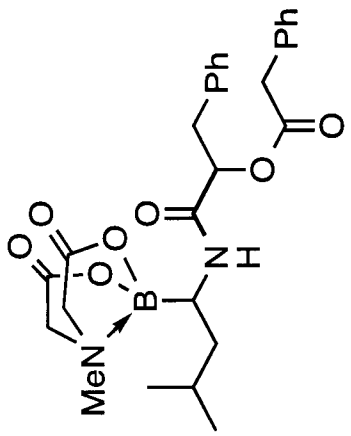

AZ-1 = 11ad
Epithelial cell permeability (CACO-2) of AZ-1
A to B
B to A
cell-surface glycan
metoprolol (positive control)
atenelol (negative control)
AZ-1
bortezomib
P_{App} (10^{-6} cm/s)
0
2
4
6
8
10
12
14

Figure 8


Gly 47
1.9 Å
Thr 1
1.4 Å
Thr 21
2.1 Å
Green: proteasome 20S (CT-L)

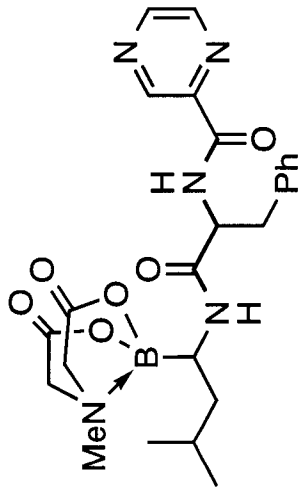
in cellulo

Figure 9



BMN precursor 10

425 nM IC_{50} for CT-L 20S proteases



MIDA bortezomib 7

22 nM IC_{50} for CT-L 20S proteases

Figure 10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2014/000307

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***C07F 5/02*** (2006.01), ***C07K 5/06*** (2006.01), ***C07K 5/08*** (2006.01), ***C07K 5/10*** (2006.01), ***C07K 7/06*** (2006.01), *C07K 1/13* (2006.01)

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07F 5/02 (2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
None

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
STN (CAplusTM and RegistryTM, no keywords); Canadian Patent Database Scopus ("MIDA boronate", "peptide", "amino acid"); Scopus ("MIDA boronate", "peptide", "amino acid")

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P/X	ZAJDLIK, A., *et al.*, "α-boryl isocyanides enable facile preparation of bioactive boropeptides", *Angew. Chem. Intl. Ed., Engl.*, **5 August 2013**, 52(32), 8411-8415 The whole document	1-31
X	Zhi, H., *et al.*, "Boroalkyl group migration provides an versatile entry into α-amionoboronic acid derivatives", *J. Am. Chem. Soc.*, 2012, 134/24, 9926-9929 Compound 10	6-17
X	CA 2 799 202, Eliasof, S. D., 24 November 2011 (24-11-2011) Compounds on pages 413, 414 and 419 (top)	6-17
X	CA 2 757 463, Bricout, D., et al., 07 October 2010 (07-10-2010) Compounds 12 (p. 6), and 15 (p. 7)	6-17

☐ Further documents are listed in the continuation of Box C.

☑ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier application or patent but published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 5 May 2014 (05-05-2014)	Date of mailing of the international search report 09 July 2014 (09-07-2014)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	Authorized officer Michael Ganton (819) 994-3425

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2014/000307

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
CA2799202A1	24 November 2011		
		AU2011255647A1	15 November 2012 (15-11-2012)
		CN103037903A	10 April 2013 (10-04-2013)
		EA201201400A1	29 March 2013 (29-03-2013)
		EP2571525A1	27 March 2013 (27-03-2013)
		IL222800D0	31 December 2012 (31-12-2012)
		JP2013526549A	24 June 2013 (24-06-2013)
		MX2012013100A	22 January 2013 (22-01-2013)
		WO2011146638A1	24 November 2011 (24-11-2011)
		WO2013025490A1	21 February 2013 (21-02-2013)
		US2011300150A1	08 December 2011 (08-12-2011)
		US2012064107A1	15 March 2012 (15-03-2012)
		US2013059816A1	07 March 2013 (07-03-2013)
CA2757463A1	07 October 2010 (07-10-2010)		
		AU2005271573A1	16 February 2006 (16-02-2006)
		AU2005271573B2	27 May 2010 (27-05-2010)
		BRPI0514042A	27 May 2008 (27-05-2008)
		CN1993453A	04 July 2007 (04-07-2007)
		EP1778825A1	02 May 2007 (02-05-2007)
		JP2008509249A	27 March 2008 (27-03-2008)
		KR20070048766A	09 May 2007 (09-05-2007)
		MX2007001349A	23 April 2007 (23-04-2007)
		US2006030497A1	09 February 2006 (09-02-2006)
		US7592296B2	22 September 2009 (22-09-2009)
		WO2006017503A1	16 February 2006 (16-02-2006)
		WO2006017503B1	06 April 2006 (06-04-2006)