CHAPTER-III

Regio- and Stereocontrolled Access to
\( \gamma \)-Boronated Unsaturated Amino Esters and
Derivatives from (Z) -Alkenyl 1,2-Bis(boronates)
INTRODUCTION

Structure and properties of boronic acids and their derivatives

Boronic acids are defined as organometallic compounds containing a trivalent boron atom that is covalently attached to one carbon substituent and two hydroxyl groups.\(^1\) The ground state boron atom is \(\text{sp}^2\)-hybridized, with a trigonal planar geometry and only six valence electrons, which gives the atom Lewis acidic properties due to the two electron deficiency and associated empty \(p\)-orbital. The moderate stability of boronic acids can be attributed to short B-O bonds (typically 1.35-1.38 Å) that are significantly stronger than C-O bonds (130 kcal/mol vs 92 kcal/mol)\(^2\) due to donation of lone pair electrons on oxygen to the empty \(p\) orbital on boron, giving rise to partial double bond character. Conversely, the B-C bond is slightly weaker than a typical C-C bond (77 kcal/mol vs 85 kcal/mol)\(^2\) and is typically 1.55-1.59 Å.

![Figure 1. Structures of boronic acid derivatives](image)

Diverse derivatives of boronic acids were synthesized to circumvent the difficulties such as stability, reactivity, ease of purification and others. The pinacol boronic ester 2 prepared from 1 though is typically less reactive than 1, it has increased stability with longer shelf-life\(^3\) and facile purification. Chiral boronates such as (\(+\))-pinanediolato boronic ester 3, though can be prepared, are more expensive to prepare, while efficient methods have been developed for chiral induction.\(^4\)

Diethanolamine adduct 4 and potassium trifluoroborinate salt 5, are developed as alternatives to \(sp^2\)-hybridized organoboron compounds and have been studied extensively. The diethanolamine derivatives like 4 are white powders that are easily purified by precipitation and filtration. Upon coordination of an additional bonding heteroatom, 4 adapts a distorted tetrahedral structure when boron’s octet is filled by a dative bonding lone pair of electrons and the boron atom rehybridizes to a \(sp^3\) center.\(^5\) Potassium trifluoroborate 5 is a unique variant that has proven to be exceptionally air stable and
highly reactive in a diverse set of cross-coupling and addition reactions. Similar to 4, the fluoroborate 5 assumes a tetrahedral geometry and $sp^3$-hybridization on boron.

**General Nomenclature of Boronic Acid Derivatives**

The reactivity and properties of boronic acids depend upon the nature of the substituent, more specifically, on the type of carbon group (R, Figure 2) directly bonded to boron. The boronic acids are classified into subtypes such as alkyl-, alkenyl-, alkynyl-, and arylboronic acids, based on R group present. For cyclic derivatives such as boronic esters, the IUPAC RB-1-1 rules for small heterocycles (i.e., the Hantzsch-Widman system) are employed along with the prefix boro. Thus, saturated five- and six-membered cyclic boronic esters are, respectively, named as dioxaborolanes and dioxaborinanes. For example, the formal name of the pinacol ester of phenylboronic acid is 2-phenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. The corresponding nitrogen analogues are called diazaborolidines and diazaborinanes, and the mixed nitrogen-oxygen heterocycles are denoted by the prefix oxaza. Unsaturated heterocycles wherein the R group and the boron atom are part of the same ring are named as boroles.

![Figure 2. Nomenclature of oxygen containing organoboron compounds](image)

The successful synthesis of boronic acid derivatives and further reactions of the organoboron compounds, originates from the theory of their reactivity, which is similar to a carboxylate carbon. Thus, the reactions on these derivatives usually proceed stepwise through a tetrahedral intermediate to a trigonal planar geometry, with a few exceptions. Though the balance of the equilibrium in the reaction is controlled by thermodynamic stability, however, the rate of reaction is highly dependent on: a) the electrophilicity of the boron atom, b) the Lewis basicity of the nucleophile and c) the steric interactions (Scheme...
1). In fact, formation of stable \( sp^3 \)-hybridized boron adducts like potassium organotrifluoroborates provides an exceptional resistance to autoxidation, which is a highly favourable process as a result of the 53 Kcal/mol greater bond strength of B-O bonds in comparison to B-C bonds.\(^8\) Through careful consideration of these properties, we can predict and exploit the reactivity of an element that has largely been underutilized in both medicinal and synthetic chemistry.

\[
\begin{align*}
{\text{OR}_1} & \quad +{\cdot}\text{Y} & \quad \text{Y} \\
{\text{R}^\prime \text{B}^\prime} & \quad -{\cdot}\text{Y} & \quad \text{Y} \\
{\text{OR}_1} & \quad -{\cdot}\text{OR}_1 & \quad +{\cdot}\text{OR}_1
\end{align*}
\]

**Scheme 1.** Model of equilibrium between a nucleophile, \( Y \), and boronic acid/ester

### Pharmaceutical applications of organoboron compounds

Medicinal chemists are rapidly acclimating to the idea of boronic acid derivatives as therapeutics for their interesting physiochemical characteristics. The ability of boronic acids to form covalent bonds provides the opportunity to design inhibitors with much higher affinities (and consequently, slower dissociation rates) towards a physiological target than typical pharmaceuticals, which often rely on weaker forces such as hydrophobic interactions, hydrogen bonding and electrostatic attractions. Additionally, organoboron compounds differ from suicide inhibitors because the formation of the covalent bond through dative donation of lone pair electrons is reversible. Strong boron-oxygen bonds (130 kcal/mol) contribute to the selectivity of boronic drug candidates towards the alcohol functionalities found on serine and threonine residues\(^9,10\) over other nucleophilic side chains, such as thiols and amines. Although excellent candidacy as inhibitors has been demonstrated for serine proteases (such as thrombin,\(^11\) elastase,\(^12\) dipeptidyl IV,\(^13\) hepatitis C virus protease,\(^14\) \( \beta \)-lactamase\(^15\) and ClpXP\(^16\) and threonine hydrolases (\( \gamma \)-glutamyl transpeptidase\(^17\) and autotaxin\(^18\)) these properties introduce inherent limitations because they are less likely to be effective on other targets, such as cysteine proteases though rare examples of binding alternative structures such as manganese-dependent arginase\(^19\) and tRNA (\textit{vide infra}) have been reported. Investigations of organoboron-based therapeutics are proliferating and traditional concerns of toxicity and poor stability are waning.\(^20\)
Velcade (bortezomib),\textsuperscript{21} a boronic acid-containing dipeptide (Figure 3; 6), is the best example to date as the first boron-containing drug, approved by the FDA in 2003 for the treatment of multiple myeloma and relapsed mantle cell lymphoma. The dipeptide interacts specifically with threonine residues in the active sites of various $\beta$-subunits of the 20S proteasome as shown by crystallographic studies,\textsuperscript{22} however the exact interaction responsible for the desired phenotype response has not yet been determined.\textsuperscript{23}

\[
\text{Ki} = 0.62 \text{ nM} \quad \text{Ki} = 1600 \text{ nM}
\]

\textbf{Figure 3.} Structures and binding affinities of Velcade 6 and peptidyl aldehydes 7

Another drug candidate Tavaborole (AN2690), reported in 2006, contains a benzoxaborole functionality (Figure 4), which was shown to be an effective anti-fungal agent in the treatment of onychomycosis\textsuperscript{24} and is currently in Phase 3 clinical trials. Interestingly, 8 exhibits a different mechanism of action through a spiro complex of 8 with the \textit{cis} 2\textsuperscript{'}- and 3\textsuperscript{'}-hydroxyls of the terminal adenosine (Figure 5). In fact, complexation of boron with \textit{cis}-diols has recently been found to play a crucial role in natural processes of several organisms including animals, plants, and bacteria. Although research on the role of boron in living organisms is in an early stage, the known functions of these complexes\textsuperscript{25,26} and the recent success of boronic acids as therapeutic tools, provide the fuel for their incorporation into potential drugs.\textsuperscript{27}

\textbf{Figure 4.} Structure of Tavaborole (8)  
\textbf{Figure 5.} Spiro complex of AN2690 and leucyl tRNA synthetase
Synthetic intermediates-transforming the C-B bond

Boronic acids defined as organometallic compounds, combine the aspects of both organic and inorganic chemistry, with unusual mixture of properties with reference to the reactivity of the carbon-boron bond. Exchange of the boryl moiety for a variety of carbon, nitrogen and oxygen linked functionalities provides a convenient route to complex structures that may be difficult to achieve by other means. Transformations of boron-containing intermediates date back to 1956, when Brown reported the anti-Markovnikov hydration of terminal alkenes 9 to provide the primary alcohols 11 using a 2-step procedure through the alkylborane intermediate 10 and subsequent oxidation (Scheme 2).\textsuperscript{28,29} Unfortunately, the instability of boranes deterred synthetic chemists from pursuing organoboron intermediates for quite some time.\textsuperscript{30} In 1979, Suzuki and Miyaura revitalized the field when they pioneered a transition metal-catalyzed procedure to transform a carbon-boron bond into a carbon-carbon bond by cross-coupling a stable boronic ester with an alkenyl or alkynyl halide.\textsuperscript{31} Unperceived at the time, this single discovery led to an exponential growth of research on organoboron intermediates. Indeed, the Nobel Prize in Chemistry was awarded, in part, to Professor Suzuki in 2010 for his contributions to the field.

\begin{equation}
\begin{array}{c}
\text{Scheme 2. Oxidation of borane intermediate}
\end{array}
\end{equation}

A unique feature of organoboron compounds, independent of the hybridization of the central carbon, is the transfer of stereochemical integrity to the product when reacted with either stoichiometric reagents\textsuperscript{32} or cross-coupled using transition metal-catalysis.\textsuperscript{33} A retention of configuration is typically observed, however, examples of inversion exist.\textsuperscript{34} As a general rule, \textit{sp}2 C-B bonds are more likely to produce the desired product in transition metal-catalyzed couplings due to conformational restrictions-which greatly decrease the
decomposition of intermediates by β-hydride elimination-and the enhanced stability from back bonding in organometallic intermediates.\textsuperscript{35}

Copper (II) salts have shown to be versatile catalysts in the oxidation of boronic acid/ester 12 to either amine 13 or ether 14 (Scheme 3) under similar conditions as disclosed by Chan, Evans and Lam in 1998.\textsuperscript{36-38} General reaction conditions are operationally simple, utilizing a stoichiometric amine base and atmospheric oxygen to re-oxidize the catalyst and provide moderate to excellent yields typically ranging from 50-98%. The limited number of reports involving copper-catalyzed transformations is likely due to the instability of organocuprates at room temperature.\textsuperscript{39,40}

\textbf{Scheme 3}

Alternatively, using copper (II) as a stoichiometric oxidant in the presence of a palladium catalyst a Mizoroki-Heck type of reaction on boronate 12 with alkenes formed a new C-C bond to afford 15\textsuperscript{41} (Scheme 4). Further, optimization of these conditions led to the report of a base- and oxidant-free oxidative Heck coupling in 2007 and expansion of the substrate scope to include vinyl ethers, which provide an interesting route to aryl ketone 16\textsuperscript{42} (Scheme 4). Stable organopalladium complexes have indeed been isolated and characterized,\textsuperscript{43} providing both mechanistic insight into cross-coupling reactions and motivation to pursue palladium as an effective catalyst.

