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Development of a Modular Approach for the Synthesis of Teraryl-based alpha-Helix Mimetics for the Inhibition of Protein-Protein-Interactions

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„Die Chemie und mit ihr allgemein gesprochen die gesamte
Naturwissenschaft ist das wahre Land der unbegrenzten Möglichkeiten“
Emil Fischer

Meiner Familie

Abstract

Proteins are playing an essential role in different cellular functions, but they do not act as isolated entities. They are operating by complex interaction mechanisms and a whole network of non-covalently interacting proteins exists in the human proteome. The dysfunction of protein-protein-interactions (PPIs) are linked to various diseases and PPIs are promising targets for next-generation therapeutics.[1] As PPIs lack well-defined binding cavities like enzymes and consist of large, uncontinous binding epitopes, targeting PPIs with small molecules remain a challenge.[2] In human cells the number of different PPIs is estimated to be approximately 650 000[3] and in more than 60 % only one site of an α-helical secondary structure motif is essential for sufficient binding.[4] HAMILTON et al. have presented the terphenyl-structure, a completely nonpeptidic scaffold that could mimic larger areas of the protein surface such as an α-helix[5] and they showed several applications where terphenyls selectively inhibit various PPIs.[6,7]

Time consuming linear reaction sequences and poor solubility under physiological conditions of terphenyls led to the development of other types of α-helix mimetics containing more polar heterocycles.[8] Pyridine containing teraryls are known, but no general modular synthesis had been developed so far.[9] In this thesis a building block concept for the synthesis of teraryls was developed and two sets of building blocks, core unit fragments and pyridine boronic acid esters, mimicking the side chains of natural amino acids relevant for PPI were provided. The assembly of the building blocks was performed by Pd-catalyzed cross-coupling reactions whereby selectivity was gained by the core unit fragment featuring two leaving groups with differentiated reactivity.

Kurzfassung

Proteine spielen eine wichtige Rolle bei verschiedensten Funktionen in der Zelle und es konnte gezeigt werden, dass einzelne Proteine nicht als isolierte Einheiten arbeiten. Proteine agieren über komplexe, nicht kovalente Mechanismen und ein ganzes Netzwerk aus Protein-Protein-Interaktionen (PPI) existiert im menschlichen Proteom. Verschiedene Krankheiten können mit inkorrekten PPI in Verbindung gebracht werden, weswegen PPI vielversprechende Ziele für Medikamente der nächsten Generation sind.[1] Da in PPI keine definierten, aktiven Zentren wie in Enzymen vorkommen und sie große, flache Bindungsoberflächen besitzen, können kleine organische Moleküle nur schwer interagieren und PPI inhibieren.[2] Die Anzahl verschiedener PPI in der menschlichen Zelle beträgt ungefähr 650.000,[3] wobei in über 60 % nur eine Seite einer α-Helix für die Interaktion von Bedeutung ist.[4] HAMILTON et al. entwickelten das Terphenyl-Gerüst, eine Struktur die keine Peptidbindungen enthält und durch ähnliche Abstände der Seitenketten trotzdem gut mit einer α-Helix überlappt.[5] In verschiedenen Beispielen konnte gezeigt werden, dass Terphenyle selektiv unterschiedliche PPI inhibieren.[6,7] Aufgrund zeitaufwändiger, linearer Syntheserouten und schlechter Wasserlöslichkeit unter physiologischen Bedingungen wurden alternative α-Helix-Mimetika, die Heterozyklen enthalten, entwickelt.[8] Teraryle die Pyridine enthalten wurden schon hergestellt, aber auch für diese Verbindungsklasse ist keine flexible, modulare Syntheseroute bekannt. In dieser Arbeit wurde ein Konzept zur modularen Synthese von Terarylen, die zwei Pyridin-Ringe enthalten, entwickelt. Das Konzept baut auf zwei Arten von Bausteinen auf, den Kern-Baustein und den Pyridin-Boronsäureester-Baustein, welche die Seitenketten von natürlichen Aminosäuren imitieren sollen. Um das Teraryl-Gerüst aufzubauen werden diese Bausteine durch eine Pd-katalysierte Kreuzkupplung verknüpft. Selektivität wird durch den Kern-Baustein erhalten, welcher zwei Abgangsgruppen enthält, die unterschiedlich schnell in Pd-katalysierten Kreuzkupplungen reagieren.

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1 Introduction

Proteins are playing an essential role in various fundamental biological processes, such as DNA replication, transcription, translation, and transmembrane signal transduction. In the last decades it was recognized, that proteins do not act as isolated entities but are operating by complex interaction mechanisms. A whole network of non-covalently interacting proteins exists in the human proteome and they are regulating each other. By screening a protein matrix of 4456 baits and 5632 preys using an automated yeast two hybrid (Y2H) interaction mating STELZL *et al.* were able to identify new PPIs and they could develop a map of the highly connected human proteome (Figure 1). Among them 195 proteins involved in diseases were found and also placed in a new context with their previous unknown interaction partners. Therefore systematic screens of PPIs will lead to a better understanding of cellular processes in the human proteome and will help do identify new drug targets.[1]

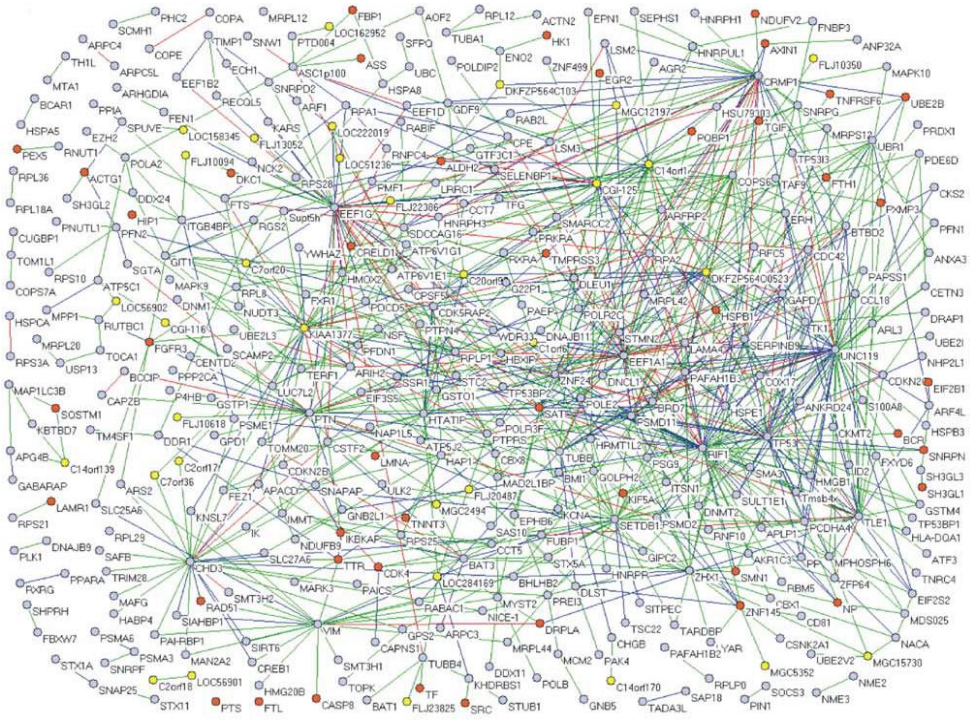
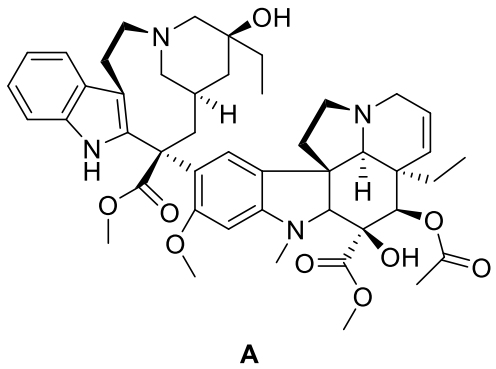


Figure 1: A graph of the human PPI network involving 401 proteins linked via 911 interactions (disease proteins: orange), picture taken from Ref. [1].

Many new techniques for the prediction of lead structures like protein-crystallography, computational chemistry as well as genetics and the rapid synthesis of these molecules by combinatorial chemistry in combination with high-throughput screenings were developed in the past decades. Nevertheless the clinical validation of new drugs and the admission to market is rather stagnating. Over a quarter of drugs that enter clinical development fail because they are

ineffective.[10] Since the druggable genome - a subset of the ~30,000 genes in the human genome that express proteins involved in diseases and are able to bind drug-like molecules – is estimated to encompass around 600-1500 drug targets, the majority of target proteins remain still to be identified.[11] Nevertheless a variety of different methods for druggability prediction have been published in the past six years and will further improve the selection of new drug targets.[12] As the dysfunction of PPIs is linked to various diseases, PPIs are promising candidates for next-generation therapeutics. Until recently, the list of common targets was restricted to enzymes, ion channels or receptors with well-defined binding sites, which are easily addressable by small molecules. Enriching this list with PPIs will access new targets, but will also lead to new challenges. Since PPIs lack well defined binding-cavities that are necessary for sufficient binding, it is rather difficult to find small molecules which are interacting sufficiently with large protein surfaces. However, there are already small molecules derived from nature which are used in anti-cancer therapy (Figure 2).[2] One example is the natural product vinblastine (**A**) which belongs to the vinca alkaloids and was isolated from the Madagascan periwinkle plant *Catharanthus roseus*. Vinblastine (**A**) and other vinca alkaloids prevent the polymerisation of tubulin to microtubules by destabilizing them. Since the proper formation of mitotic spindle, which is made of microtubules, is necessary for cell separation the depolymerisation of microtubules leads to mitotic block and apoptosis.[13]14]



A

Figure 2: Vinblastine (Velbe®), a vinca alkaloid which acts as mitotic inhibitor.[14]

These promising applications encourage to find even smaller and easier to synthesise molecules with similar properties. Nevertheless, considerable efforts will be necessary to synthesize these molecules and test for their ability to act as therapeutics.

2 Theoretical Background

In human cells the number of different PPIs is estimated to be approximately 650 000.[3] Therefore selective molecules, which interact with one particular target protein, are needed for pharmaceutical applications. In the beginning, short peptide chains were used to study these interactions, but they have several drawbacks in their application as drugs such as conformational lability, proteolytic instability and poor bioavailability. Different strategies have been explored to overcome these limitations including stapled peptides, *N*-terminal caps, and peptide foldamers.[15] But all these strategies have still peptidic character. HAMILTON *et al.* sought a completely nonpeptidic scaffold that could mimic larger areas of the protein surface such as an α-helix. With this approach HAMILTON *et al*. invented a fourth general strategy for targeting α-helix containing PPIs, the structural mimetics (Figure 3).[5]

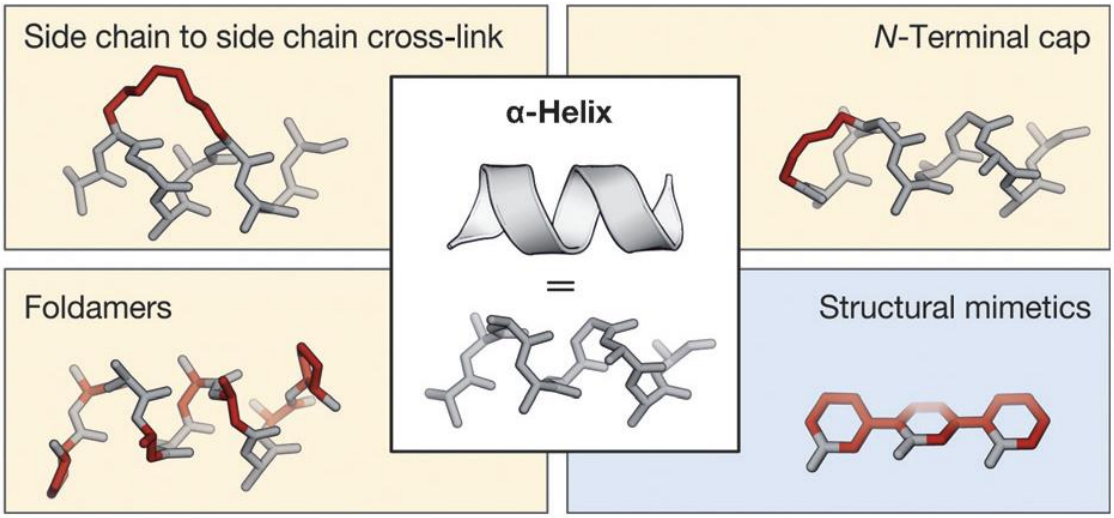


Figure 3: Schematic representation of an a-helix together with general strategies of helix stabilization and mimicry, picture taken from Ref. [15].

HAMILTON´s scaffold can be synthesized rather simply but contain similar distances and angular relationships to those found in α-helices. An X-ray crystal structure showed that a tris-functionalized 3,2´,2´´-terphenyl derivative in a staggered conformation has corresponding distances between the substituents, as it is given between the i, i+3 and i+7 β-carbons in an α-helical peptide (Figure 4). Although there might be other low-energy conformers be present in solution, HAMILTON *et al.* assumed the desired terphenyl conformation will be accessible. The staggered conformation of the crystalline molecule as well as low rotational barriers strongly point to this conformation. Predominantly, in the presence of a complementary recognition site, this conformation will be favored. Interestingly, the unsubstituted terphenyl is a very weak binder, which suggests that the backbone does not engage in non-specific interactions.[5]

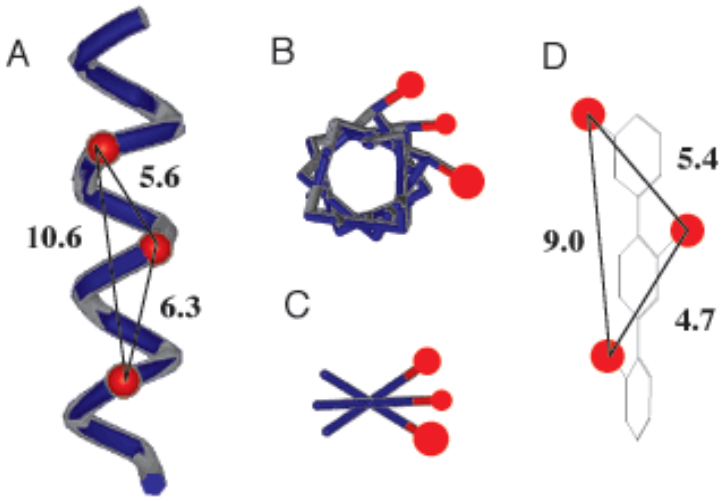


Figure 4: (A) Schematic representation of an R-helical 12-mer peptide with i, i + 3, and i + 7 substituents, side view; (B) top view; (C) 3,2´,2"- trisubstituted terphenyl, top view; (D) side view, picture taken from Ref. [5].

2.1 Proof of concept

HAMILTON *et al.* were able to show the universal application of this concept on several protein-protein-interactions.

2.1.1 Smooth muscle myosin light chain kinase (smMLCK) with calmodulin (CaM)

Earlier work from DEGRADO *et al.* has shown that an effective recognition site for α-helical peptides is present in CaM and this PPI is also an interesting target in ongoing research due to its influence in cell cycle events.[16] By mutational studies three amino acids were associated with high binding energy contribution. The amino acids playing a key role in the interaction are present in the i, i+3 and i+7 (Trp800, Thr803 and Val807) position. These key residues can be mimicked by the corresponding tris-functionalized 3,2´,2´´-terphenyl **B1-4** (Figure 5).[5]

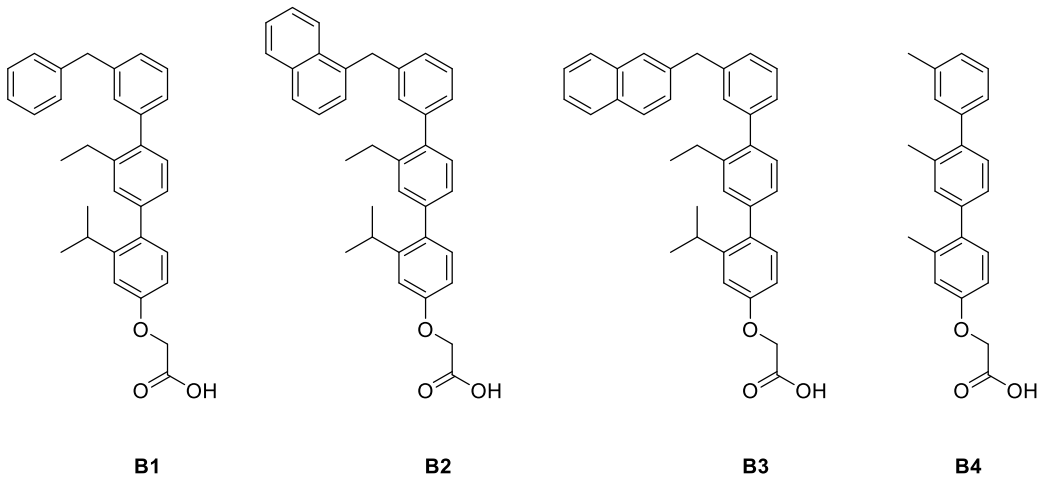


Figure 5: Simpified synthesized terphenyls for the inhibition of smMLCK/CaM.[5]

The additional added free carboxylic acid was converted to the corresponding ammonium salt, which proved to be soluble in buffer with <1 % DMSO. Affinity of the synthesized terphenyls to CaM was tested by affinity chromatography and competition assays. The 1-naphthyl derivative **B2** was characterized as the most potent inhibitor with an IC_{50} = 9 nM. The terphenyls belong to the most potent CaM antagonists and have an 8-fold improvement over the helical peptide RS20 from smMLCK.[5]

2.1.2 Bak BH3 with Bcl-x_L

The anti-apoptotic protein Bcl-x_L is overexpressed in many types of cancer and leads to uncontrolled cell growth.[17] It protects mutated cells from cell death even if apoptotic signals are present, which are generated by chemo- or radiotherapy. Pro-apoptotic Bak- and Bad-proteins, interact by heterodimerization with the anti-apoptotic protein Bcl-x_L and enable the apoptotic cascade leading to cell death.[18] In accordance with crystal structures and based on alanine scans of the Bak/Bcl-x_L complex four hydrophobic residues (Val74, Leu78, Ile81, Ile85) along one edge of the helix were identified as hotspots. Additionally Asp83 forms an ion pair with a lysine residue of Bcl-x_L (Figure 6).[6,19,20]

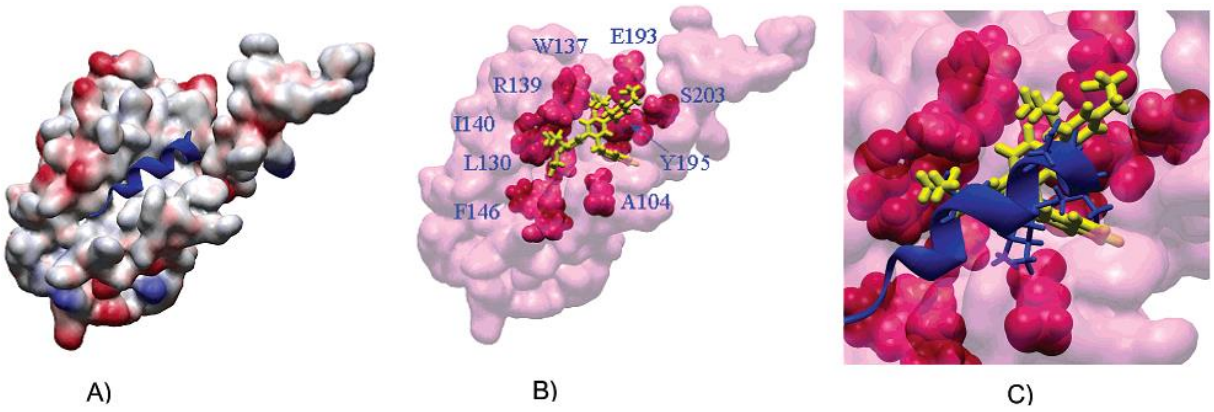


Figure 6: (A) Bak-BH3-peptide/Bcl-xL complex. (B) Docking results and residues shifted in the NMR experiment of a terphenyl and Bcl-x_L. (C) Overlay of peptide, picture taken from Ref. [6].

Based on these structural requirements, a series of terphenyls **C1-4** substituted on the three ortho-positions were designed (Figure 7). On the helical exterior an additional carboxylic acid was introduced to mimic the ion pair interaction.

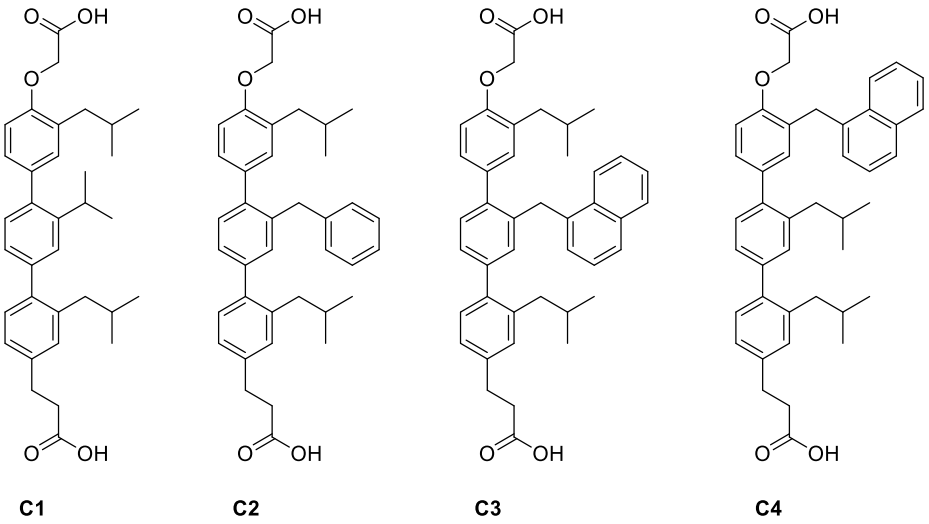


Figure 7: Synthesized Teraryls for the inhibition of Bak/Bcl-x_L.[6]

The binding affinity of these molecules was assessed by a fluorescence polarization assay using fluorescein-labeled 16-mer Bak-peptide. K_D values were measured between 100 nM and 3 µM. The most potent molecule was the Leu,- 1-Naph-, Leu-containing analog **C3**. Both carboxylic acids seems to be crucial for sufficient inhibition.[19,19]

2.1.3 Human double minute 2 (HDM2) and p53

The transcription factor p53 plays a key role in the apoptosis pathway. In unstressed cells p53 is present in very low cellular concentrations and its degradation is regulated by HDM2 via the ubiquitin-dependent proteasome pathway.[21] HDM2 binds to p53 and acts as ubiquitin E3 ligase which promotes ubiqutination and further degradation. Mutated or inactive p53 was found in over 50 % of cancerous tumors and also overexpression of HDM2 can be linked to tumors such as osteogenic sarcomas and soft-tissue sarcomas.[22]

According to the crystal structure, HDM2 binds to p53 via a pocket-ligand type interaction whereas p53 forms an amphipathic α-helix and interacts with a hydrophobic groove on the globular HDM2 domain (Figure 8). The predominant role of three amino acid residues (Phe19, Trp23 and Leu26) was further confirmed by computational and NMR spectroscopy experiments.[23]

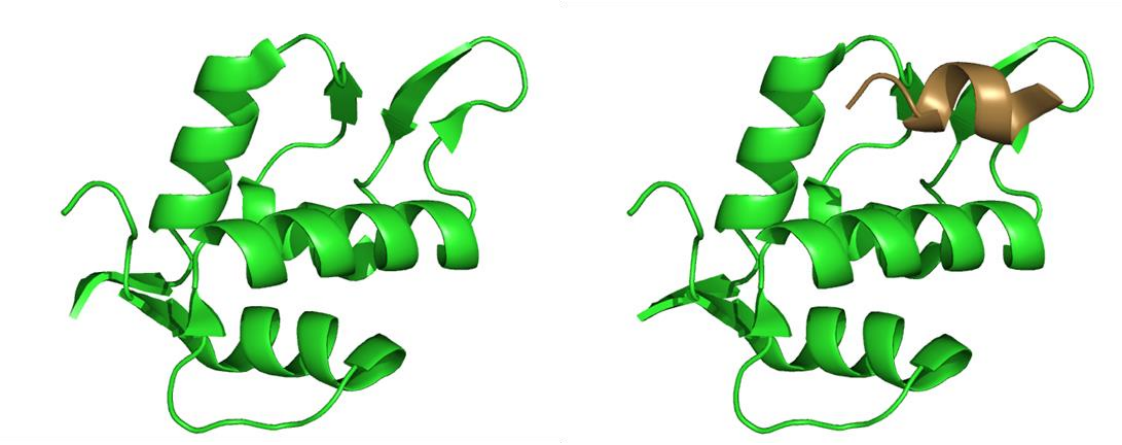


Figure 8: HDM2 and HDM2/p53-complex, picture taken from Ref. [24].

A set of terphenyls **D1-3** was prepared by HAMILTON *et al*. and tested in a fluorescence polarization competition assay with fluorescein-labeled p53 peptide for their binding affinities to HDM2 (Figure 9). Binding of terphenyls into the hydrophobic cleft leads to displacement of the fluorescent probe and decreases the fluorescent polarization.[7]

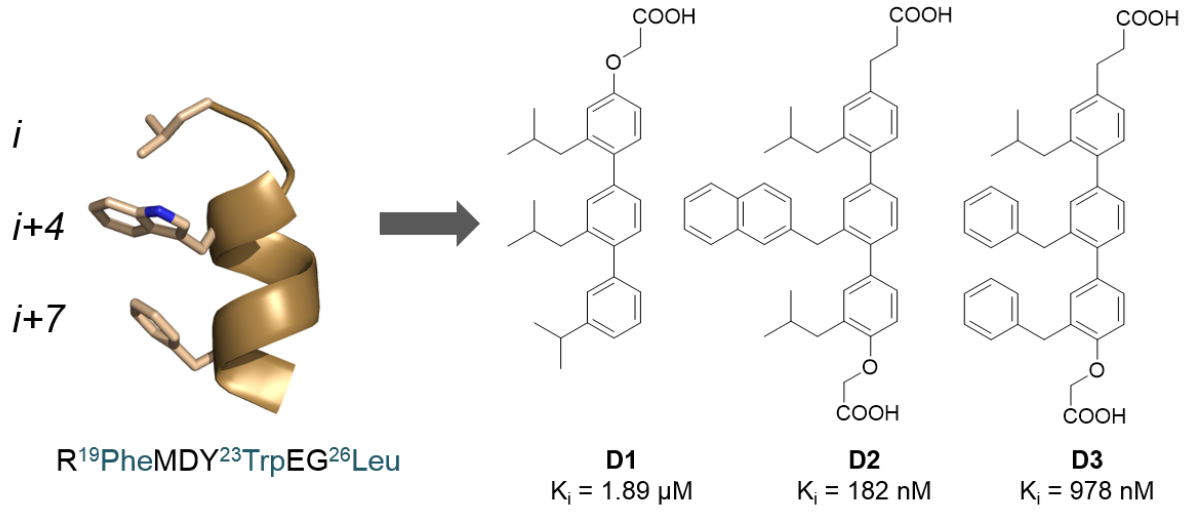


Figure 9: α-helix of p53 and synthesized terphenyl mimetics, picture taken from Ref. [24].

Low in vitro inhibition constants in the µM to nM range encouraged further in vivo studies of these terphenyls.[25] It was shown that terphenyls do not activate p53 by partially inhibiting RNA polymerase II, which reduces the expression level of HDM2. In contrast activation of p53 correlates with the ability of terphenyls to inhibit the formation of the HDM2-p53 complex. In in vivo experiments several terphenyls were identified to be membrane permeable – a consequence of their hydrophobic nature. They were also able to activate p53 in tumor cells and induce accumulation of this protein.[7]

2.2 Computational validation

Four years after HAMILTON had established his concept of small-molecule peptidomimetics ARORA *et al.* analyzed the protein structure data bank with computational methods focusing on protein-protein-interactions. They aimed identifying common features of protein complexes with their analysis and predict PPI that can be affected by small molecules.[26] Furthermore they wanted to investigate secondary structure motifs involved in PPIs. The most frequent occurring motif was indeed the α-helical peptide chain found in more than 60 % of all recorded PPIs.[27]

2.2.1 Alanine scanning mutagenesis

Hotspots are referred to residues with very strong contribution to the binding energy. When the binding energy decreased by more than 4.18 kJ.mol^{-1} upon mutation to alanine, this amino acid belongs to a hotspot-area. By applying alanine scanning mutagenesis, previously unknown interactions with α-helices involved could be identified.[4] Domains containing α-helices were further investigated upon their composition and characteristics. Position and location of hotspot residues on helices were determined and also the overall energy-contribution and occurrence frequency of different amino acids were calculated (Figure 10).

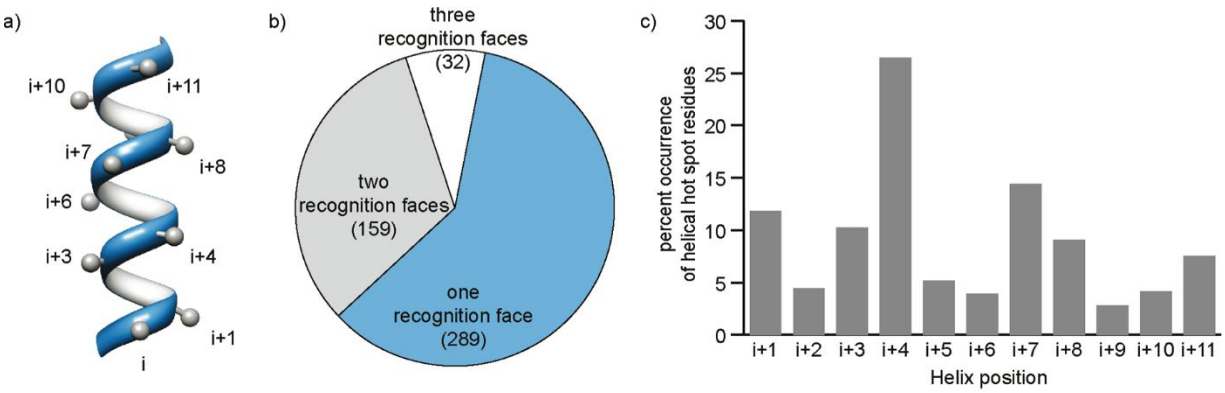


Figure 10: Energetic contributions of residues on different faces of interfacial helices. (a) Positioning of side-chain residues on a canonical R-helix. (b) Percent occurrence of hotspot residues on one, two, or three helical faces (the total number of helices in each category is shown in parentheses). (c) Percent occurrence of hotspot residues as a function of helix position, picture taken from Ref. [4].

In more than 60 % of the analyzed PPIs only one site of the α-helix is essential for sufficient binding. The positions with the highest contribution to hotspots are the i+1, i+3 or 4 and i+7 residues. They were most frequently detected as hotspots. This suggests that helix surface mimetics may be highly effective as PPI-inhibitors.[4,28]

The percentage of each helical residue that contributes strongly to binding was calculated. Leucine was found most frequently in the interface area, but after normalizing to the natural abundance of the single amino acids also amino acids with aromatic residues and arginine were

found frequently. The major energy contribution was found for hydrophobic interactions, but also salt bridges and polar interactions were located in the binding energy landscape (Figure 11).

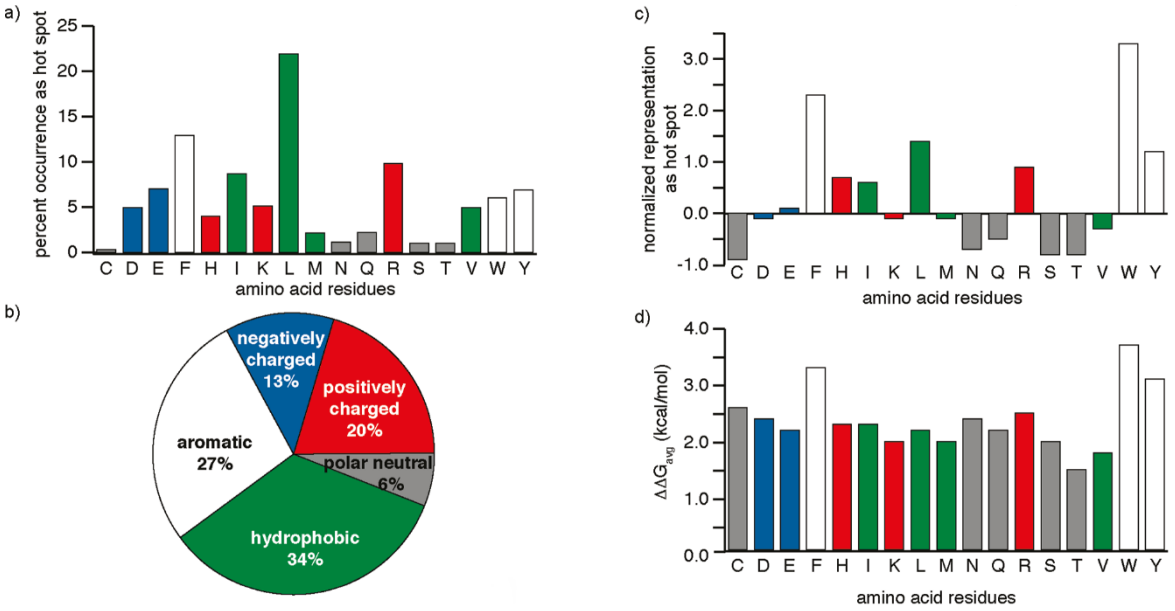


Figure 11: (a) Percent occurrence of hotspot amino acids in helix-mediated protein interfaces. (b) Percent occurrence of hotspot residues classified into similar groups. (c) Representation of hotspot amino acids normalized to the natural abundance of amino acids normalized to the natural abundance of amino acids in proteins. (d) Average predicted decrease in binding energy of helical interfaces upon mutation of hotspot residues to alanine. Color code: aromatic (phenylalanine, tryptophan, and tyrosine), white; hydrophobic (isoleucine, leucine, and valine), green; negatively charged (aspartic acid and glutamic acid), blue; polar neutral (asparagine, cysteine, glutamine, serine, and threonine), gray; positively charged (arginine, histidine, and lysine), red, picture taken from Ref. [4].

This computational approach by ARORA *et al.* should help to combine the design of helix mimetics and their application in biology. Since the use of helix mimetics in biology has been limited to a set of model protein complexes ARORA *et al*. simplified the search for new PPI-targets. By providing a list of targetable protein-complexes different options for applying small molecule α-helix mimetics were generated.

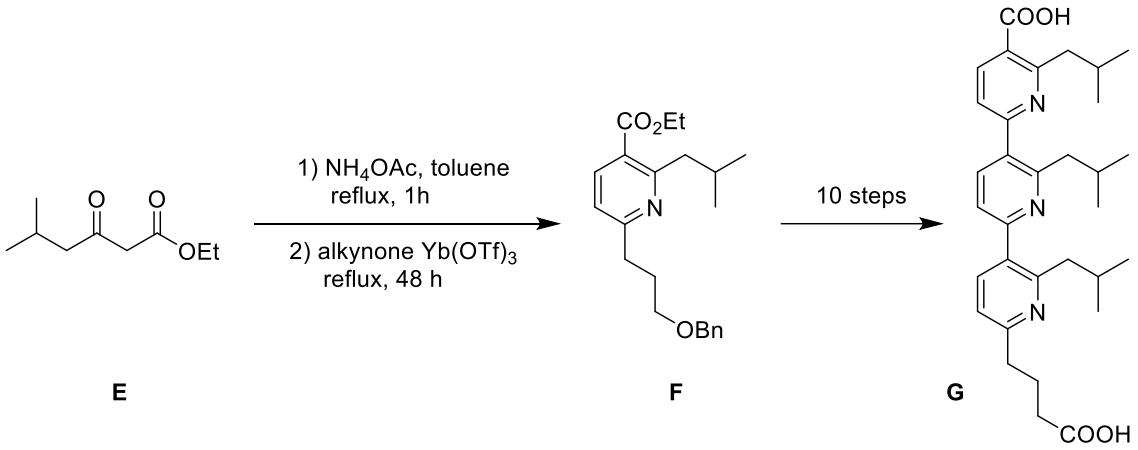
2.3 α-Helix peptidomimetics

Despite the fact that HAMILTON *et al*. developed a fascinating structural concept for α-helix mimetics, terphenyls have still several limitations, which need to be overcome. One drawback is the strong hydrophobic character of these molecules. Without additionally attached highly polar functional groups, they would not be soluble under physiological conditions.[29] To achieve more polar structures, heterocycles were introduced into the terphenyl scaffold. In addition to better water solubility also an amphiphilic character was generated. The

hydrophobic part of the molecule is responsible for the PPI and the hydrophilic part gives improved solubility properties.[30] Many different heterocycles were used.