\textbf{Scheme 4}
The true foundation for palladium-catalyzed cross-coupling of organoboronic acids can be traced much further back to the aforementioned report of the Suzuki-Miyaura cross-coupling (SMC) reaction in 1979. A great deal of research has been done to expand the scope of organic halides for the synthesis of 17 (Scheme 5) resulting in the synthesis of complex therapeutics and natural products alike and established this reaction as one of the most efficient and broadly applicable protocols in the history of synthetic chemistry.

Diboron reagents are utilized in the presence of a transition metal catalyst, which assist in breaking the moderately strong boron-boron bond (68 kcal/mol) for the construction of C-B bonds. This approach is very effective for the mono- and diboration of alkenes and the boryl substitution of C-H and C-X bonds, significantly expanding the breadth of achievable organoboron structures. The structure of the borated product can easily be controlled through the choice of catalyst and conditions starting from the most common diboron reagent 18 [bis(pinacolato)diboron] (Scheme 6). Notable milestones in this field include: the diboration of both terminal and internal alkynes with > 99% cis-selectivity using a platinum(0) catalyst to produce diboryl alkene 19 (Scheme 6) and the following extension to alkene substrates, C-H activation of simple alkanes by a rhodium(I) catalyst at high temperature to provide alkylboronic ester 20 (Scheme 6).
SMC-type cross-coupling of 18 with aryl halides in the presence of a palladium(0) source generated aryboronic ester 21 (Scheme 7), which was later extended to other substrates. Copper-catalyzed conjugate addition of 18 to electron-deficient alkenes for the preparation of β-boryl carbonyl compounds 22 (Scheme 7), which provided a route to boron-substituted amino acid analogs. A few reports using gold or iridium catalysts to affect these transformations have emerged, however, more preferable conditions are available with other metals.
PRESENT WORK

Alkenyl boronates constitute an important family of organoboron compounds whose utility in organic synthesis has been extensively illustrated. However, among this class of versatile intermediates, 1-alkene-1,2-diboronic esters 23, have been relatively poor studied. Since the discovery of an efficient cis-selective route to these species by platinum-catalyzed diboration of alkynes in 1993, most of the work related to these compounds has been focused on their metal-catalyzed cross-coupling reactions (Scheme 6). 50,59 Regioselective palladium Suzuki coupling at the terminal C-B bond can be followed by the introduction of a second aryl or heteroaryl moiety to afford unsymmetrical tetrasubstituted alkenes (Scheme 8). 50,61

By contrast, the use of a differently protected diboron 25, instead of the classical bis-(pinacolato)diboron, allowed internal selective cross coupling 62 using Pd catalyst and base in THF at 80 °C to afford regioselective cross coupled product 26 (Scheme 9).

Other convincing examples of the interest of compounds 23 were provided by couplings with 2 equiv. of the same electrophile (Scheme 10) 50,63 to give bis coupled product 27.
Yamamoto et al.\textsuperscript{64} reported double carbomethoxylation of bis boronate 23 using Pd(OAc)\(_2\), PPh\(_3\) and CO in MeOH to give the diester 28 (Scheme 11).

\begin{center}
\textbf{Scheme 11}
\end{center}

```
\begin{align*}
\text{Pd(OAc)\(_2\), PPh\(_3\), CO, MeOH} & \rightarrow \text{R}^1 \text{Bpin} \\
\text{23} & \rightarrow \text{CO\(_2\)Me} \\
\text{R}^1 \text{Bpin} & \rightarrow \text{CO\(_2\)Me} \\
\text{28}
\end{align*}
```

Andersson et al.\textsuperscript{65} reported catalytic enantioselective hydrogenation of bis boronate 23 in CH\(_2\)Cl\(_2\) to afford the enantiomerically pure bis boronate 29 (Scheme 12).

\begin{center}
\textbf{Scheme 12}
\end{center}

```
\begin{align*}
\text{H\(_2\), catalyst} & \rightarrow \text{R}^1 \text{Bpin} \\
\text{23} & \rightarrow \text{Bpin} \\
\text{R}^1 = \text{aryl} \\
\text{29}
\end{align*}
```

Fernandez et al.\textsuperscript{66} described fluorodeboronation on bis boronate 23 using electrophilic fluorination with Selectfluor to give \(\alpha,\alpha\)-difluorinated carbonyl derivative 30 (Scheme 13).

\begin{center}
\textbf{Scheme 13}
\end{center}

```
\begin{align*}
\text{F\(^+\), NaOH} & \rightarrow \text{CHF\(_2\)O} \\
\text{23} & \rightarrow \text{CHF\(_2\)O} \\
\text{30}
\end{align*}
```
Shimizu et al.\textsuperscript{67} reported annulation reactions with bis boronates 31 and aromatic dihalides in the presence of Pd catalyst and base to derive annulated compounds 32 or 33 (Scheme 14), while Singleton et al.\textsuperscript{68} reported Diels-Alder cycloaddition on bis catechol borane 31 with dienes at higher temperatures gave the Diels-Alder adducts 35 (Scheme 14).

**Scheme 14**

PETASIS REACTION

Borono-Mannich reaction is referred to as the Petasis reaction, which is a multicomponent reaction (MCR) that enables the preparation of amines and their derivatives. It is a powerful method for the synthesis of α-amino acids and derivatives. However, a literature survey revealed that reactions on Borono-Mannich type have been hitherto carried out with the 1,2-diboronic esters as substrates.

If the carbonyl compounds were engaged as one of the components in the Petasis reaction the products would be the amines, similarly if glyoxylic acid is the component the products would be amino acids (Scheme 15).

**Scheme 15**
Mechanism

\[
\begin{align*}
R^2O
\end{align*}
\]

SUZUKI REACTION

Suzuki reaction reported in 1979, is the coupling of an aryl or vinyl boronic acid with an aryl or vinyl halide or triflate using a palladium catalyst. It is a powerful cross coupling method that allows the synthesis of conjugated olefins, styrenes and biphenyls.

Scheme 16

**Mechanism**

\[
\begin{align*}
\text{Path A} & \quad R-Pd-R^1 \\
\text{Path B} & \quad R-Pd-X
\end{align*}
\]

Scheme 17. Suzuki-Miyaura catalytic cycle. Dashed boxes identify the "active" intermediates
From the preceding discussion it is amply evident that boron containing organometallic compounds have versatile utility. Though a variety of bis-boronates are reported, their synthetic utility has been not well studied. Thus, the use of such bis-boronates for C-C, C-O and C-N bond forming reactions would be very attractive for the synthesis of novel scaffolds for drug discovery, besides the synthesis of complex natural products. Hence, it was proposed to use the bis-boronates for different reactions and establish new chemical reactions for synthetic exploitation. In addition, the thus made boron compounds can be validated for their biological activity. Thus, in this chapter, we describe the regioselective Petasis reaction of alkenyl bis(boronates), the reactions of thus derived boronated amino esters under Suzuki-Miyaura cross-coupling conditions with different aromatic halides to give diversely substituted amino esters. Further, Petasis products would be subjected to other synthetic transformations.

Accordingly, (Z)-alkenyl 1,2-bis(boronates) 37a-d were prepared using known protocol\textsuperscript{50,59,66} from the corresponding alkynes 36a-d. Thus, 1-hexyne (36a), propargyl trimethylsilane (36b), phenylacetylene (36c) and 3-hexyne (36d) independently on reaction with bis(pinacolato)-diboron in the presence of tetrakis(triphenylphosphine)-platinum as catalyst in DMF:toluene at 80 °C for 18 h gave the corresponding alkenyl 1,2-bis(boronates) in good yields (Scheme 18).

**Scheme 18**

\[
\begin{align*}
R & \overset{\text{pinB-Bpin, Pt(PPh\textsubscript{3})\textsubscript{4}}}{\longrightarrow} \overset{\text{DMF/Toluene, 80 °C}}{\longrightarrow} \text{pinB} & \overset{\text{Bpin}}{\longrightarrow} \\
36a & \quad R = n\text{-Bu, } R^1 = H & 37a & \quad R = n\text{-Bu, } R^1 = H & 78\% \\
36b & \quad R = \text{CH}_2\text{TMS, } R^1 = H & 37b & \quad R = \text{CH}_2\text{TMS, } R^1 = H & 80\% \\
36c & \quad R = \text{Ph, } R^1 = H & 37c & \quad R = \text{Ph, } R^1 = H & 85\% \\
36d & \quad R = \text{Et, } R^1 = \text{Et} & 37d & \quad R = \text{Et, } R^1 = \text{Et} & 82\%
\end{align*}
\]

Having synthesized the requisite bis-boronates 37a-d, the study was then extended first to a regioselective Petasis reaction. Accordingly, when 37a was subjected to Petasis reaction as previously reported in methanol or THF,\textsuperscript{69} poor yields were obtained (Scheme 19).
However, bis-boronic ester 37a on Petasis reaction with morpholine and glyoxylic acid in HFIP (1,1,1,3,3,3 hexafluoropropan-2-ol) at room temperature for 8 h gave the corresponding γ-borated unsaturated amino acids 38a. The thus prepared amino acid 38a was directly subjected to esterification with an ethereal solution of CH$_2$N$_2$ to afford the corresponding γ-borated ester 39a in 69% yield over two steps (Scheme 20). Such an improvement in yield was attributed to the positive effect of HFIP on the formation of ionic intermediates and stabilization of polarized transition states. Structure of ester 39a was confirmed from the $^1$H NMR (Spectrum 1), where resonances for the lone olefinic proton was observed at $\delta$ 5.96 as a doublet ($J = 9.8$ Hz), while CαH proton resonated at $\delta$ 4.32 as a doublet ($J = 9.8$ Hz), four morpholine protons (2 x CH$_2$) resonated at $\delta$ 3.73 as a triplet, whereas OMe resonated at $\delta$ 3.69 as a singlet, remaining morpholine protons (2 x CH$_2$) resonated at $\delta$ 2.59-2.48 as a multiplet. Four methyl protons appeared at $\delta$ 1.27 as a singlet, the terminal Me group protons at $\delta$ 0.86 as a triplet, while the remaining protons resonated at the respective positions. In the $^{11}$B NMR of 39a (Spectrum 2), the appearance of broad single at $\delta$ 30 ppm correspond to one boron unit. HRMS showed $m/z$ 368.2608 (M$^+$+H) for C$_{19}$H$_{35}$NO$_5$B further confirming the product.
The study was then extended to the bis-boronates 37b and 37c. Accordingly, 37b and 37c independently underwent facile Petasis reaction under the above reaction conditions to give the respective acids 38b and 38c. Reaction of 38b and 38c with ethereal CH₂N₂ afforded the esters 39b (60%) and 39c (53%) respectively (Scheme 21). Structures of esters 39b and 39c were confirmed from the ¹H NMR (Spectrum 3 and 5), where resonances for aromatic protons in 39c were observed at δ 7.42-7.22 as a multiplet, olefinic protons for 39b and 39c were observed at δ 5.80 (J = 9.9 Hz) and 6.40 (J = 9.9 Hz) as doublets respectively, while, CαH protons for 39b and 39c resonated at δ 4.47 (J = 9.9 Hz) and 4.32 (J = 9.9 Hz) as a doublets respectively. Four morpholine protons (2 x CH₂) corresponding to 39b resonated at δ 3.74 as a triplet, whereas for 39c resonances for morpholine protons (2 x CH₂) were observed at δ 3.78-3.74 as a multiplet. The OMe protons for 39b and 39c resonated at δ 3.68 and 3.74 as a singlets respectively, while, remaining four morpholine protons (2 x CH₂) resonated at δ 2.60-2.46 and 2.67-2.54 as a multiplets for 39b and 39c respectively, allylic CH₂ for 39b resonated at δ 1.67 as a singlet. Resonances of four methyl groups (4 x CH₃) of boronate ester appeared as two singlets at δ 1.25, 1.24 for 39b and at δ 1.35, 1.34 for 39c corresponding to the boronate unit. Three of methyl group (3 x CH₃) protons of TMS were resonated at δ -0.05 as a singlet for 39b. In the ¹¹B NMR of 39b and 39c appearance of broad signals at δ 29.7 and 30.3 ppm respectively correspond to one boron unit. HRMS showed m/z 420.2351 (M⁺+Na) for
Chapter III, Present work

C_{19}H_{36}NO_{5}BNaSi (39b) and m/z 410.2112 (M^+Na) for C_{21}H_{30}BNO_{5}Na (39c) further confirming the products.

In this Petasis reaction a single isomer was identified with an $E$ stereochemistry as evidenced from NOESY experiments. Similarly, the reaction was found to be highly regioselective and no product from a double Petasis condensation was detected under the above reaction conditions.

In a further study, bis-boronic acid 37d, prepared from a disubstituted acetylene, was subjected to Petasis reaction. However, 37d met with failure to give 38d (Scheme 22).

**Scheme 22**

Likewise, bis boronic esters 37a and 37c independently were subjected to Petasis reaction using dibenzylamine and glyoxylic acid in HFIP at room temperature for 8 h to give the corresponding $\gamma$-boronated unsaturated amino acids 38e and 38f, which were directly subjected for esterification with an ethereal solution of CH$_2$N$_2$ to afford corresponding $\gamma$-boronated esters 39d (50%) and 39e (54%) (over two steps) respectively (Scheme 23). In the $^1$H NMR (Spectrum 6 and 7), the resonances for olefinic protons of 39d and 39e were observed at $\delta$ 6.16 ($J = 9.3$ Hz) and 6.53 ($J = 9.3$ Hz) respectively as doublets, while, CαH protons appeared at $\delta$ 4.74 ($J = 9.3$ Hz) and 4.73 ($J = 9.5$ Hz) respectively as a doublets. Benzylic CH$_2$ protons appeared at $\delta$ 3.76 and 3.81 as a singlets, whereas, OMe protons were observed at $\delta$ 3.69 as a singlet for both the products. The remaining protons resonated at the expected positions. In the $^{11}$B NMR of 39d and 39e appearance of broad signals at $\delta$ 30.4 and 30.3 ppm respectively corresponding to one boron unit gave proof for the products. HRMS showed m/z 478.3129 (M$^+$H) for
C$_{29}$H$_{41}$NO$_4$B (39d) and m/z 498.2809 (M$^+$+H) for C$_{31}$H$_{37}$NO$_4$B (39e), further confirming the products.

Similarly, bis-boronic ester 37a subjected to Petasis reaction with pyridyl piperazine (A) and Boc piperazine (B) independently with glyoxylic acid in HFIP at room temperature for 8 h to give the corresponding γ-boronated acids 38g and 38h, which were directly subjected to esterification to afford the corresponding esters 39f (57%) and 39g (63%) (over two steps) respectively (Scheme 24). Structures of esters 39f and 39g were confirmed by $^1$H NMR spectra, where, olefinic proton resonances appeared at $\delta$ 5.99
(J = 9.8 Hz) and 5.90 (J = 9.7 Hz) as a doublets for 39f and 39g respectively. The CαH protons for 39f and 39g were resonated at δ 4.40 (J = 9.8 Hz) and 4.29 (J = 9.7 Hz) as a doublets respectively. Boc protons (4 x CH₃) appeared at δ 1.22 as a singlet, while the remaining protons were resonated at their respective positions. Further, HRMS showed m/z 444.3037 (M⁺+H) for C₂₄H₃₉N₃O₄B (39f) and m/z 489.3112 (M⁺+Na) for C₂₄H₄₃N₂O₆BNa (39g) confirming the products.

Similarly, bis boronic ester 37b was subjected to Petasis reaction with N-Methyl benzylamine and glyoxylic acid in HFIP gave the corresponding acid 38i, which on esterification with an ethereal solution of CH₂N₂ to give corresponding γ-boronated ester 39h in 53% yields (over two steps) (Scheme 25), while boronate 37a on Petasis reaction with primary amine (benzylamine) failed to give the corresponding amino acid 38j (Scheme 25). Structure of 39h was confirmed by ¹H NMR (Spectrum 12), where, resonances for the aromatic protons appeared at δ 7.40-7.19 as a multiplet and olefinic proton resonated at δ 5.97 (J = 9.6 Hz) as a doublet. The CαH proton resonated at δ 4.73 (J = 9.6 Hz) as a doublet, while, benzylic CH₂ protons resonated at δ 3.76-3.54 as a multiplet and two singlets appeared at δ 3.73 and 2.21 corresponding to OMe and NMe respectively. Further, HRMS showed m/z 432.2738 (M⁺+H) for C₂₃H₃₉NO₄BSi confirming the product.
Diastereo Selective Petasis Reaction:

Regioselective Petasis reaction was also investigated for diastereoselectivity using (S)-(−)-N-benzyl-α-methylbenzylamine 40. Accordingly, 37a on reaction with 40, a more sterically demanding amine than dibenzylamine, and glyoxylic acid in HFIP for 8 h gave the corresponding amino acid, which on further esterification using in situ generated CH$_2$N$_2$ in diethylether for 2 h gave an inseparable diastereomeric mixture of 41 in 58% yield with 58:42 ratio (Scheme 26). Structure of 41 was confirmed from the $^1$H NMR (Spectrum 13), where, resonances for the one olefinic proton was observed at δ 6.16 and 6.0 as doublets for distereomeric mixture. The CαH proton resonated at δ 4.93 and 4.86 as doublets. OMe resonated at δ 3.65 and 3.47 as singlets, while the remaining protons resonated at the expected chemical shifts. Further, HRMS showed m/z 492.3279 (M$^+$+H) for C$_{30}$H$_{43}$NO$_4$B confirming the product.

Scheme 26

Suzuki reactions on γ-boronated amino esters:

After the successful conversion of bis-boronates regioselectivley into amino esters 39a-h by Petasis multicomponent reaction, the study was then extended to the Suzuki reaction on the thus obtained Petasis products. Accordingly, ester 39a was subjected to Suzuki-Miyaura cross-coupling reaction with 4-bromo toluene in the presence of [1,1-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) and potassium phosphate tribasic monohydrate in THF:H$_2$O at reflux$^{70}$ for 8 h to give the corresponding ester 42a in 75% yield (Scheme 27). In the $^1$H NMR spectrum of 42a, aromatic proton resonances appeared at δ 7.14 and 7.02 as two doublets ($J = 7.9$ Hz), the lone olefinic proton at δ 5.48 as a doublet, OMe protons at δ 3.73 as a singlet, while CαH appeared at δ 3.52 as a doublet ($J =$
Scheme 27

\[
\begin{align*}
\text{MeO}_2C & \quad \text{N} \\
\text{Bnip} & \quad \text{n-Bu}
\end{align*}
\]

\[
\begin{align*}
\text{4-bromo toluene,} & \\
\text{PdCl}_2(\text{dppf}), \text{K}_3\text{PO}_4, \text{H}_2\text{O} & \\
\text{THF/H}_2\text{O, 8 h, reflux, 75\%}
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \\
\text{CO}_2\text{Me} & \\
\text{N} & \\
\text{O}
\end{align*}
\]

\[
\begin{align*}
\text{42a}
\end{align*}
\]

9.9 Hz). A singlet resonated at \(\delta\) 2.36 corresponding to \(\text{Ar-CH}_3\) and the other protons resonated at the expected chemical shifts. HRMS showed \(m/z\) 354.2042 (M\(^+\)+Na) for C\(_{20}\)H\(_{29}\)NO\(_3\)Na further confirming the product.

Having the conditions established for Suzuki cross coupling on the Petasis ester 39a, the reaction was extended to different aromatic halides with boronate esters 39. Accordingly, 39c and 39b were subjected for Suzuki reaction with 4-bromo toluene and 4-bromo anisole respectively in the presence of PdCl\(_2\)(dppf) and potassium phosphate tribasic monohydrate in THF:H\(_2\)O at reflux for 8 h to give the corresponding esters 42b and 42c respectively in 80% yields (Scheme 28). In the \(^1\)H NMR spectra of 42b and 42c, the lone olefinic proton resonated at \(\delta\) 6.15 and 5.29 as a doublet respectively, OMe protons appeared at \(\delta\) 3.76 corresponding to 42b, whereas two singlets at \(\delta\) 3.82 and 3.74 corresponding to two OMe groups for 42c and the other protons resonated at the expected chemical shifts. HRMS showed \(m/z\) 374.1736 (M\(^+\)+Na) for C\(_{22}\)H\(_{25}\)NO\(_3\)Na (42b) and \(m/z\) 400.1913 for C\(_{20}\)H\(_{31}\)NO\(_4\)SiNa (42c) further confirming the product.
Likewise, 39a independently on Suzuki coupling with 2-bromo toluene and 3-bromopyridine in the presence of PdCl₂(dppf), K₃PO₄.H₂O gave the respective esters 42d and 42e in 82% and 60% yields (Scheme 29). Structures of esters 42d and 42e were confirmed by ¹H NMR (Spectrum 18 and 19), where, olefinic proton of 42d resonated at δ 5.58 and 5.56 as a doublet, while the olefin proton of 42e resonated at δ 5.65 as a doublet. Similarly, OMe protons for 42d appeared at δ 3.71 and 3.68 as singlets, whereas OMe protons of 42e appeared at δ 3.72 as a singlet. HRMS showed m/z 354.2047 (M⁺+Na) for C₂₀H₂₉NO₃Na (42d) and m/z 319.2017 (M⁺+H) for C₁₈H₂₇N₂O₃ (42e) further confirming the products.