2.3.1 Terpyridine scaffold

HAMILTON *et al.* improved their originally presented terphenyl concept and introduced pyridine rings. They used a heteroannulation method developed by BOHLMANN und RAHTZ[31] and further developed by BAGLEY[32] via an one pot condensation of a β-keto ester **E** and a ketoalkyne **F** (Scheme 1). The terpyridine **G** should be tested for their ability to inhibit the interaction between Bcl-x_L and Bak, but results to that studies were never published.[9]



Scheme 1: Terpyridine synthesis.[9]

2.3.2 Pyrrolopyrimidine scaffold

LIM *et al.* prepared a pyrrolopyrimidine-based scaffold **H1-2** via solid-phase synthesis. Different derivatives were tested in a high-throughput screen whereby potent dual inhibitors could be identified that disrupt the interaction between p53 and MDMX/HDM2 (Figure 12).[33]

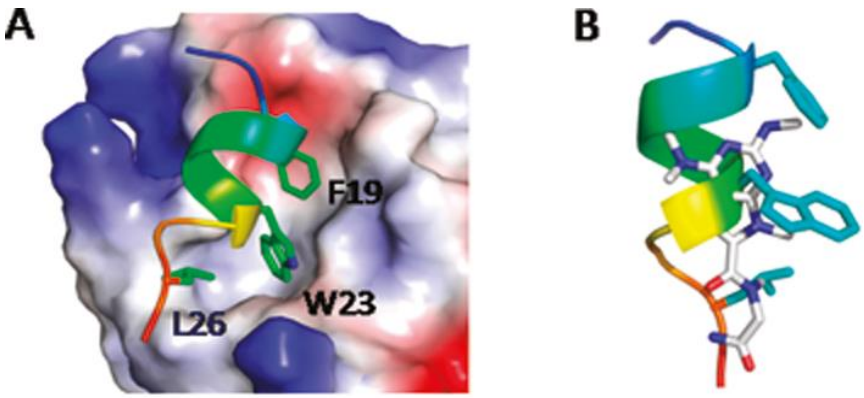


Figure 12: (A) Crystal structure of MDMX in complex with a p53peptide (PDB entry: 2Z5S). (B) Overlay of compound 3 (R_1, R_2, R_3 = CH_3) and an MDMX-bound p53 peptide, picture taken from Ref. [33].

The pyrrolopyrimidine scaffolds **H1-2** have several advantages such as conformational rigidity, improved water solubility, excellent cell-permeability and easy access by solid-phase synthesis. Two inhibitors with submicromolar K_i values were identified in a fluorescent polarization-based competitive assay (Figure 13).[33]

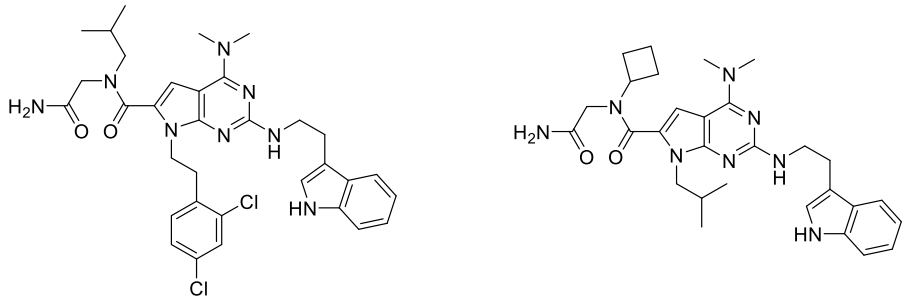


Figure 13: Identified inhibitors against p53/HDMX.[33]

Several other heterocycle containing templates are reported in the literature, but many of them have never been tested for their biological activity.[8,29,30,34]

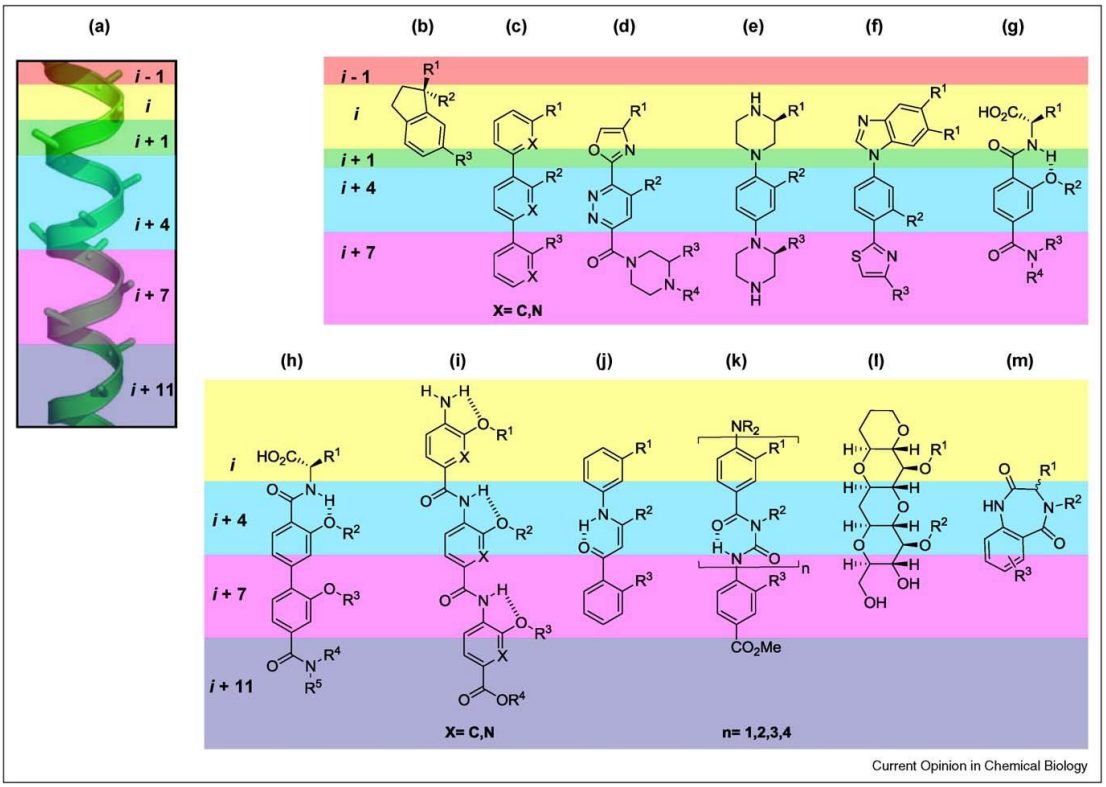


Figure 14: Figure 15: Schematic representations of (a) a natural α-helix with the i−1, i, i+1, i+4, i+7 and i+11 residues, (b) the 1,1,6-trisubstituted indane, (c) the terphenyl (when X = C) and the terpyridine (when X = N), (d) oxazole-pyridazine piperazine, (e) 1,4-dipiperazino benzene, (f) 5-6-5 imidazole-phenyl-thiazole, (g) terephthalamide, (h) biphenyl 4,4'-dicarboxamide, (i) oligobenzamide (when X = C) and oligopyridine (when X = N), (j) enaminone, (k) benzoylurea, (l) 6/6/6/6 trans*-fused polycyclic ether and (m) benzodiazepinedione based α-helix mimetics, picture taken from Ref. [8].*

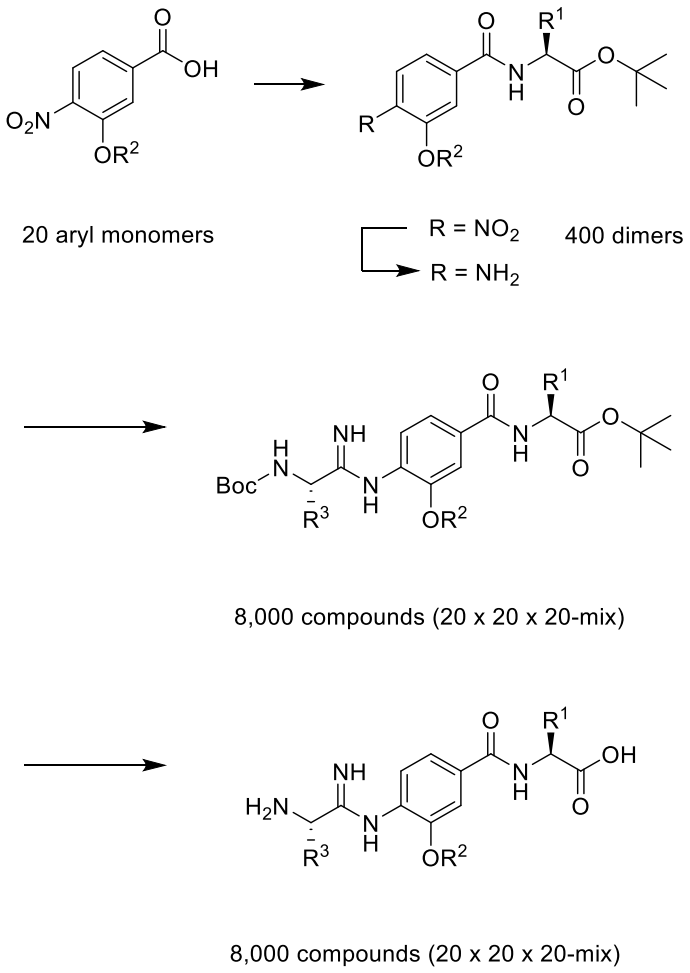
2.4 Modular synthesis of α-helix mimetics

Although promising results were achieved in biological screenings long and time consuming linear synthesis limited the application of these molecules. To generate access via a highly modular building block based strategy would allow larger screening collections and more rapid identification of new bioactive molecules as in many cases synthesis is the rate limiting step.[35,36]

Considerable successful strategies have been reported on synthesizing libraries of α-helix mimetics by modular or combinatorial approaches.

2.4.1 Triaryl amide scaffold

BOGER *et al.* established a solution-phase synthesis for triaryl amide scaffolds, which were inspired by HAMILTON´s terphenyls. Easy synthesis and a more polar character mediated by amide-bonds are several advantages of this scaffold.[37]

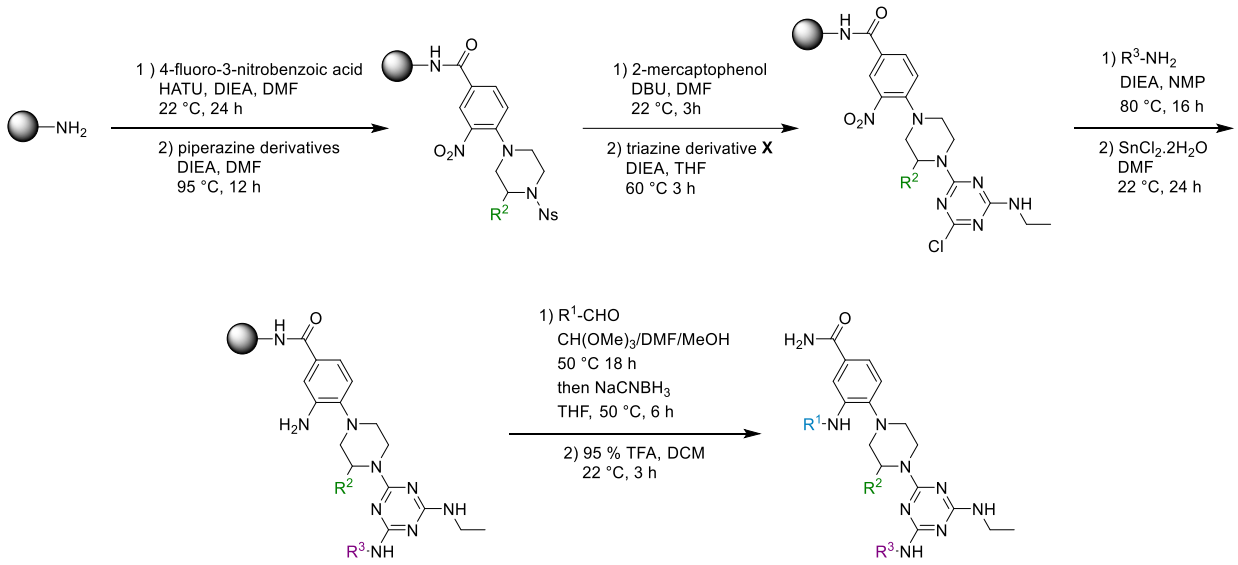


Scheme 2: Library synthesis of triaryl amide scaffolds.[38]

The synthetic strategy is based on building blocks containing an amine and a carboxylic acid, which are connected by simple amide coupling (Scheme 2). For amide coupling a series of highly efficient methods are availabele as they hyve been developed for peptide synthesis.
20 amino acid side chain variants were used and 8,000 compounds representing all permutations of these variants were assembled. To facilitate the isolation and purification of each intermediate an acid/base extraction purification protocol was established.[38] By screening the compound-pool against the NHR hydrophobic pocket of the HIV-1 envelope glycoprotein gp41 and inhibiting of the CHR α-helix submicromolar K_i-values were measured.[39] Solid phase synthesis for the preparation of triaryl amide scaffolds were been reported as well.[36,40]

2.4.2 Piperazine-triazine scaffold

Piperazine-triazine based scaffolds were developed by LIM *et al.* and were assembled by solid phase synthesis. By introducing heterocycles the water solubility was improved in comparison to terphenyls and via solid-phase synthesis easy and rapid access to a library of different compounds is guaranteed (Scheme 3).



Scheme 3: Solid phase synthesis for piperazine-triazine library.[41]

By screening the library a selective inhibitor for the Mcl-1/BH3 has been found and the ability of this scaffold to serve as α-helix mimetics has been proven. The most potent inhibitor found contains three phenyl residues at R^1, R^2 and R^3, which are predicted to overlay with the three key residues Val^{220}, Val^{216} and Leu^{213} on the α-helical BH3 peptide by molecular modeling

(Figure 15). The binding affinity was determined by a competitive fluorescent polarization assay in the submicromolar range.[41]

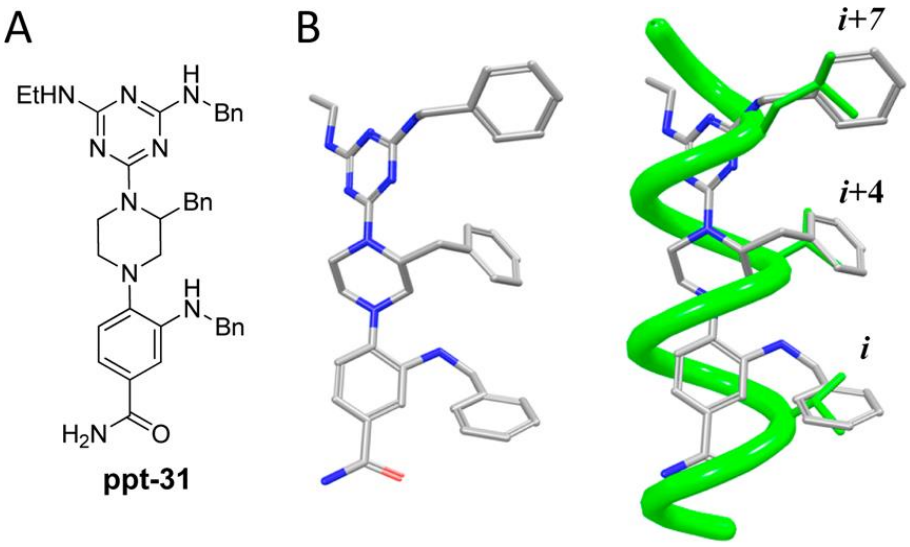


Figure 15: (A) Chemical structure of hit compound, PPT-31. (B) An energy-minimized structure of PPT-31 and overlay with an α-helical peptide, picture taken from Ref. [41].

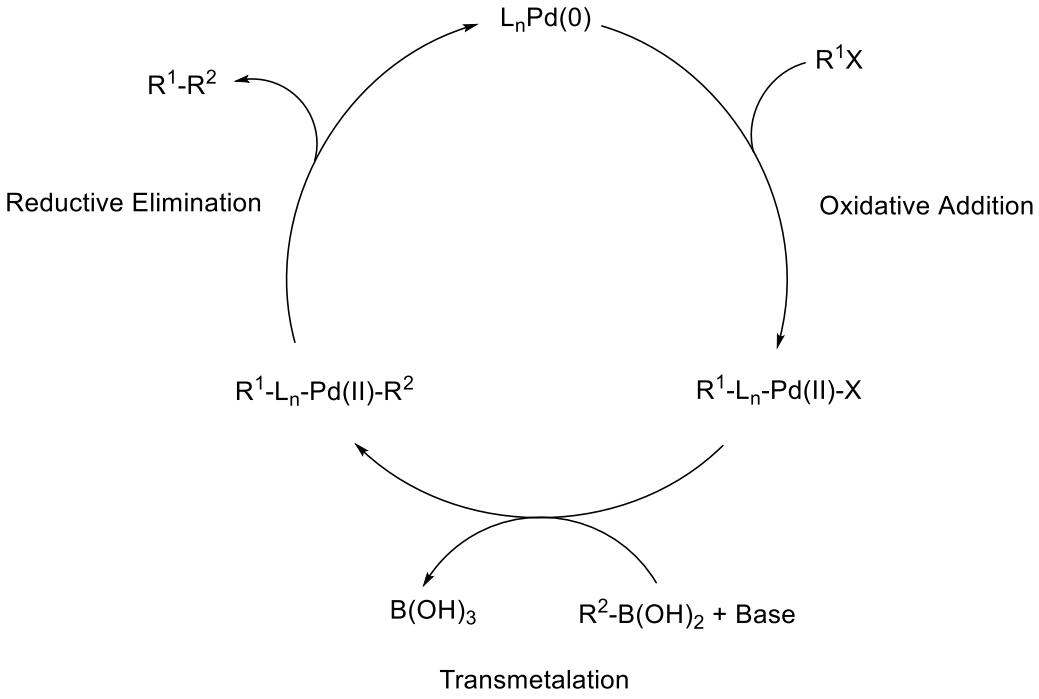
2.5 Palladium-catalyzed cross-coupling reactions

Today cross-coupling reactions are the most straightforward and general method for carbon-carbon bond formation. In the beginning, C-C bond formation was typically achieved by stoichiometric reactions using reactive nucleophiles or pericyclic reactions.[42] 60 years ago only Li- and Mg-organyls were used in cross-coupling, which undergo many side reactions and have a low chemoselectivity. KUMADA *et al*. discovered in 1972 the cross-coupling of GRIGNARD reagents by Ni-catalysis. A first catalytic cycle was described and phosphine ligands were used for the first time, which made the catalytic system widely applicable.[43] In the same year HECK published a protocol for the coupling of iodobenzene with styrene, which was a milestone in further development of numerous palladium-catalyzed reactions. NEGISHI *et al.* improved the reaction developed by KUMADA *et al*. by replacing Mg with Al and later with Zn and Zr. Instead of a Ni-catalyst they used Pd-catalysis.[44] Only a few years later, also B, Sn and Si were used in cross-coupling reactions. Boron-reagents, which are used for SUZUKI-MIYAURA coupling are the most prominent. These improvements were able to overcome side reactions and tolerate many different functional groups. Honoring their pioneering work HECK, NEGISHI and SUZUKI were awarded with the Nobel Prize in 2010.[42] The broad application of palladium-

catalyzed cross-coupling reactions in academia as well as industry demonstrate the importance of their discovery.[45]

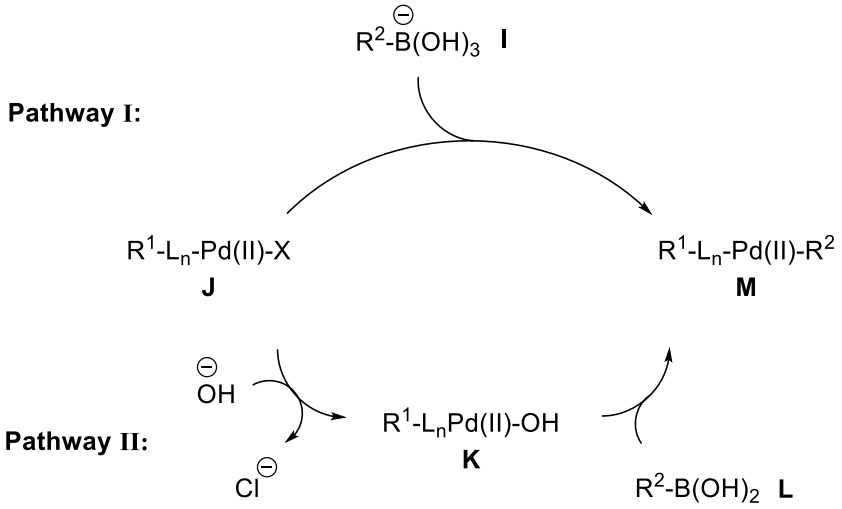
2.5.1 Mechanistic studies towards the SUZUKI-MIYAURA coupling

A general mechanism for palladium-catalyzed cross-coupling reactions can be proposed, which proceeds via three mechanistic key steps: oxidative addition, trans-metalation and reductive elimination (Scheme 4).[46]



Scheme 4: Mechanistic cycle for the SUZUKI cross-coupling reaction.[46]

Especially oxidative addition and reductive elimination were extensively studied and are today well understood. Less attention has been paid towards the understanding of the transmetalation step, but in general two pathways are proposed for that step. The first one suggests nucleophilic attack of a preformed borate **I** to the palladium halide **J** (pathway I). The second one involves the formation of a nucleophilic palladium hydroxo complex **K** and trans-metalation via a neutral boronic acid **L** (Scheme 5).[47] This pathway was originally proposed by SUZUKI and MIYAURA themselves. According to DFT calculations pathway II is energetically more favored.[48]



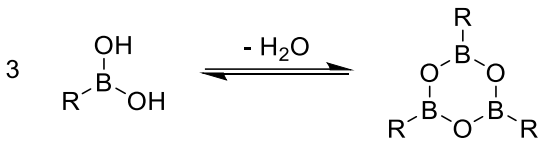
Scheme 5: Two pathways for the key transmetalation step.[46]

In recent years various catalystsystems and ligands were developed to improve the reaction and apply cross-coupling to synthesize more and more complex molecules.[49] General coupling procedures for heterocycles were also described and effective ligands for heterocycles with rather low reactivity were found.[50]

2.5.2 Boron reagents

In the SUZUKI-MIYAURA coupling usually mild reaction conditions can be used and lead to a high functional group tolerance. Organoboron reagents and also the boronic side products formed in the reaction are in general environmentally unproblematic and can be easily removed from the products. Organoboron reagents have the advance of being bench stable and many different protocols have been established for their preparation.[51]

2.5.2.1 Boronic acids



Scheme 6: General structure of boronic acids and entropically favored boroxines.[51]

Boronic acids (Scheme 6) were first used in palladium-catalyzed cross-coupling reactions in 1981, but are still very popular especially for their high atom-economy.[51,52] The primary method for the preparation of boronic acids is via other organometallic reagents, like organolithium- or organomagnesium-species. Thereby the organometallic reagent is reacted

with boric esters ($B(OiPr)_3$ or $B(OMe)_3$) as an electrophile followed by hydrolysis to release the free boronic acid. Since this method proceeds via highly reactive organometallic intermediates, some functional groups are not tolerated.[53,54,55] Boronic acids can also be directly prepared via palladium catalysis similar to the MIYAURA-borylation protocol by using bisboronic acid instead of B_2Pin_2. Further conversion to other boron reagents like esters or BF_3-salts is also possible.[53,56]

2.5.2.2 Boronic esters

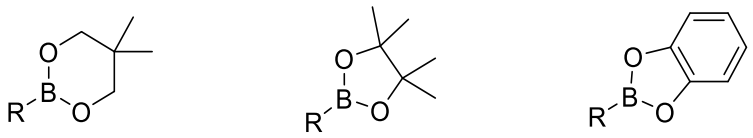
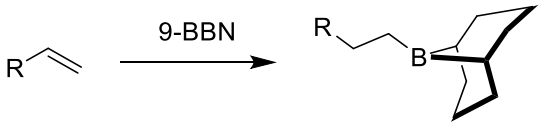


Figure 16: Examples for boronic esters used in SUZUKI-MIYAURA coupling.[57]

Like boronic acids, boronic esters (Figure 16) can be prepared via organometallic species such as GRIGNARD- or organolithium reagents.[58] By using KNOCHEL-type GRIGNARD-chemistry a broader range of functional groups is tolerated.[59] The most popular way to introduce boronic esters is the Pd-catalyzed MIYAURA borylation. This highly functional group tolerant method converts aryl- or alkenyl halides to the corresponding boronic esters using B_2Pin_2 as a boron-source.[60] The transformations proceeds via a mechanism similar to the SUZUKI-MIYAURA cross-coupling involving oxidative addition, trans-metalation and reductive elimination.[61] Also other methods are described in the literature including direct Ir-catalyzed CH-borylation,[62] introduction via radical, metal-free pathway from aryl amines,[63] electrophilic arene borylation[64] or hydroboration with catecholborane.[65]

2.5.2.3 Organoboranes

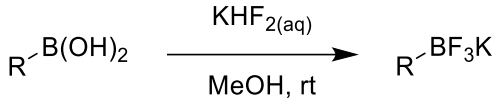


Scheme 7: General example for preparation of organoborones via hydroboration.[55]

Most commonly organoborones are prepared via hydroboration (Scheme 7). This route is also a convenient way to achieve sp^3-hybridised boron-reagents. When alkenes are treated with

$NaBH_4$ and dialkyl boron a *syn*-selective anti-MARKOVNIKOV addition to the olefin occurs and trialkylboranes are formed with the boron on the less hindered position.[55,66]

2.5.2.4 Organotrifluoroborate salts



Scheme 8: General procedure for the synthesis of BF_3K-salts.[67]

BF_3K-salts are generally prepared from boronic acids via treatment with KHF_2 and isolated by precipitation or evaporation of the solvent (Scheme 8).[68] An alternative method for preparation of BF_3K-salts proceeds via KF and tartaric acid and avoids the direct use of KHF_2 and HF.[69] Since prior to the coupling hydrolysis of the BF_3K-salt is required to convert it into a species suitable for transmetalation, water is used as co-solvent in most cases, but even traces of water in not absolute solvents are sufficient for hydrolysis. Using BF_3K-salts is also a convenient method for coupling of base labile substrates since the boron species is already present as boronate.[67,70]

2.5.2.5 MIDA boronates and derivatives

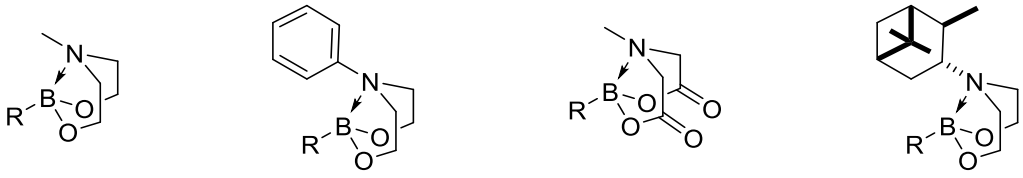


Figure 17: Examples for N-coordinated boronates.[71,72]

A broad range of different *N*-methyliminodiacetic acid (MIDA) boronates (Figure 17) is already commercially available.[73] Nonetheless, some general and convenient procedures for preparation of MIDA boronates have been established. In the first one boronic acids are used as starting material and converted to the corresponding MIDA derivatives by heating under reflux with MIDA ligand and removal of water via DEAN-STARK or drying agents.[74] The second procedure was developed for labile boronic acids and proceeds via a one-pot lithiation/borylation protocol to avoid isolation of the instable boronic acid.[75] As pioneered by BURKE et al. MIDA boronates are used for iterative cross-coupling since the MIDA boronate

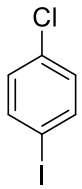
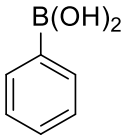
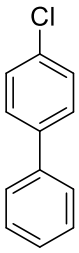
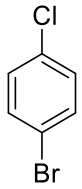
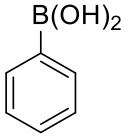
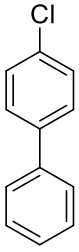
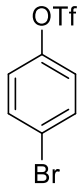
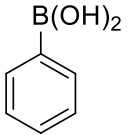
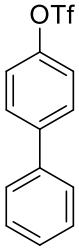
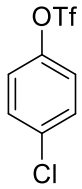
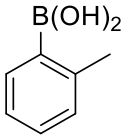
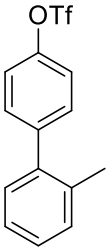
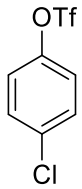
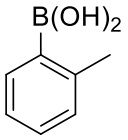
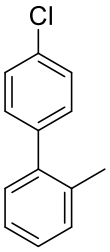
itself does not undergo coupling reactions. Only after hydrolysis in $NaOH_{(aq)}$ the latent functionality is deprotected and the reactive free boronic acid is released.[71,72,76] For unstable boronic acids the so called slow-release cross-coupling was established by BURKE et al. For this procedure, mild bases and water as cosolvent are used to get in situ hydrolysis of MIDA boronates at a slower rate than catalyst turnover.[75]

Also boronates, which are presumed to be environmentally friendly due to reactions in water at RT and low catalyst loadings without ligand can be performed as well as boronamides, which can also be used in iterative cross-coupling.[51]

2.5.3 Chemoselective SUZUKI-MIYAURA cross-coupling

For control of the chemoselectivity of cross-coupling reactions a broad range of new opportunities has been presented. By tuning the catalytic systems high chemoselectivity could be achieved.[77] The rate of oxidative addition is different for carbon-halogen bonds and correlates in general with the order of reactivity of halides and pseudo-halides (I > Br ~ OTf > Cl). Various applications of chemoselective SUZUKI-MIYAURA coupling reactions have been reported.[78,79,80] FU *et al.* were also able to turn the rate of oxidative addition and couple chlorides selectively in presence of triflates, which should react faster under normal conditions.[79] While the selectivity between different halogens is in general very high, it has also been shown that chemoselective control is possible between the same halogens either by substrate- or catalyst-control.[81] In substrate controlled reactions steric and electronic properties of the substrate determine the reaction site. In catalyst-controlled reactions the reaction site can be controlled by switching the catalyst (Table 1).[82]

Table 1: Examples for chemoselective cross-coupling.[79]

Entry	Aryl Halide	Boronic Acid	Product	Conditions[a]	Yield
1				0.5 % $Pd_2(dba)_3$ 1.2 % P(*t*-Bu)$_3$	98 %
2				0.5 % $Pd_2(dba)_3$ 1.2 % P(*t*-Bu)$_3$	97 %
3				0.5 % $Pd_2(dba)_3$ 1.2 % P(*t*-Bu)$_3$	98 %
4				1.5 % $Pd_2(dba)_3$ 3.0 % P(*t*-Bu)$_3$	95 %
5				3.0 % $Pd(OAc)_2$ 6.0 % PCy_3	87 %

[a] Standard conditions: 1.0 eq aryl halide, 1.0 eq boronic acid, 3.0 eq KF, THF, RT

Chemoselectivity within the trans-metalation is mainly achieved by using MIDA-protected boronic acids, which do not undergo cross-coupling reactions until deprotection with mild aqueous bases (Figure 18).[71]

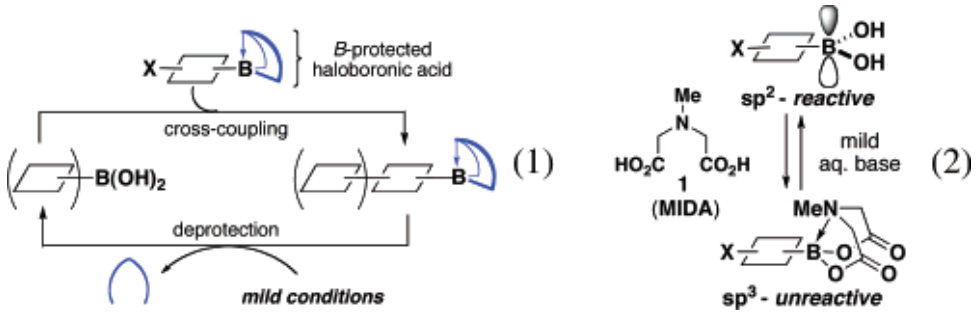


Figure 18: Iterative cross-coupling and MIDA protection/deprotection, picture taken from Ref. [71].

3 Aim of work

By comparing the crystal structure of a poly-alanine α-helix and a substituted teraryl, HAMILTON *et al.* found a well-fitting backbone structure to mimic α-helical peptide chains. (Figure 19). [5,19]

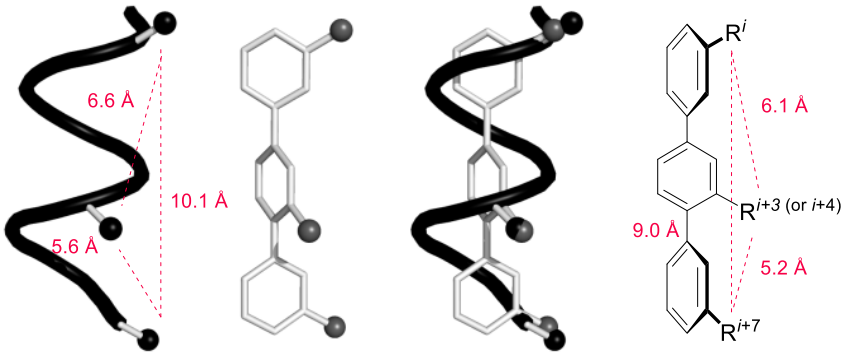


Figure 19: Overlay of a alpha-helix and a teraryl, picture taken from Ref. [24].

Due to several limitations of short peptides as drugs, the use of small-molecules, which are able to adopt the role of the alpha-helical peptide, is desirable. For high efficiency and rapid access to small molecule inhibitors, a short and easy reaction sequence needs to be developed. HAMILTON´s terarylic backbones seem to be promising scaffolds, but time consuming reaction sequences made the synthesis difficult. Since no modular synthetic approach is known for this compound-class and all teraryls were synthesized in a linear fashion the rapid generation of diverse molecules was not possible. The modular synthesis for triaryl amides established by BOGER *et al.* is a powerful synthetic strategy, which provides rapid excess to diverse libraries. Since the building blocks of these molecules are connected via an amide bond they might be easier degraded by peptidases. Teraryls lack this peptide-like connections and should therefore be more stable against fast degradation. In a retrosynthetic approach teraryls can be divided into three single building blocks, which can be connected via C-C-bond formation. Cross-coupling reactions were extensively investigated in the past ten years and are now well established in organic synthesis. To connect the building blocks with each other a robust SUZUKI-MIYAURA cross-coupling protocol should be developed. The ultimate goal will be to find one system for the coupling of all different building blocks containing diverse functional groups.

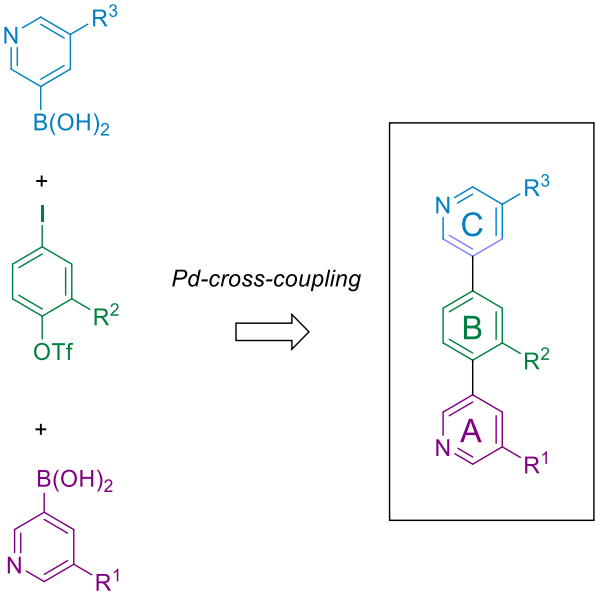


Figure 20: Retro-synthetic approach for teraryl assembly.[83]

By providing two sets of building blocks, teraryls can be assembled in a two-step sequential SUZUKI-MIYAURA coupling procedure (Figure 20). Necessary for this strategy is the central core unit fragment. This kind of building blocks features two leaving groups differentiated by their reactivity in cross-coupling reactions, which should enable a chemoselective teraryl synthesis without using protecting groups.[83] In certain cases unprotected functional groups are not suitable for the use in SUZUKI-MIYAURA coupling, which would make the use of protecting groups for these side chains necessary.

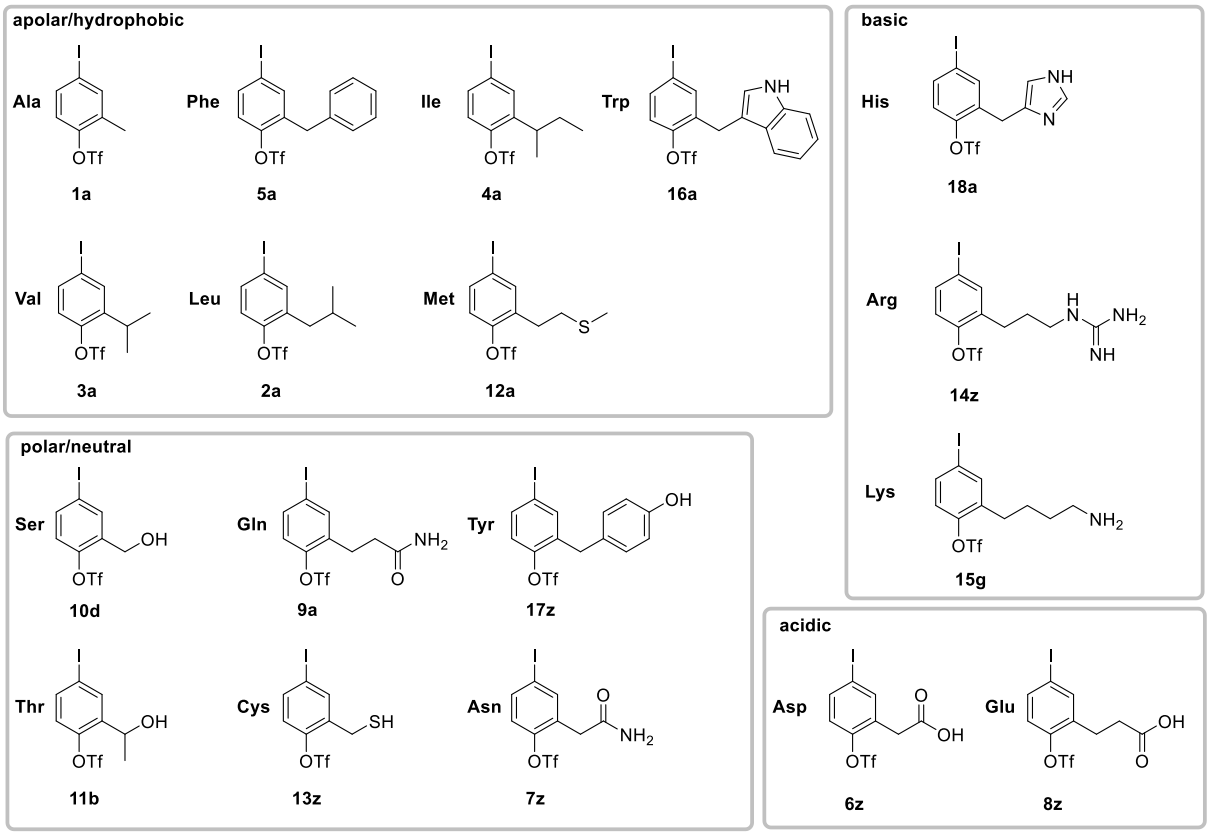


Figure 21: Target molecules for the core unit fragment library.