Scheme 29

Similarly, esters 39d and 39e independently on Suzuki coupling with 4-bromo toluene and 1-bromo-4-nitrobenzene respectively, the above reaction conditions gave the corresponding esters 42f (86%) and 42g (78%) respectively (Scheme 30). In the ¹H NMR spectrum of 42f and 42g, olefinic proton resonances appeared at δ 5.69 and 6.43 as a doublet respectively, while CαH appeared at δ 4.07 and 4.10 as a doublet corresponding to 42f and 42g respectively. OMe protons resonated at δ 3.69 and 3.83 as a singlets respectively, while other protons resonated at the expected chemical shifts. HRMS showed m/z 442.2742 (M⁺+H) for C₃₀H₃₆NO₂ (42f) and m/z 515.1948 (M⁺+Na) for C₃₁H₂₈N₂O₄Na (42g) further confirming the products.
Similarly, esters 39f and 39g independently were subjected to Suzuki reaction with 1-bromo-4-nitrobenzene and 4-bromo anisole respectively to give the corresponding esters 42h (82%) and 42i (89%) respectively (Scheme 31). Structures of esters 42h and 42i were confirmed by $^1$H NMR, where, olefinic proton resonances appeared at δ 5.72 and 5.49 as a doublet corresponding to 42h and 42i respectively, while OMe appeared at δ 3.75 and 3.72 as a singlet respectively. CαH corresponding to 42h and 42i resonated at δ 3.47 and 3.56 as a doublet respectively, while all the other protons resonated at the expected chemical shifts.
HRMS showed m/z 439.2342 (M⁺+H) for C_{24}H_{31}N_{4}O_{4} (42h) and m/z 447.2858 (M⁺+H) for C_{25}H_{39}N_{2}O_{5} (42i) further confirming the products.

Further, ester 39h on Suzuki coupling with 4-bromo toluene in the presence of PdCl\textsubscript{2}(dppf), potassium phosphate tribasic monohydrate in THF:H\textsubscript{2}O at reflux for 8 h gave corresponding ester 42j in 69% yield (Scheme 32). In the \textsuperscript{1}H NMR spectrum of 42j, olefinic proton appeared at δ 5.48 as a doublet, CαH resonated at δ 3.94-3.86 as a multiplet, while OMe appeared at δ 3.73 as a singlet and the other protons resonated at the expected chemical shifts. HRMS showed m/z 396.2361 (M⁺+H) for C_{24}H_{34}NO_{2}Si further confirming the product.

**Scheme 32**

```
\begin{align*}
\text{39h} & \xrightarrow{4\text{-bromo toluene, PdCl}_2(dppf), K_3PO_4, H_2O} \text{42j} \\
\text{MeO}_2C & \text{N} \quad \text{Ph} \\
\text{pinB} & \text{CH}_2\text{TMS} \\
\end{align*}
```

 Synthentic transformations of γ-boronated amino esters:

The synthetic utility of the γ-borylated amino esters 39 was also demonstrated by several transformations of the boronic ester group. Accordingly, oxidation of 39a with sodium perborate in THF:H\textsubscript{2}O afforded γ-oxo-α-aminoester 43 in 74% yield (Scheme 33). In the \textsuperscript{1}H NMR spectrum of 43, CαH resonated at δ 3.77-3.73 as a multiplet, OMe protons at δ 3.67 as a singlet, one of the CβH protons at δ 2.99 as a doublet of doublet, terminal CH\textsubscript{3} at δ 0.84 as a triplet, while the other protons resonated at the expected positions. HRMS showed m/z 280.1523 (M⁺+Na) for C_{13}H_{23}NO_{4}Na further confirming the product.

**Scheme 33**

```
\begin{align*}
\text{MeO} & \text{N} \quad \text{O} \\
\text{pinB} & \text{n-Bu} \\
\text{39a} & \xrightarrow{NaBO_3, H_2O} \text{43} \\
\text{MeO} & \text{N} \quad \text{O} \\
\text{pinB} & \text{n-Bu} \\
\end{align*}
```
Similarly, ester 39a on treatment with NaN₃ in the presence of copper catalyst (CuSO₄) in MeOH gave alkenyl azide 44 in 71% yield (Scheme 34). In the ¹H NMR spectrum of 44, olefinic proton resonated at δ 4.74 as a doublet (J = 9.5 Hz), CαH proton at δ 3.95 as a doublet (J = 9.5 Hz), while, OMe protons at δ 3.66 as a singlet and the remaining protons were resonated at expected positions. HRMS showed m/z 277.1530 (M⁻N₂Na⁺) for C₁₃H₂₂N₂O₃Na further confirming the product.

Scheme 34

The alkenyl azide 44 on reaction with phenyl acetylene and sodium ascorbate under ‘click’ reaction conditions resulted a trizole derivative 45 in 36% yield (over two steps) (Scheme 35). Structure of triazole 45 was confirmed by ¹H NMR spectrum, where triazole proton resonated at δ 8.01 as a singlet, aromatic protons resonated at δ 7.80 as a doublet, δ 7.39 as a triplet and at δ 7.29 as one more doublet. Olefinic proton resonated at δ 5.71 as a doublet, one singlet at δ 3.69 corresponding to OMe, while the other protons resonated at the expected positions. Further, HRMS showed m/z 407.2054 (M⁺+Na) for C₂₁H₂₈N₄O₃Na confirmed the product.

Scheme 35

Conclusion

In conclusion, a regioselective Petasis reaction has been performed for the first time at the terminal C-B bond of (Z)-1-alkene-1,2-diboronic esters. The resulting amino esters were then subjected to Suzuki coupling with the second boronate moiety to give the corresponding amino esters. This protocol provides an opportunity not only for the conversion of bisboronates into Petasis/Suzuki products but also to other functionalized amino ester derivatives by exploiting the versatility of the boronic ester group.
EXPERIMENTAL SECTION

Methyl 4-(4,4,4,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(morpholino)-oct-3-enoate (39a): To a stirred solution of ester 37a (0.1 g, 0.30 mmol) in hexafluoropropan-2-ol (0.5 mL/0.15 mmol), glyoxylic acid monohydrate (0.03 g, 0.32 mmol) and morpholine (30 µL, 0.32 mmol) were added under argon atmosphere at room temperature. The reaction mixture was stirred for 8 h, solvent was evaporated under reduced pressure to give acid residue 38a, which was directly used for further esterification reaction.

To a solution of the crude acid 38a in diethyl ether (5 mL/0.29 mmol) at 0 °C, a solution of CH₂N₂ in ether was added until the persistence of yellow colour. After 2 h, the solvent was evaporated under reduced pressure and purified the residue by column chromatography (230-400 mesh Silica gel, 20% ethyl acetate in cyclohexane) to afford 39a (0.076 g, 69%) as a colorless oil; ¹H NMR (300 MHz, CDCl₃, 298 K): δ 5.96 (d, 1H, J = 9.8 Hz, olefinic), 4.32 (d, 1H, J = 9.8 Hz, CαH), 3.73 (t, 4H, J = 4.3 Hz, 2 x CH₂), 3.69 (s, 3H, OCH₃), 2.59-2.48 (m, 4H, 2 x CH₂), 2.24-2.07 (m, 4H, allylic CH₂), 1.41-1.21 (m, 4H, 2 x CH₂), 1.27 (s, 12H, 4 x CH₃), 0.86 (t, 3H, J = 7.0 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃, 298 K): δ 171.8, 140.4 (br), 136.7, 83.4, 69.1, 66.7, 51.9, 51.0, 36.4, 31.7, 24.8, 24.7, 22.2, 13.9; ¹¹B NMR (96 MHz, CDCl₃, 298 K): δ 30.0 (brs); HRMS (ESI+): m/z calculated for C₁₉H₃₅NO₅¹¹B (M⁺+H), 368.26083, found 368.2608.

Methyl-4-(4,4,4,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(morpholino)-5-(trimethyl silyl)-pent-3-enoate (39b): To a stirred solution of ester 37b (0.11 g, 0.30 mmol) in hexafluoropropan-2-ol (0.5 mL/0.15 mmol), glyoxylic acid monohydrate (0.03 g, 0.33 mmol) and morpholine (29 µL, 0.33 mmol) were added under argon atmosphere at room temperature and stirred for 8 h. Work up, esterification as described for 39a and purification of the residue by column chromatography (230-400 mesh Silica gel, 10% ethyl acetate in cyclohexane) afforded 39b (0.071 g, 60%) as a colorless oil; ¹H NMR (300 MHz, CDCl₃, 298 K): δ 5.80 (d, 1H, J = 9.9 Hz, olefinic), 4.47 (d, 1H, J = 9.9 Hz, CαH), 3.74 (t, 4H, J = 4.0 Hz, 2 x CH₂), 3.68 (s, 3H, OCH₃), 2.60-2.46 (m, 4H, 2 x CH₂), 1.67 (s, 2H, allylic CH₂), 1.25 (s, 6H, 2 x CH₃), 1.24 (s, 6H, 2 x CH₃), -0.05 (s, 9H, 3 x CH₃); ¹³C NMR (100 MHz, CDCl₃, 298 K): δ 171.9, 137.2 (br), 135.1, 83.5, 69.0, 66.7, 51.8, 51.0, 26.6.
24.9, -1.5; $^1$B NMR (96 MHz, CDCl$_3$, 298 K): δ 29.7 (brs); HRMS (ESI+): m/z calculated for C$_{19}$H$_{36}$NO$_5$$^{11}$BNaSi (M$^+$+Na) 420.23535, found 420.2351.

Methyl 4-(4,4,4,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(morpholino)-4-phenyl-but-3-enoate (39c): To a stirred solution of ester 37c (0.11 g, 0.30 mmol) in hexafluoropropan-2-ol (0.5 mL/0.15 mmol), glyoxylic acid monohydrate (0.031 g, 0.34 mmol) and morpholine (29 μL, 0.34 mmol) were added under argon atmosphere at room temperature and stirred for 8 h. Work up, esterification as described for 39a and purification of the residue by column chromatography (230-400 mesh Silica gel, 20% ethyl acetate in cyclohexane) afforded 39c (0.062 g, 53%) as a colorless oil; $^1$H NMR (400 MHz, CDCl$_3$, 298 K): δ 7.42-7.22 (m, 5H, Ar-H), 6.40 (d, 1H, J = 9.9 Hz, olefinic), 4.32 (d, 1H, J = 9.9 Hz, CaH), 3.78-3.74 (m, 4H, 2 x CH$_2$), 3.74 (s, 3H, OCH$_3$), 2.67-2.54 (m, 4H, 2 x CH$_2$), 1.35 (s, 6H, 2 x CH$_3$), 1.34 (s, 6H, 2 x CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$, 298 K): δ 171.3, 141.3, 138.2 (br), 135.8, 128.7, 128.3, 127.3, 126.6, 84.1, 70.0, 66.8, 52.1, 51.3, 24.9, 24.7; $^{11}$B NMR (96 MHz, CDCl$_3$, 298 K): δ 30.3 (brs); HRMS (ESI+): m/z calcd for C$_{21}$H$_{30}$BNO$_3$Na (M$^+$+Na) 410.21147, found 410.2112.

Methyl-2-dibenzyldiamo-4-(4,4,4,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-oct-3-enoate (39d): To a stirred solution ester 37a (0.10 g, 0.30 mmol) in hexafluoropropan-2-ol (0.5 mL/0.15 mmol) glyoxylic acid monohydrate (0.03 g, 0.32 mmol) and dibenzyldiamine (30 μL, 0.32 mmol) were added under argon atmosphere at room temperature and stirred for 8 h. Work up, esterification as described for 39a and purification of the residue by column chromatography (230-400 mesh Silica gel, 20% ethyl acetate in cyclohexane) afforded 39d (0.072 g, 50%) as a colorless oil; $^1$H NMR (300 MHz, CDCl$_3$, 298 K): δ 7.39-7.40 (m, 4H, Ar-H), 7.29-7.26 (m, 4H, Ar-H), 7.20-7.19 (m, 2H, Ar-H), 6.16 (d, 1H, J = 9.3 Hz, olefinic), 4.74 (d, 1H, J = 9.3 Hz, CaH), 3.76 (s, 4H, 2 x benzylic CH$_2$), 3.69 (s, 3H, OCH$_3$), 2.26-2.11 (m, 2H, allylic CH$_2$), 1.42-1.29 (m, 4H, 2 x CH$_2$), 1.09 (s, 6H, 2 x CH$_3$), 1.05 (s, 6H, 2 x CH$_3$), 0.91 (t, 3H, J = 7.0 Hz, CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$, 298 K): δ 173.2, 139.8, 137.7, 128.7, 128.0, 126.6, 83.0, 63.2, 54.9, 51.4, 36.5, 31.9, 26.9, 24.6, 24.4, 22.3, 14.0 (Ca to boron is not visible); $^{11}$B NMR (96 MHz, CDCl$_3$, 298 K): δ 30.4 (brs); HRMS (ESI+): m/z calculated for C$_{29}$H$_{41}$NO$_4^{11}$B (M$^+$+H) 478.31286, found 478.3129.
**Methyl-2-dibenzylamino-4-(4,4,4,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-phenyl-but-3-enoate (39e):** To a stirred solution of ester 37c (0.11 g, 0.30 mmol) in hexafluoropropan-2-ol (0.5 mL/0.15 mmol), glyoxylic acid monohydrate (0.031 g, 0.34 mmol) and dibenzyl amine (65 µL, 0.34 mmol) were added under argon atmosphere at room temperature and stirred for 8 h. Work up, esterification as described for 39a and purification of the residue by column chromatography (230-400 mesh Silica gel, 8% ethyl acetate in cyclohexane) afforded 39e (0.081 g, 54%) as a colorless oil; $^1$H NMR (400 MHz, CDCl$_3$, 298 K): δ 7.39 (d, 4H, $J = 7.8$ Hz, Ar-H), 7.33-7.24 (m, 8H, Ar-H), 7.21-7.15 (m, 3H, Ar-H), 6.53 (d, 1H, $J = 9.3$ Hz, olefinic), 4.73 (d, 1H, $J = 9.5$ Hz, CαH), 3.81 (s, 4H, 2 x benzylic CH$_2$), 3.69 (s, 3H, OCH$_3$), 1.09 (s, 6H, 2 x CH$_3$), 1.06 (s, 6H, 2 x CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$, 298 K): δ 172.4, 142.2, 139.9, 139.5, 128.7, 128.15, 128.1, 127.4, 126.8, 126.7, 83.7, 63.7, 55.0, 51.6, 24.6, 24.5; $^{11}$B NMR (96 MHz, CDCl$_3$, 298 K) δ 30.3 (brs); HRMS (ESI+): m/z calculated for C$_{31}$H$_{37}$NO$_4^{11}$B (M$^+$+H) 498.28156, found 498.2809.

**Methyl 4-(4,4,4,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(pyridin-4-yl)piperazino-oct-3-enoate (39f):** To a stirred solution of ester 37a (0.10 g, 0.30 mmol) in hexafluoropropan-2-ol (0.5 mL/0.15 mmol) glyoxylic acid monohydrate (0.03 g, 0.32 mmol) and 1-(pyridin-4-yl)piperazine (0.053 g, 0.32 mmol) were added under argon atmosphere at room temperature and stirred for 8 h. Work up, esterification as described for 39a and purification of the residue by column chromatography (230-400 mesh Silica gel, 30% ethyl acetate in cyclohexane) afforded 39f (0.076 g, 57%) as a colorless oil; $^1$H NMR (300 MHz, CDCl$_3$, 298 K): δ 8.18 (d, 1H, $J = 3.9$ Hz, Ar-H), 7.46 (t, 1H, $J = 7.4$ Hz, Ar-H), 6.64-6.59 (m, 2H, Ar-H), 5.99 (d, 1H, $J = 9.8$ Hz, olefinic), 4.40 (d, 1H, $J = 9.8$ Hz, CαH), 3.72 (s, 3H, OCH$_3$), 3.57 (t, 4H, $J = 4.9$ Hz, 2 x CH$_2$), 2.66-2.53 (m, 4H, 2 x CH$_2$), 2.18-2.02 (m, 2H, allylic CH$_2$), 1.41-1.26 (m, 4H, 2 x CH$_2$), 1.26 (s, 12H, 4 x CH$_3$), 0.87 (t, 3H, $J = 7.2$ Hz, CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$, 298 K): δ 172.2, 159.4, 147.8, 137.5, 137.2, 113.2, 107.0, 83.4, 68.9, 51.9, 50.4, 45.1, 36.5, 31.8, 24.8, 24.7, 22.3, 13.9; $^{11}$B NMR (96 MHz, CDCl$_3$, 298 K): δ 29.8 (brs); HRMS (ESI+): m/z calculated for C$_{24}$H$_{39}$N$_5$O$_4^{11}$B (M$^+$+H) 444.30336, found 444.3037.
Methyl-4-(4,4,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-[4-(1,1-dimethylethoxy)carbonyl] piperazino-oct-3-enoate (39g): To a stirred solution of ester 37a (0.10 g, 0.30 mmol) in hexafluoropropan-2-ol (0.5 mL/0.15 mmol), glyoxylic acid monohydrate (0.03 g, 0.32 mmol) and tert.-butyl piperazine-1-carboxylate (0.06 g, 0.32 mmol) were added under argon atmosphere at room temperature and stirred for 8 h. Work up, esterification as described for 39a and purification of the residue by column chromatography (230-400 mesh Silica gel, 30% ethyl acetate in cyclohexane) afforded 39g (0.088 g, 63%) as a colorless oil; $^1$H NMR (300 MHz, CDCl$_3$, 298 K): $\delta$ 5.90 (d, 1H, $J$ = 9.7 Hz, olefinic), 4.29 (d, 1H, $J$ = 9.7 Hz, CH), 3.65 (s, 3H, OCH$_3$), 3.41-3.39 (m, 4H, 2 x CH$_3$), 2.56-2.40 (m, 4H, 2 x CH$_3$), 2.23-207 (m, 2H, allylic CH$_2$), 1.40 (s, 9H, Boc), 1.34-1.22 (m, 4H, 2 x CH$_2$), 1.22 (s, 12H, 4 x CH$_3$), 0.93 (t, 3H, $J$ = 7.2 Hz, CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$, 298 K): $\delta$ 172.0, 154.6, 139.8 (br), 137.1, 83.3, 79.4, 68.5, 51.7, 50.2, 43.9 (br), 43.0 (br), 36.4, 31.7, 28.3, 24.7, 24.6, 22.2, 13.8; $^{11}$B NMR (96 MHz, CDCl$_3$, 298 K): $\delta$ 30.2 (brs); HRMS (ESI+): m/z calculated for C$_{24}$H$_{43}$N$_{2}$O$_6^{11}$BNa (M$^+$+Na) 489.31119, found 489.3112.

Methyl-2-benzyl(methyl)amino-4-(4,4,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(tri methylsilyl)-pent-3-enoate (39h): To a stirred solution of ester 37b (0.11 g, 0.30 mmol) in hexafluoropropan-2-ol (0.5 mL/0.15 mmol), glyoxylic acid monohydrate (0.03 g, 0.33 mmol) and N-methyl benzylamine (42 µL, 0.33 mmol) were added under argon atmosphere at room temperature and stirred for 8 h. Work up, esterification as described for 39a and purification of the residue by column chromatography (230-400 mesh Silica gel, 8% ethyl acetate in cyclohexane) afforded 39h (0.069 g, 53%) as a colorless oil; $^1$H NMR (400 MHz, CDCl$_3$, 298 K): $\delta$ 7.40-7.19 (m, 5H, Ar-H), 5.97 (d, 1H, $J$ = 9.6 Hz, olefinic), 4.73 (d, 1H, $J$ = 9.6 Hz, CH), 3.76-3.54 (m, 2H, benzylic CH$_2$), 3.73 (s, 3H, OCH$_3$), 2.21 (s, 3H, NCH$_3$), 1.73 (s, 2H, allylic CH$_2$), 1.23 (s, 6H, 2 x CH$_3$), 1.21 (s, 6H, 2 x CH$_3$), 0.00 (s, 9H, 3 x CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$, 298 K): $\delta$ 173.1, 147.6, 139.2 (br), 136.1, 129.2, 128.1, 126.9, 83.3, 67.0, 58.5, 51.6, 38.7, 26.6, 24.9, 24.8, -1.5; $^{11}$B NMR (96 MHz, CDCl$_3$, 298 K): $\delta$ 29.6 (brs); HRMS (ESI+): m/z calculated for C$_{23}$H$_{39}^{11}$BNO$_4$Si (M$^+$+H) 432.27414, found 432.2738.