The second set of building blocks contains a boronic acid derivative, which undergoes the trans-metalation step in the catalytic cycle of cross-coupling reactions. HAMILTON *et al*. used three phenyl rings for their teraryls. These rather unpolar molecules caused solubility issues under physiological conditions, which could be overcome by introducing highly polar functional groups at the terminus of the terphenyls. To avoid additional functional groups it was desirable to make the terphenyl itself more polar and the route of choice was to introduce more polar heterocycles instead of the former used carbocycles. To keep a similar geometry as in terphenyls the six-membered pyridine rings were used. We introduced 3,5-substituted pyridines as building blocks, which allows that in the assembled teraryls the nitrogen is located on the opposite site as the functional groups (Figure 20). It is assumed that as soon as the teryryl interacts with a protein, the backbone containing the nitrogens points into the aqueous media and by the reduced cost of solvation energy the binding to the protein might be improved. Similar to the core unit fragments for some functional groups in the pyridine boronic acid esters protecting groups are required.

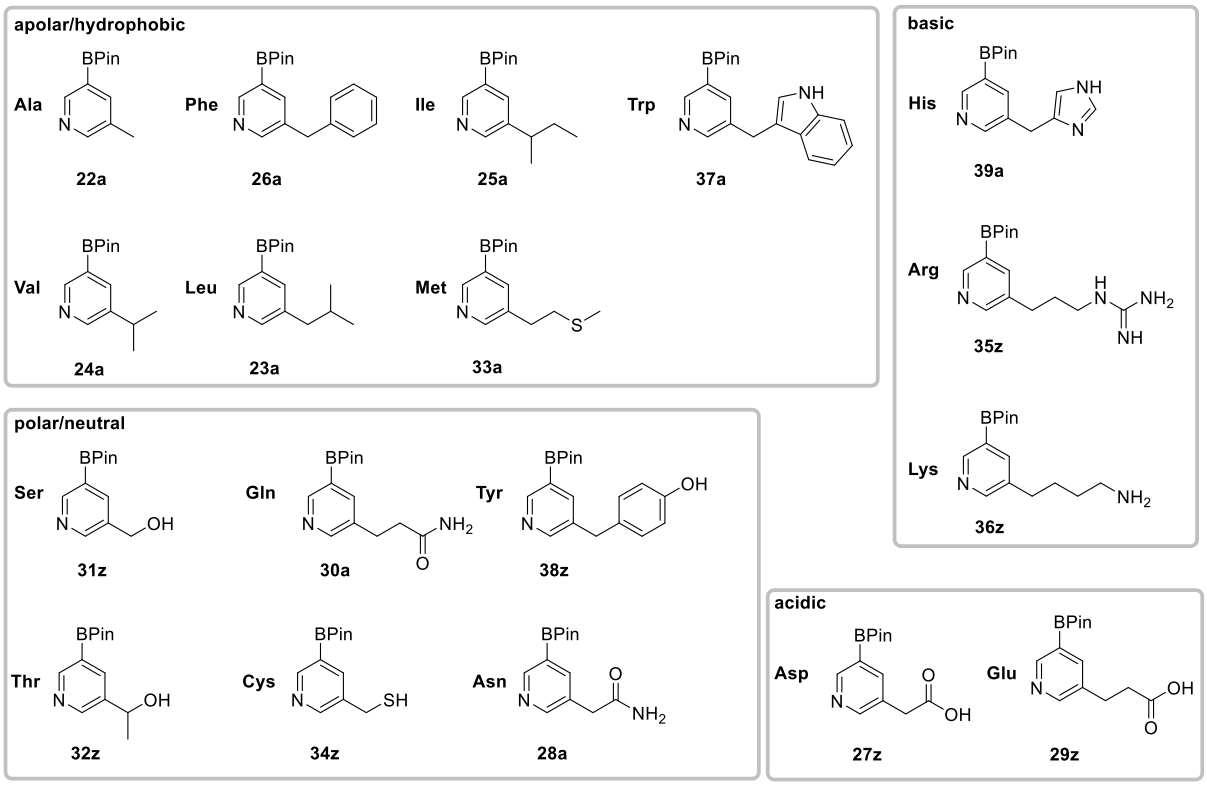


Figure 22: Target molecules for pyridine boronic acid fragment library.

For canonical mimicking of α-helical peptides, the same side chains as occurring in natural amino acids were chosen for the synthesis of a small library of building blocks. In this work short and efficient synthetic routes for core unit fragments as well as pyridine boronic acid building blocks to complete this library should be established. Since some building blocks are needed in large amounts, high yielding and scalable reaction sequences are desired.

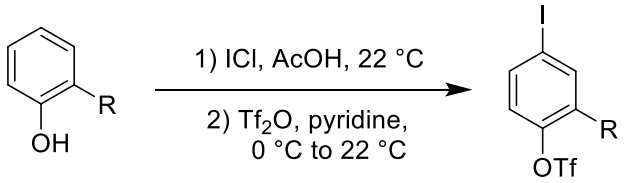
4 Results and Discussion

4.1 Core Unit Fragments

The core unit fragments contain two leaving groups with differentiated reactivity in Pd-catalyzed cross-coupling reactions. As leaving groups were used iodine, which reacts in the first step, followed by the coupling of the second leaving group, an OTf-group, in the second cross-coupling step. A lot of different ortho-substituted phenol derivatives are commercially available and the introduction of an iodine in para-position to a HO-group is a well-established procedure in arene chemistry.[84] Therefore this compound class appeared to be very attractive and provide a great variety of different starting materials, which are well accessible. The side chains of the first set of core unit fragments should contain the same side chains found in natural amino acids relevant for protein-protein-interactions. In the following discussion part they are referred to the common three letter code used in amino acid nomenclature.

4.1.1 Synthesis of Ala-, Val-, Leu-, Ile- , Phe- and Asp-building blocks

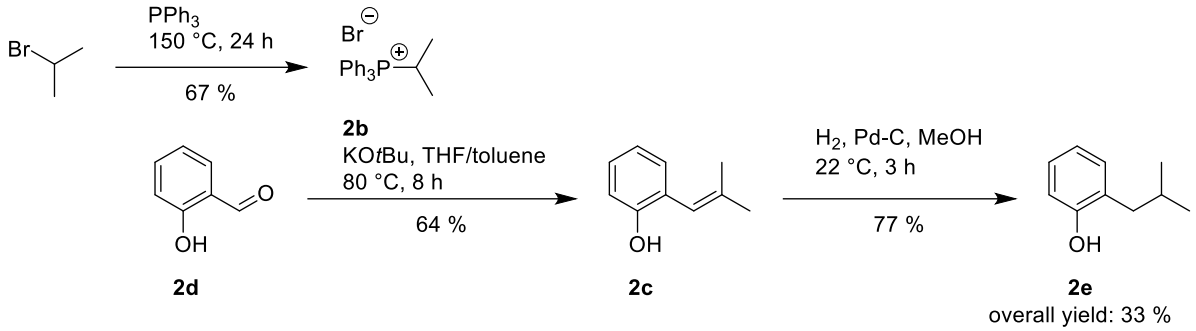
For all building blocks containing an aliphatic side chain and also for the Phe-building block containing an aromatic side chain the same reaction sequence was used.[80] Since all phenol precursors (except for the Leu-building block) were commercially available the desired final building blocks were synthesized in only two steps in high yields. Two well established reaction procedures could be adopted for the preparation of these molecules.[85,86] The introduction of iodine in para-position of an -OH followed by conversion of the -OH to an -OTf-function was performed (Scheme 9).



Scheme 9: General reaction scheme for the synthesis of aliphatic building blocks.[80]

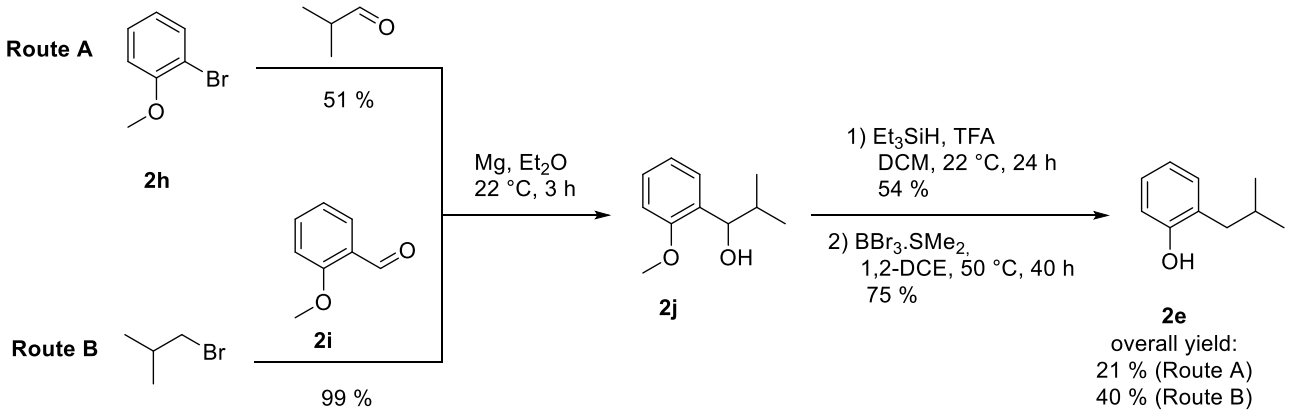
Since the phenol-precursor for the Leu-building block was not commercially available, a short, simple and high yielding reaction sequence had to be established. In the first attempt a WITTIG-reaction was used to introduce the iso-butyl side chain (Scheme 10).[80] Due to the formation of a sensitive destabilized ylide product **2e** was isolated only in poor yields. Also problems in reproducibility occurred since the ylide started to hydrolyze in the presence of traces of water. Especially on larger scales the hygroscopic KO*t*Bu, which was used as base, dragged moisture

into the reaction. A base switch to *n*BuLi did not improve results and only poor yields (~50 %) could be achieved in this case too.



Scheme 10: Synthesis of Leu-building block via WITTIG-reaction.[80]

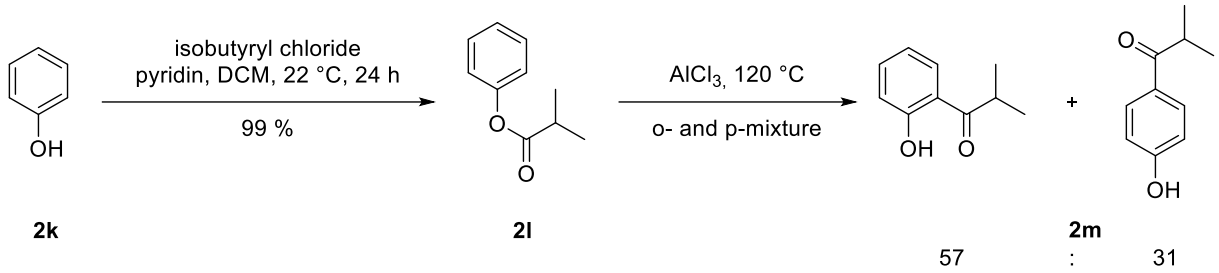
In order to get a scalable reaction route two different GRIGNARD reactions were performed. On the one hand, the GRIGNARD reagent was prepared from Mg and iso-propyl bromide and as electrophile 2-methoxybenzaldehyde (**2i**) was used. On the other hand, the GRIGNARD reagent was prepared from Mg and 2-bromobenzalehyde (**2h**) and isobutyraldehyde was used as electrophile. The GRIGNARD reaction was followed by the removal of the formed HO-function with Et_3SiH and TFA. For this reaction strategy a protecting group for the phenol-function was necessary, because unprotected phenol would quench 1 eq GRIGNARD reagent or would prevent the formation of GRIGNARD reagent in the same molecule. In this case a methyl group was used to protect the phenol. The cleavage of the methoxy-function was performed by BBr_3 in DCM and gave **2e** in 21 % overall yield for Route A and 40 % overall yield for Route B (Scheme 11).



Scheme 11: Synthesis of Leu-building block via GRIGNARD-reaction.

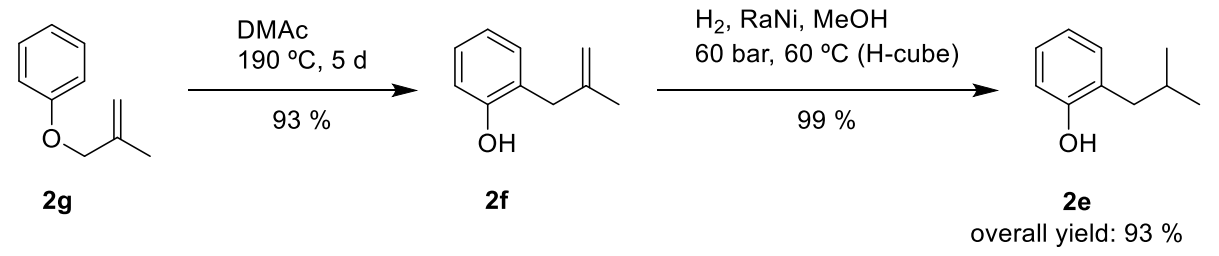
To avoid an inconvenient protecting group strategy another reaction sequence was tested. By using a FRIES rearrangement the corresponding ketone **2m** was prepared, but could only be

isolated as product mixture (Scheme 12). Therefore this strategy was rejected immediately without testing the subsequently planned WOLFF KISHNER- or CLEMMENSEN-reduction.



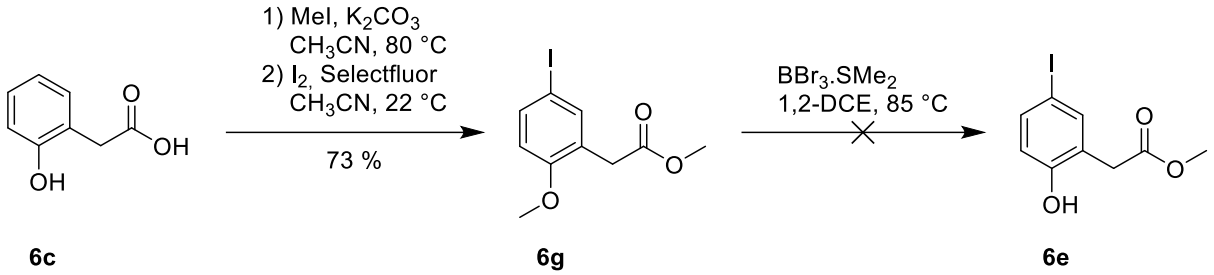
Scheme 12: Attempted synthesis of Leu-building block via FRIES-rearrangement.

A second rearrangement was also tested. The precursor for a CLAISEN rearrangement, methallyl phenyl ether (**2g**), was commercially available. For this type of rearrangement very high temperatures and long reaction times are required. The reaction was performed in a pressure tube and DMF was used as solvent. It was necessary to keep the reaction for 5 days at 190 °C but the reaction mixture became black after one day and when the reaction vessel was opened an amine like smell passed off. Conversion stopped at around 75 % due to thermic decomposition of DMF. Instead of DMF *N*,*N*-dimethyl acetamide (DMAc) was used, which is thermally more stable. The product was isolated by aqueous extraction. The phenol was deprotonated with 2 M NaOH solution and dissolved in the aqueous phase. The very unpolar unreacted starting material **2g** was removed by extraction into pentane. After neutralization the product **2f** was extracted with Et_2O while the highly polar DMAc remained in the aqueous phase. On GC-MS and in NMR isomerization of the double bond to the thermodynamically more stable, higher substituted double bond **2c** was detected, but in the next step the double bond should be hydrogenated so that both isomers **2c** and **2f** lead to the same saturated product **2e**. Hydrogenation was performed with an H-cube flow reactor with Raney-Ni as catalyst. After removing the solvent under reduced pressure pure product **2e** could be isolated. In this reaction sequence only two steps were needed for the synthesis of the desired phenol precursor **2e** for the leucine building block **2a** and it could be isolated in very high overall yields (Scheme 13).



Scheme 13: Synthesis of Leu-building block via CLAISEN-rearrangement.

For the Asp-building block **6a** 2-(2-hydroxyphenyl)acetic acid (**6c**) was used as starting material in the first reaction sequence. A methyl ether and a methyl ester were introduced in one step via alkylation with MeI followed by iodination with Selectfluor® and I_2. When the methyl ether in **6g** was attempted to be cleaved by using $BBr_3.SMe_2$ no product **6e** could be detected (Scheme 14).



Scheme 14: First synthetic route for Asp-core unit fragment.

By NMR and GC-MS analysis the main product was identified as the corresponding lactone **6b** (Figure 23).

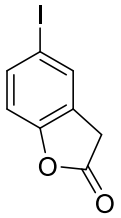
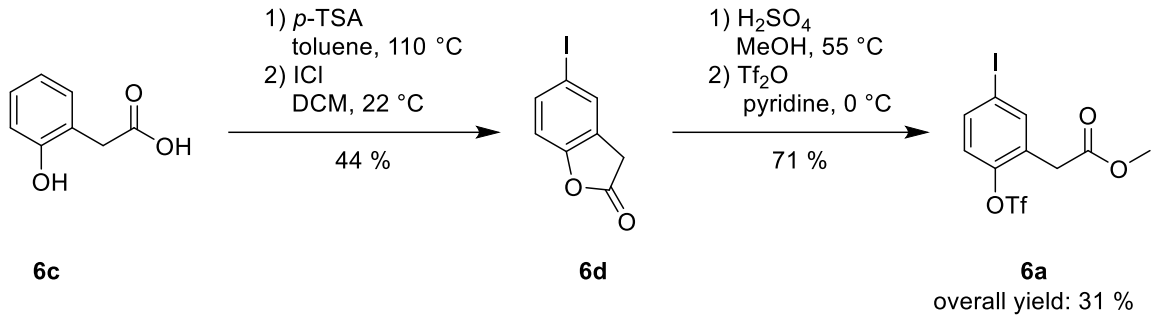


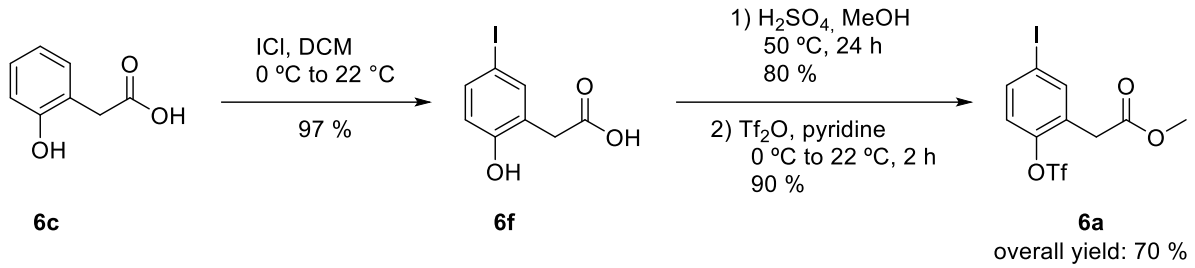
*Figure 23: Isolated main product, which was identified as the corresponding lactone **6d**.*

To avoid the protection and deprotection step the thermodynamically stable lactone **6d** was used as an intermediate in the next reaction route. The lactone was synthesized from 2-(2-hydroxyphenyl)acetic acid (**6c**) via acid catalyzed lactonisation under DEAN-STARK conditions. Then the iodide was introduced, followed by transesterification to the methyl ester and the introduction of the triflate. Product **6a** was isolated in 31 % overall yield (Scheme 15).



Scheme 15: Second reaction route for the synthesis of the Asp-core unit fragment.

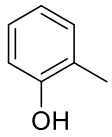
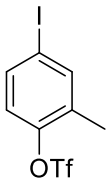
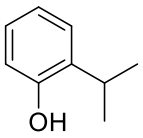
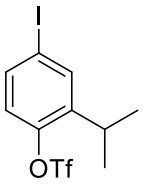
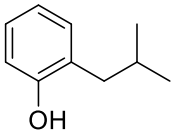
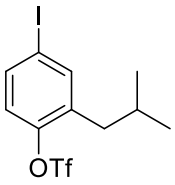
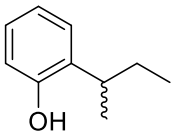
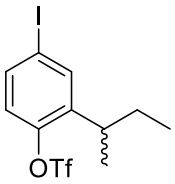
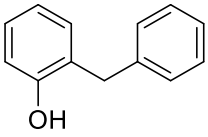
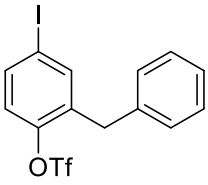
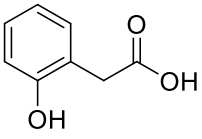
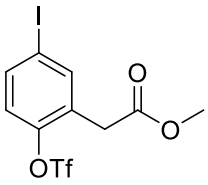
The second reaction route contains still four steps and the final product **6a** was isolated in moderate overall yield. Again a protection and deprotection step was used. For further improvement of the reaction sequence directly 2-(2-hydroxyphenyl)acetic acid (**6c**) was used in the iodination reaction and the same reaction sequence as for the aliphatic core unit fragments was used. The conditions for the introduction of the iodine had to be slightly adjusted and one additional step, the conversion of the free carboxylic acid **6f** to the corresponding methyl ester **6e**, was necessary. Product **6f** from the first step was isolated using a very simple work up procedure. By quenching the reaction with half-saturated Na_2SO_3 solution remaining iodine was reduced to iodide. Due to the high pH-value of the Na_2SO_3 solution the carboxylic acid as well as the HO-function were deprotonated and the product was also extracted into the aqueous phase. Neutralization with 2 M $KHSO_4$ solution led to reprotonation and precipitation of pure product **6f**. For the introduction of the triflate the same conditions as before could be used and **6a** was isolated in 70 % overall yield (Scheme 16).



Scheme 16: Optimized synthesis of Asp-building block.

This synthetic strategy allows the easy and rapid synthesis of all aliphatic building blocks from commercially available starting materials.[80] Also the synthesis of the aromatic Phe-building block and the acidic Asp-building block is possible. The overall yields are given in Table 2.

Table 2: Overview over the synthesized aliphatic core unit building blocks.

Entry	Starting Material	Product	Overall Yield
1	 **1c**	 **1a**	71 %
2	 **3c**	 **3a**	59 %
3	 **2e**	 **2a**	77 %
4	 **4c**	 **4a**	59 %
5	 **5c**	 **5a**	69 %
6	 **6c**	 **6a**	70 %

4.1.2 Synthesis of Ser-, Thr-, Cys-and Gln-building blocks

Another commercially available ortho-substituted phenol derivative is salicylic aldehyde (**2d**). This molecule ia a perfect precursor for the serine building block.[80] In the first step the iodine was introduced. The same reaction conditions as used for the aliphatic building blocks yielded no satisfying conversion of the starting material. Therefore various iodination methods were screened (Table 3).

Table 3: Iodination conditions for salicylic aldehyde.

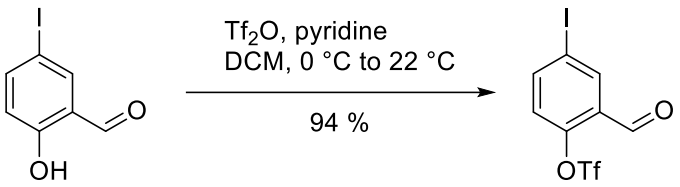
Entry	Reagent	Solvent	Temperature	Time	Conversion[a]
1	ICl	AcOH	22 °C	3 d	45 %
2	ICl	AcOH	22 °C	8 d	94 %[b]
3[87]	ICl	AcOH	40 °C	8 d	96 %[b]
4[88]	I_2, ICl	THF	22 °C	48 h	32 %
5[88]	I_2, ICl	THF	40 °C	24 h	39 %
6[89]	ICl	DCM	0 °C to 22 °C	48 h	91 % (68 % yield)

[a] Conversion according to GC-MS, [b] Additional 0.5 eq ICl were added.

Conversion and yield strongly depend on the quality of ICl. Batches from diverse sources were used and different results were achieved. The best results were achieved with ICl from Acros Organics (A0246742) in DCM at RT (Entry 6). Among the desired para-iodinated salicylic aldehyde also ortho-iodinated and di-iodinated side products were detected. The detected amount differs from reaction to reaction. In some cases also chlorinated product was detected. All by-products could be separated by column chromatography.

Since iodinated salicylic aldehyde **10b** was used as precursor for six building blocks, a large amount of this strategic starting material was synthesized. As column chromatography is not convenient for big batches, recrystallization from cyclohexane was used as alternative purification method. Purification by recrystallization led to slightly lower yields, but was much faster and cheaper than column chromatography on a multigram scale.

The same problem occurred in the second reaction step, the introduction of the triflate. By using standard conditions only 12 % of product **10c** could be isolated. By slightly adapting the conditions the yield could be improved to 94 %. Instead of pyridine DCM was used as solvent and pyridine was only added as stoichiometric base (Scheme 17).[90]

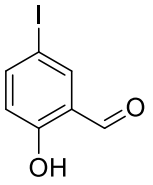
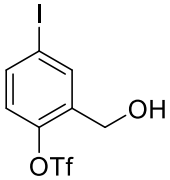


10b **10c**

Scheme 17: Triflation of iodinated salicylic aldehyde.

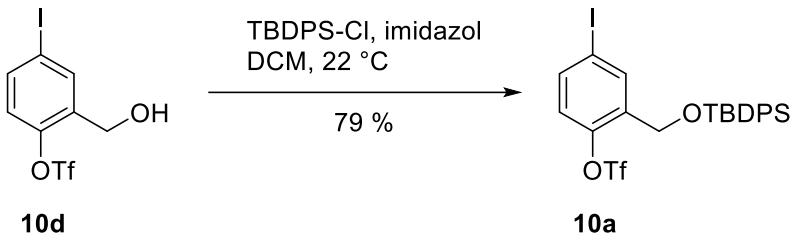
To install the serine side chain the aldehyde had to be reduced to the corresponding hydroxy group. At first sight it seemed very easy to reduce an aldehyde, but due to other functional groups in the molecule $NaBH_4$ was no suitable option. After testing different reducing agents only reduction with DIBAL-H resulted in the desired product. With this reaction set-up quite high yields were achieved (Table 4).

Table 4: Reduction of aldehyde.

Entry	Reagent	Solvent	Temperature	Time	Product[a]
1	$NaBH_4$	DCM	22 °C	24 h	No conversion
2	$NaBH_4$	EtOH	22 °C	24 h	No conversion
3	$NaBH_4$	EtOH	80 °C	24 h	No conversion
4	$NaBH_4$	THF	22 °C	24 h	No conversion
5	$NaBH_4$	THF	80 °C	24 h	No conversion
6	$LiBEt_3H$	THF	22 °C	1 h	 **10b**
7	DIBAL-H	DCM	-78 °C	2 h	 **10d** 94 % yield[b]

[a] According to GC-MS, [b] isolated yield.

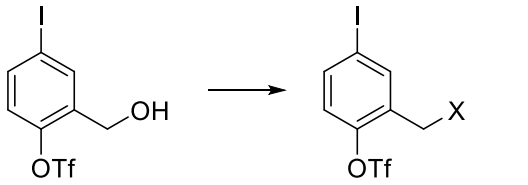
In the last step the free hydroxy function was protected with a silyl protecting group for the SUZUKI-MIYAURA cross-coupling (Scheme 18).



10d **10a**

Scheme 18: TBDPS-prodection of hydroxy function.

For the cysteine building block also alcohol intermediate **10d** could be used. The hydroxy function had to be transformed into a leaving group, which was then converted by a nucleophilic substitution reaction into a thioacetic acid derivative. Various leaving groups were tried, but the results were rather disappointing as the nucleophile was either not successfully introduced or isolated in rather poor yields (Scheme 19, Table 5).



10d **13b-e**
X = -I, -Br, -Cl or -OTf

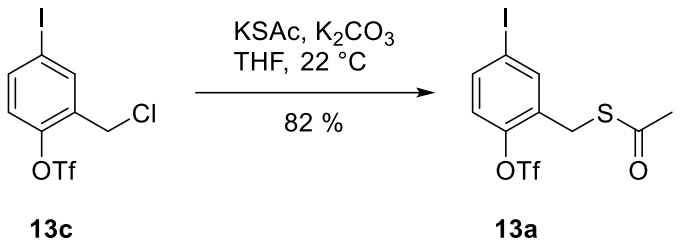
Scheme 19: Conversion of hydroxy function into different leaving groups.

Table 5: Introduction of leaving groups.

Entry	Reagents	Solvent	Temperature	Yield[a]	X
1	$SOBr_2$, Pyridine	Toluene	22 °C	28 %	-Br
2	$SOBr_2$	DCM/DMF	22 °C	38 %	-Br
3	$SOBr_2$	DCM/DMF	22 °C to 50°C	42 %	-Br
4	CBr_4/PPh_3	Et_2O	22 °C	44%	-Br
5	Hexabromoacetone, PPh_3	DCM	30°C	40%	-Br
6	$SOCl_2$	-	0 °C to 22 °C	58 %	-Cl
7	KI, $SOCl_2$ benzotriazole	DCM/DMF	22 °C	crude	-Cl
8	NaI, Amberlyst15	CH_3CN	22 °C	No conversion	
9	Tf_2O, Et_3N	DCM	0°C to 22 °C	Degradation	

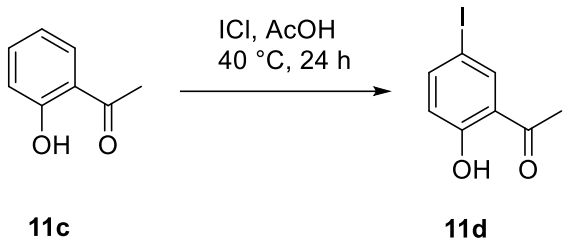
[a] Isolated yield.

The best results were achieved with $SOCl_2$ neat at 22 °C (Entry 6). The low yields in the bromination reactions might be explained by undesired bromination of the ring-structure. These by-products might be less prominent in the chlorination reaction due to less reactive $SOCl_2$ in comparison to $SOBr_2$. According to literature, entry 7 should give iodinated product, but only the chlorinated **13c** was detected.[91] In the last step the chlorine was substituted with thioacetic acid to get a protected thiol-function **13a** (Scheme 20).[92] Thioacetic acid derivatives can undergo cross-coupling reactions by themselves and act as leaving group too. According to literature the 2-methoxy-2-methylpropanethioate group is stable under cross-coupling conditions.[93] This protecting group was not commercially available and had to be synthesized. Cysteine belongs to the rarest amino acid residues occurring in hotspots and therefore a commercially available thio acid was used to prove the concept.



Scheme 20: Introduction of thioacetic acid as protected thiol function.

The first attempt for the synthesis of the threonine building block **11a** was adopted from the serine building block **10a** synthesis. To end up with a secondary alcohol the aldehyde functionality was replaced with a ketone functionality in the starting material (Scheme 21).



Scheme 21: Iodination of threonine precursor.

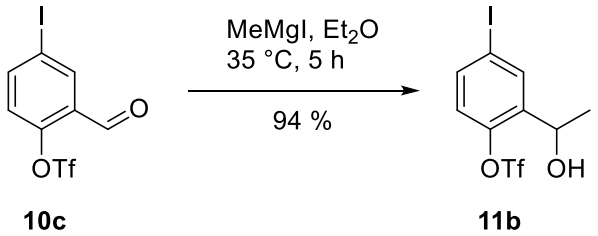
In comparison to salicylic aldehyde, 1-(2-hydroxyphenyl)ethan-1-one was much faster converted. Unfortunately, several by-products were formed. To achieve higher yields other iodination methods were screened (Table 6).

Table 6: Screening of iodination methods.

Entry	Reagent	Solvent	Temperature	Time	Conversion[a]
1	ICl	AcOH	40 °C	3 d	96 % (52 % product)[b]
2	ICl	AcOH	22 °C	48 h	93 % (51 % product)[a]
3[94]	I_2, HIO_3	EtOH/H_2O	100 °C	5 min	94 % (13 % product)

[a] According to GC-MS, [b] additional 1.0 eq ICl were added.

In all three cases too many by-products and unselective iodination was detected. Therefore another approach to generate secondary alcohols was needed. The route of choice was the synthesis via aldehyde **10c** which had already been synthesized (see synthesis of Ser-core unit fragment **10a**). By addition of Methyl-GRIGNARD, the aldehyde was reduced and the corresponding secondary hydroxy function **11b** was formed in one step (Scheme 22). The reaction did not work in THF since the boiling point of MeI is lower than the boiling point of THF. No GRIGNARD reagent was formed at all because MeI was evaporated out of the reaction mixture. When Et_2O was used the Mg-turnings were completely converted to MeMgI and a slightly cloudy, grey solution was formed. It is also possible to use commercially available MeMgBr and run the reaction at room temperature overnight. In both cases ~95 % yield were achieved.

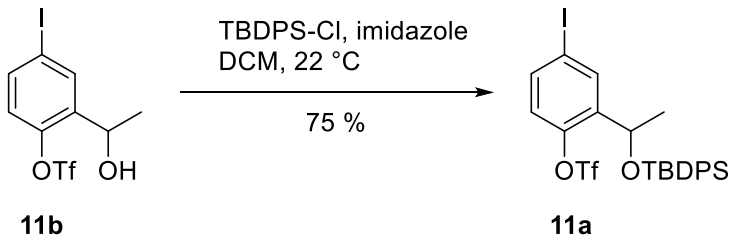


10c **11b**

Scheme 22: Grignard reaction for introducing methyl group.

In comparison to the first route a racemic product mixture was formed whereby the ketone could be reduced enantioselectively to the desired enantiomerically pure secondary alcohol. Many different methods for stereoselective reduction of ketones are established. The racemate formed in the GRIGNARD reaction can still be converted into an enantiomerically pure compound by re-oxidation and stereoselective reduction of the ketone.

Like for the serine building block the final step was the introduction of a silyl protecting group to yield **11a** (Scheme 23).



Scheme 23: Protection of threonine building block.

Aldehyde **10c** could be used again as intermediate for the synthesis of the glutamine building block **9a**. The side chain, containing already the free amide, was introduced via WITTIG reaction. In the last step only the double bond had to be reduced. In this case it was not possible to use H_2 and Pd/C since under these conditions also the iodine will be removed. As an alternative to hydrogenation reactions with Pd a diimide reduction was considered. Diimide transfers two hydrogens to the double bond and is oxidized to N_2 which is the driving force of this reaction. Since diimide itself is very unstable, different precursors (Figure 24) can be used and diimide is released in situ by treatment of the precursors with acid or base.

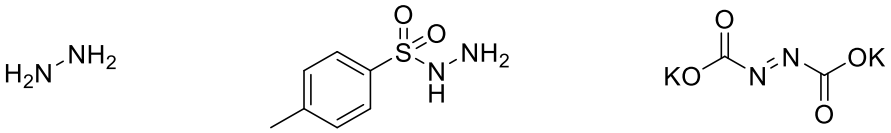


Figure 24: Diimide precursor: hydrazine, p-tosyl hydrazide (p-THA), potassium azadicarboxylate (PADA).