Methyl 2-(S)-Benzyl-$\alpha$-methylbenzylamino-4-(4,4,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-oct-3-enoate (41): To a stirred solution of ester 37a (0.10 g, 0.30 mmol) in
hexafluoropropan-2-ol (0.5 mL/0.15 mmol), glyoxylic acid monohydrate (0.03 g, 0.32 mmol) and (S)-(−)-N-benzyl-α-methylbenzylamine 40 (0.069 g, 0.32 mmol) were added under argon atmosphere at room temperature and stirred for 8 h. Work up, esterification as described for 39a and purification of the residue by column chromatography (230-400 mesh Silica gel, 9% ethyl acetate in cyclohexane) afforded mixture of 2 diastereomers (58:42) 41 (0.085 g, 58%) as a colorless oil; $^1$H NMR (400 MHz, CDCl$_3$, 298 K): δ 7.45-7.43 (m, 3H, Ar-H), 7.36-7.15 (m, 7H, Ar-H), 6.16 (d, 0.55H, $J = 9.3$ Hz, olefinic), 6.00 (d, 0.45H, $J = 9.1$ Hz, olefinic), 4.93 (d, 0.45H, $J = 9.2$ Hz, CaH), 4.86 (d, 0.55H, $J = 9.4$ Hz, CaH), 4.12-4.06 (m, 1H, benzylic CH), 3.98 (d, 0.55H, $J = 15.2$ Hz, benzylic CH$_2$), 3.93 (d, 0.55H, $J = 15.4$ Hz, benzylic CH$_2$), 3.89 (d, 0.45H, $J = 15.4$ Hz, benzylic CH$_2$), 3.81 (d, 0.45H, $J = 15.2$ Hz, benzylic CH$_2$), 3.65 (s, 3 x 0.45H, OCH$_3$), 3.47 (s, 3 x 0.55H, OCH$_3$), 2.20-2.04 (m, 2H, allylic CH$_2$), 1.40 (d, 3 x 0.45H, $J = 7.2$ Hz, CH$_3$), 1.38 (d, 3 x 0.55H, $J = 7.4$ Hz, CH$_3$), 1.34-1.25 (m, 4H, 2 x CH$_2$), 1.19 (s, 12 x 0.45H, 4 x CH$_3$), 1.16 (s, 12 x 0.55H, 4 x CH$_3$), 0.89 (t, 3 x 0.45H, $J = 7.1$ Hz, CH$_3$), 0.88 (t, 3 x 0.55H, $J = 7.0$ Hz, CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$, 298 K): δ 174.1, 173.6, 144.35, 143.8, 141.9, 141.7, 139.7, 139.2, 136.6 (br), 28.2, 128.1, 127.95, 127.9, 127.85, 127.8, 126.55, 126.5, 126.3, 126.1, 83.0, 83.0, 62.8, 62.5, 59.0, 58.35, 51.7, 51.6, 51.4, 51.2, 36.4, 36.2, 31.8, 31.6, 24.7, 24.5, 24.4, 22.3, 22.2, 16.9, 14.0; $^{11}$B NMR (96 MHz, CDCl$_3$, 298 K): δ 30.0 (brs); HRMS (ESI+): m/z calculated for C$_{30}$H$_{43}$NO$_4$ $^{11}$B (M$^+$+H) 492.3285, found 492.3279.

Methyl 4-(4-methylphenyl)-2-(morpholino)-oct-3-enoate (42a): To a solution of ester 39a (0.05 g, 0.14 mmol) in THF (1.2 mL/0.14 mmol) and water (30 μL/0.14 mmol) under argon atmosphere, [1,1’-bis (diphenyl phosphino)ferrocene] dichloropalladium(II) (2 mg, 2.7 mmol), potassium phosphate tribasic monohydrate (0.093 g, 0.41 mmol) and 4-bromo toluene (0.046 g, 0.27 mmol) were added at room temperature. The reaction mixture was heated at reflux for 18 h, cooled to room temperature, diluted with water and extracted with Et$_2$O (2 x 15 mL). The combined organic extracts were dried (MgSO$_4$) evaporated the solvent under reduced pressure and purified the residue by column chromatography (230-400 mesh Silica gel, 10% ethyl acetate in cyclohexane) to afford 42a (0.035 g, 75%) as a colorless oil; $^1$H NMR (300 MHz, CDCl$_3$, 298 K): δ 7.14 (d, 2H, $J = 7.9$ Hz, Ar-H), 7.02 (d, 2H, $J = 7.9$ Hz, Ar-H), 5.48 (d, 1H, $J = 9.9$ Hz, olefinic), 3.73 (s, 3H, OMe), 3.69 (t, 4H, $J = 4.5$ Hz, 2 x CH$_2$), 3.52 (d, 1H, $J = 9.9$ Hz, CaH), 2.58-2.45 (m, 2H, CH$_2$), 2.38-2.26 (m,
4H, 2 x CH₂), 2.36 (s, 3H, Ar-CH₃), 1.33-1.22 (m, 4H, 2 x CH₃), 0.84 (t, 3H, J = 7.0 Hz, CH₃); ^{13}C NMR (100 MHz, CDCl₃, 298 K): δ 171.8, 149.3, 136.9, 136.8, 128.9, 128.0, 120.0, 67.9, 66.7, 52.0, 50.9, 39.4, 29.8, 22.2, 21.2, 13.8; HRMS (ESI+): m/z calculated for C₂₀H₂₉NO₃Na (M⁺+Na) 354.20451, found 354.2042.

**Methyl 4-(4-methylphenyl)-2-(morpholino)-4-phenyl-but-3-enoate (42b):** To a solution of ester 39c (0.054 g, 0.14 mmol) in THF (1.2 mL/0.14 mmol) and water (30 μL/0.14 mmol) under argon atmosphere, [1,1’-bis (diphenyl phosphino)ferrocene] dichloropalladium(II) (2 mg, 2.8 μmol), potassium phosphate tribasic monohydrate (97 mg, 0.42 mmol) and 4-bromo toluene (0.047 g, 0.27 mmol) were added at room temperature and heated at reflux for 18 h. Work up as described for 42a and purification of the residue by column chromatography (230-400 mesh Silica gel), 10% ethyl acetate in cyclohexane afforded 42b (0.039 g, 80%) as a colorless oil; ^{1}H NMR (300 MHz, CDCl₃, 298 K): δ 7.30-7.25 (m, 5H, Ar-H), 7.21 (d, 2H, J = 7.8 Hz, Ar-H), 7.10 (d, 2H, J = 7.9 Hz, Ar-H), 6.15 (d, 1H, J = 10.1 Hz, olefinic), 3.77-3.72 (m, 5H, CαH and 2 x CH₂), 3.76 (s, 3H, OCH₃), 2.65-2.58 (m, 2H, 2 x CH₂), 2.44-2.38 (m, 2H, allylic CH₂), 2.40 (s, 3H, Ar-CH₃); ^{13}C NMR (100 MHz, CDCl₃, 298 K): δ 171.4, 148.0, 141.5, 137.5, 135.7, 129.7, 129.0, 128.2, 128.0, 127.5, 122.2, 68.3, 66.8, 52.1, 51.1, 21.3; HRMS (ESI+): m/z calculated for C₂₂H₂₅NO₃Na (M⁺+Na) 374.17321, found 374.1736.

**Methyl-2-(morpholino)-4-(4-methoxyphenyl)-5-(trimethylsilyl)-pent-3-enoate (42c):** To a solution of ester 39b (0.055 g, 0.14 mmol) in THF (1.2 mL/0.14 mmol) and water (30 μL/0.14 mmol) under argon atmosphere, [1,1’-bis (diphenyl phosphino)ferrocene] dichloropalladium(II) (2 mg, 2.7 μmol), potassium phosphate tribasic monohydrate (97 mg, 0.41 mmol) and 4-bromo anisole (34 μL, 0.27 mmol) were added at room temperature and heated at reflux for 18 h. Work up as described for 42a and purification of the residue by column chromatography (230-400 mesh Silica gel, 9% ethyl acetate in cyclohexane) to afford 42c (0.042 g, 80%) as a colorless oil; ^{1}H NMR (300 MHz, CDCl₃, 298 K): δ 7.17 (d, 2H, J = 8.7 Hz, Ar-H), 6.86 (d, 2H, J = 8.8 Hz, Ar-H), 5.29 (d, 1H, J = 10.1 Hz, olefinic), 3.82 (s, 3H, OCH₃), 3.74 (s, 3H, OCH₃), 3.70-3.67 (m, 4H, 2 x CH₂), 3.62 (d, 1H, J = 10.1 Hz, CαH), 2.55-2.45 (m, 2H, CH₂), 2.33-2.23 (m, 2H, CH₂), 1.91 (s, 2H, allylic CH₂), -0.17 (s, 9H, 3 x CH₃); ^{13}C NMR (100 MHz, CDCl₃, 298 K): δ 172.2, 158.8, 146.2, 133.3, 129.6,
Methyl 4-(2-Methylphenyl)-2-(morpholino)-oct-3-enoate (42d): To a solution of ester 39a (0.037 g, 0.10 mmol) in THF (1.2 mL/0.14 mmol) and water (30 μL/0.14 mmol) under argon atmosphere, [1,1'-bis (diphenyl phosphino)ferrocene] dichloropalladium(II) (1.4 mg, 2.0 μmol), potassium phosphate tribasic monohydrate (0.036 g, 0.30 mmol) and 2-bromo toluene (0.047 g, 0.27 mmol) were added at room temperature and heated at reflux for 18 h. Work up as described for 42a and purification of the residue by column chromatography (230-400 mesh Silica gel, 25% ethyl acetate in cyclohexane) afforded 42d (0.02 g, 60%) as a colorless oil; mixture of 2 diastereomers (58:42). $^1$H NMR (300 MHz, CDCl$_3$, 298 K): δ 7.22-7.12 (m, 3H, Ar-H), 6.93 (d, 0.4H, J = 6.9 Hz, Ar-H), 6.92 (d, 0.6H, J = 6.6 Hz, Ar-H), 5.58 (d, 0.4H, J = 9.6 Hz, olefinic), 5.56 (d, 0.6H, J = 10 Hz, olefinic). 3.73-3.68 (m, 4H, 2 x CH$_2$), 3.71 (s, 3 x 0.4H, CH$_3$), 3.68 (s, 3 x 0.6H, CH$_3$), 3.28 (d, 0.4H, J = 9.6 Hz, CaH), 3.23 (d, 0.6H, J = 9.9 Hz, CaH), 2.56-2.47 (m, 2H, allylic CH$_2$), 2.33-2.23 (m, 4H, 2 x CH$_2$), 2.23 (s, 3 x 0.4H, CH$_3$), 2.15 (s, 3 x 0.6H, CH$_3$), 1.43-1.29 (m, 4H, 2 x CH$_3$), 0.88 (t, 3 x 0.6H, J = 7.0 Hz, CH$_3$), 0.86 (t, 3 x 0.4H, J = 7.1 Hz, CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$, 298 K): δ 171.7, 171.6, 148.6, 148.6, 139.4, 139.0, 135.5, 134.1, 130.0, 129.5, 128.0, 127.1, 127.0, 125.2, 125.1, 121.2, 120.8, 68.4, 68.3, 66.7, 51.7, 51.7, 51.1, 51.05, 38.6, 38.2, 29.6, 29.4, 22.4, 22.2, 19.2, 18.9, 13.8; HRMS (ESI+): m/z calculated for C$_{20}$H$_{29}$NO$_3$Na (M$^+$Na) 354.20451, found 354.2047.