When p-tosyl hydrazide was used, an inseparable mixture of product and degradation products of p-tosyl hydrazide was formed. Therefore another diimide-precursor was needed (Table 7). Using a continuous flow reactor (Figure 25) and hydrazine monohydrate as precursor gives the desired product in ~40 % yield. But drastic conditions led to several by-products and lowering the temperature to incomplete conversion. The flow experiments were performed by Bartholomäus PIEBER from the group of Prof. Oliver KAPPE.[95]

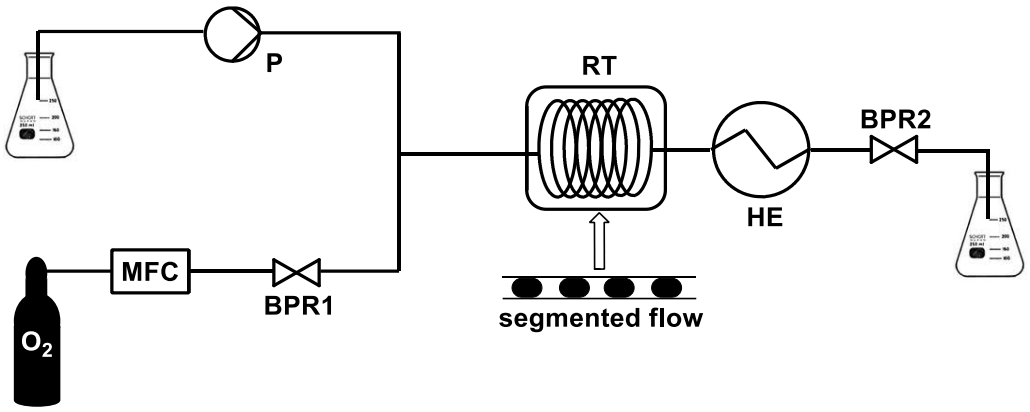


Figure 25: Diimide reduction performed with a continuous flow-reactor[95]

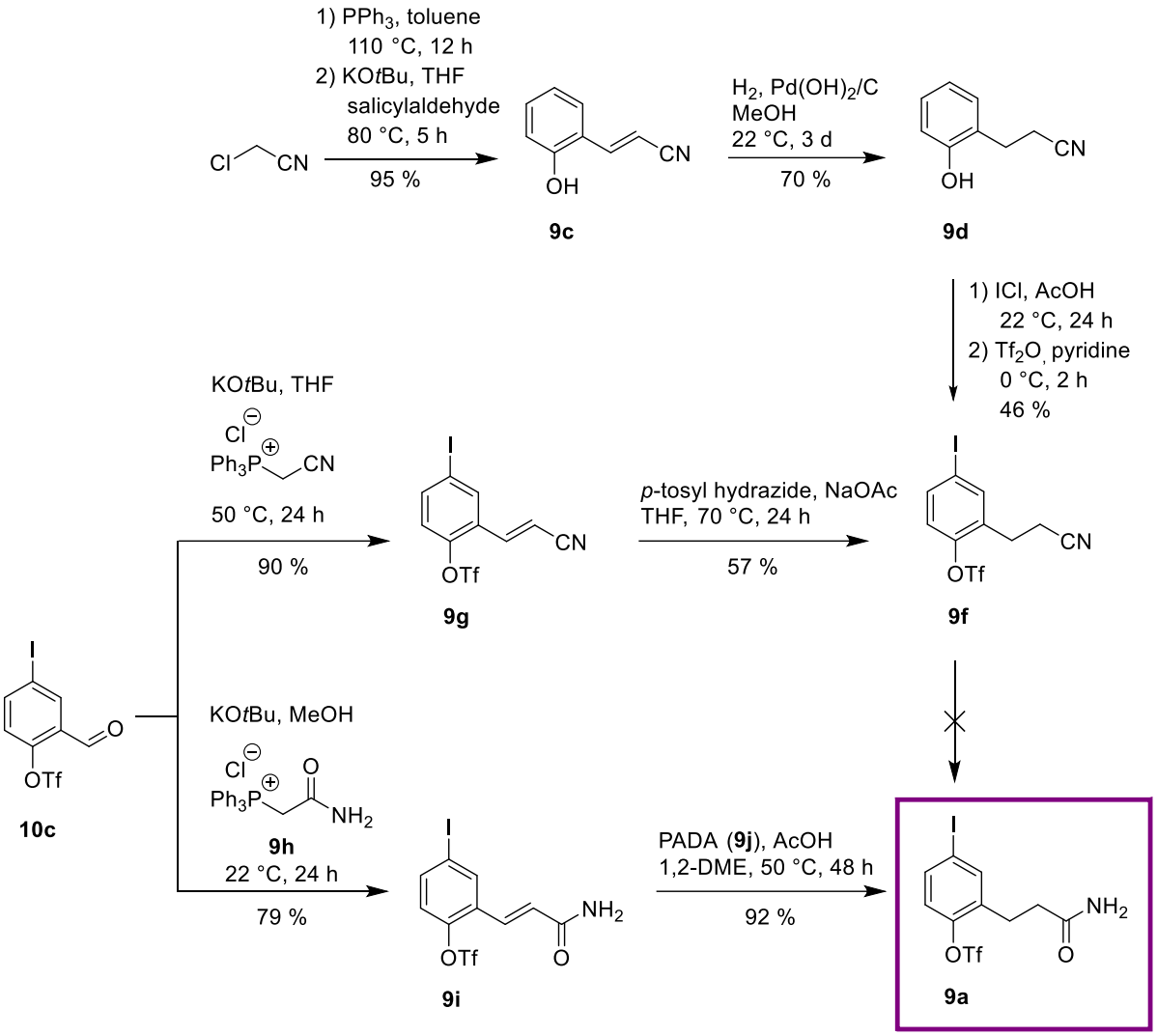
As third diimide-precursor potassium azadicarboxylate was used. When diimide is generated this precursor decomposes under acidic conditions to CO_2 and the corresponding potassium salt of the acid. A big advantage of this precursor is, that no degradation-products of the precursor remain in the reaction and unreacted potassium azadicarboxylate is removed simply by filtration since the salt is insoluble in the organic solvent used for the reaction. It was observed that slightly longer reaction times were necessary in this batch process.

Table 7: Conditions for Diimide reduction.

Entry	Reagents	Additive	Solvent	Temperature	Yield[a]
1	p-THA,	NaOAc	THF	70 °C	Product mixture
2[b]	$N_2H_4.H_2O$	O_2	n-propanol	120 °C	80 %
3[b]	$N_2H_4.H_2O$	O_2	n-propanol	100 °C	86 % (40 %)
4	PADA	HOAc	MeOH	70 °C	23 %
5	PADA	HOAc	1,2-DME	50 °C	99 % (92 %)

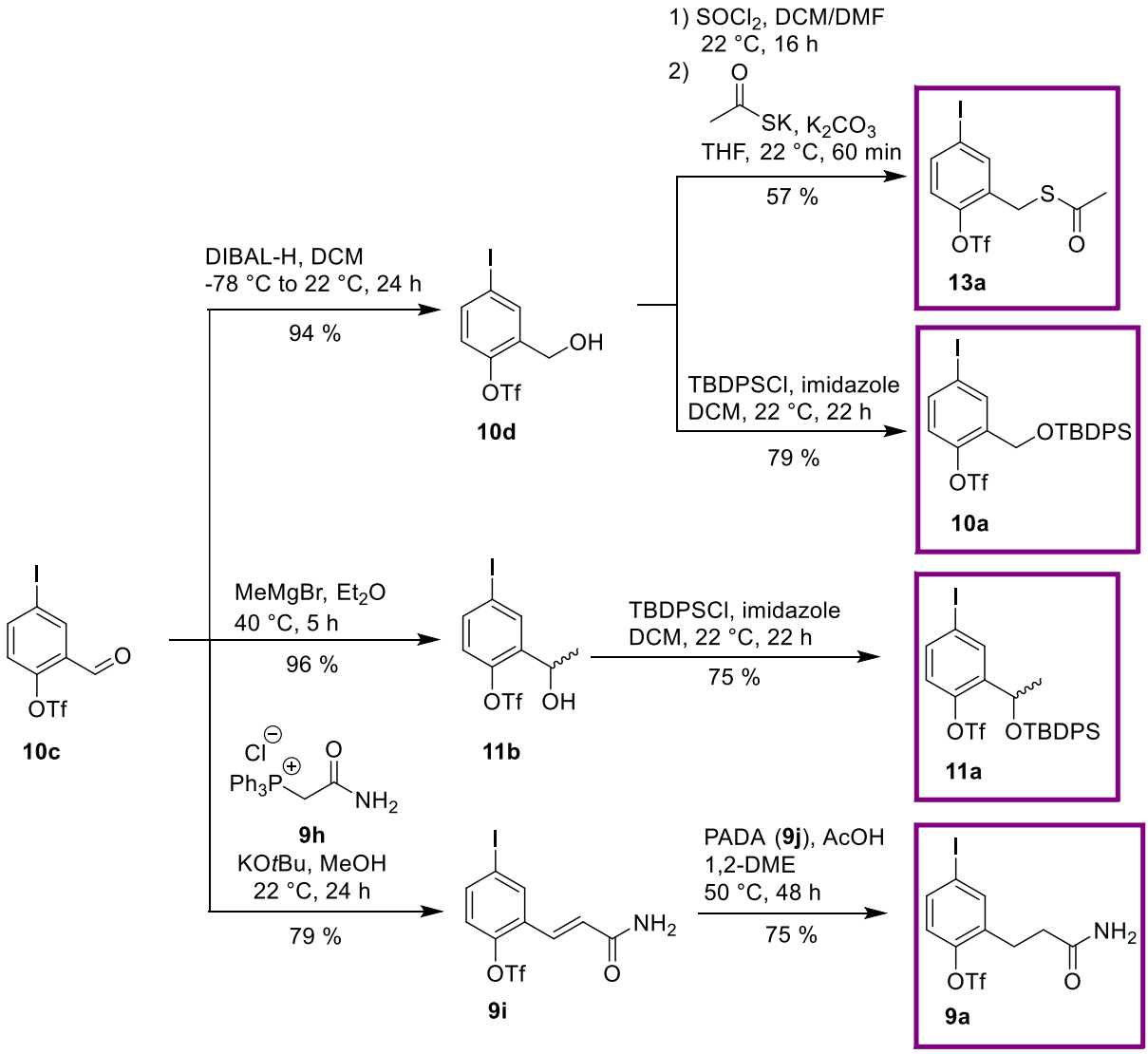
[a] Yield according to HPLC-MS, isolated yields in parenthesis, [b] performed in flow-reactor.

In previous reaction sequences the amide was masked as nitrile, but also introduced via WITTIG reaction.[58] The conversion of the nitrile to the corresponding amide was not possible before teraryl assembly as either the iodide or the triflate were cleaved under the rather harsh conditions required for the conversion of nitriles into amides. In comparison with the former reaction sequence several improvements were achieved through the new reaction route. The most important one is that the free amide can be used and no protecting group or masked form is necessary. Furthermore the general intermediate aldehyde **10c** can be used as precursor which shortens the longest linear reaction sequence from 5 to 4 steps (Scheme 24).



Scheme 24: Comparison between the reaction sequences for the glutamine building block.

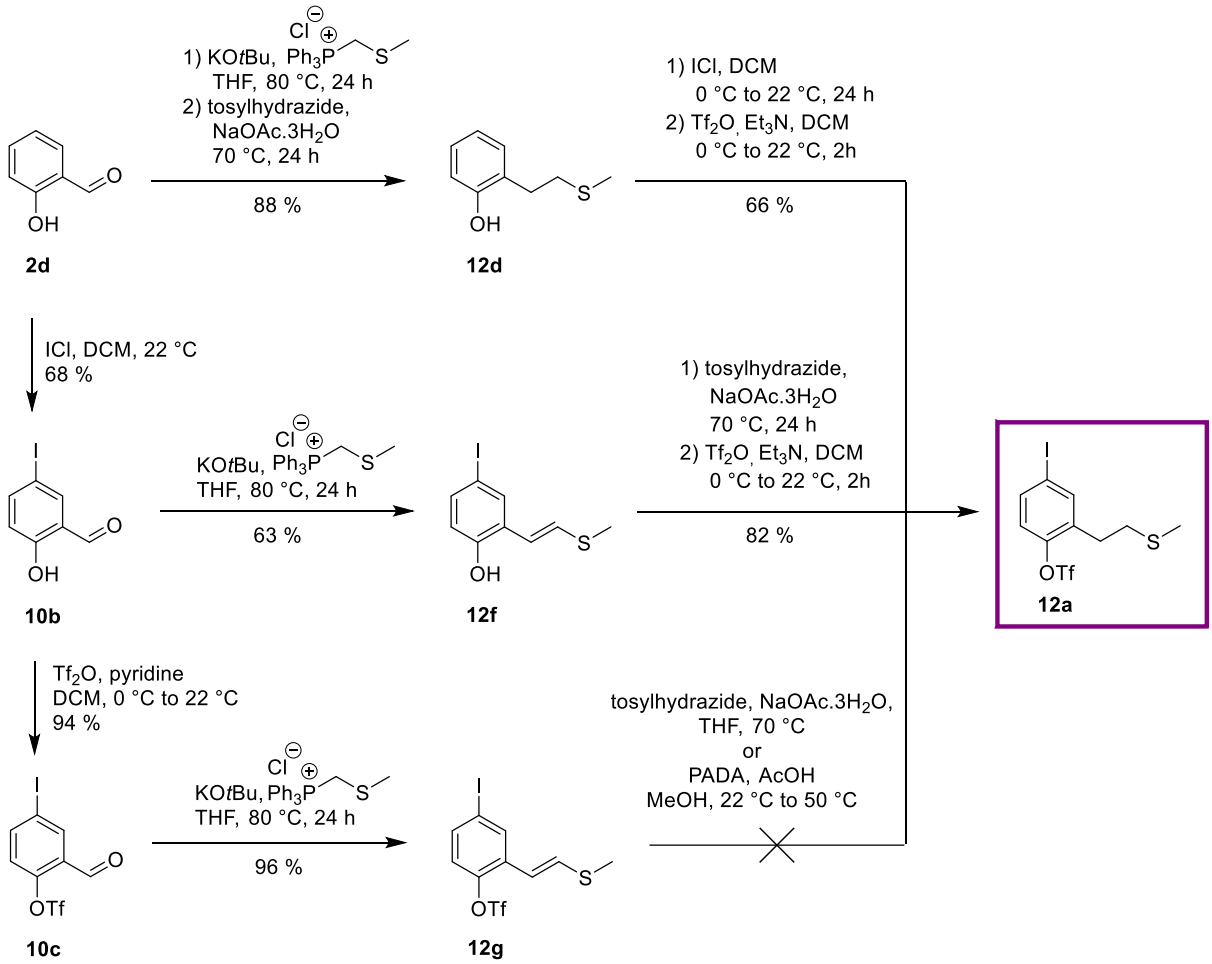
The already iodinated and triflated aldehyde intermediate **10c** was used as precursor for four different building blocks (Scheme 25).[80]



Scheme 25: Overview over the final reaction sequences for Cys-, Ser-, Met- and Gln-building blocks.

4.1.3 Synthesis of Met- and Trp-building blocks

The synthesis of the Met-building block starting from aldehyde **10c** via WITTIG reaction was attempted, but it was not possible to reduce the double bond in presence of all functional groups. Therefore also the routes starting from salicylic aldehyde and 4-iodo salicylic aldehyde (**10b**) were explored.



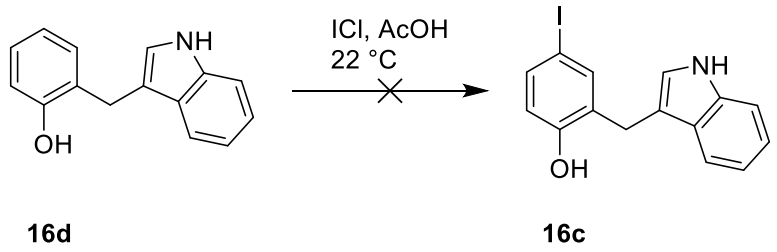
Scheme 26: Tested reaction sequences for the synthesis of Met-building block.

The overall yields in the first and in the second reaction sequence were in the same order of magnitude. It was again necessary to use the diimide reduction on the one hand because iodine was already introduced and would be removed by hydrogenation using Pd and on the other hand due to catalyst poisoning by sulfur. In the second route a higher functionalized precursor was used and the longest linear reaction sequence is also one step shorter. Therefore the second reaction route was selected as route of choice (Scheme 26). Starting from **10b** WITTIG reaction resulted in thioenolether **12f**, which by a sequence of diimide reduction and triflation furnish Met-core unit fragment **12a** in 35 % overall yield.

For the tryptophan building block several methods were tried to introduce a halogen into indole or a protected indole which should be followed by a GRIGNARD reaction or lithiation. The halogenated indoles are very instable and sensitive to light. It was not possible to introduce bromine into the protected indole. Due to the difficult handling of halogenated indoles this route was discarded.

In literature a FRIEDEL-CRAFTS type alkylation of indoles to salicylic alcohols has been described.[96] When this route was used no halogenation of indole or derivatives would be

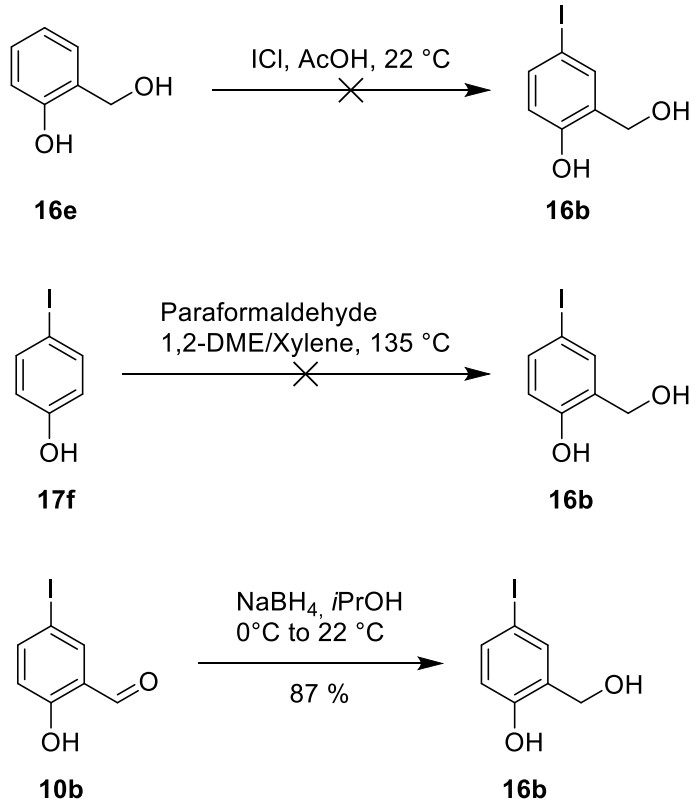
necessary. Unfortunately iodination of 2-((1*H*-indol-3-yl)methyl)phenol (**16d**) resulted in a complex product mixture and the desired product **16c** could not be isolated (Scheme 27).



16d **16c**

*Scheme 27: Iodination of indole-derivative **16d**.*

The reaction sequence was changed and the iodine introduced before the indole was attached. Iodination of salicylic alcohol (**16e**) did not give the desired product and the reaction between formaldehyde and *para*-iodophenol (**17f**) gave no conversion. Again 4-iodosalicylic aldehyde (**10b**) was used as precursor and by reduction of the aldehyde to the corresponding benzylic alcohol the desired product **16b** was achieved (Scheme 28).



16e **16b**

17f **16b**

10b **16b**

Scheme 28: Synthesis of 4-iodosylicylic alcohol.

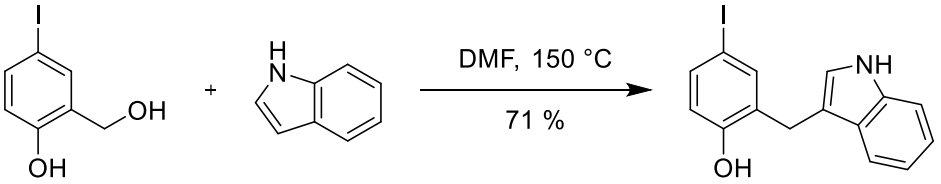
Several reducing agents were tested to find the optimal conditions for the reduction of 4-iodosalicylic aldehyde (Table 8).

*Table 8: Conditions for the reduction of **10b.***

Entry	Reagents	Solvent	Temperature	Yield[a]
1	DIBAL-H	DCM	-78 °C	11 %
2	$BH_3.SMe_2$	THF	22 °C	No product
3	$LiAlH_4$	THF	0 °C to 22 °C	No product
4	$LiBEtH_3$	THF	22 °C	No product
5	$NaBH_4$	EtOH	0 °C to 22 °C	32 %
6	$NaBH_4$	*i*PrOH	0 °C to 22 °C	87 %

[a] Isolated yields.

The FRIEDEL-CRAFTS type alkylation was performed according to literature[96] and 71 % product could be isolated (Scheme 29).



16b **16c**

Scheme 29: Friedel-Crafts type alkylation for the synthesis of Trp-core unit fragment.

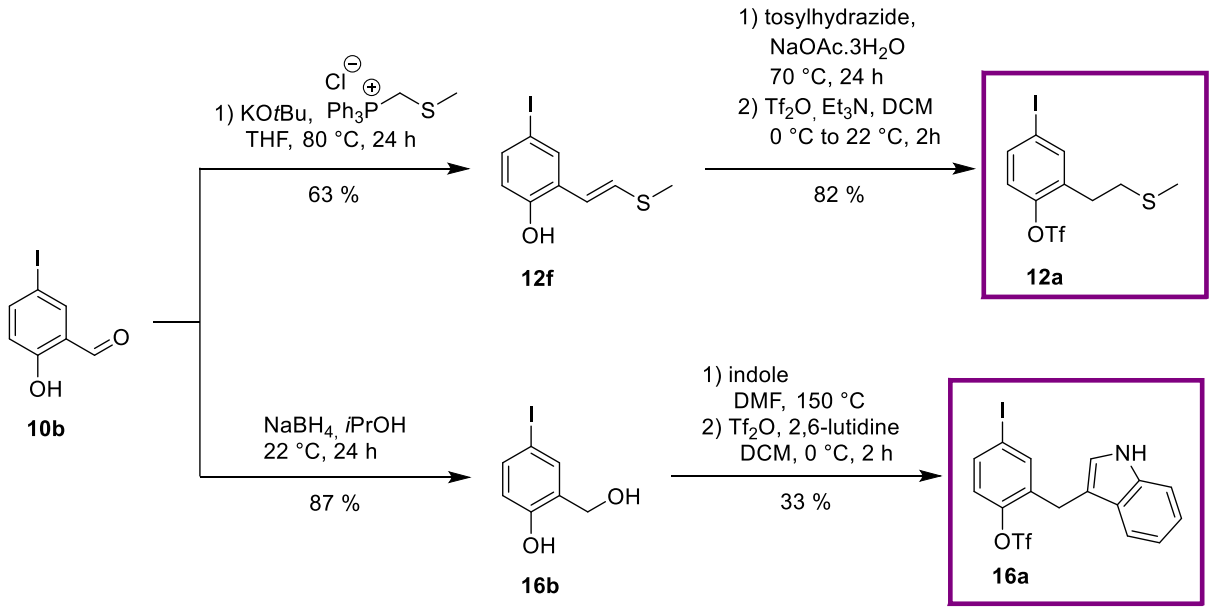
In the final step the triflate was introduced. A procedure for a similar molecule was already reported and in this case 2,6-lutidine was used as base and DCM as solvent.[97] The reaction was run at -78 °C. By using the described conditions only 40 % product could be isolated, but by optimization of the reaction conditions the yield could be improved to 79 %. (Table 9, Entry 7).

*Table 9: Conditions for introducing the triflate-function on **16c.***

Entry	Base	Solvent	Temperature	Yield
1	Pyridine	-	0 °C	TLC
2	Pyridine	DCM	0 °C	TLC
3	Et_3N	DCM	0 °C	TLC
4	DBU	DCM	0 °C	TLC
5	2,6-lutidine	DCM	-78 °C	40 %
6	2,6-lutidine	-	0 °C	No conversion
7	2,6-lutidine	DCM	0 °C	79 %

[a] Isolated yields.

For the Trp- as well as the Met-building block 4-iodosalicylic aldehyde (**10b**) could be used as precursor. The side chains were introduced for Met via WITTIG-reaction followed by diimide reduction and for Trp via FRIEDEL-CRAFTS alkylation followed be introduction of the triflate function (Scheme 30).

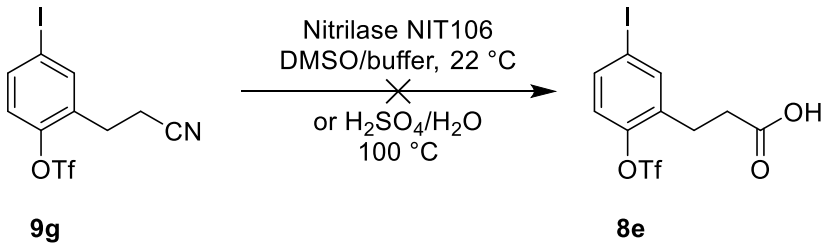


Scheme 30: General reaction route for Met- and Trp-building block.

4.1.4 Synthesis of Glu-, Arg- and Lys-building blocks

The original synthesis route for the Glu-building block developed by our group implied the same nitrile-intermediate **9g** as used for the Gln-building block.[80] The nitrile should then be converted to the corresponding carboxylic acid (**8e**) by enzyme catalysis, but no conversion was detected by HPLC-MS (Scheme 31). Even addition of dithiothreitol, to prevent oxidation of the

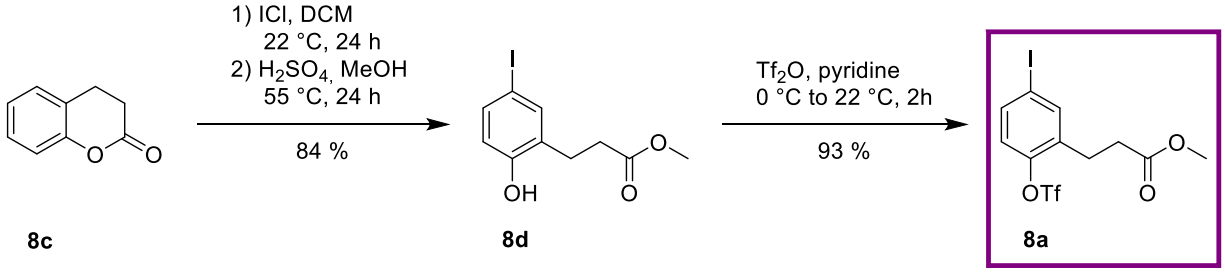
cysteine-rich active site of the enzyme to disulfide, gave no conversion.[98] Chemical methods using H_2SO_4/H_2O did not lead to the carboxylic acid either as only decomposition of the starting material was observed.



9g **8e**

Scheme 31: Conversion of nitrile to corresponding carboxylic acid.

In the second reaction sequence dihydrocoumarine (**8c**) was used as starting material and iodinated in the first step.[99] The lactone **8b** was transesterified to the methyl ester giving access to the phenol, which was converted to the triflate in the last step. The methyl ester is kept as protecting group for SUZUKI-MIYAURA cross-coupling (Scheme 32).

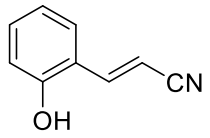
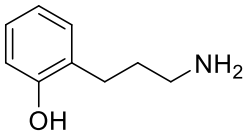
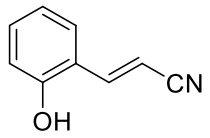
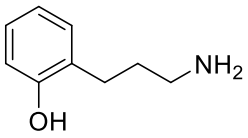
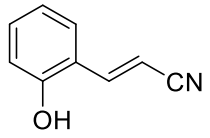
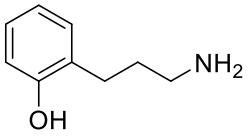
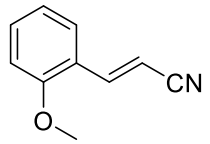
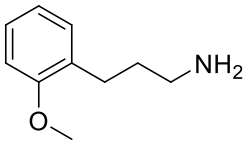
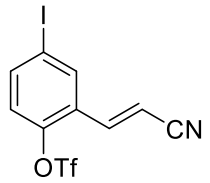
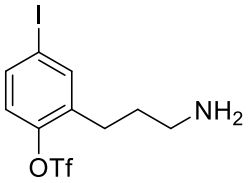
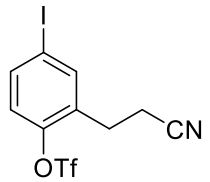
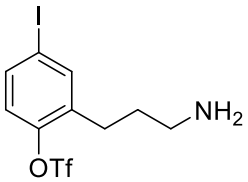
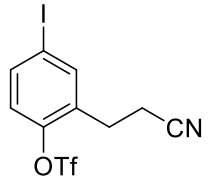
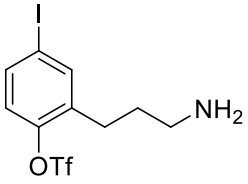


8c **8d** **8a**

Scheme 32: Reaction sequence for Glu-building block.

As precursor for the Arg-building block also a nitrile should be used which can then be reduced to the corresponding amine (Table 10).

*Table 10: Reduction conditions for the preparation of Arg-core unit fragment **14a***

Entry	Starting material[a]	Conditions	Product	Yield[b]
1	 **9c**	Pd/C, 70 °C, 50 bar, EtOH (H-cube)	 **8f**	No conversion
2	 **9c**	Raney-Ni, 70 °C, 50 bar, EtOH (H-cube)	 **8f**	74 %
3	 **9c**	Raney-Ni, 70 °C, 50 bar, MeOH (H-cube)	 **8f**	44 %
4	 **8e**	Raney-Ni, 70 °C, 50 bar, $MeOH/NH_3$ (H-cube)	 **8g**	90 %
5	 **9h**	$LiAlH_4$, Et_2O, 22 °C	 **8h**	45 %
6	 **9g**	$LiAlH_4$, Et_2O, 22 °C	 **8h**	No product
7	 **9g**	DIBAL-H, $NaBH_4$ THF, -78 °C	 **8h**	54 %

[a] Synthesized via WITTIG-reaction (see Gln-core unit fragment **9a**), [b] isolated yields.

Entries 1-3 were not followed up because they could not be successfully iodinated. Rather low yields in entries 2 and 3 are caused by side reactions during the reduction. By adding aqueous ammonia (entry 4) the side reactions could be prevented and only the desired amine was formed. In this case iodination with Selectfluor® and I_2 gave selective iodination, but cleavage of the methoxy-group led to partial cleavage of the iodine and resulted in complex, hardly separable product mixtures. In entries 5-7 relatively harsh reduction conditions are needed and many by-products like the dehalogenated substrate were observed.

Milder reaction conditions could be used for reducing an ester. The Glu-building block was reduced to the corresponding alcohol **14b**. Via MITSUNOBU-STAUDINGER sequence the hydroxy group was converted to the corresponding amine. The intermediate azide was not isolated and the amine was used without further purification in the guanylation reaction. The desired Arg-building block **14a** was isolated in 80 % yield over 3 steps starting from the reduced Glu-building block **14b**. For the guanylation reaction two different reagents were used leading to isolated yields in the same range (Figure 26).

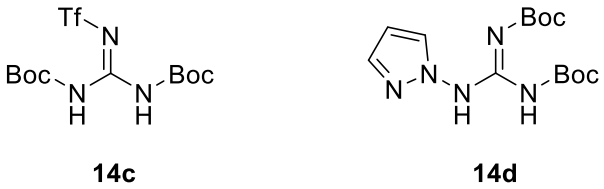
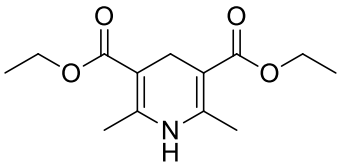


Figure 26: Guanylating reagents.

The triflate-containing reagent is not commercially available and had to be synthesized in a one-step procedure starting from 1,3-bis(*tert*-butoxycarbonyl)guanidine **14e**, therefore reagent **14d** was used for the scaled up procdure of the Arg-building block **14a**.[100,101]

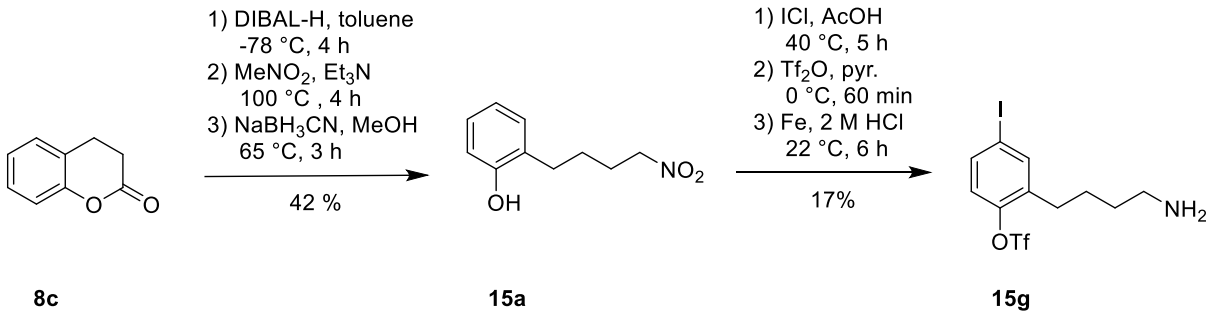
The first route for the synthesis of the Lys-building block involved a HENRY-reaction and started from dihydrocoumarine (**8c**), which was reduced to the corresponding lactole **15b**. Since the lactole and the open chain aldehyde are in an equilibrium, nitromethane can react with the aldehyde shifting the equilibrium again and allow full conversion of lactole **15b** (Scheme 33). According to GC-MS the elimination product was isolated, but NMR showed still a molecule containing a hydroxy function (thermal elimination in GC-inlet). Therefore reduction with hydrogen and Pd failed and another method to remove the hydroxy-group had to be found (Table 11).

Table 11: Reaction conditions for removing the hydroxy function.

Entry	Reagents	Solvent	Temperature	Conversion[a]
1	$NaBH_3CN$	MeOH	22 °C	No conversion
2	$NaBH_3CN$	MeOH	70 °C	> 99 %
3	$NaBH_4$	CH_3CN	0 °C	No conversion
4	$NaBH_4$	CH_3CN	22 °C	71 %
5	$NaBH_4$, SiO_2	DCM/*i*PrOH	22 °C	No conversion
6	$NaBH_4$, SiO_2	DCM/*i*PrOH	70 °C	5 %
7		H_2O	100 °C	No conversion

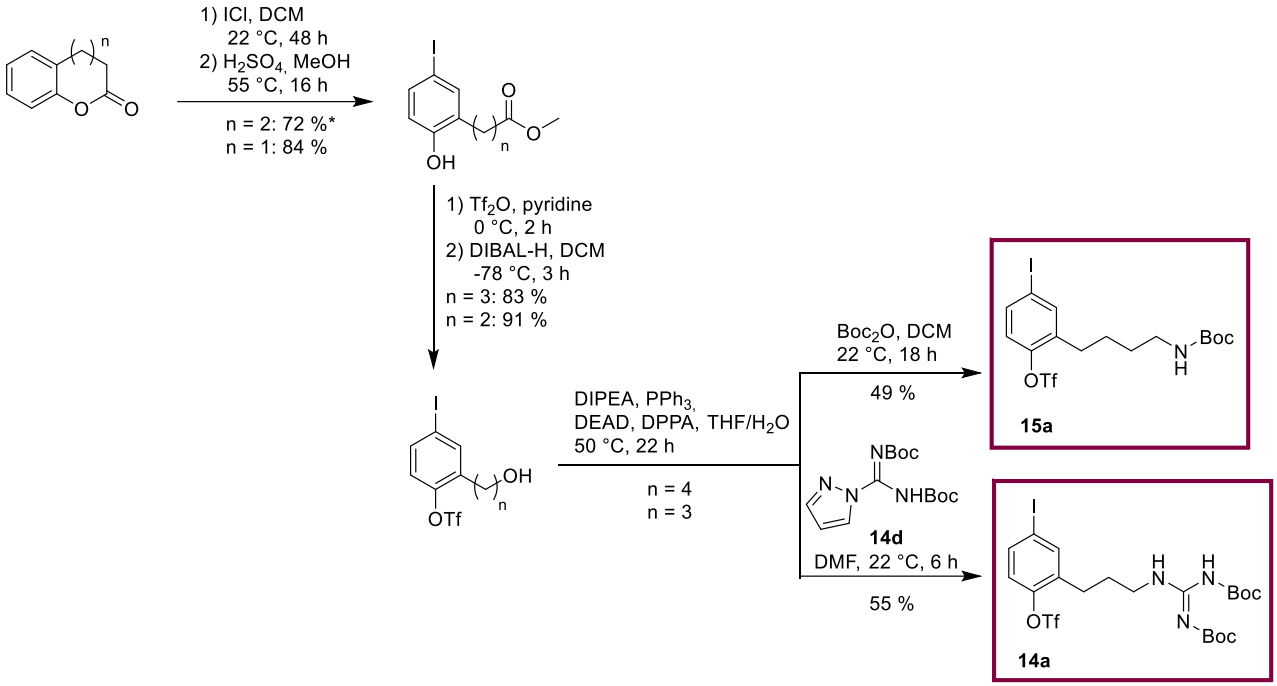
[a] According to GC-MS.

The best results were achieved by using $NaBH_3CN$ in MeOH under reflux temperature, but the isolated yield was only 60 %. Iodination and introduction of the triflate function worked straightforward according to already established procedures. In the last step the nitro-group was reduced to the corresponding amine **15g** via Sn and acetic acid, but elevated temperatures were necessary to achieve full conversion (80 °C). Therefore, Fe in 2 M aqueous HCl was tested as an alternative and full conversion was detected after stirring at RT for 4 h.



Scheme 33: First route for the synthesis of Lys-core unit fragment.

A long linear reaction sequence and a low overall yield made an improved reaction route necessary (Scheme 33). As good results had been achieved with the MITSUNOBU-STAUDINGER sequence applied for the synthesis of the Arg-building block **14a**, the same sequence was used for the synthesis of the Lys-building block **15a** starting from the 7-membered lactone **15h** (Scheme *34*). The lactone was synthesized from α-tetralone (**15i**) via BAEYER-VILLIGER oxidation[102] and in the final step the amine was simply Boc-protected.

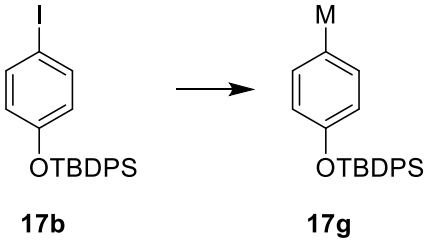


* for n = 2 the seven-membered lactone was synthesized via Baeyer-Villiger oxidation from tetralone

Scheme 34: Final reaction routes for Lys- and Arg-core unit fragment.

4.1.5 Synthesis of Tyr- and His-building blocks

The introduction of the Tyr-side chain was accomplished by nucleophilic attack of a metal-organic reagent at a carbonyl-compound. The phenol was protected by a silyl-protecting group. The very stable TBDPS-group was used, which can be easily removed after teraryl-coupling under mild conditions using fluoride. The TBDPS-group donates electrons to the aromatic ring and generates an electron rich system. Therefore insertion of Mg into the Br-C and also the I-C bond was not possible. Metall-halogen exchange with different Grignard reagents or *n*BuLi was very slow. *t*BuLi gave the best results to ensure complete metal-halogen exchange in a reasonable time without further optimization (Scheme 35, Table 12).



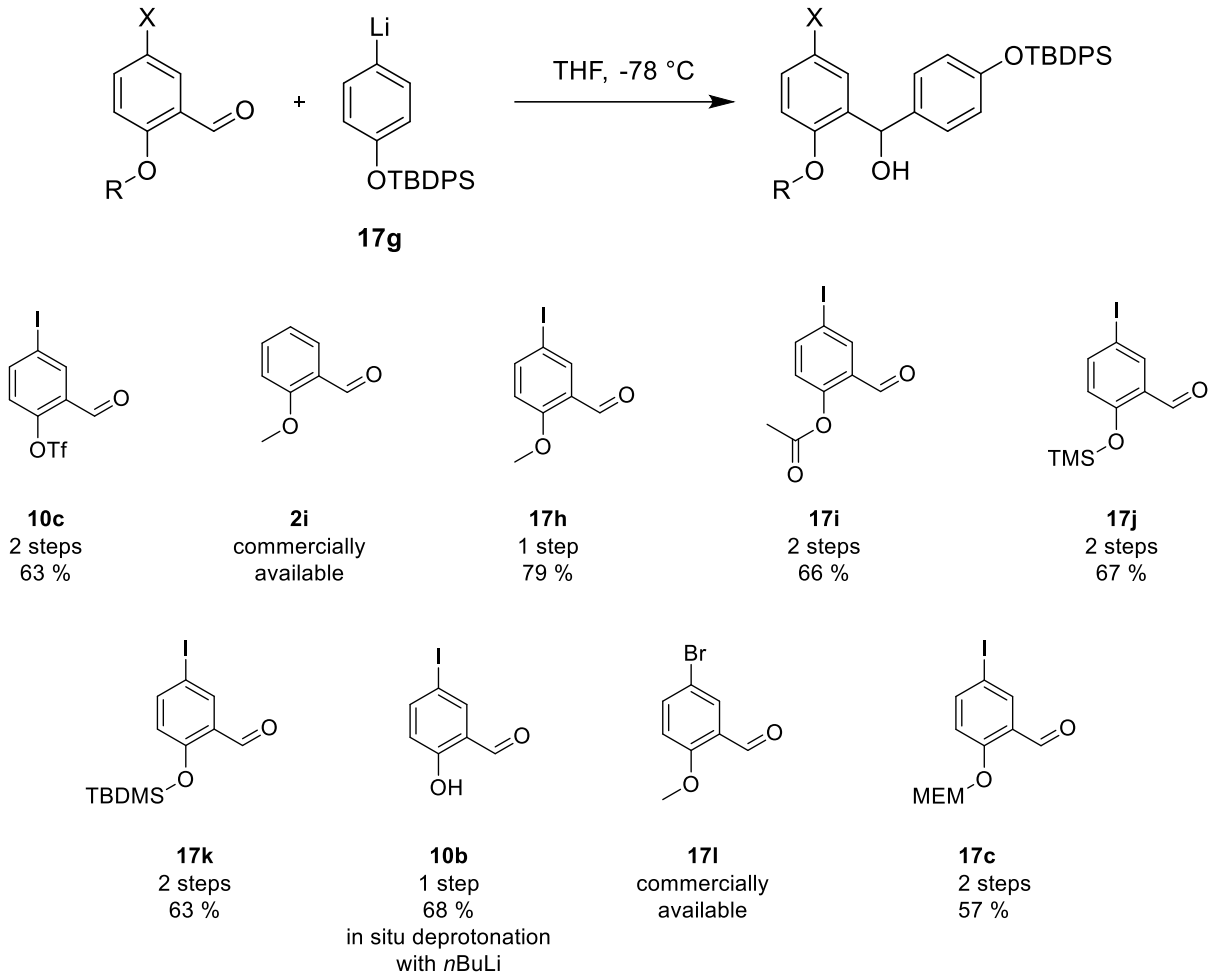
*Scheme 35: Formation of metal-organic reagent for the synthesis of Tyr-building block **17a**.*

*Table 12: Conditions for the metal-halogen exchange of **17b**.*

Entry	Reagent	Solvent	Temperature	Time	Conversion[a]
1	Mg	Et_2O	22 °C to 50 °C	2 h	No conversion
2	Mg	THF	22 °C to 70 °C	2 h	No conversion
3	EtMgBr	DCM	22 °C	2 h	2 %
4	EtMgBr	Et_2O	22 °C	2 h	5 %
5	EtMgBr	THF	22 °C	2 h	49 %
6	EtMgBr	1,4-Dioxane	22 °C	2 h	18 %
7	EtMgBr.LiCl	THF	22 °C	30 min	> 99 %
8	*t*BuMgBr	THF	22 °C	30 min	No conversion
9	*i*PrMgCl.LiCl	THF	-78 °C	2 h	60 %
10	*n*BuLi	THF	-78 °C	1 h	70 %
11	*t*BuLi	THF	-78 °C	20 min	> 99 %

[a] According to GC-MS.

With the lithium-organyl in hands the conversion with different carbonyl compounds were tested (Scheme 36, Table 13).



Scheme 36: General reaction scheme for the lithiation reaction and different carbonyl derivatives.

*Table 13: Isolated yields for the lithiation reaction with **17g**.*

Entry	Starting material	X	R	Yield[a]
1	**10c**	I	Tf	decomposition
2	**2i**	H	Me	91 % [b]
3	**17h**	I	Me	51 %
4	**17i**	I	COMe	80 % [c,d]
5	**17j**	I	TMS	decomposition
6	**17k**	I	TBS	23 %
7	**10b**	I	Li	decomposition
8	**17k**	Br	Me	99 %
9	**17c**	I	MEM	83 %

[a] Isolated yields, [b] product dimerizes, [c] cleavage of methyl-ester via addition of 3.0 eq MeMgBr, [d] benzylic-hydroxy function oxidizes to ketone.

After isolation of the reaction product from entry 3 double peaks looking like doublets were detected in NMR and after a HRMS analysis the molecule was identified as ether-bridged dimer **17m** (Figure 27). Interestingly, this dimer was observed only in this special case. All other products were isolated as monomers with free benzylic hydroxy functions. The iodine in presence with the carbonyl group was not affected due to the faster nucleophilic attack than metal-halogen exchange and accurate 1:1 stoichiometry.

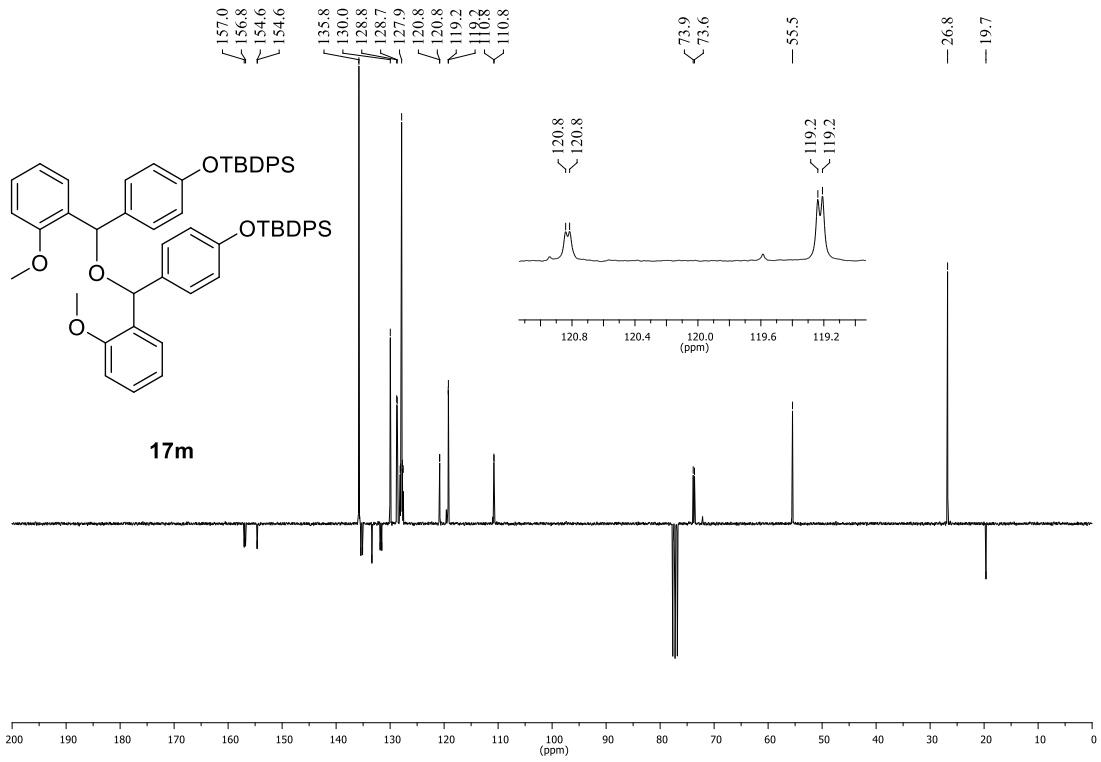
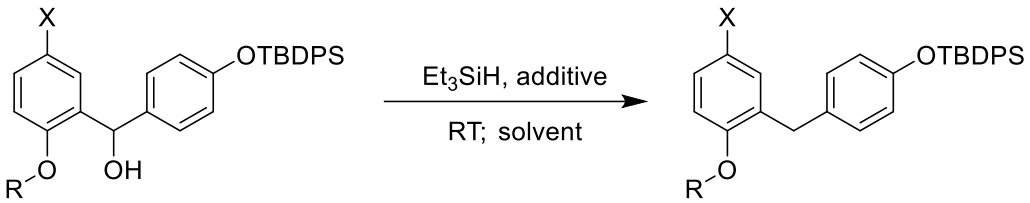


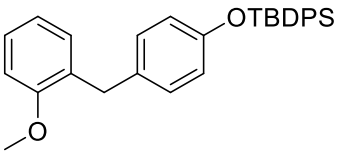
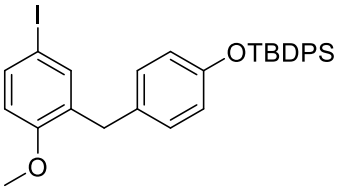
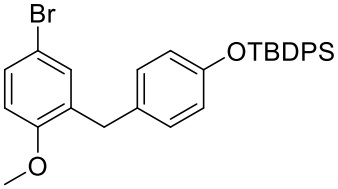
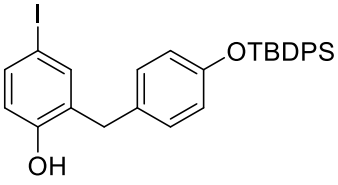
*Figure 27: Structure of **17m** identified by HRMS and corresponding ^{13}C-APT-NMR-spectrum.*

After introduction of the Tyr-side chain the benzylic hydroxy-function formed during the reaction of lithium-organyls with aldehydes had to be removed. While a two-step procedure via chlorination with $SOCl_2$ and dechlorination with Sn and acetic acid had already used been used within this project,[58] two more convenient one-step procedures were explored (Scheme 37, Table 14). The first one uses $PdCl_2$ and Et_3SiH which has the same disadvantage like the two step procedure with Sn, as it will remove the hydroxyl-function as well as the iodine.[103] This procedure could be used for compounds without halogens. The second one was a metal-free procedure with Et_3SiH and TFA.



Scheme 37: Removal of the hydroxy function formed during lithiation reaction.

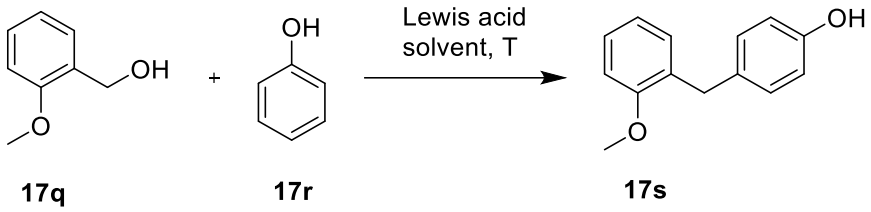
Table 14: Conditions for the removal of the hydroxyl function.

Entry	X	R	Additive	Solvent	Yield[a]	Product
1	H	Me	$PdCl_2$	EtOH	Decomposition	-
2	H	Me	TFA	DCM	99 %	 **17n**
3	I	Me	TFA	DCM	99 %	 **17o**
4	I	H	TFA	DCM	No conversion	-
5	I	TBS	TFA	DCM	Decomposition	-
6	Br	Me	TFA	DCM	99 %	 **17p**
7	I	Mem	TFA	DCM	68 %	 **17e**

[a] Isolated yields.

Another possibility for the introduction of the side chain was a FRIEDEL-CRAFTS alkylation.[104] The advantage of this method is that the dehydroxylation step would be obsolete, but it is known that FRIEDEL-CRAFTS alkylation reactions are not selective and are prone to overalkylation.

Therefore different conditions were screened to find suitable conditions with the *p*-alkylated product as main product (Scheme 38, Table 15, Table 16 Table 17).



Scheme 38: General reaction scheme for the screening of the FRIEDEL-CRAFTS alkylation.

Table 15: Lewis acid screening (1.2 eq phenol, CS_2, RT, 60 min).

Entry	Lewis Acid (0.5 eq)	Conversion[a]	Product[a]
1	$AlCl_3$	19 %	8 %
2	$FeCl_3$	> 99 %	56 %
3	$TiCl_4$	> 99 %	52 %
4	$SnCl_4$	> 99 %	55 %
5	$LaCl_3$	No conversion	-

Table 16: Solvent screening (1.2 eq Phenol, 0.5 eq $TiCl_4$, RT, 60 min).

Entry	Solvent	Conversion[a]	Product[a]
1	CS_2	> 99 %	52 %
2	DCM	> 99 %	58 %
3	1,2-DCE	> 99 %	58 %
4	Petrolether	> 99 %	48 %
5	1,4-DCB	> 99 %	49 %
6	CH_3NO_2	> 99 %	64 %
7	Sulfolane	78 %	33 %

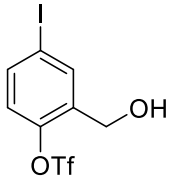
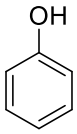
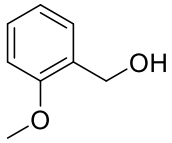
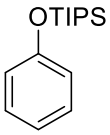
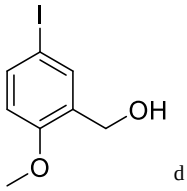
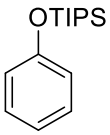
Table 17: Temperature screening (1.2 eq Phenol, 0.5 eq $TiCl_4$, CH_3NO_2, RT, 60 min).

Entry	Temperature	Conversion[a]	Product[a]
1	0 °C	93 %	66 %
2	RT	> 99 %	64 %
3	40 °C	> 99 %	69 %

[a] According to GC-MS, by-products are ortho-alkylated products or di-alkylated products.

By using the optimized conditions ($TiCl_4$, CH_3NO_2, RT, 60 min) on larger scale (1.6 g) only 23 % pure *p*-product **17s** could be isolated and the free phenol had to be protected because otherwise no differentiation after cleavage of the methyl ether between the two phenols would be possible. Therefore already protected phenols **17t** (TIPS-protected) respectively already iodinated and triflated benzylic alcohol **10d** were tested with the optimized conditions (Table 18). The TIPS-protection group was used instead of TBDPS because TIPS contains only aliphatic residues. TBDPS with two phenyl rings provide more possible alkylation sites.

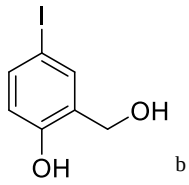
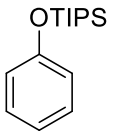
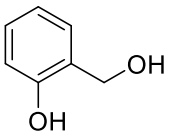
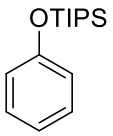
Table 18: Screening the scope of the FRIEDEL-CRAFTS alkylation by using different benzylic alcohol- and phenol-derivatives ($TiCl_4$, CH_3NO_2, RT, 60 min).

Entry	Starting material	Reagent	Product[a]
1	 **10d**	 **17r**	No conversion[b]
2	 **17q**	 **17t**	No product[c]
3	 [d] **17u**	 **17t**	No product[c]

[a] According to GC-MS, by-products are ortho-alkylated products or di-alkylated products, [b] no conversion detectable, even at 100 °C, [c] cleavage of TIPS-group, [d] for synthesis of benzylic alcohol **17u** see Trp-core unit fragment **16a**.

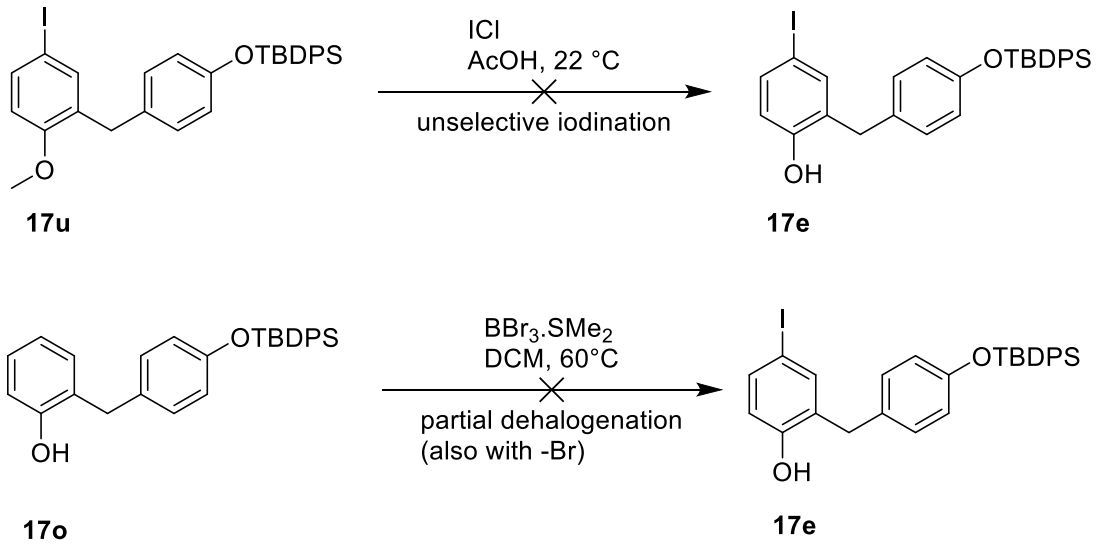
$TiCl_4$ seems to be too harsh for the TIPS-protecting group. Since similar results were achieved with $FeCl_3$, a milder LEWIS acid, TIPS protected phenols **17t** were converted again under $FeCl_3$ catalysis (Table 19).

Table 19: Screening the scope of the FRIEDEL-CRAFTS alkylation by using different benzylic alcohol- and phenol-derivatives ($FeCl_3$, CH_3NO_2, RT, 60 min).

Entry	Starting material	Reagent	Product[a]
1	 **16b** [b]	 **17t**	15 %
2	 **16e**	 **17t**	3 %

[a] According to GC-MS, by-products are ortho-alkylated products or di-alkylated products, [b] for synthesis of benzylic alcohol **17u** see Trp-core unit fragment **16a**.

While the FRIEDEL-CRAFFTS-alkylation led to the desired products, higher yields were obtained via the lithiation reaction although one additional step had to be performed, and therefore we pursued the latter strategy for scale-up.

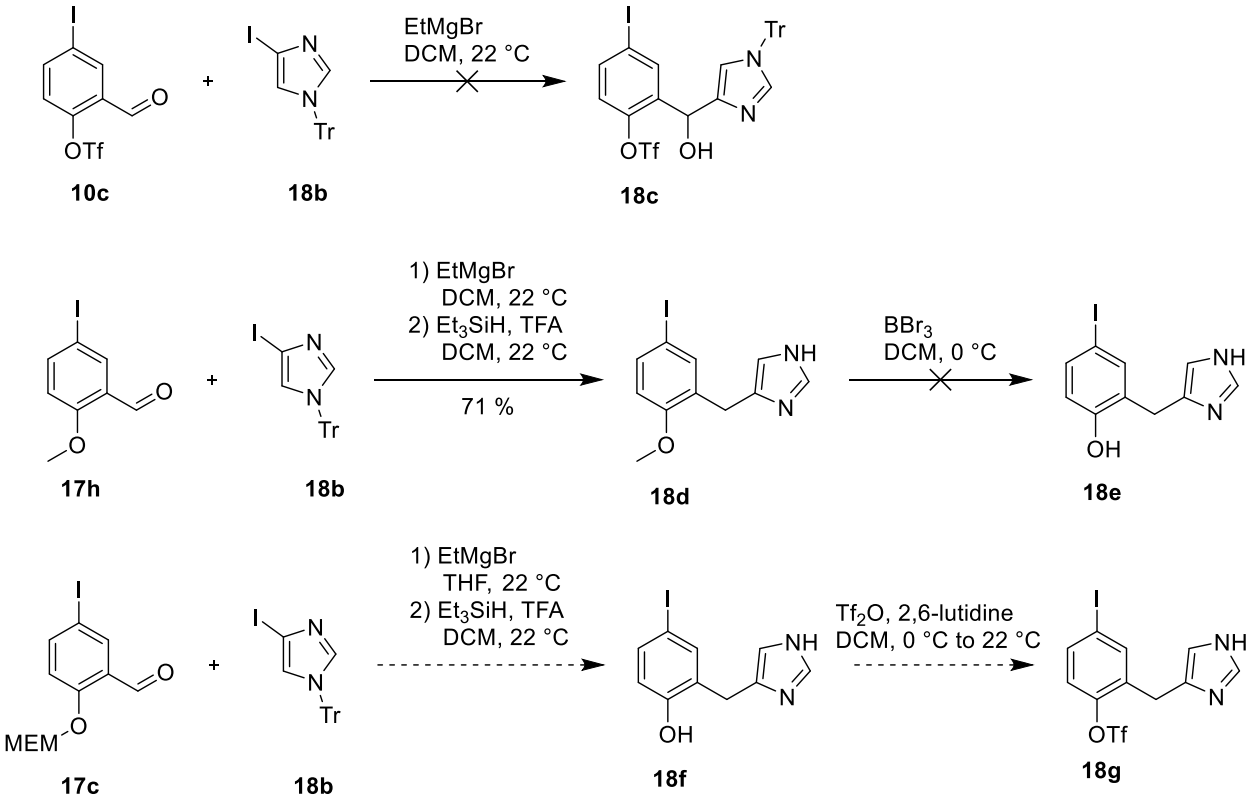


*Scheme 39: Failed reactions in the synthesis of Tyr-core unit fragment **17a**.*

Cleavage of the methyl-ester with $BBr_3.SMe_2$ worked well with **17n** and 79 % product could be isolated. In case of the already iodine **17p** or bromine **17f** containing intermediate the ether-cleavage led to dehalogenation and a complex product mixture. Iodination with the ICl-method or the Selectfluor®-method of **17u** resulted in a mixture of *o*- and *p*-iodinated products (Scheme

39). Due to the size of the molecule it was nearly impossible to separate these product isomers via column chromatography. Therefore using the more expensive, but easily cleavable MEM-protecting group was the route of choice (Scheme 41). An additional advantage is that the MEM-protecting group was already cleaved during the dehydroxylation reaction and no additional cleavage was required. For the conversion of phenol **17e** into the triflate the standard procedure with Tf_2O and pyridine was used, resulting in 63 % isolated yield of **17a**.

According to literature protected halogenated imidazoles undergo metal halogen exchange with EtMgBr.[105] Therefore, for the His-building block basically the same reaction sequence was used as for the Tyr-building block. The trityl protected imidazole **18b** was treated with EtMgBr to form an organo-metal species, which should be quenched with an electrophile. At first the methylether protected salicylaldehyde **17h** was used as electrophile, but during cleavage of the methyl ether dehalogenation occurred and resulted in an inseparable product mixture. As the MEM-protecting group gave good results for the Tyr-core unit fragment **17a**, it should also be used for the synthesis of the His-core unit fragment **18a** (Scheme 40).

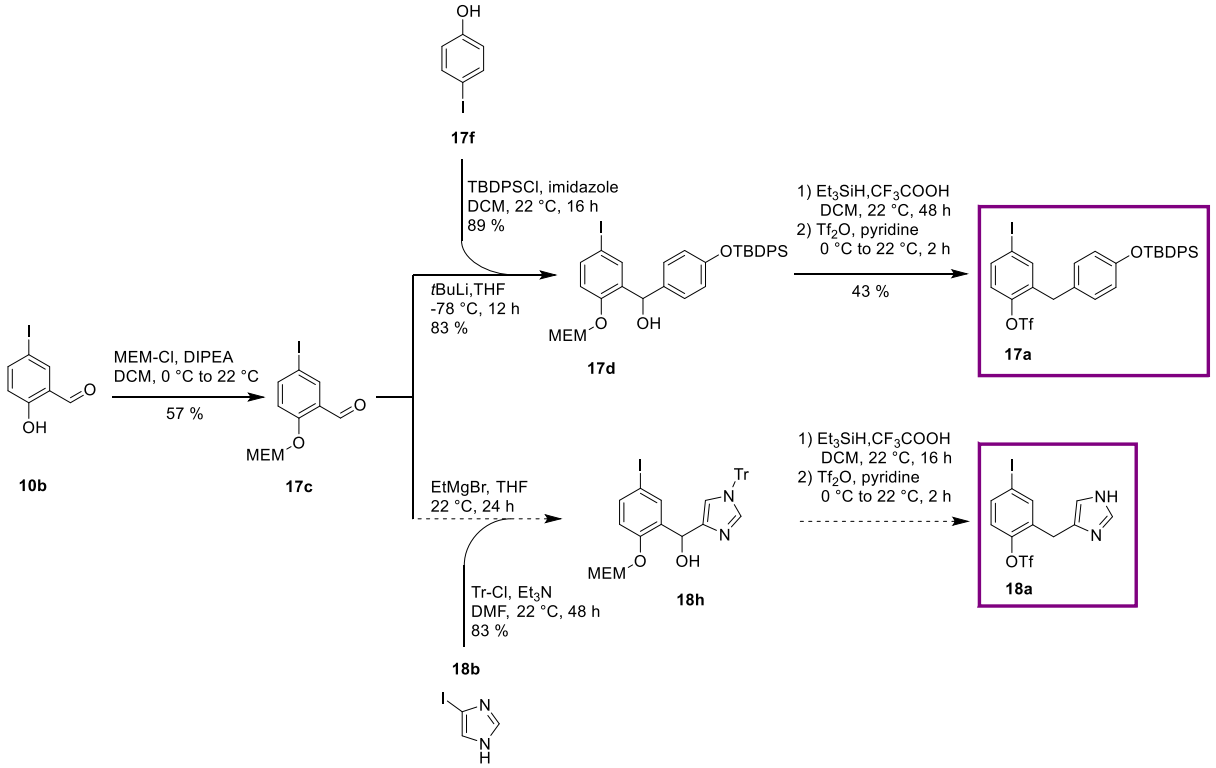


Scheme 40: Different routes for the synthesis of His-core unit fragment.

An alternative route for the synthesis of His-building block is to assemble the imidazole ring instead of attaching it. A TosMIC mediated synthesis of imidazoles starting from an aldehyde was described in the literature.[106] As shown before MeO- was no suitable protecting group due

to cleavage problems in presence of halogens. Either the unprotected phenol or the already triflated phenol should be used. With the unprotected phenol no aldehyde/lactole was produced due to sensitivity upon reduction and oxidation of that molecule. It either resulted in the diol or the lactone.

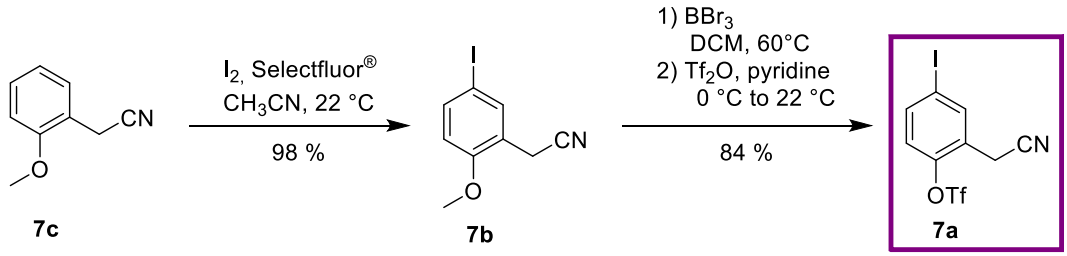
In the course of the PhD thesis the His-core unit fragment **18a** could not be produced yet.



Scheme 41: Final reaction route for the Tyr-core unit fragment and planned reaction route for the His-core unit fragment.

4.1.6 Synthesis of Asn-building block

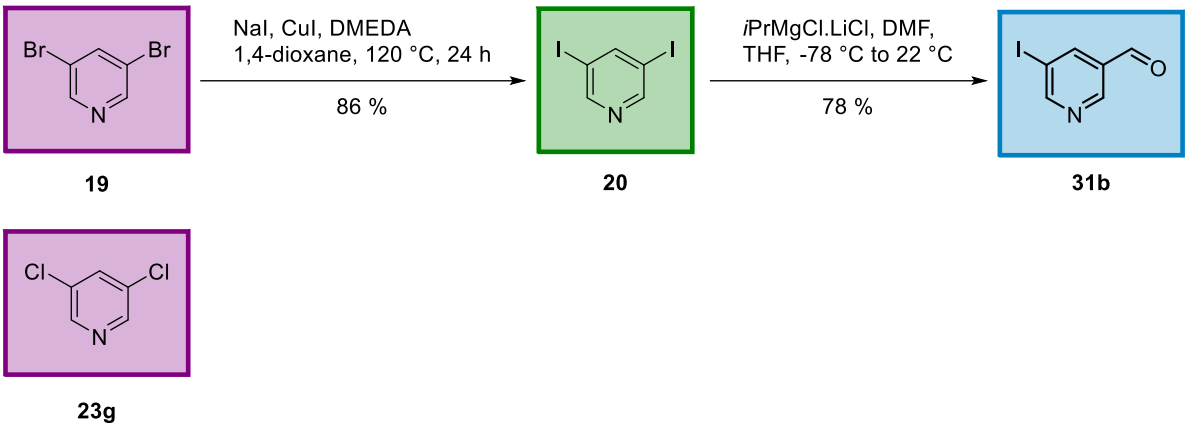
The Asn-building block was already synthesized in a masked form as nitrile (Scheme 42).[80] It would be more convenient to have access to the free amide because otherwise an additional step after the SUZUKI-MIYAURA coupling would be necessary, but no suitable reaction sequence has been conveived at present.



Scheme 42: Synthesis of the Asn-core unit fragment.

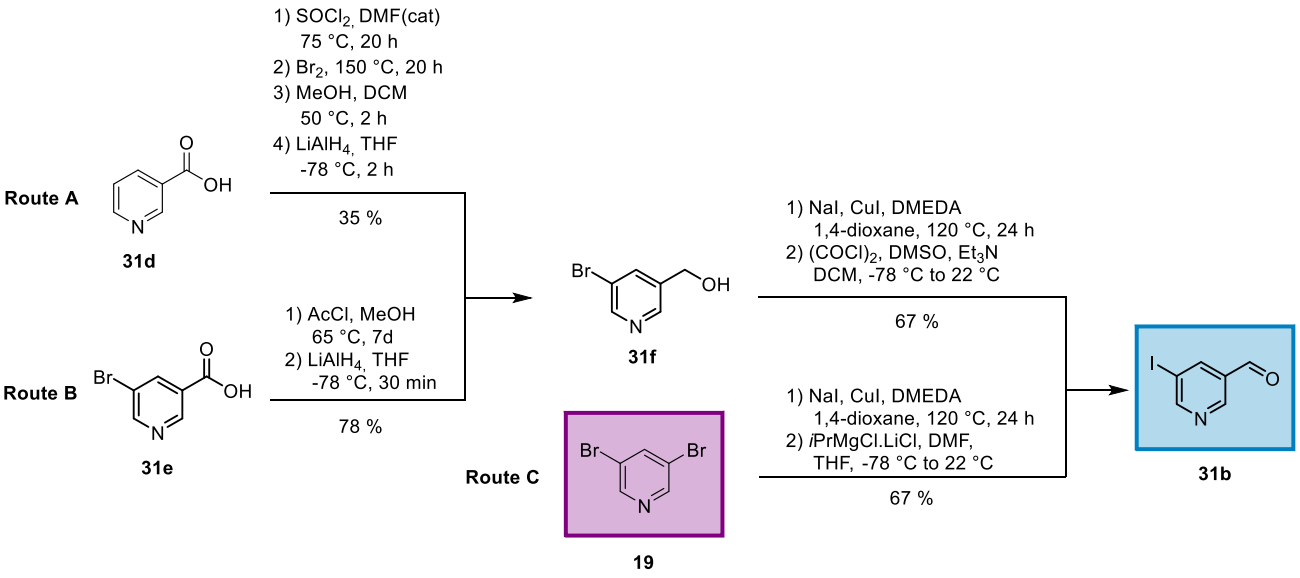
4.2 Pyridine boronic acid esters

For the synthesis of the pyridine boronic acid esters only four general intermediates, starting from two different commercially available starting materials had to be used (Scheme 43).



Scheme 43: Intermediates for pyridine boronic acid ester synthesis.

The Br-I-exchange via a BUCHWALD-modification of the FINKELSTEIN-reaction was established and optimized by Martin Peters.[58] For the synthesis of 3-iodonicotinic aldehyde (**31b**) two rather long reaction sequences were explored by Sebastian GRIMM (Route B)[107] and Bernhard WÖLFL (Route A),[108] which could be shortened in this thesis by applying KNOCHEL-GRIGNARD chemistry.[109] After a metal-halogen exchange and quenching with DMF, the desired aldehyde **31b** could be isolated in two steps and overall yield of 67 %, which compares well with the previous approaches. Since in Route A six steps, containing one with boiling Br_2, were required and in Route B the very expensive substrate **31e** was converted in four steps to the desired product (Scheme 44).



Scheme 44: Synthesis of 3-iodonicotinic aldehyde.

With these general intermediates access to all desired pyridine boronic acid ester should be possible. In Figure 28 an overview of the reaction sequences for all pyridine boronic acid esters is outlined except the Leu-pyridine boronic acid ester **23a**, since that building block could be synthesized from 3,5-dichloropyridine (**23g**) as starting material.

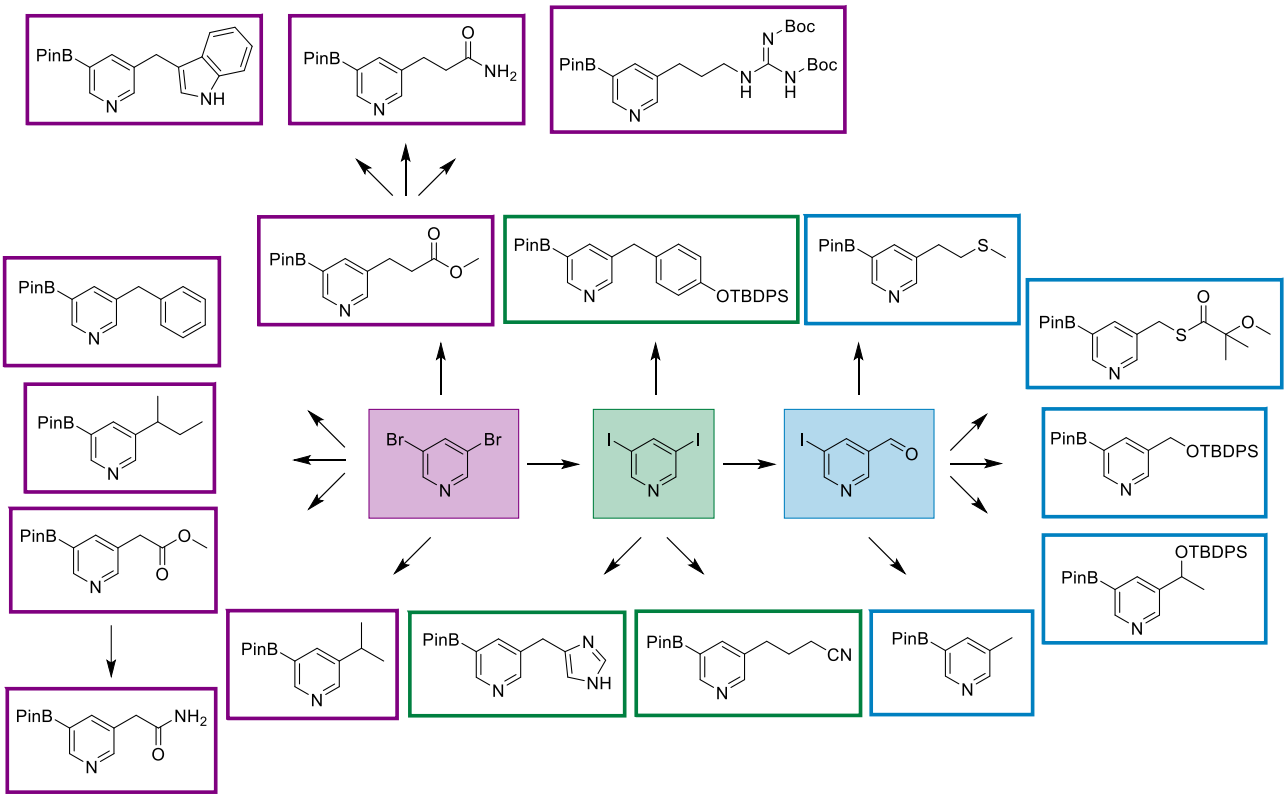
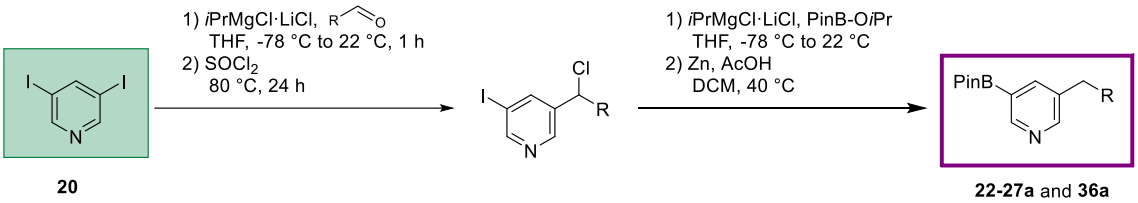


Figure 28: General reaction scheme for the synthesis of pyridine boronic acid esters.