Methyl 4-(Pyridin-3-yl)-2-(morpholino)-oct-3-enoate (42e): To a solution of ester 39a (0.052 g, 0.14 mmol) in THF (1.2 mL/0.14 mmol) and water (30 μL/0.14 mmol) under argon atmosphere, [1,1'-bis (diphenyl phosphino)ferrocene] dichloropalladium(II) (2 mg, 2.8 μmol), potassium phosphate tribasic monohydrate (0.097 g, 0.42 mmol) and 3-bromo pyridine (0.047 g, 0.27 mmol) were added at room temperature and heated at reflux for 18 h. Work up as described for 42a and purification of the residue by column chromatography (230-400 mesh Silica gel, 30% ethyl acetate in cyclohexane) afforded 42e (37 mg, 82%) as a colorless oil; $^1$H NMR (300 MHz, CDCl$_3$, 298 K): δ 8.54 (d, 1H, J = 3.6 Hz, Ar-H), 8.50 (s, 1H, Ar-H), 7.49 (dt, 1H, J = 1.9, 7.8 Hz, Ar-H), 7.30 (dd, 1H, J = 4.9, 7.5 Hz, Ar-H), 5.65 (d, 1H, J = 10 Hz, olefinic), 3.72 (s, 3H, OCH$_3$), 3.68 (t, 4H, J = 4.6 Hz, 2 x CH$_2$),...
Methyl 2-dibenzylamino-4-(4-methylphenyl)-oct-3-enoate (42f): To a solution of ester 39d (0.066 g, 0.14 mmol) in THF (1.2 mL/0.14 mmol) and water (30 μL/0.14 mmol) under argon atmosphere, [1,1’-bis (diphenyl phosphino)ferrocene] dichloropalladium(II) (2 mg, 2.7 μmol), potassium phosphate tribasic monohydrate (0.095 g, 0.41 mmol) and 4-bromo toluene (0.032 g, 0.27 mmol) were added at room temperature and heated at reflux for 18 h. Work up as described for 42a and purification of the residue by column chromatography (230-400 mesh Silica gel, 7% ethyl acetate in cyclohexane) afforded 42f (0.053 g, 86%) as a colorless oil; ¹H NMR (400 MHz, CDCl₃, 298 K): δ 7.19-7.16 (m, 10H, Ar-H), 7.0 (s, 4H, Ar-H), 5.69 (d, 1H, J = 9.8 Hz, olefinic), 4.07 (d, 1H, J = 9.8 Hz, CαH), 3.69 (s, 3H, OCH₃), 3.66 (s, 4H, 2 x benzylic CH₂), 2.45-2.40 (m, 2H, allylic CH₂), 2.33 (s, 3H, Ar-CH₃), 1.31-1.28 (m, 4H, 2 x CH₂), 0.86 (t, 3H, J = 7.0 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃, 298 K): δ 173.4, 147.6, 139.6, 136.9, 136.4, 128.7, 128.0, 127.9, 126.6, 120.1, 60.6, 54.9, 51.4, 39.3, 30.1, 22.2, 21.1, 13.9; HRMS (ESI+): m/z calculated for C₃₀H₃₆NO₂ (M⁺+H) 442.2746, found 442.2742.

Methyl- 2-dibenzylamino-4-(4-nitrophenyl)-4-phenyl-but-3-enoate (42g): To a solution of ester 39e (0.070 g, 0.14 mmol) in THF (1.2 mL/0.14 mmol) and water (30 μL/0.14 mmol) under argon atmosphere, [1,1’-bis (diphenyl phosphino)ferrocene] dichloropalladium(II) (2 mg, 2.8 μmol), potassium phosphate tribasic monohydrate (97 mg, 0.42 mmol) and 1-bromo-4-nitrobenzene (0.057 g, 0.28 mmol) were added at room temperature and heated at reflux for 18 h. Work up as described for 42a and purification of the residue by column chromatography (230-400 mesh Silica gel, 10% ethyl acetate in cyclohexane) afforded 42g (0.054 g, 78%) as a colorless oil; ¹H NMR (400 MHz, CDCl₃, 298 K): δ 8.03 (d, 2H, J = 8.7 Hz, Ar-H), 7.35-7.17 (m, 17H, Ar-H), 6.43 (d, 1H, J = 9.8 Hz, olefinic), 4.10 (d, 1H, J = 9.8 Hz, CαH), 3.86 (d, 2H, J = 13.7 Hz, benzylic CH₂), 3.83 (s, 3H, OCH₃), 3.72 (d, 2H, J = 13.7 Hz, benzylic CH₂); ¹³C NMR (100 MHz, CDCl₃, 298
K): δ 172.2, 147.0, 145.6, 144.8, 140.7, 139.0, 130.4, 128.7, 128.4, 128.3, 128.2, 127.6, 127.0, 124.6, 123.4, 60.4, 55.0, 51.8; HRMS (ESI+): m/z calculated for C_{31}H_{28}N_{2}O_{4}Na (M^+ + Na) 515.19468, found 515.1948.

**Methyl 4-(4-nitrophenyl)-2-(pyridin-4-yl)piperazino-oct-3-enoate (42h):** To a solution of ester 39f (0.063 g, 0.14 mmol) in THF (1.2 mL/0.14 mmol) and water (30 µL/0.14 mmol) under argon atmosphere, [1,1’-bis (diphenyl phosphino)ferrocene] dichloropalladium(II) (2 mg, 2.8 µmol), potassium phosphate tribasic monohydrate (98 mg, 0.42 mmol) and 1-bromo-4-nitrobenzene (0.057 g, 0.28 mmol) were added at room temperature and heated at reflux for 18 h. Work up as described for 42a and purification of the residue by column chromatography (230-400 mesh Silica gel, 20% ethyl acetate in cyclohexane) afforded 42h (0.05 g, 82%) as a colorless oil; ¹H NMR (300 MHz, CDCl₃, 298 K): δ 8.21 (d, 2H, J = 8.7 Hz, Ar-H), 8.17-8.15 (m, 1H, Ar-H), 7.49-7.42 (m, 1H, Ar-H), 7.36 (d, 2H, J = 8.7 Hz, Ar-H), 6.65-6.58 (m, 2H, Ar-H), 5.72 (d, 1H, J = 10.0 Hz, olefinic), 3.75 (s, 3H, OMe), 3.56-3.49 (m, 4H, 2 x CH₂), 3.47 (d, 1H, J =10.0 Hz, CaH), 2.64-2.57 (m, 2H, allylic CH₂), 2.47-2.40 (m, 4H, 2 x CH₂), 1.35-1.25 (m, 4H, 2 x CH₂), 0.87 (t, 3H, J = 6.6 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃, 298 K): δ 171.4, 159.2, 147.9, 147.1, 146.6, 137.5, 129.2, 123.5, 122.9, 113.4, 107.0, 67.6, 52.1, 50.3, 45.1, 38.9, 29.7, 22.1, 13.8; HRMS (ESI+): m/z calculated for C_{31}H_{31}N_{4}O_{4} (M^+ + H) 439.23453, found 439.2342.

**Methyl-4-(4-methoxyphenyl)-2-[4-(1,1-dimethylethoxy)carbonyl]piperazino-oct-3-enolate (42i):** To a solution of ester 39g (0.065 g, 0.14 mmol) in THF (1.2 mL/0.14 mmol) and water (30 µL/0.14 mmol) under argon atmosphere, [1,1’-bis (diphenyl phosphino)ferrocene] dichloropalladium(II) (2 mg, 2.7 µmol), potassium phosphate tribasic monohydrate (0.096 g, 0.42 mmol) and 4-bromo anisole (35 µL, 0.27 mmol) were added at room temperature and heated at reflux for 18 h. Work up as described for 42a and purification of the residue by column chromatography (230-400 mesh Silica gel, 10% ethyl acetate in cyclohexane) afforded 42i (0.056 g, 89%) as a colorless oil; ¹H NMR (300 MHz, CDCl₃, 298 K): δ 7.08 (d, 2H, J = 8.7 Hz, Ar-H), 6.87 (d, 2H, J = 8.7 Hz, Ar-H), 5.49 (d, 1H, J = 10.0 Hz, olefinic), 3.81 (s, 3H, OCH₃), 3.72 (s, 3H, OCH₃), 3.56 (d, 1H, J = 9.9 Hz, CaH), 3.40 (t, 4H, J = 4.5 Hz, 2 x CH₂), 2.49-2.39 (m, 2H, CH₂), 2.39-2.29 (m, 2H, CH₂), 2.29-2.19 (m, 2H, CH₂).

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2.29-2.19 (m, 2H, allylic CH₂), 1.42 (s, 9H, Boc), 1.34-1.21 (m, 4H, 2 x CH₂), 0.84 (t, 3H, J = 7.0 Hz, CH₃); ¹³C NMR (75 MHz, CDCl₃, 298 K): δ 172.1, 158.7, 154.6, 148.5, 132.2, 129.3, 120.5, 113.5, 79.6, 67.6, 55.2, 51.9, 50.3, 43.7, 43.0, 39.4, 29.8, 28.4, 22.1, 13.8; HRMS (ESI+): m/z calculated for C₂₅H₃₉N₂O₅ (M⁺H) 447.2859, found 447.2858.

**Methyl-2-(benzyl(methyl)amino)-4-p-tolyl-5-(trimethylsilyl)pent-3-enoate (42j):** To a solution of ester 39h (0.06 g, 0.14 mmol) in THF (1.2 mL/0.14 mmol) and water (30 µL/0.14 mmol) under argon atmosphere, [1,1’-bis (diphenyl phosphino)ferrocene] dichloropalladium(II) (2 mg, 2.8 µmol), potassium phosphate tribasic monohydrate (0.096 g, 0.42 mmol) and 4-bromo toluene (32 µL, 0.28 mmol) were added at room temperature and heated at reflux for 18 h. Work up as described for 42a and purification of the residue by column chromatography (230-400 mesh Silica gel, 6% ethyl acetate in cyclohexane) afforded 42j (0.025 g, 69%) as a colorless oil; ¹H NMR (300 MHz, CDCl₃, 298 K): δ 7.29-7.21 (m, 5H, Ar-H), 7.18 (d, 2H, J = 8.1 Hz, Ar-H), 7.09 (d, 2H, J = 8.1 Hz, Ar-H), 5.48 (d, 1H, J = 10.1 Hz, olefinic), 3.94-3.86 (m, 1H, CaH), 3.73 (s, 3H, OCH₃), 3.62-3.45 (s, 2H, benzylic CH₂), 2.34 (s, 3H, Ar-CH₃), 2.16 (brs, 3H, NCH₃), 1.97 (d, 2H, J = 4.8 Hz, CH₂), -0.15 (s, 9H, 3 x CH₃); ¹³C NMR (100 MHz, CDCl₃, 298 K): δ 173.0, 145.6, 138.1, 136.8, 129.0, 128.7, 128.3, 128.1, 126.9, 118.7, 66.0, 58.6, 51.6, 38.3, 30.7, 29.7, 21.2, -1.4; HRMS (ESI+): m/z calculated for C₂₄H₃₄NO₂Si (M⁺Na) 396.23588, found 396.2361.