4.2.1 Synthesis of Val-, Ile- and Phe-pyridine boronic acid ester

In the initial route developed by Martin PETERS a twofold KNOCHEL-GRIGNARD-reaction sequence was used for the synthesis of the aliphatic side-chain containing pyridine boronic acid esters.[58] The first metal-halogen exchange was quenched with various aldehydes to introduce the side chains and the second metal halogen exchange was quenched with PinBO*i*Pr. The big drawback of this reaction sequence was the fact that it required several steps to remove the hydroxy function formed during the first GRIGNARD reaction. Martin PETERS established a two-step procedure whereby the hydroxy-group is first converted into a chloride and after introduction of the boronic acid pinacol ester the chloride could be removed with Zn and acetic acid. Removal of the chloride before iodide to boronic acid ester conversion led to deiodination (Scheme 45).



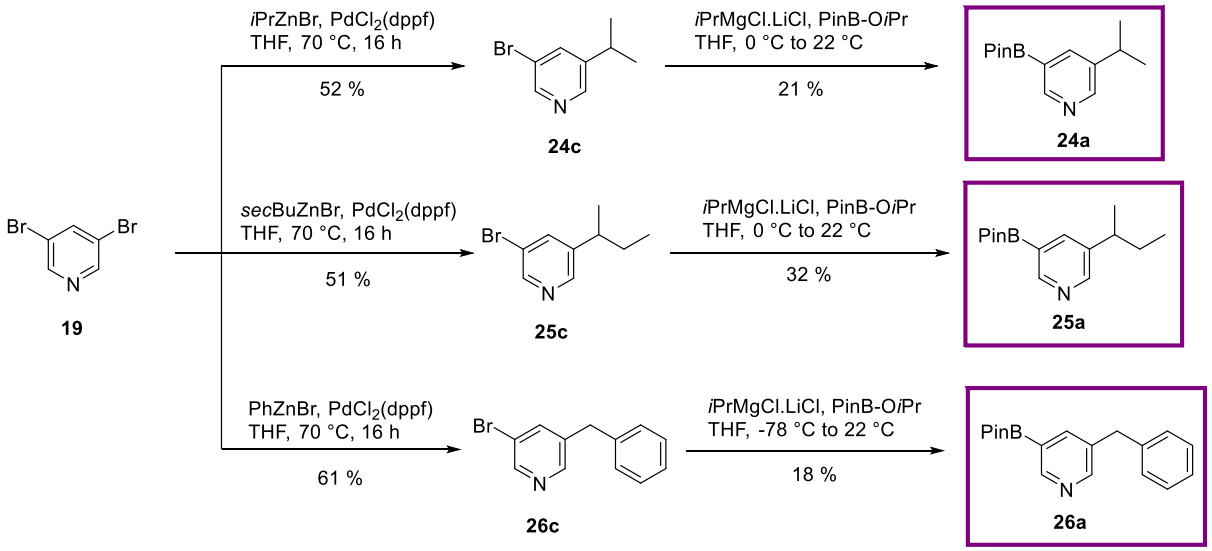
Scheme 45: Original reaction sequence for the synthesis pyridine boronic acid ester.[58]

With this route the Leu-, Val-, Ile-, Phe-, Lys- and Asp-pyridine boronic acid ester could be synthesized.[58] The Asp-pyridine boronic acid ester was converted to the Asn-pyridine boronic acid ester by aminolysis. The products were purified by sublimation or Kugelrohr-distillation. Especially when boronic acid esters with a higher molecular weight were sublimed, product was lost by decomposition. Most of the isolated yields were still moderate, but they could be much higher as predicted by crude product NMR (purity ~95 %). This observation and the long reaction sequence turned out to be problematic for scale up. Since bigger amounts were required for teraryl coupling, an alternative reaction sequence was investigated. The key step of this sequence was the NEGISHI-coupling of halogen pyridine with Zn-organyls.

The direct insertion of zinc into organic halides was achieved by RIECKE-zinc until a new procedure was established by KNOCHEL *et al.* whereby 1,2-dibromoethane and TMS-Cl are used for the activation of commercially available zinc dust.[110] By adopting the activation method of KNOCHEL the desired Zn-organyls **24c-26c** could be prepared and coupled via NEGISHI-coupling. The concentration of Zn-organyls can be determined by titration with iodine,[111] but was calculated according to the peak areas detected by GC-FID. Unfortunately, the NEGISHI-coupling did not work well with 3,5-diiodopyridine (**20**), only 9 % product were isolated for

Phe-pyridine boronic acid ester and several by-products were detected on GC-MS. In contrast, by use of less expensive 3,5-dibromopyridine (**19**) this method was suitable for the synthesis of Val-, Ile- and Phe-pyridine boronic acid esters in which a second bromide metal-exchange was used for the introduction of the boronic acid ester (Scheme 46). For the second magnesium-bromide exchange rather harsh conditions and long reaction times were necessary and in some cases incomplete conversion was detected as observed by Martin PETERS before.[58] Therefore the exchange of bromide to iodide before the second metal-halogen exchange should result in cleaner reactions and higher yields, since after addition of the boronic pinacol ester purification due to instability on silica gel is getting more challenging.

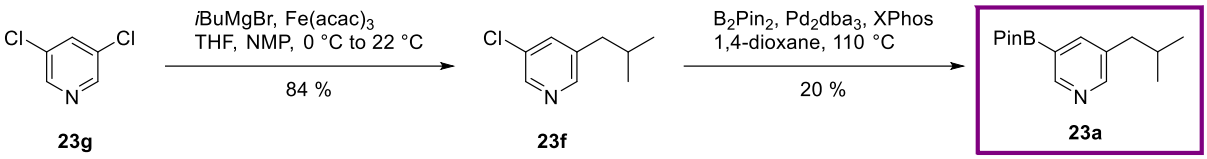
In general the conversion of iodides to pinacol boronic acid ester via KNOCHEL-GRIGNARD-chemistry is a very clean reaction and no further purification should be necessary in many cases as the purity of crude product is > 95 % according to NMR. If the products are sublimed a lot of product gets lost due to thermal decomposition. Another method of purification is recrystallization but only poor yields could be isolated again. Therefore either a very clean reaction is desirable to use directly the crude product and avoid product lost by purification or another purification method needs to be established.



Scheme 46: Synthesis of Val-, Ile- and Phe-pyridine boronic acid ester.

4.2.2 Synthesis of Leu-pyridine boronic acid ester

The synthesis of Leu-pyridine boronic acid ester **23a** was not accsessible via a NEGISHI coupling because this substrate is prone to β-hydride elimination. Therefore a Fe-catalyzed FÜRSTNER-modification of the KUMADA-coupling was used (Scheme 47).[112]



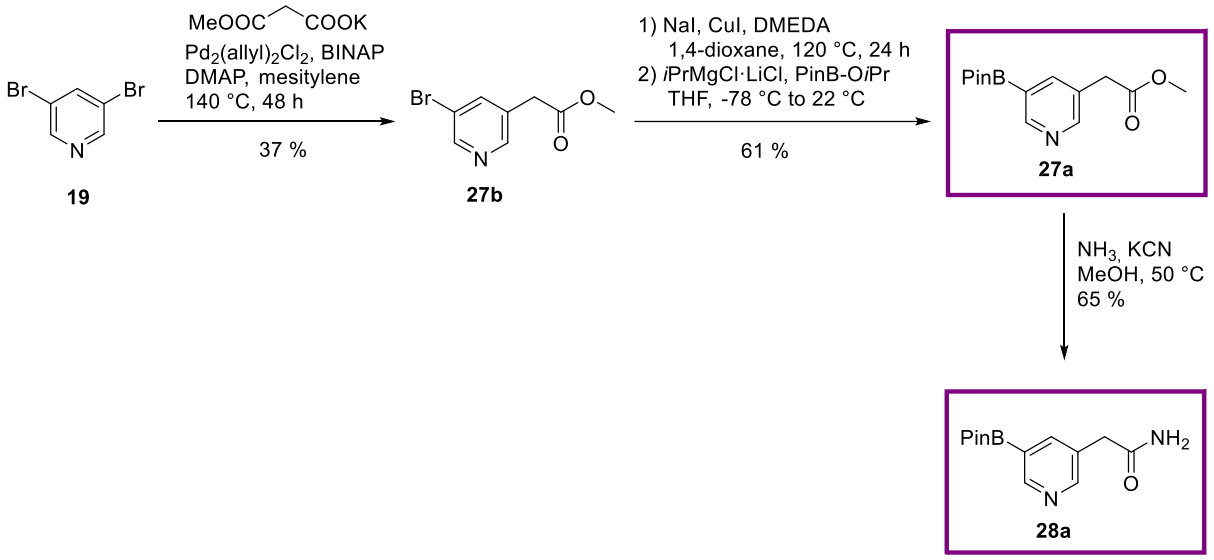
Scheme 47: Synthesis of Leu-pyridine boronic acid ester.

The chloride could not be converted to the boronic acid pinacol ester via a metal halogen exchange instead a MYAURA borylation was performed giving product **23a** in 20 % yield.

4.2.3 Synthesis of Asp- and Asn-pyridine boronic acid esters

The Asp-pyridine boronic acid ester was also tried to be synthesized via a REFORMATZKY reaction followed by NEGISHI coupling, but no conversion could be detected. As an alternative route a decarboxylative cross-coupling procedure was used, starting from 3,5-dibromopyridine (**19**) and monopotassium methyl malonate (Scheme 48). The reaction was tried once and 37 % yield were isolated under non-optimized conditions. Further optimization should improve this reaction and result in higher yields. A major side product was the homo-coupling of two 3,5-dibromopyridines. Despite full conversion of the starting material, it was not sure if the carboxylic acid intermediate was fully decarboxylated, since the intermediate could not be detected via GC-MS. If carboxylic acid intermediate was not fully converted it was separated via column chromatography due to the higher polarity and led to low yields.

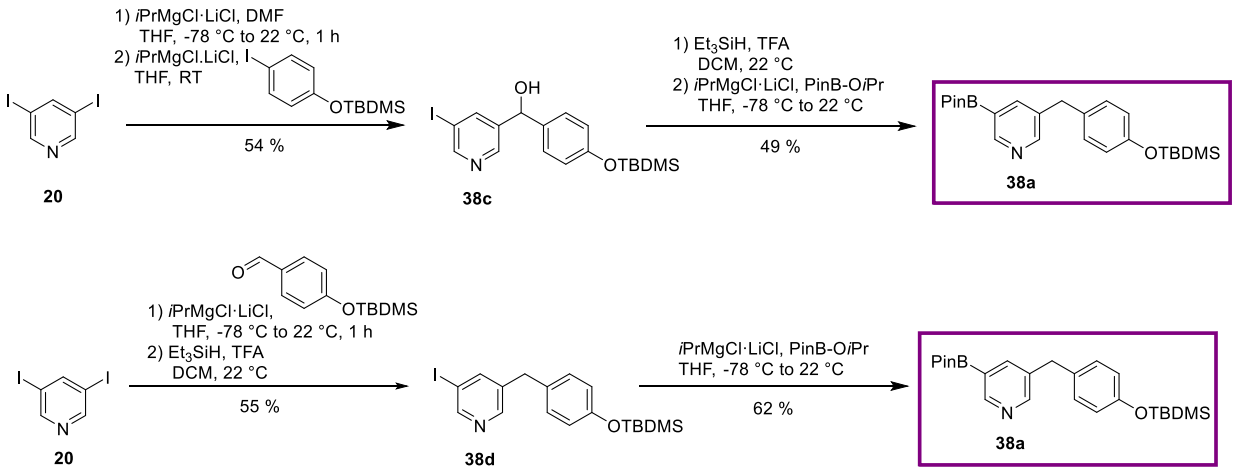
Aminolysis was performed to generate the Asn-pyridine boronic acid ester **28a**. In the case of the Asp-pyridine boronic acid ester **27a** a bromide-iodide exchange was indispensable because the reaction of the KNOCHEL-GRIGNARD-reagent with an ester is faster than the metal-bromide exchange. In contrast the metal-iodide exchange is faster than the reaction of *i*PrMgCl.LiCl with an ester.



Scheme 48: Synthetic route for the preparation of Asp- and Asn-pyridine boronic acid ester.

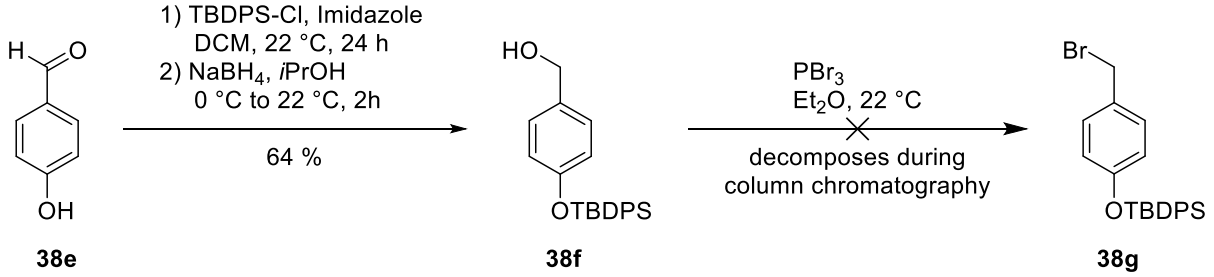
4.2.4 Synthesis of Lys-, Tyr- and His-pyridine boronic acid esters

For the Tyr-pyridine boronic acid ester **38a** the original two-fold KNOCHEL-GRIGNARD-route was the route of choice. Since this molecule contains a second, electron rich aromatic ring the hydroxy function formed during introduction of the side chain could be removed in a one-step procedure with Et_3SiH and TFA. The proposed mechanism proceeds via a carbocation which is stabilized by electron rich aromatic rings. With only four steps this route is the shortest route developed so far. In the former route 3-iodonicotinic aldehyde **(31b)** was used as starting material and even with the improved synthesis for 3-iodnicotinic aldehyde (**31b**) the longest linear reaction sequence contains five steps (Scheme 49).[108]



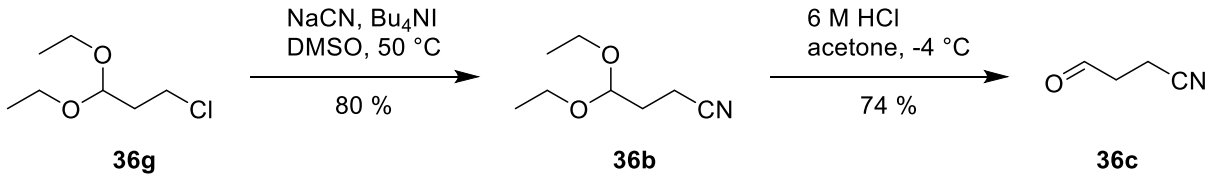
*Scheme 49: Synthesis of the Tyr-pyridine boronic acid ester **38a**.*

The TBDMS-group was used instead of the TBDPS-group to be able to monitor the second metal-halogen exchange still via GC-MS, which was the fastest and easiest method to detect the conversion of the metal-halogen exchange. With the TBDPS-group the molecule could not be detected on GC-MS as it would have a molecular weight which would hinder volatilization. The benzylic bromide **38g** was synthesized for application in a NEGISHI coupling but this sequence was abandoned due to the instable, difficult to handle benzylic bromide **38g** and no shortening of the reaction sequence (Scheme 50).



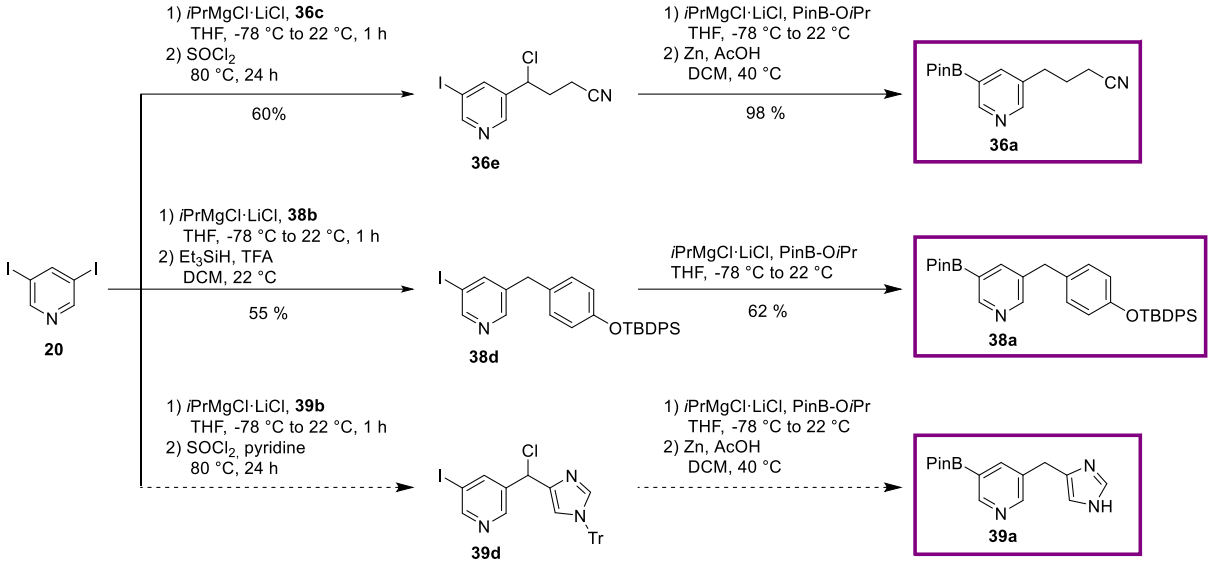
*Scheme 50: Synthesis of benzylic bromide **38g** for the use in NEGISHI coupling.*

For the Lys-pyridine boronic acid ester no improved route was found and this building block was synthesized according to the original two fold KNOCHEL-GRIGNARD-procedure.[58] Although 4,4-diethoxybutanenitrile is commercially available it was synthesized from the corresponding chloride via a nucleophilic substitution as the chloride is much cheaper than the nitrile.[113] The acetale was cleaved under acidic conditions to yield the corresponding aldehyde (Scheme 51).



Scheme 51: Preparation of 4-oxobutanenitrile.

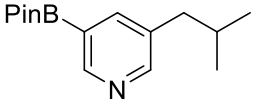
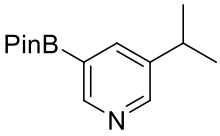
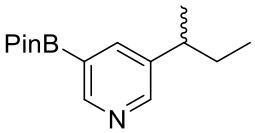
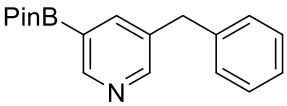
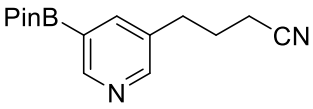
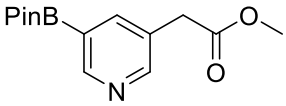
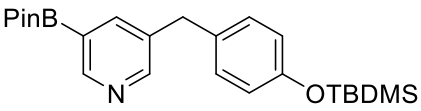
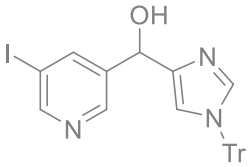
The His-pyridine boronic acid ester could within this thesis not be synthesized yet, but should be accessible via a similar reaction sequence (Scheme 52). The first KNOCHEL-GRIGNARD-reaction has already been performed and product **39c** was isolated in 56 % yield.



Scheme 52: Reaction sequence for the Lys- and Tyr-boronic acid ester and the planned route for the His-pyridine boronic acid ester.

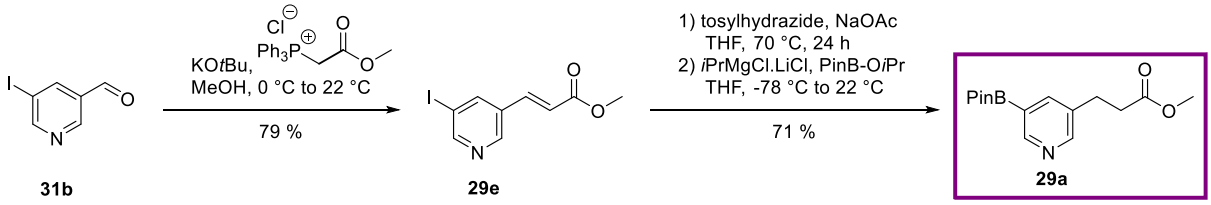
By using transition metal (TM) catalyzed reactions several reaction routes could be shortened. Nevertheless the overall yields are still very poor and need to be improved. The main issue was the purification of pyridine boronic acid esters, since they were not stable during purification via column chromatography. Sublimation and recrystallization provide pure product, but are associated with big losses in yield (Table 20).

Table 20: Comparison between Knochel Grignard und transition metal catalyzed reaction routes.

Entry	Product	KNOCHEL GRIGNARD Overall yield	TM catalyzed Overall yield
1	 **23a**	39 % (5 steps)	17 % (2 steps)
2	 **24a**	32 % (4 steps)	11 % (2 steps)
3	 **25a**	21 % (5 steps)	16 % (2 steps)
4	 **26a**	65 % (5 steps)	11 % (2 steps)
5	 **36a**	51 % (5 steps)	-
6	 **27a**	55 % (5 steps)	23 % (3 steps)
7	 **38a**	29 % (4 steps)	-
8	 **39c**	48 % (2 steps)	-

4.2.5 Synthesis of Glu-, Gln-, Arg and Trp-pyridine boronic acid esters

In the original route Sebastian Grimm used a WITTIG reaction to introduce the Glu-side chain (Scheme 53).[107] The WITTIG product **29e** resembles products generated by a HECK coupling.



Scheme 53: Original route for the synthesis of Glu-pyridine boronic acid ester.

By using a HECK coupling the much better accessible 3,5-dibromopyridine (**19**) yould serve as inexpensive starting material. Furthermore instead of a stoichiometric reaction a catalytic reaction can be performed. The more reactive 3,5-diiodopyridine (**20**) was also used in a HECK coupling reaction, but gave more side products by coupling with both iodides and homo-coupling. These by-products were also observed in the coupling with 3,5-dibromopyridine (**19**), but in less amounts. For the optimization of this reaction extensive screening of reaction parameters was performed.

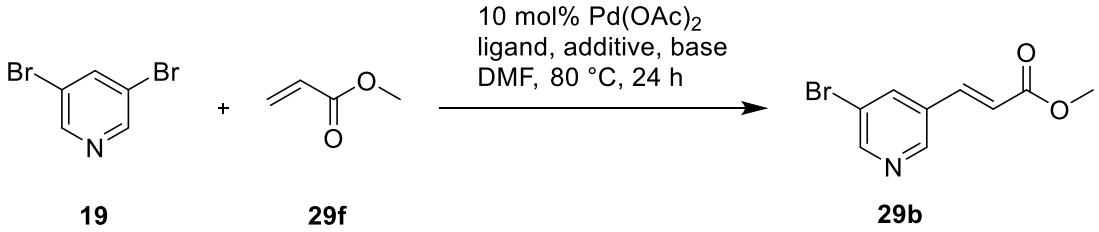
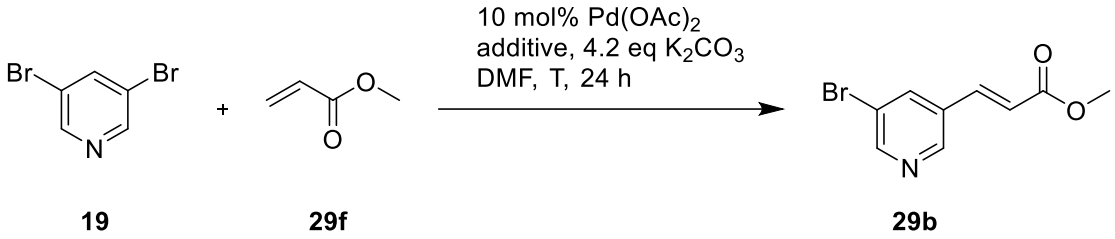


Table 21: Ligand screening to optimize Heck coupling conditions.

Entry	Ligand (0.2 eq)	Additive (0.1 eq)	Base (4.2 eq)	Product[a]
1	PPh_3		Et_3N	5 %
2	PPh_3	Bu_4NCl	Cy_2MeN	54 %
3	PBu_3		K_2CO_3	60 %
4	PPh_3	Bu_4NCl	K_2CO_3	-
5	$P(OPh)_3$		K_2CO_3	-
6	$P(OPh)_3$	Bu_4NCl	K_2CO_3	-
7	-	-	K_2CO_3	78 %
8	-	Bu_4NCl	K_2CO_3	66 %

[a] According to GC-FID.

After screening of different ligands it turned out, that using $Pd(OAc)_2$ without additive gave the best results (Table 21).

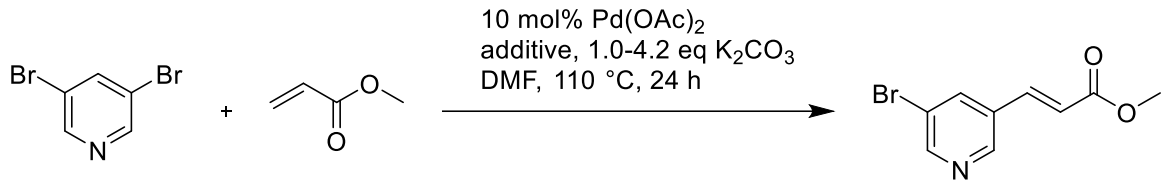


19 **29f** **29b**

Table 22: Temperature screening to optimize Heck coupling conditions.

Entry	Additive (0.1 eq)	Temperature	Product[a]
1	-	65 °	-
2	-	80 °C	78 %
3	Bu_4NCl	80 °C	66 %
4	-	100 °C	66 %
5	Bu_4NCl	100 °C	66 %
6	-	110 °C	63 %
7	Bu_4NCl	110 °C	59 %

[a] According to GC-FID.



19 **29f** **29b**

Table 23: Base screening to optimize Heck coupling conditions.

Entry	Additive (0.1 eq)	eq Base	Product[a]
1	-	4.2	63 %
2	Bu_4NCl	4.2	59 %
3	-	2.0	77 %
4	Bu_4NCl	2.0	77 %
5	-	1.5	81 %
6	-	1.2	79 %
7	-	1.0	5 %

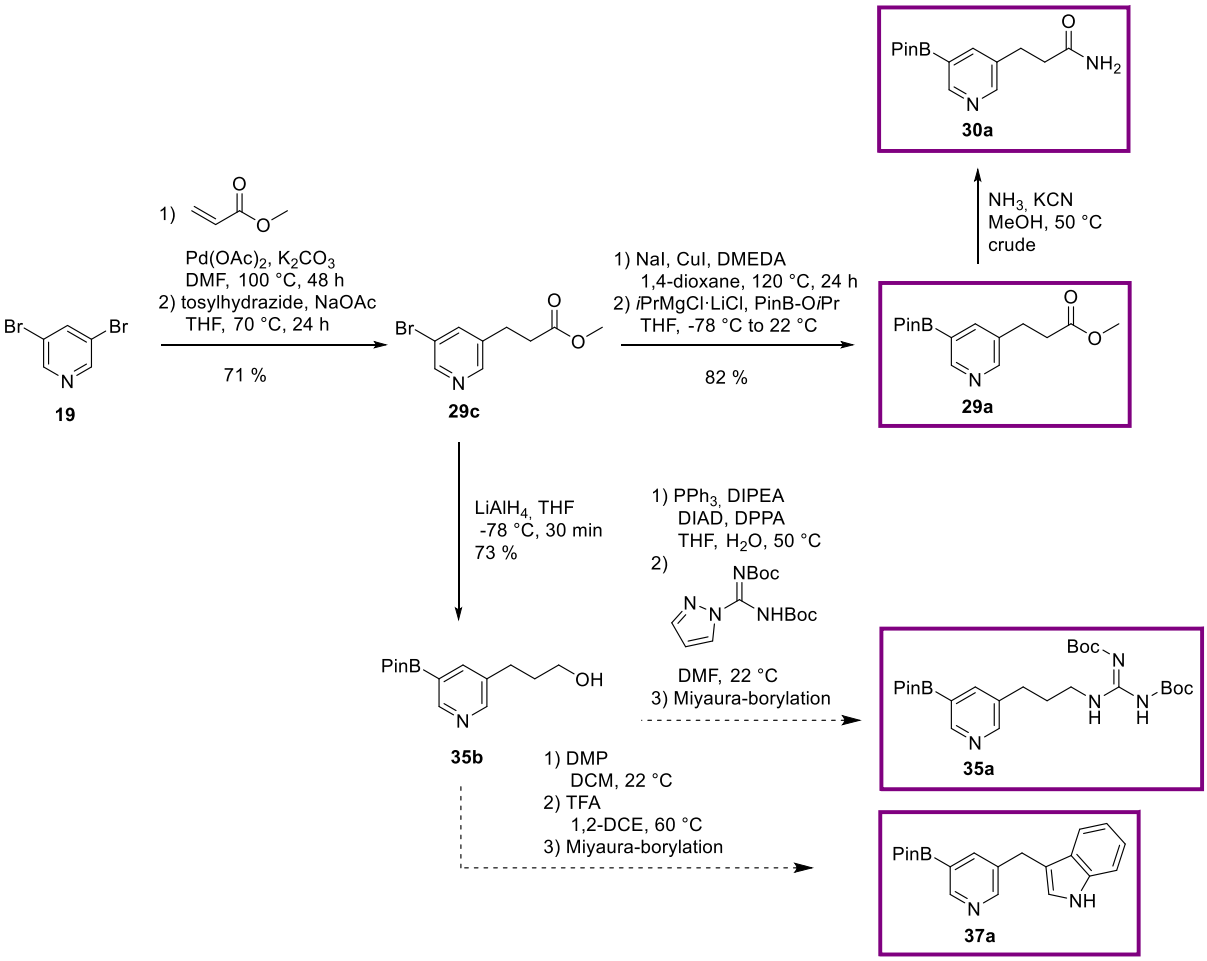
[a] According to GC-FID.

With optimized reaction conditions (10 mol% $Pd(OAc)_2$, 1.5 eq K_2CO_3, DMF, 100 °C, 48 h) 81 % product were formed according to GC-FID and 71 % could be isolated (Table 22 and Table 23). The next step was a diimide reduction as used in the former route, followed by bromide-iodide exchange due to the same reasons as described for the Asp-pyridine boronic ester **27a** and the conversion to the boronic acid pinacol ester. The Gln-pyridine boronic acid ester **30a** was synthesized via aminolysis. Deborylation of the product occurred during sublimation and an alternative purification method needs to be established to isolate pure product.

For the Arg- and Trp-pyridine boronic acid ester the corresponding alcohol **35b** was synthesized. The same conditions as for the reduction of methyl 5-bromonicotinate were used. Then for the Arg-pyridine boronic acid a MITSUNOBU-STAUDINGER sequence as described for the Arg-core fragment followed by introduction of the guanidine-mojety was performed. The boronic acid pinacol ester should be attached via a MIYAURA borylation, but was not finished within this thesis. The intermediate **35d** was isolated in 16 % overall yield.

The indole ring for the Trp-pyridine boronic acid **37a** should be introduced via a FISCHER indole synthesis. As precursor for this reaction the corresponding aldehyde **37b** was required. No direct reduction of ester **29c** to aldehyde **37b** was possible. A two-step procedure had to be used following reduction of ester **29c** to alcohol **35b** and subsequent oxidation to the corresponding

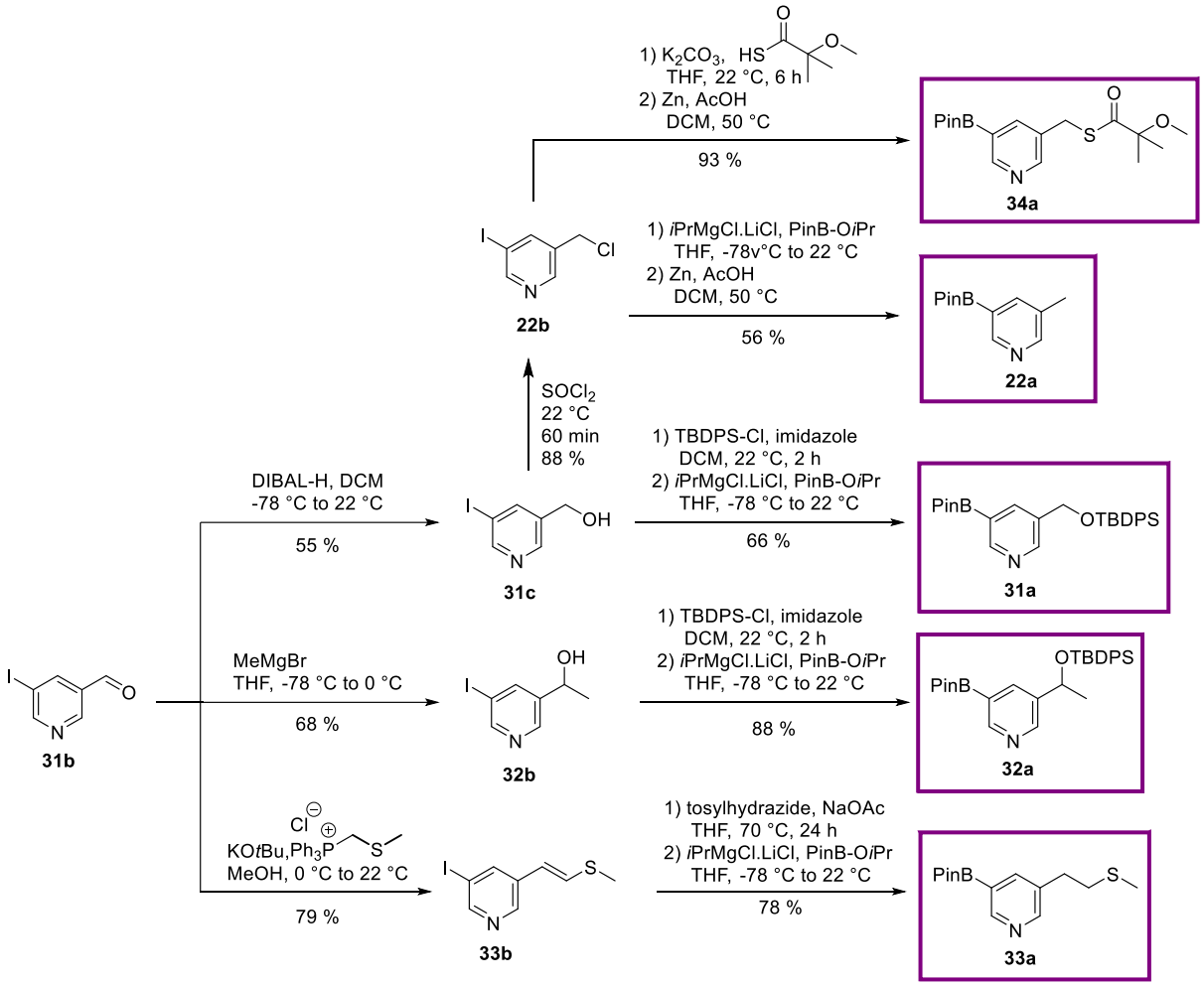
aldehyde **37b** using DESS MARTIN reagent. The aldehyde was further converted to the indole ring via a FISCHER indole synthesis with phenyl hydrazine. Intermediate **37c** was isolated in 11 % overall yield. The last step should be the attachment of the boronic acid pinacol ester via MIYAURA borylation, but this step was not finished within this thesis. (Scheme 54).



Scheme 54: Synthetic route for the preparation of Glu-, Gln-, Arg- and Trp-pyridine boronic acid ester.