**Methyl 2-(morpholino)-4-oxo-octanoate (43):** To a stirred solution of ester 39a (0.05 g, 0.14 mmol) in THF (2 mL) and water (2 mL), sodium perborate monohydrate (0.045 g, 0.45 mmol) was added and stirred at room temperature for 12 h. The reaction mixture was diluted with water (4 mL) and extracted with Et₂O (2 x 5 mL). The combined organic extracts were dried (MgSO₄) and evaporated under vacuum. The resulting residue was purified by column chromatography (230-400 mesh Silica gel, 8% ethyl acetate in cyclohexane) to afford γ-keto amino ester 43 (0.026 g, 74%) as a colorless oil; ¹H NMR (400 MHz, CDCl₃, 298 K): δ 3.77-3.73 (m, 1H, CaH), 3.67 (s, 3H, OCH₃), 3.67-3.61 (m, 5H, 2 x CH₂, C₂H), 2.99 (dd, 1H, J = 17.0, 9.2 Hz, C₃H), 2.75-2.64 (m, 2H, CH₂), 2.56-2.47 (m, 2H, CH₂), 2.37 (t, 2H, J = 7.3 Hz, CH₂), 1.86 (t, 2H, J = 7.4 Hz, CH₂), 1.49 (quint, 2H, J = 7.4 Hz, CH₂), 1.24 (hex, 2H, J = 7.4 Hz, CH₂), 0.84 (t, 3H, J = 7.3 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃, 298 K): δ 207.3, 169.8, 65.9, 61.9, 50.7, 49.2, 41.8, 40.6, 24.7, 185
21.3, 12.8; HRMS (ESI+): m/z calculated for C_{13}H_{23}NO_{4}Na (M^+ + Na) 280.1525, found 280.1523.

**Methyl 2-(morpholino)-4-azido-oct-3-enoate (44):** To a stirred solution of boronic ester 39a (0.056 g, 0.15 mmol) in MeOH (2 mL), sodium azide (0.012 g, 0.18 mmol) and copper sulfate (0.015 g, 0.095 mmol) were added at room temperature and stirred for 24 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried (MgSO_4), evaporated under vacuum and purified the residue by column chromatography (230-400 mesh Silica gel, 10% ethyl acetate in cyclohexane) to afford γ-azido amino ester 44 (0.03 g, 71%) as a colorless oil; ^1H NMR (400 MHz, CDCl_3, 298 K): δ 4.74 (d, 1H, J = 9.5 Hz, olefinic), 3.95 (d, 1H, J = 9.5 Hz, CαH), 3.67 (t, 4H, J = 4.6 Hz, 2 x CH_2), 3.66 (s, 3H, OCH_3), 2.56-2.49 (m, 2H, allylic CH_2), 2.45-2.38 (m, 2H, CH_2), 2.26 (t, 2H, J = 7.5 Hz, CH_2), 1.47 (quint, 2H, J = 7.5 Hz, CH_2), 1.32 (hex, 2H, J = 7.5 Hz, CH_2), 0.87 (t, 3H, J = 7.3 Hz, CH_3); ^13C NMR (75 MHz, CDCl_3, 298 K): δ 171.3, 141.2, 109.2, 66.8, 65.35, 52.0, 50.9, 32.2, 29.4, 21.9, 13.7; HRMS (ESI+): m/z calculated for C_{13}H_{22}N_{3}O_{3}Na (M-N_2^+ + Na) 277.1528, found 277.1530.

**Methyl 2-(morpholino)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)-oct-3-enoate (45):** To a stirred solution of ester 39a (0.04 g, 0.11 mmol) in MeOH (2 mL), sodium azide (9 mg, 0.13 mmol) and copper sulfate (0.011 g, 0.07 mmol) were added at room temperature and stirred for 24 h. Sodium ascorbate (0.011 g, 0.05 mmol) and phenylacetylene (0.012 g, 0.12 mmol) were added to the reaction mixture and stirred for 24 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried (MgSO_4), evaporated under vacuum and purified the residue by column chromatography (230-400 mesh Silica gel, 12% ethyl acetate in cyclohexane) to afford γ-triazolyl amino ester 45 (15 mg, 36%) (over two steps); ^1H NMR (400 MHz, CDCl_3, 298 K): δ 8.01 (s, 1H, Ar-H), 7.80 (d, 2H, J = 7.1 Hz, Ar-H), 7.39 (t, 2H, J = 7.3 Hz, Ar-H), 7.29 (d, 1H, J = 7.4 Hz, Ar-H), 5.71 (d, 1H, J = 9.4 Hz, olefinic), 3.75-3.70 (m, 1H, CαH), 3.69 (s, 3H, OCH_3), 3.65 (t, 4H, J = 4.4 Hz, 2 x CH_2), 2.63 (t, 2H, J = 7.3 Hz, CH_2), 2.70-2.43 (m, 4H, 2 x CH_2), 1.37-1.26 (m, 4H, 2 x CH_2), 0.83 (t, 3H, J = 7.1 Hz, CH_3); ^13C NMR (75 MHz, CDCl_3, 298 K): δ 169.9, 147.3, 141.9, 130.1, 129.0, 128.4, 125.7, 120.7,
66.6, 65.4, 52.0, 50.6, 35.9, 28.8, 21.9, 13.7; HRMS (ESI+): $m/z$ (M+H)$^+$ calculated for C$_{21}$H$_{28}$N$_4$O$_3$Na 407.2059, found 407.2054.
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Spectrum 1. $^1$H NMR Spectrum of 39a (300 MHz, CDCl$_3$) 

$^{13}$C NMR Spectrum of 39a (100 MHz, CDCl$_3$)
Spectrum 2. $^{11}$B NMR Spectrum of $39a$ (96 MHz, CDCl$_3$)
Spectrum 3. $^1$H NMR Spectrum of 39b (300 MHz, CDCl₃)

$^{13}$C NMR Spectrum of 39b (100 MHz, CDCl₃)
**Spectrum 4.** $^{11}\text{B}$ NMR Spectrum of 39b (96 MHz, CDCl$_3$)
Spectrum 5. $^1$H NMR Spectrum of 39c (400 MHz, CDCl$_3$)

$^{13}$C NMR Spectrum of 39c (75 MHz, CDCl$_3$)
Spectrum 6. $^1$H NMR Spectrum of 39d (300 MHz, CDCl$_3$)

$^{13}$C NMR Spectrum of 39d (75 MHz, CDCl$_3$)
**Spectrum 7.** $^1$H NMR Spectrum of 39e (400 MHz, CDCl$_3$)

$^{13}$C NMR Spectrum of 39e (75 MHz, CDCl$_3$)
Spectrum 8. $^{11}$B NMR Spectrum of 39e (96 MHz, CDCl$_3$)
Spectrum 9. $^1$H NMR Spectrum of 39f (300 MHz, CDCl$_3$)

$^{13}$C NMR Spectrum of 39f (75 MHz, CDCl$_3$)
Spectrum 10. $^1$H NMR Spectrum of 39f (96 MHz, CDCl$_3$)
Spectrum 11. $^1$H NMR Spectrum of 39g (300 MHz, CDCl$_3$)
13C NMR Spectrum of 39g (100 MHz, CDCl$_3$)
**Spectrum 12.** $^1$H NMR Spectrum of 39h (400 MHz, CDCl₃) $^{13}$C NMR Spectrum of 39h (100 MHz, CDCl₃)
Spectrum 13. $^1$H NMR Spectrum of 41 (400 MHz, CDCl$_3$)

$^{13}$C NMR Spectrum of 41 (100 MHz, CDCl$_3$)
Spectrum 14. $^{11}$B NMR Spectrum of 41 (96 MHz, CDCl$_3$)
Spectrum 15. $^1$H NMR Spectrum of 42a (300 MHz, CDCl$_3$)

$^{13}$C NMR Spectrum of 42a (100 MHz, CDCl$_3$)
**Spectrum 16.** $^1$H NMR Spectrum of 42b (300 MHz, CDCl$_3$)

$^{13}$C NMR Spectrum of 42b (100 MHz, CDCl$_3$)
Spectrum 17. $^1$H NMR Spectrum of 42c (300 MHz, CDCl$_3$)

$^{13}$C NMR Spectrum of 42c (100 MHz, CDCl$_3$)
Spectrum 18. $^1$H NMR Spectrum of 42d (300 MHz, CDCl$_3$)

$^{13}$C NMR Spectrum of 42d (75 MHz, CDCl$_3$)
Spectrum 19. $^1$H NMR Spectrum of 42e (300 MHz, CDCl$_3$)

$^{13}$C NMR Spectrum of 42e (100 MHz, CDCl$_3$)
Spectrum 20. $^1$H NMR Spectrum of 42f (400 MHz, CDCl$_3$)

$^{13}$C NMR Spectrum of 42f (100 MHz, CDCl$_3$)
Spectrum 21. $^1$H NMR Spectrum of 42g (400 MHz, CDCl$_3$)

$^{13}$C NMR Spectrum of 42g (100 MHz, CDCl$_3$)
Spectrum 22. $^1$H NMR Spectrum of 42h (300 MHz, CDCl₃)

$^{13}$C NMR Spectrum of 42h (100 MHz, CDCl₃)
Spectrum 23. $^1$H NMR Spectrum of 42i (300 MHz, CDCl$_3$)

$^{13}$C NMR Spectrum of 42i (75 MHz, CDCl$_3$)
Spectrum 24. $^1$H NMR Spectrum of 42j (300 MHz, CDCl$_3$)

$^{13}$C NMR Spectrum of 42j (100 MHz, CDCl$_3$)
Spectrum 25. $^1$H NMR Spectrum of 43 (400 MHz, CDCl$_3$)

$^{13}$C NMR Spectrum of 43 (100 MHz, CDCl$_3$)
Spectrum 26. $^1$H NMR Spectrum of 44 (400 MHz, CDCl$_3$)

$^{13}$C NMR Spectrum of 44 (75 MHz, CDCl$_3$)
Spectrum 27. $^1$H NMR Spectrum of 45 (400 MHz, CDCl$_3$)

$^{13}$C NMR Spectrum of 45 (75 MHz, CDCl$_3$)