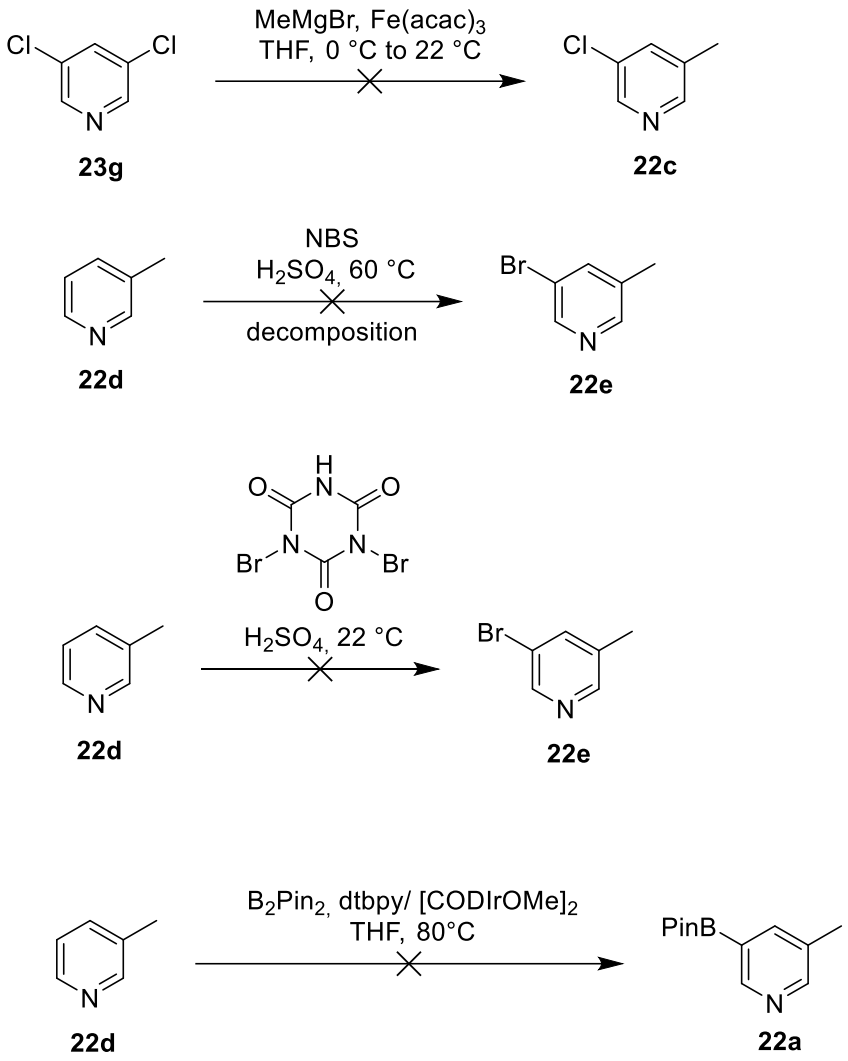
4.2.6 Synthesis of Ala-, Cys-, Ser-, Thr- and Met-pyridine boronic acid esters

These building blocks were synthesized by Sebastian Grimm[107] and Bernhard Wölfl[108] and are depicted here for the sake of completeness (Scheme 55). The only alteration was the synthesis of aldehyde **31b** described before and the reduction of this aldehyde via DIBAL-H to the corresponding alcohol **31c**.



Scheme 55: Synthesis of Cys-, Ala-, Ser-, Thr- and Met-pyridine boronic acid ester.

For the synthesis of Ala-pyridine boronic acid ester **22a** several other methods were tested, but none of them gave the desired product (Scheme 56). This long reaction sequence seems to be too complicated for such a simple building block. It is worth considering to buy the more expensive 3-bromo-5-methylpyridine **22e**. On the one hand the Ala-pyridine boronic acid ester **22a** is usually needed as reference and therefore only little amounts are necessary. On the other hand synthesizing the Ala-building block **22a** via 5-iodonicotinaldehyde (**31b**) is overall as expensive as buying the already correct functionalized precursor **22e**.

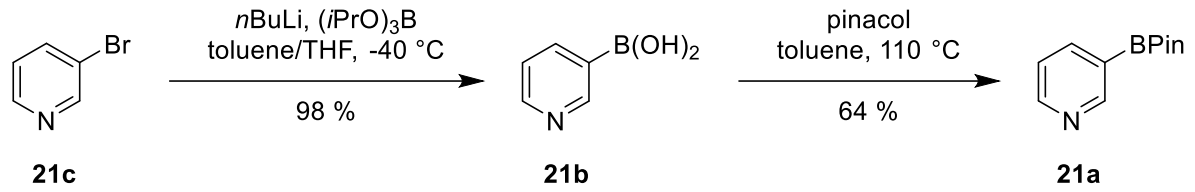


Scheme 56: Alternative routes for the Ala-pyridine boronic acid ester.

The KUMADA-coupling showed desired product but very poor yields were isolated. Bromination with NBS led to decomposition and bromination with 1,3-dibromo-1,3,5-triazinane-2,4,6-trione showed product on GC-MS but the majority of the starting material also decomposed.

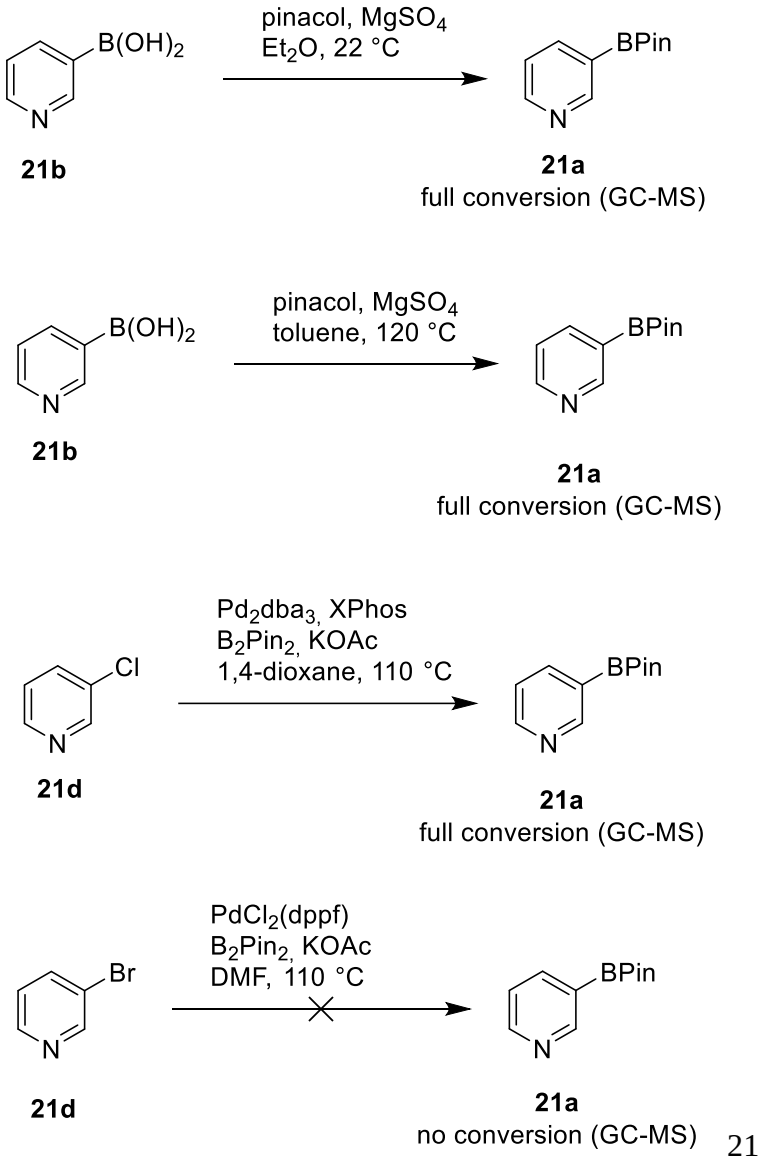
4.2.7 Synthesis of Gly-pyridine boronic acid ester

The Gly-pyridine boronic acid ester **21a** was synthesized as test-substrate to explore suitable conditions for the SUZUKI-MIYAURA cross-coupling. Since larger amounts were needed, a short and inexpensive reaction sequence was desirable. Due to purification or scale-up difficulties with the other pyridine boronic acid ester the simplest one was chosen as test substrate. The Gly-pyridine boronic acid ester **21a** was prepared following a procedure from *Org. Synth.* in a straightforward two step synthesis and was isolated in moderate yields. The product could be easily purified by recrystallization from cyclohexane (Scheme 57).[53]



Scheme 57: Synthesis of Gly-pyridine boronic acid ester as test-substrate.

Some alternative routes were tested for the synthesis of Gly-pyridine boronic acid ester **21a**. Three of them showed full conversion by GC-MS, but were not further proceeded (Scheme 58).

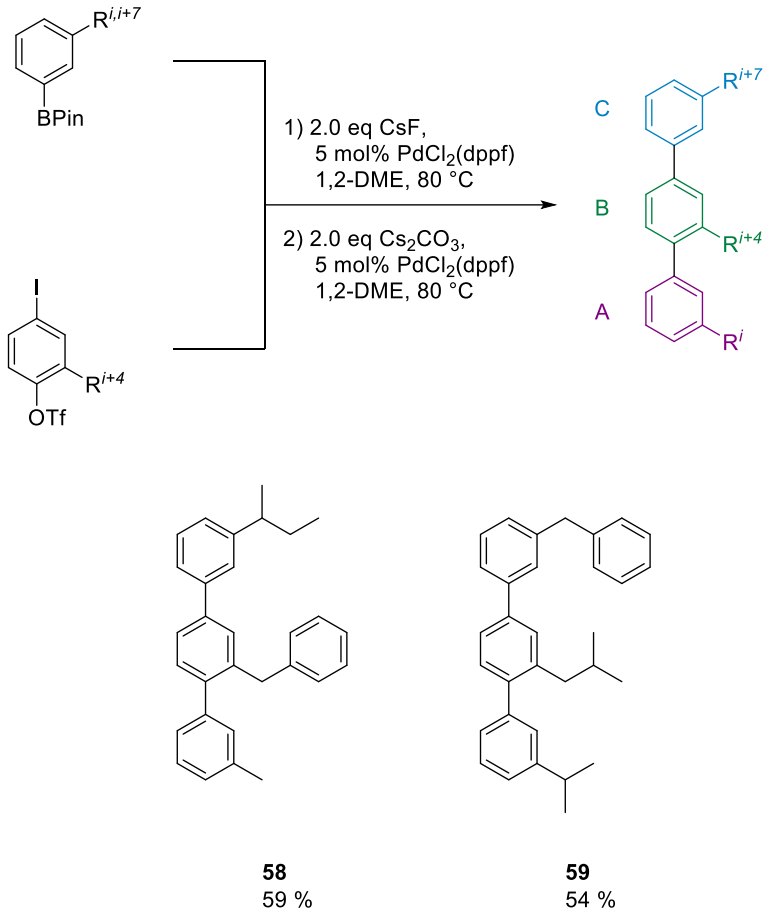


21

Scheme 58: Alternative synthetic routes for the preparation of Gly-pyridine boronic acid ester.

4.3 Assembly of teraryls

The original procedure for teraryl assembly was used for the coupling of phenyl rings. In the first step selectively the iodide underwent cross-coupling reaction followed by the triflate in the second reaction step (Scheme 59). Chemoselectivity was reached by a base-switch from CsF to Cs_2CO_3. No unselective coupling-products were observed.[80]



58
59 %

59
54 %

Scheme 59: Two-step coupling procedure for terphenyl assembly.

The same conditions were also applied for the coupling of pyridine boronic acid esters (Figure 29).

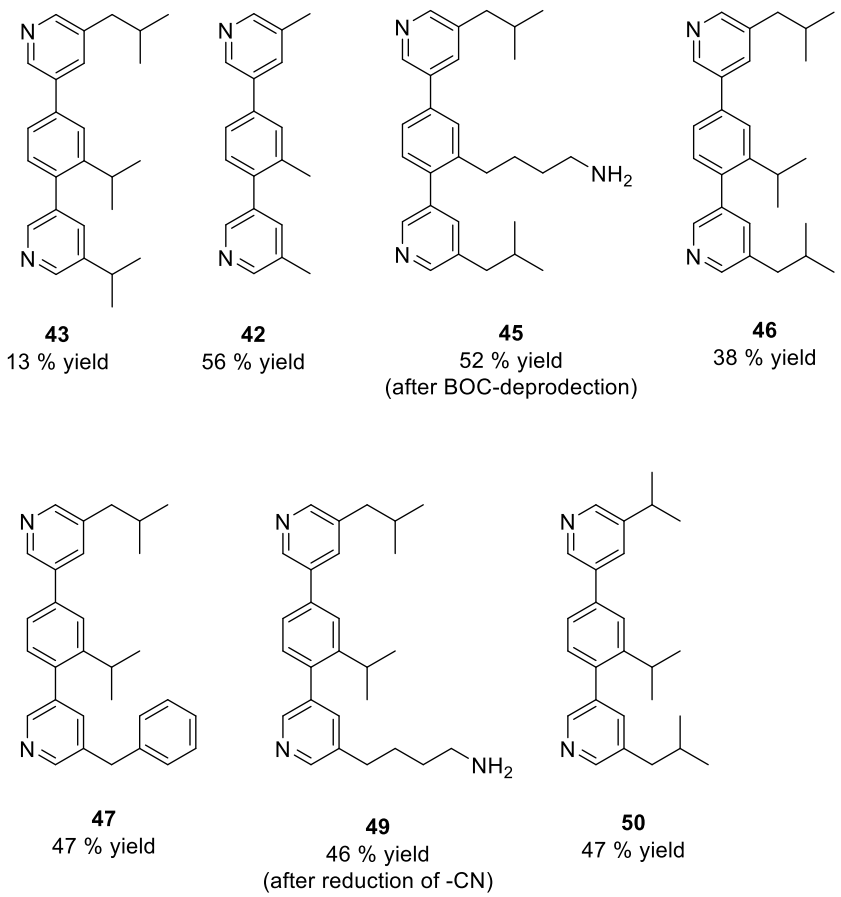
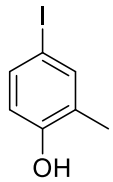


Figure 29: Synthesized Teraryls; conditions 1st coupling: 2.0 eq CsF, 5 mol% $PdCl_2$(dppf), 1,2-DME, 80 °C; conditions 2nd coupling: 2.0 eq Cs_2CO_3, 5 mol% $PdCl_2$(dppf), 1,2-DME, 80°C.

When pyridine boronic acid esters were used instead of phenyl boronic acid esters the reaction time increased significantly. In addition incomplete conversion as well as significant amounts of by-products were observed and therefore in many cases poor yields were isolated. The by-product was isolated as well and the structure was confirmed by NMR and GC-MS as hydrolyzed triflate **1b** (Figure 30).



1b

Figure 30: Isolated by-product from SUZUKI-MIYAURA coupling.

To improve the conditions for coupling reactions with the more challenging pyridine boronic acid esters a screening of reaction parameters was performed to find suitable reaction

conditions. For the screening the simplest pyridine boronic acid ester **21a** was used as considerable amount of sustrate were required.

4.3.1 Anion screening

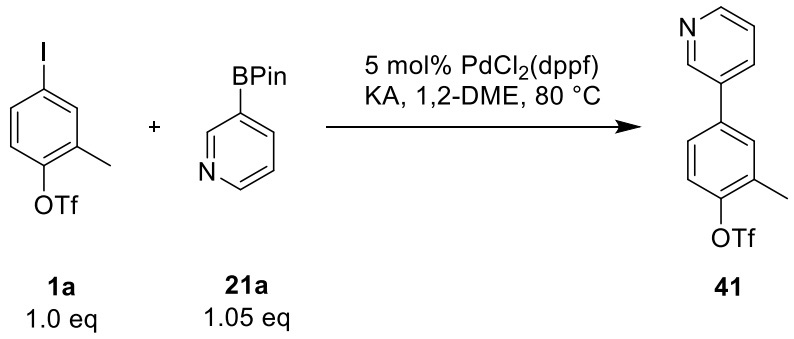


Table 24: Anion screening to optimize SUZUKI-MIYAURA coupling.

Entry	Anion	2 h		24 h	
		Conversion[a]	Selectivity[a]	Conversion[a]	Selectivity[a]
1	K_2CO_3	48 %	> 99 %	> 99 %	> 99 %
2	K_3PO_4	73 %	95 %	> 99 %	95 %
3	KOH	62 %	86 %	69 %	52 %
4	KF	-	-	11 %	> 99 %
5	KO*i*Pr	93 %	89 %	93 %	88 %
6	KOMe	74 %	86 %	51 %	86 %
7	KO*t*Bu	62 %	53 %	87 %	71 %
8	KOAc	-	-	3 %	> 99 %

[a] Conversion and selectivity were monitored via GC-MS.

The best results were achieved with K_2CO_3 and K_3PO_4 (Table 24, Entries 1 and 2). The by-products were in all cases identified as hydrolysed triflate **1b** as in the cross-couplings done before.

4.3.2 Solvent screening

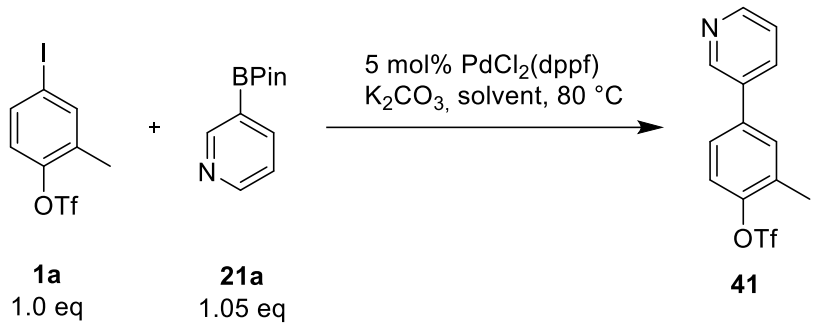


Table 25: Solvent screening to optimize SUZUKI-MIYAURA coupling.

Entry	Solvent	2 h		24 h	
		Conversion[a]	Selectivity[a]	Conversion[a]	Selectivity[a]
1	1,2-DME	20 %	> 99 %	78 %	96 %
2	THF	4 %	> 99 %	44 %	> 99 %
3	1,4-Dioxan	-	-	83 %	> 99 %
4	DMF	> 99 %	> 99 %	> 99 %	56 %
5	MeOH	-	-	-	-
6	*n*PrOH	> 99 %	> 99 %	> 99 %	> 99 %
7	CH_3CN	41 %	> 99 %	> 99 %	> 99 %
8	DMSO	> 99 %	> 99 %	> 99 %	-

[a] Conversion and selectivity were monitored via GC-MS.

The results for the cross-coupling reaction in DMF, *n*PrOH and DMSO were similar (Table 25, Entries 4, 6 and 8). Full conversion was detected within 2 h. In CH_3CN the reaction proceeds a little bit more slowly and full conversion was detected after 24 h. In DMF and DMSO the product started decomposing after a certain time and in DMSO no product was detected at all after 24 h. For further screenings DMF was used as solvent due to the fast and in the beginning very clean reaction. It was assumed that on large scale DMF can be easier removed than DMSO.

4.3.3 Cation screening

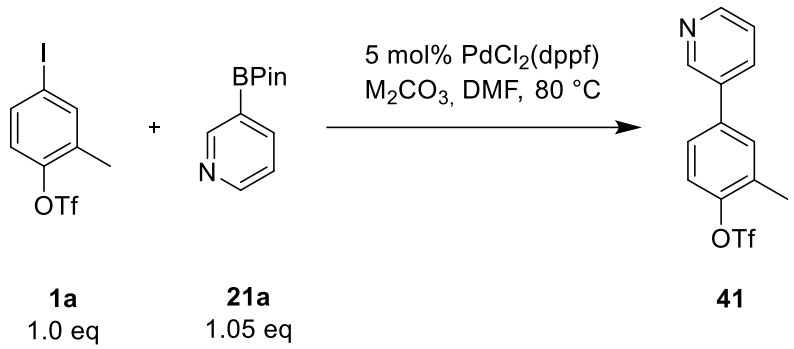


Table 26: Cation screening to optimize SUZUKI-MIYAURA coupling.

Entry	Cation	30 min		2 h		24 h	
		Conversion[a]	Selectivity[a]	Conversion[a]	Selectivity[a]	Conversion[a]	Selectivity[a]
1	K_2CO_3	94 %	> 99 %	> 99 %	> 99 %	> 99 %	24 %
2	Na_2CO_3	75 %	> 99 %	98 %	> 99 %	> 99 %	> 99 %
3	Cs_2CO_3	> 99 %	> 99 %	> 99 %	> 99 %	> 99 %	-
4	Li_2CO_3	-	-	-	-	31 %	> 99 %
5	Ag_2CO_3	> 99 %	> 99 %	> 99 %	> 99 %	> 99 %	> 99 %

[a] Conversion and selectivity were monitored via GC-MS.

With K_2CO_3 and Cs_2CO_3 decomposition of the product was detected after 24 h (Table 26). The best result was reported with Ag_2CO_3 as AgI forms an insoluable precipitate and accelerates the reaction via a cationic Pd-species. No decomposition was detected with the mild Ag_2CO_3. With Na_2CO_3 full conversion was detected after 24 h and no decomposition was reported. An additional equivalent pyridine boronic acid ester **21a** was added and the reaction was stirred overnight. 21 % conversion to the teraryl **60** was detected, which gives a hint that similar conditions will also work for the coupling of the triflate (Figure 31).

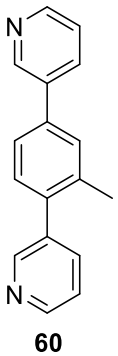
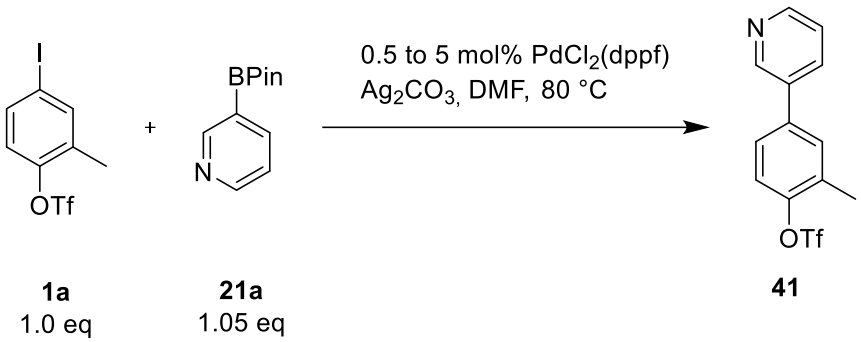


Figure 31: Synthesized teraryl.

4.3.4 Catalyst loading screening



1a 1.0 eq **21a** 1.05 eq **41**

Table 27: Catalyst loading screening to optimize SUZUKI-MIYAURA coupling.

Entry	Catalyst	30 min		2 h		24 h	
		Conversion[a]	**Selectivity[a]**	**Conversion[a]**	**Selectivity[a]**	**Conversion[a]**	**Selectivity[a]**
1	5 mol%	> 99 %	> 99 %	> 99 %	> 99 %	> 99 %	> 99 %
2	4 mol%	> 99 %	> 99 %	> 99 %	> 99 %	> 99 %	> 99 %
3	2 mol%	88 %	> 99 %	96 %	> 99 %	95 %	> 99 %
4	1 mol%	55 %	92 %	52 %	91 %	48 %	> 99 %
5	0.5 mol%	-	-	-	-	-	-

[a] Conversion and selectivity were monitored via GC-MS.

4 mol% catalyst loading were required to achieve full conversion (Table 27).

4.3.5 Temperature screening

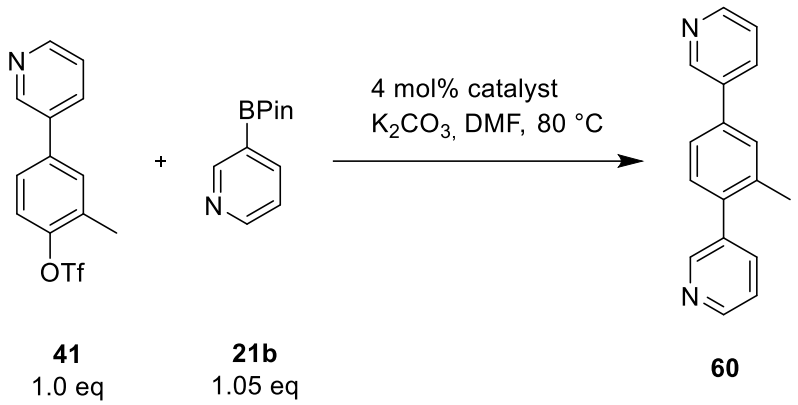
Table 28: Temperature screening to optimize SUZUKI-MIYAURA coupling.

Entry	Temperature	30 min		2 h		24 h	
		Conversion[a]	Selectivity[a]	Conversion[a]	Selectivity[a]	Conversion[a]	Selectivity[a]
1	22 °C	-	-	-	-	12 %	> 99 %
2	40 °C	19 %	> 99 %	56 %	> 99 %	93 %	> 99 %
3	60 °C	85 %	> 99 %	91 %	> 99 %	95 %	> 99 %
4	80 °C	> 99 %	> 99 %	> 99 %	> 99 %	> 99 %	> 99 %
5	80 °C[b]	77 %	> 99 %	> 99 %	> 99 %	/	/

[a] Conversion and selectivity were monitored via GC-MS, [b] K_2CO_3 was used as base, work-up after 2 h..

Full conversion was detected at 80 °C. Similar results were achieved with K_2CO_3 as base. Since Ag_2CO_3 is much more expensive than K_2CO_3 further coupling reactions were performed with K_2CO_3. Ag_2CO_3 can be used in cases with sensitive substrates as it is a weaker base (Table 28).

4.3.6 Screening for coupling of triflate



41 1.0 eq

21b 1.05 eq

60

Table 29: Catalyst screening to optimize SUZUKI-MIYAURA coupling of triflate.

Entry	Catalyst	2 h		24 h	
		Conversion[a]	Selectivity[a]	Conversion[a]	Selectivity[a]
1	$PdCl_2$(dppf)	7 %	> 99 %	15 %	> 99 %
2	$Pd(OAc)_2$/XPhos	2 %	> 99 %	87 %	30 %

[a] Conversion and selectivity were monitored via GC-MS.

The first reaction was heated to 100 °C and after 5 h 26 % conversion was detected by GC-MS (Table 29).

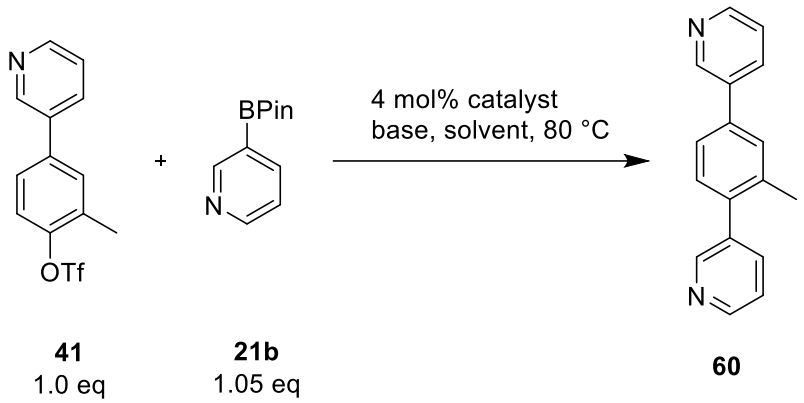
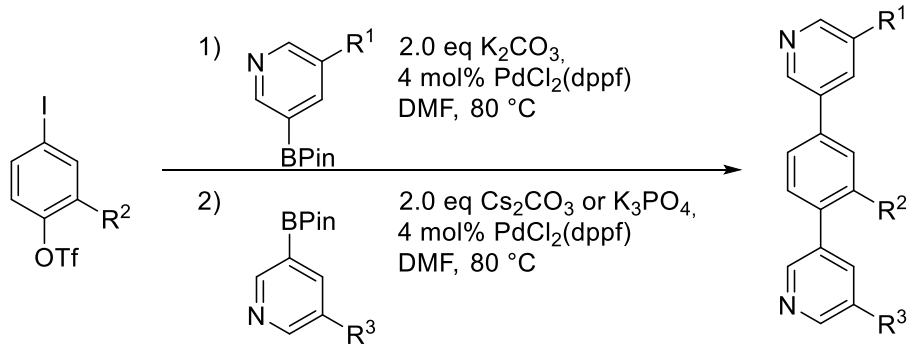


Table 30: Base screening to optimize SUZUKI-MIYAURA coupling of triflate.

Entry	Base	Solvent	2 h		24 h	
			Conversion[a]	Selectivity[a]	Conversion[a]	Selectivity[a]
1	Cs_2CO_3	DMF	> 99 %	> 99 %	> 99 %	96 %
2	K_3PO_4	DMF	> 99 %	> 99 %	> 99 %	> 99 %
3	NaOEt	DMF	> 99 %	54 %	> 99 %	-
4	NaOEt	EtOH	88 %	7 %	> 99 %	13 %

[a] Conversion and selectivity were monitored via GC-MS.

With K_3PO_4 and Cs_2CO_3 similar results were achieved (Table 30). The conditions were optimized for a simplified reaction-system and maybe need to be adjusted for more complex substrates. Nevertheless various conditions were screened and can be optimized rapidly for special substrates. The optimized conditions for the coupling of triflate were found to be 4 mol% $PdCl_2$(dppf) in DMF as solvent at 80 °C and Cs_2CO_3 or K_3PO_4 as base (Scheme 60).



Scheme 60: General reaction scheme for SUZUKI-MIYAURA cross-coupling.

5 Summary

Protein-Protein-Interactions have received increasing attention as potential drug targets. With more than 60 % involvement in PPIs alpha-helical peptide chains are the most common secondary structure motif.[4]

With the identification of hotspot areas the relevance of using small molecules as inhibitors for PPIs has been demonstrated.[114] Encouraged by these promising data various different backbone structures and synthetic strategies have been developed by chemists (Figure 32).

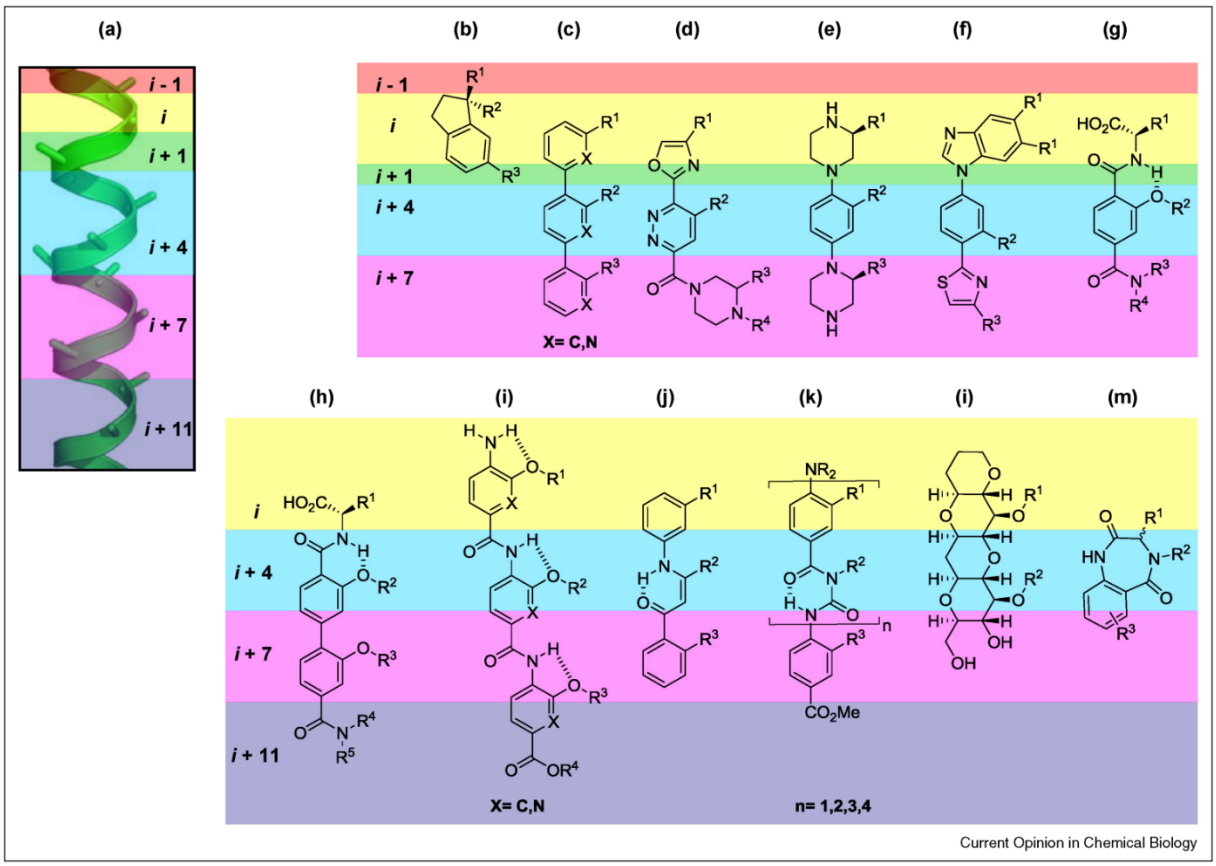


Figure 32: An overview of α-helix mimetics, picture taken from Ref. [8].

All these strategies have been highlighted with one or only few very similar structures and were designed for specific protein-complex test case. So far no general approach for the synthesis of α-helix mimetics was established with the exception of the strategy of LIM[40,41] and BOGER.[38,39] Due to the frequent occurrence of this secondary structure motif and the growing importance of PPIs in medicinal chemistry rapid access to α-helix mimicking small molecules would be desirable.

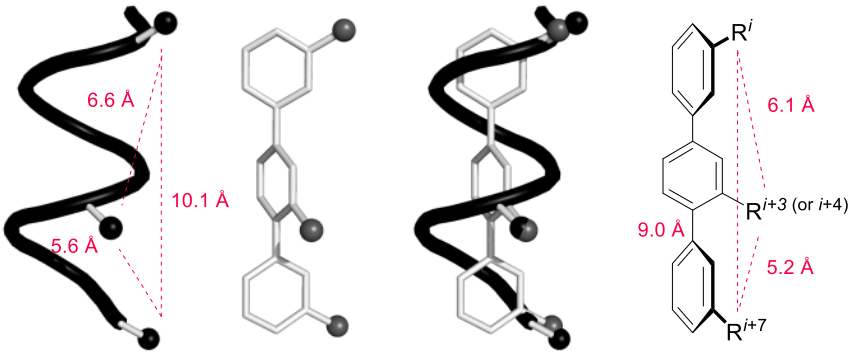
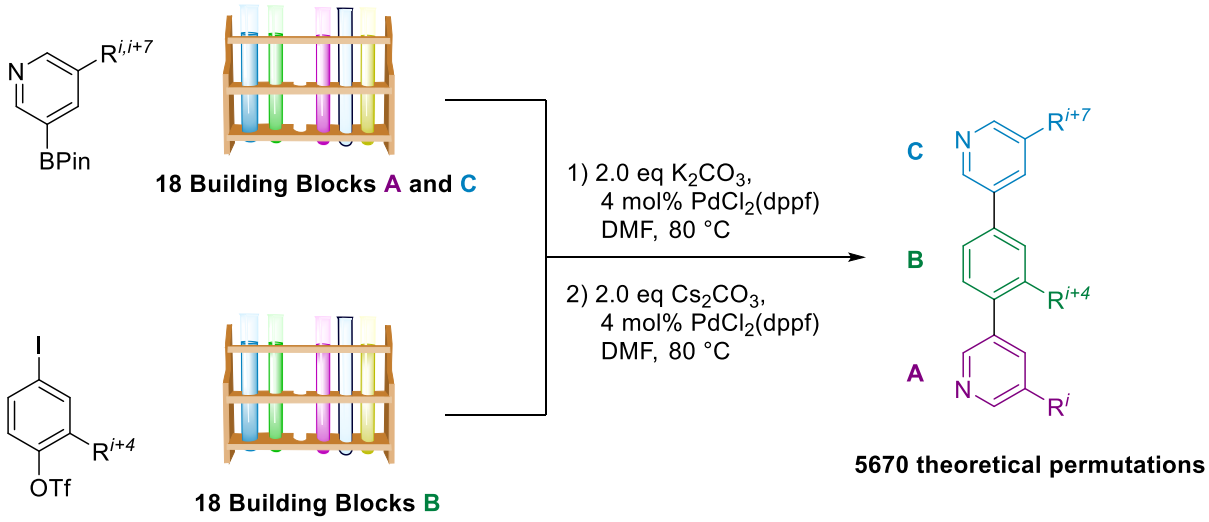


Figure 33: HAMILTON´s terphenylic scaffold, picture taken from Ref. [24].

Building on the concept by HAMILTON (Figure 33) in this thesis a general synthetic route for the synthesis of terarylic scaffolds was proposed. In contrast to HAMILTON's first suggested backbone structure two of the three phenyl rings of the very unpolar terphenyls were exchanged with more polar pyridine rings (Scheme 61). Instead of following a linear reaction pathway a modular strategy was developed using building blocks, which were assembled in a sequential two step SUZUKI-MIYAURA coupling procedure.



Scheme 61: Modular approach for teraryl synthesis.

For this approach it was necessary to provide a core unit fragment with two leaving groups suitable for Pd-catalyzed cross-coupling and differentiated in reactivity to achieve regioselectivity. As leaving groups on the one hand triflate was introduced to exploit the variety of commercially available phenol precursors and on the other hand iodine was installed by well-established electrophilic aromatic substitution chemistry. The side chains for both building block sets were chosen according to the side chains occurring in natural amino acids involved

in PPIs. The building blocks for the core unit fragment were synthesized in 2 to 6 steps and the overall yields were between 29 and 82 % (Figure 34).

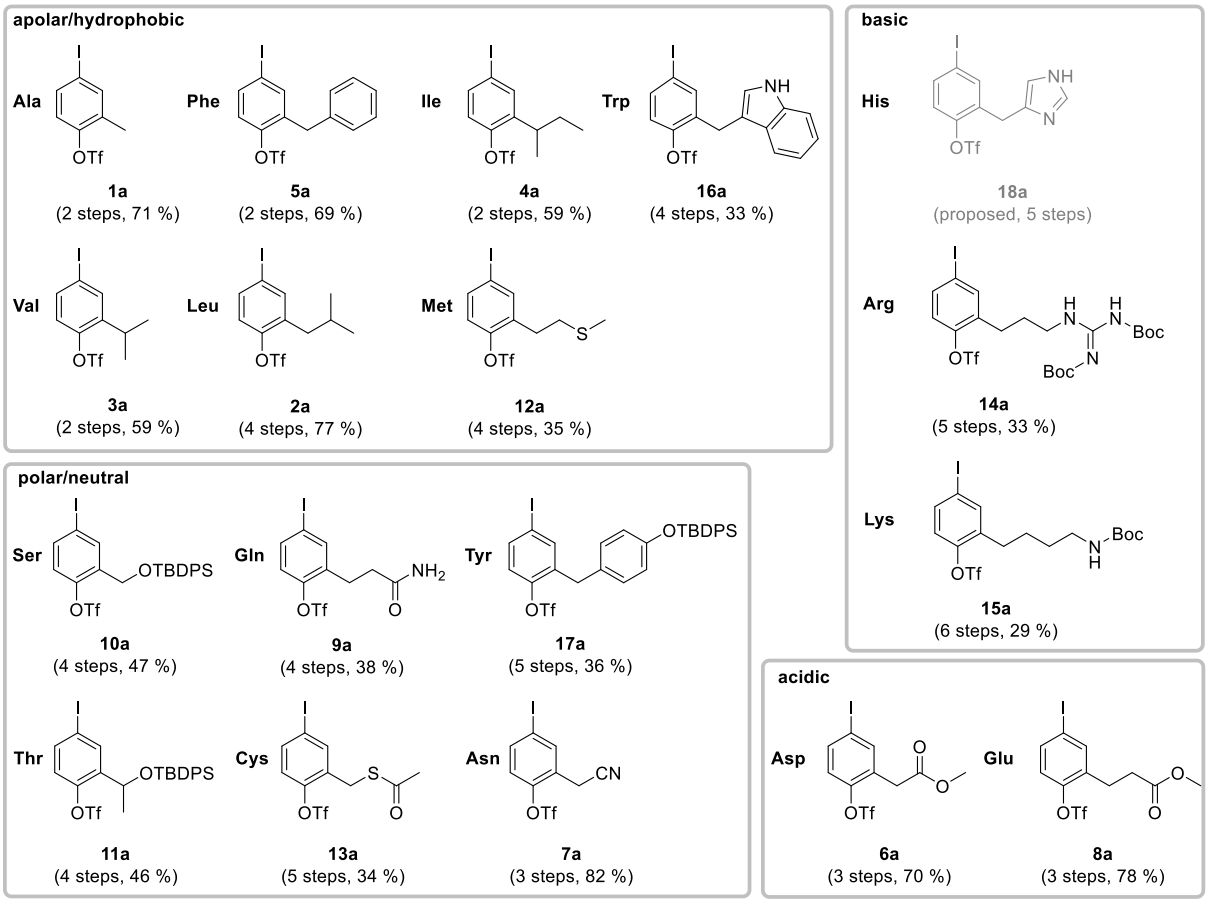


Figure 34: Overview over synthesized core unit fragments.

The second set of building blocks consists of pyridine boronic acid esters in a 3,5-substitution pattern. It is assumed that the polar nitrogen points away from the protein and is presented to the aqueous environment. By introducing more polar heterocycles a major drawback of these unpolar molecules was tackled, as the increased polarity should enhance solubility under physiological conditions and lead to better bioavailability of the synthesized molecules. Since the electronic properties of pyridines are not comparable to phenyl rings it was impossible to use the same synthetic strategies as for the synthesis of the core unit fragments. The side chains as well as the pinacol boronic acid esters were installed in every case either by using KNOCHEL-GRIGNARD type chemistry or transition metal catalysis. For all building blocks 3,5-dibromopyridine or 3,5-dichloropyridine were used as starting material providing the correct substitution pattern. All pyridine boronic acid ester building blocks were synthesized in 2 to 6 steps with overall yields between 11 and 52 % (Figure 35).

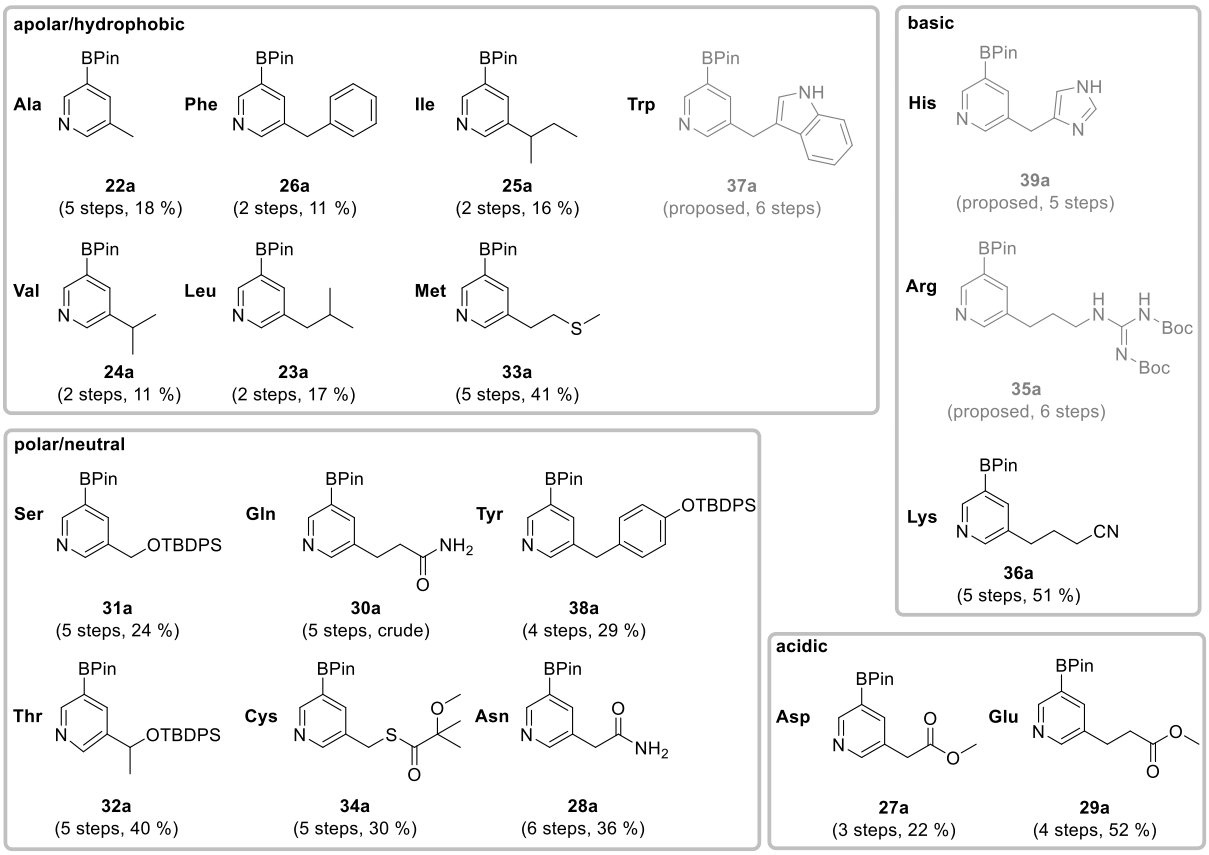
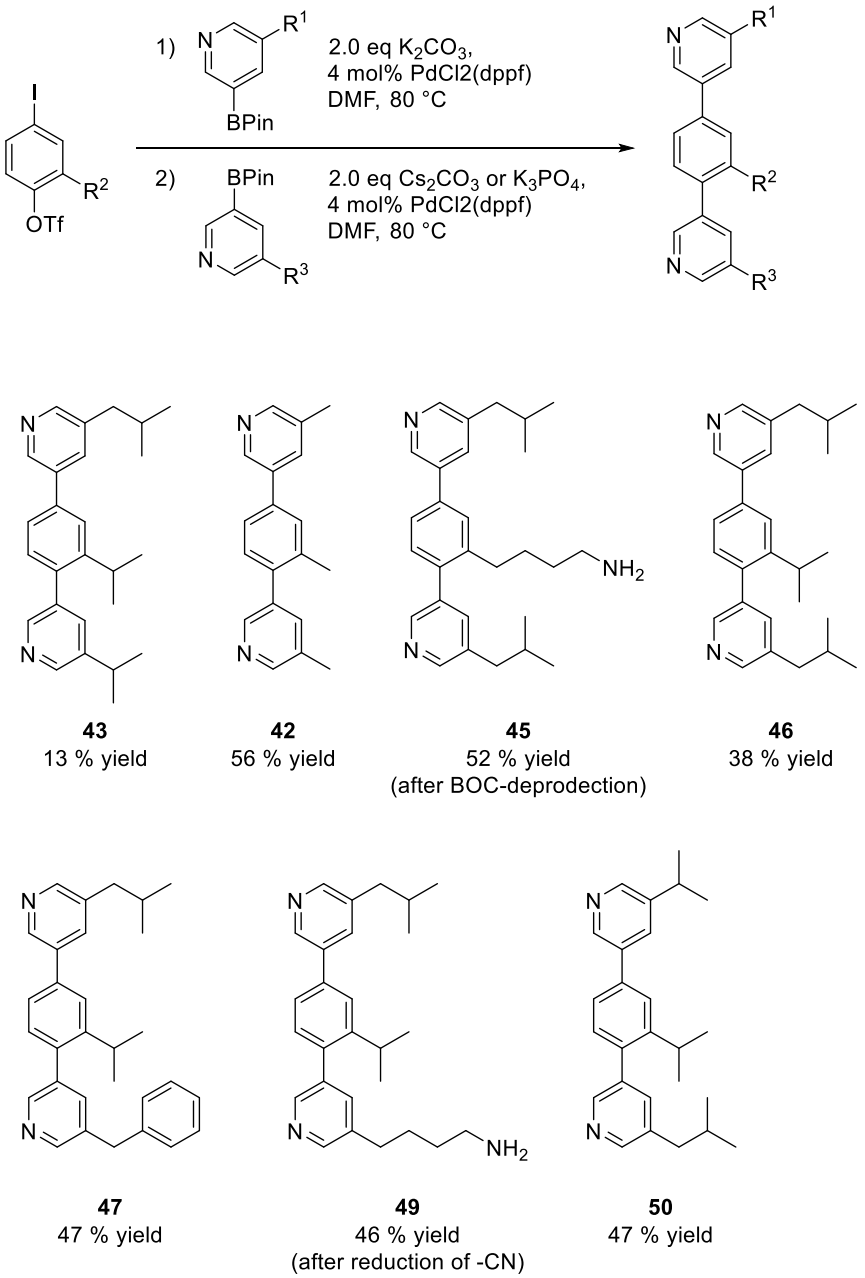


Figure 35: Overvied over synthesized pyridine boronic acid ester building blocks.

With all building blocks but His, Trp and Arg in hand the assembly of teraryls was investigated. Since pyridines can also coordinate to Pd the incomplete conversion was detected in the SUZUKI-MIYAURA coupling and the teraryls were isolated in very poor yields when the cross-coupling conditions developed for terphenyls were used. After validating the coupling conditions the reaction time was shortened and the yield could be improved. By changing 1,2-DME to DMF faster reactions and also fewer by-products were detected in both coupling steps. $PdCl_2$(dppf) was found as suitable catalyst and the reaction proceeds nicely at 80 °C. The only difference between the coupling of iodine and the coupling of triflate was the added base. To couple the triflate-group a switch from K_2CO_3 to Cs_2CO_3 or K_3PO_4 was crucial (Scheme 62). The SUZUKI-MIYAURA reaction proceeded very selectively and no undesired coupling by-products were detected.

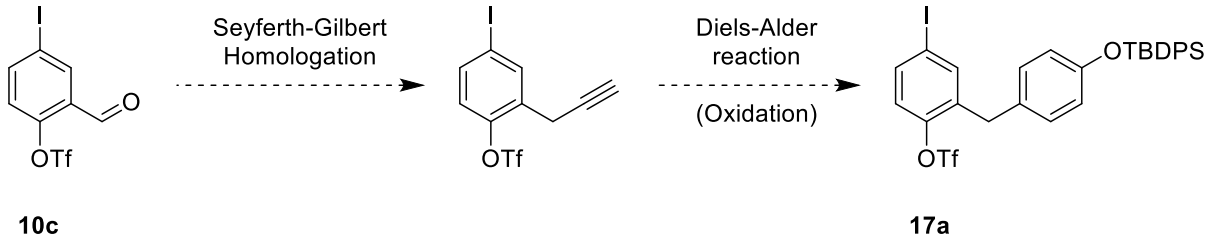


Scheme 62: General SUZUKI-MIYAURA coupling conditions and examples of synthesized teraryls.

With this method a highly modular reaction sequence was established, which provides rapid access to a functionally complex compound class (Scheme 62). Promising biological results achieved by other groups encourage the application of teraryls as α-helix mimetics and make library synthesis attractive. By this building block system various teraryls can be synthesized in short time. The building blocks are not restricted to the set shown within this work, they can be expanded and also designed for special PPI. Different methods for the building block synthesis have been shown and can be applied to introduce various other side chains extending to unnatural amino acid side chains. Stable building blocks make the handling and storage easy and ensure fast access to teraryls.

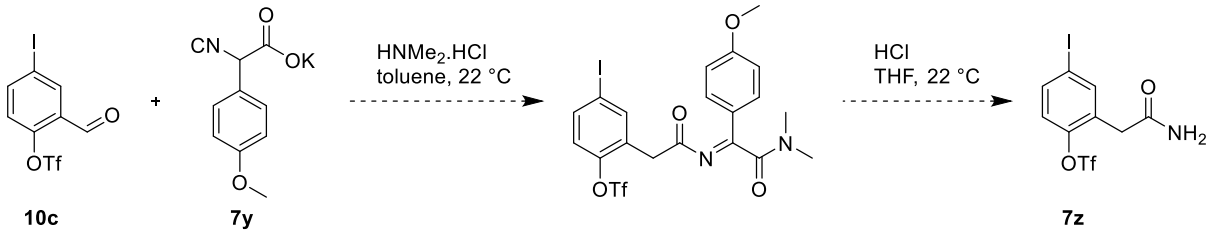
6 Outlook

Despite all building blocks mimicking the side chains of natural amino acids were synthesized for both, the core unit fragment and the pyridine boronic acid building blocks, some synthetic strategies need to be further optimized. Low yields and rather long reaction sequences impede the scale up process and the production of larger quantities of the desired building blocks. In order to guarantee rapid access to the desired teraryls, it would be preferred to have the building blocks in stock and ready for the two step coupling procedure. Alternative routes have already been initiated for the Tyr-core unit fragment and the Lys-pyridine boronic acid building block. By using a Diels-Alder reaction, protecting groups should be avoided in case of the Tyr-core unit fragment (Scheme 63).



Scheme 63: Alternative route for Tyr-core unit fragment.

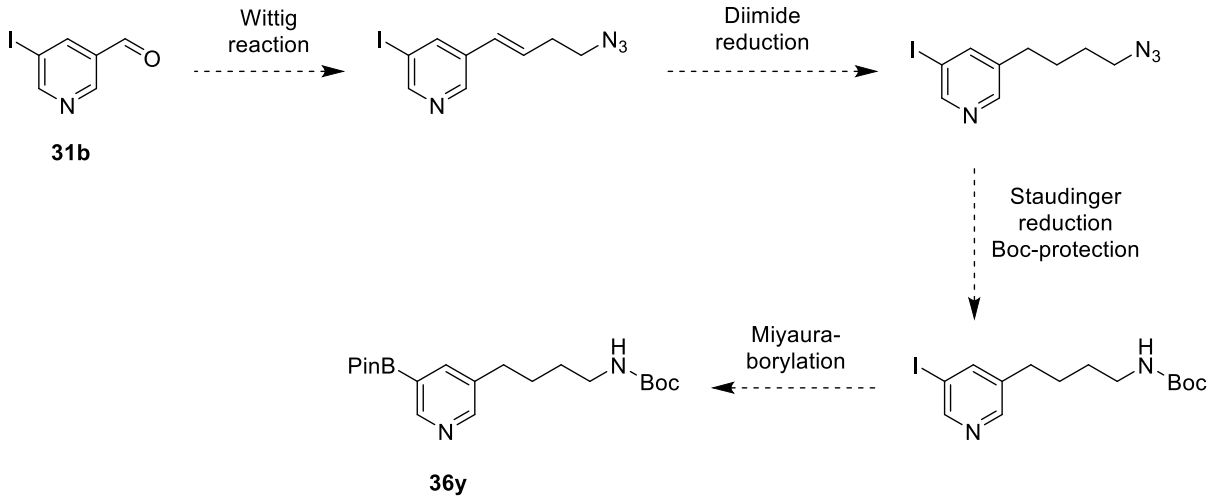
The Asn-building block was synthesized protected as nitrile, which has to be converted to the amide after teraryl assembly. It would be more convenient to have access to the free amide to avoid an additional deprotection step. An alternative route would be an oxidative homologation using the iodinated and triflated salicylic aldehyde **10c** as starting material.[115] Unfortunately, the reagent **7y** is not commercially available and has to be synthesized (Scheme 64).



Scheme 64: Alternative synthetic route for the Asn-building block.

The Lys-pyridine boronic acid ester was prepared protected as nitrile. Therefore one additional reduction step would be necessary after the teraryl-coupling. Although the alternative route requires one additional reaction step in comparison to the original route several advantages are given. Using a Boc-protecting group would facilitate the deprotection step since all other

amines (Lys- and Arg-building blocks) are also Boc-protected. In the alternative route the side chain should be introduced by a WITTIG reaction containing an azide (Scheme 65).[116]



Scheme 65: Alternative route for the Lys-paridine boronic acid building block.

In medicinal chemistry not only the synthesis of new inhibitors and biologically active substances is essential. The interface between organic synthesis and chemical biology is more and more overlapping and collaborations are playing important roles in identifying new drug-like small molecules.

The general approach presented in this work permits rapid access to a diverse set of substituted teraryls. Having established the synthetic approach to the building blocks the next step will be synthesizing sets of teraryls for chemical biology. For the beginning two different protein complexes in collaboration with two other groups were envisioned.

6.1 Rho GTPase and Rock

The Rho-Rock pathway is strongly associated with various miscellaneous cellular processes. By modulating the phosphorylation level of different signaling proteins cell migration, neurite outgrowth, and smooth muscle contraction are influenced. Abnormal activation of the Rho-Rock pathway was also linked to diseases including tumor formation, hypertension and bronchial asthma. Therefore this protein-protein-interaction might serve as a potential drug target. AHMADIAN et al. reported the crystal structure of the complex between active RhoA and the Rho-binding domain of ROCKI.[117] Two forms of ROCK are known, the inactive autoinhibited state and the active Rho-GTP bound form. Rho, activated by GTP, binds to the Rho-binding domain (RBD) which is located at the *C*-terminal end of the amphipathic α-helical coiled-coil region (Figure 36). Binding of Rho-GTP triggers a conformational change of ROCK

to expose the catalytically active kinase domain which is able to phosphorylate many signaling molecules that are critical for numerous physiological functions.

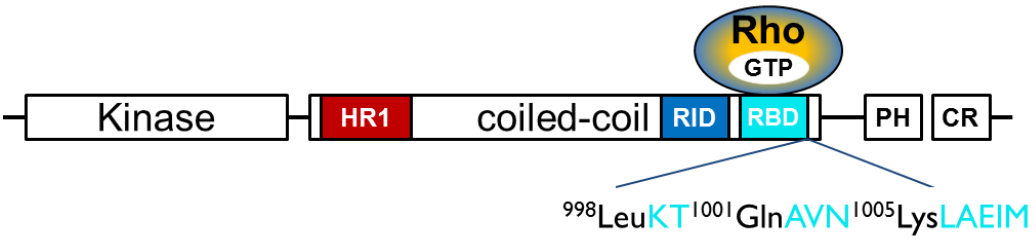


Figure 36: Schematic depiction of the ROCKI domain architecture with a kinase domain at the N-terminus, a coiled-coil region and a pleckstrin-homology domain (PH) followed by a cysteine-rich domain (CRD). The Rho-binding domain (RBD) is located at the C-terminus of the coiled coil region, picture taken from Ref. [117].

Since α-helical peptides are involved in the interaction between Rho and ROCK this protein complex is a potential target for α-helix peptidomimetics. After analysis of the crystal structure a teraryl was modelled into the "hotspot" interaction region and overlaid with the α-helical region of ROCK (Figure 37).

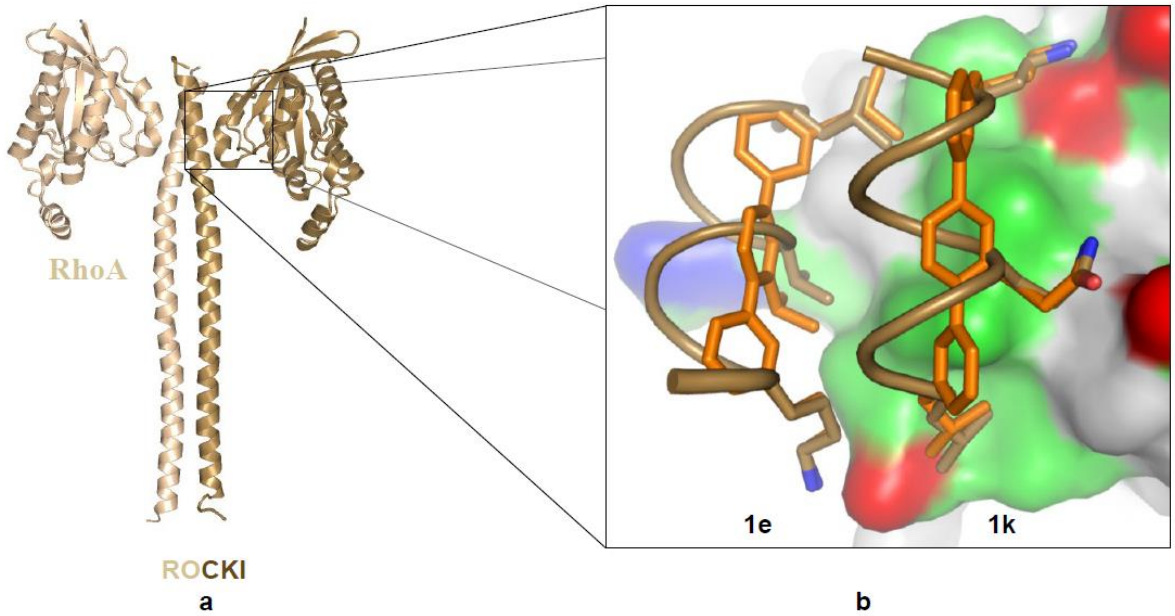


*Figure 37: Dimeric protein-complex of human ROCKI and human RhoA depicted as cartoon (**a**). The "hotspot" of interaction surface and the computer modeled lead-structures **1k** and **1e** mimicking the α-helix of ROCK (**b**); calculations were performed by DVORSKY (PDB file: 1S1C).[117] The two α-helices of human ROCKI are shown as cartoon loop (sand), lead-structures **1e** and **1k** are illustrated as sticks (orange) and human RhoA is given as surface (green, red, blue and grey), picture taken from Ref. [24].*

The calculations performed by DVORSKY leads to the target structure and also a reference structure (Figure 38). The two teraryls **51** and **52** will be synthesized using the modular approach investigated within this work.

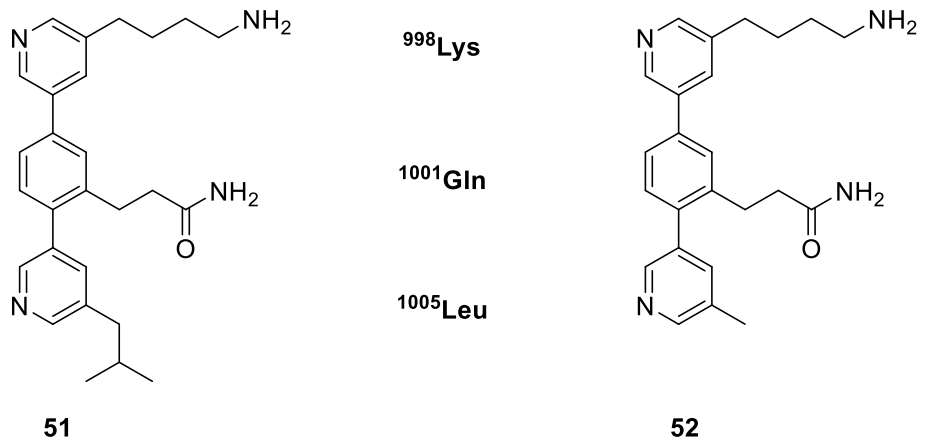


Figure 38: Target structure and reference for investigation on inhibition of Rho/Rock interaction.

6.2 Axin and beta-catenin

Wnt is a diffusible ligand protein that activates the Wnt signalling cascade. The Wnt (Wingless and INT-1) signal transduction cascade regulates the expression of numerous genes associated with cell differentiation, proliferation and survival. Unusual activated signaling by Wnt pathway is found in the onset and progression of different types of tumors including 90 % of colon cancer. The growth and survival of these tumors depends on Wnt signaling and therefore inhibition of this pathway would be an attractive therapeutic option. Most oncogenic activations of Wnt signaling show increased cellular levels of β-catenin. In the absence of Wnt, β-catenin is engaged into a multicomponent "destruction complex" formed inter alia by the proteins adenomatous polyposis coli (APC), Axin, casein kinase 1α (CK1α), and glycogen synthase kinase 3β (GSK3β). In this complex β-catenin is phosphorylated and degraded by the proteasome. This leads to low cellular levels of β-catenin in the absence of Wnt signals. Is the Wnt signalling pathway activated the destruction complex is inhibited which leads to β-catenin accumulation in the cell followed by translocation to the nucleus. There β-catenin serves as a transcriptional coactivator for T-cell factor (TCF) proteins, the downstream transcriptional regulators of the Wnt pathway (Figure 39).[118,119]

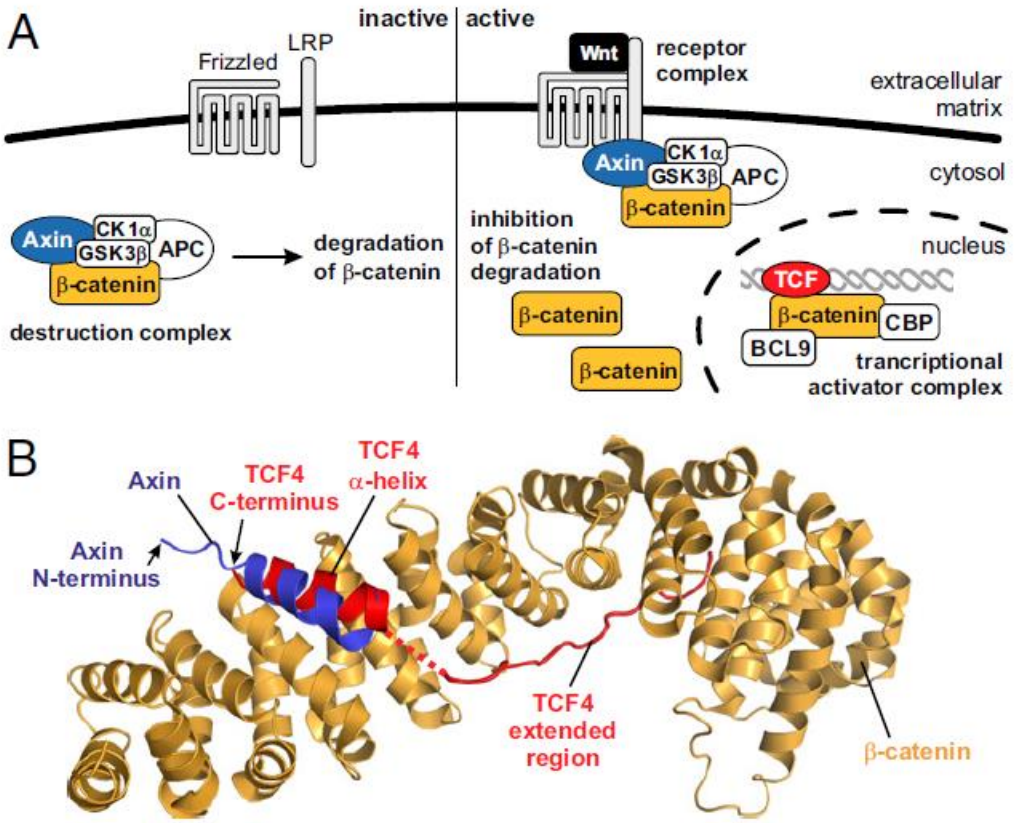


Figure 39: Wnt/β-catenin signaling. (A) The canonical Wnt signaling pathway with its major components in the inactive (Left) and active (Right) state. (B) Superimposed crystal structures of the β-catenin armadillo domain bound to the CBDs of Axin (PDB ID 1QZ7) and TCF4 (PDB ID 2GL7), picture taken from Ref. [118].

GROSSMANN et al. used the β-catenin/TCF interaction as target since this interaction is well established and it is also important in tumor cell growth maintenance.[120] They discovered a hydrocarbon-stapled peptide that directly targets β-catenin and interferes with its ability to serve as a transcriptional coactivator for T-cell factor (TCF) proteins.[118] The interaction between β-catenin and peptide ligands has been structurally characterized and it has been shown that an α-helical motif is involved. Therefore it serves also as possible target for the presented modular teraryl approach. Four teraryls **43**, **45**, **46** and **50** were already synthesized and tested but due to solubility issues no inhibition could be detected (Figure 40).

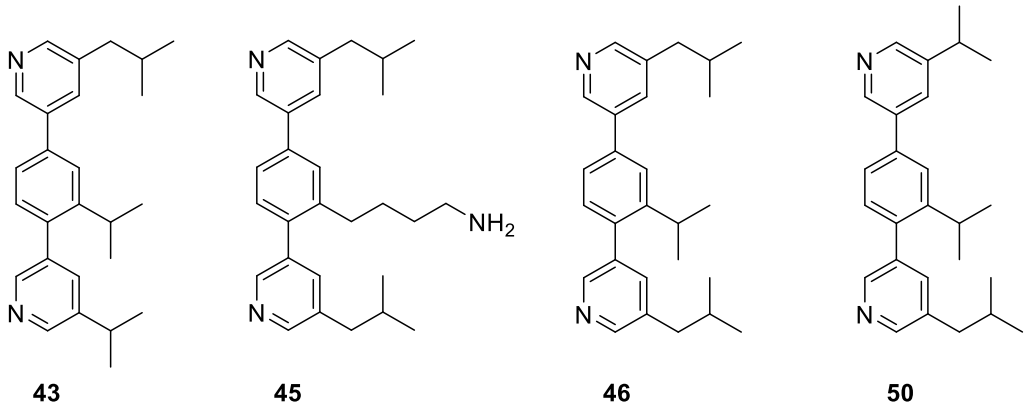


Figure 40: Synthesized Teraryls for addressing β-catenin/TCF PPI.

After calculating the "hotspots" by alanine scanning mutagenesis GROSSMANN et al. suggested five more terarylic structurs **53-57**. To overcome solubility issues more polar side chains should be incorporated (Figure 41).

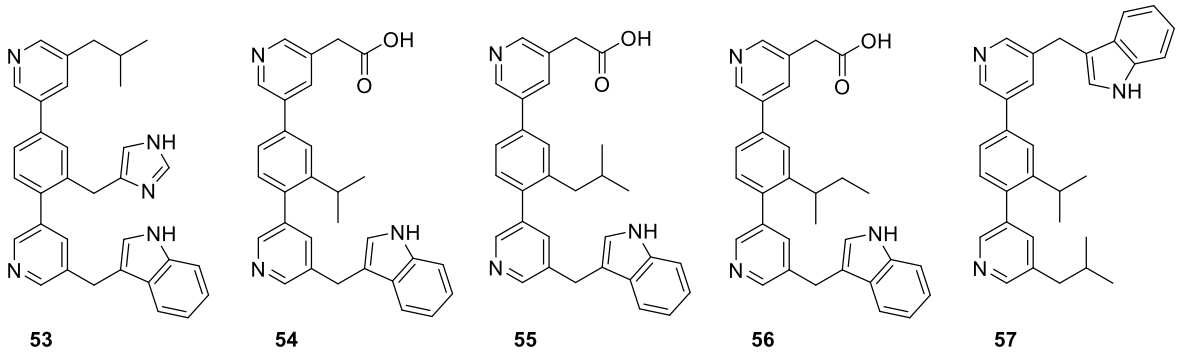


Figure 41: Improved terarylic structures.

These two cases of protein-protein-interactions are only a few representatives that are currently investigated in cooperation with the groups AHMADIAN and GROSSMANN. With the herein shown modular synthetic approach a large number of protein-protein-interactions can be addressed. Combinatorial methods might also be used to synthesize and test larger libraries. Therefore this strategy is not only suitable for PPIs with already solved crystal structures and structure based design but can also be used for random design and unbiased high throughput screenings.

7 Experimental Section

7.1 General Experimental Aspects[24]

All chemicals were purchased from Acros Organics, Alfa Aesar, Fluka, Sigma Aldrich and ABCR. They were used without further purification.

Inert reactions were carried out by using standard Schlenk technique. Oxygen and humidity sensitive reactions were performed under argon or nitrogen atmosphere using dry and degassed solvents. For degassing of solvents two different protocols were used: Low boiling solvents were frozen with liquid nitrogen and evacuated. When the solvent starts melting the Schlenk-flask was backfilled with inert gas. This procedure was repeated three times. For solvents with a high boiling point inert gas was passed through the solvent by a cannula while the flask was sonicated in an ultrasonic bath. This procedure was carried out for 20 to 30 min, depending on the amount of solvent. All reagents were added in counterstream of inert gas to keep the inert atmosphere.

7.2 Solvents[107,121]

All solvents were used at commercial quality without further purification, unless otherwise noted. Dry solvents, which were not commercially available, were prepared according to the following procedures and stored over activated molecular sieves in dark Schlenk-bottles under light exclusion and argon. For that purpose 3Å or 4Å molecular sieves were activated at oil pump vacuum (0.02 mbar) at 200 °C for 2 days.

Acetic acid: Acetic acid (96%) was purchased from Acros Organics and stored in brown glass bottles.

Acetonitrile (CH_3CN): CH_3CN was bought from Acros Organics in a 2.5 L brown glass bottle and used as received.

Chloroform: was bought from VWR Chemicals and used as received.

Cyclohexane: Cyclohexane was bought from Fisher Chemicals and stored in 5 L plastic bottles.

1,2-Dichloroethane (DCE): 1,2-Dichloroethane was purchased from ACROS Organics as extra dry solvent (99.8 %, H2O <50 ppm, AcroSeal®) and directly used in the reactions.

Dichloromethane (DCM): DCM was bought from Fisher Chemicals in 5 L plastic bottles and used as received.

DCM stabilized with EtOH was first dried with P_4O_{10}, distilled and than heated under reflux over CaH_2 and distilled into a brown glass bottle where it was stored over 4 Å molecular sieves under argon.

Diethylether (Et_2O): Et_2O was bought from VWR in a 25 L metal can and distilled on a rotary evaporator to remove the stabilisers. Et_2O was stored over KOH in brown glass bottles to bind formed peroxides.

1,2-Dimethoxyethane (1,2-DME): 1,2-DME was bought from Sigma-Aldrich in 1 L glass bottles an used directly in the reactions.

Dry 1,2-DME was prepared by filtering through an alox-column (Pure Solv by Innovative Technology) and it was stored over 4 Å molecular sieve in brown glass bottles under Ar or 1,2-DME was refluxed over metallic sodium. Benzophenone was used as indicator, turning blue when the solvent was dry. The dried 1,2-DME was further distilled and stored in a brown glass bottle over 4 Å molecular sieves under argon.

***N*,*N*-Dimethylacetamide (DMAc):** *N*,*N*-Dimethylacetamide was purchased from Merck-Schuchardt and directly used in the reactions.

***N*,*N*-Dimethylformamide (DMF):** DMF was purchased from Merck-Schuchardt in brown glass bottles and directly used in the reactions.

Dry *N*,*N*-Dimethylformamide was purchased from ACROS Organics as extra dry solvent (99.8 %, over 3 Å molecular sieves, H_2O <50 ppm, AcroSeal®) and transferred into a brown glass bottle where it was storred over 3 Å molecular sieves under argon atmosphere.

Dimethylsulfoxide (DMSO): DMSO was bought from Alfa Aesar in 1 L glass bottles and used directly in the reactions.

1,4-Dioxane: Under inert conditions 1,4-dioxane was dried at reflux temperature over sodium and benzophenone until ketyl radical indicated dryness by the appearance of a deep blue color. 1,4-dioxane was distilled and stored over 4 Å molecular sieves in a brown glass bottle under argon atmosphere.

Ethanol (EtOH): EtOH was bought in 25 L plastic cans from Merck and used as received.

Ethyl acetate (EtOAc): Ethyl acetate was bought from Fisher Chemicals and stored in 5 L plastic bottles.

Mesitylene: Mesitylene was bought from Fluka and storred in a brown glass bottle.

Methanol (MeOH): MeOH was bought from Fisher Chemicals, stored in 5 L plastic bottles and used as received.

Methanol was distilled over Mg, activated with I_2 and stored over 3 Å molecular sieves in brown glass bottles under argon.

Nitromethane: Nitromethane was bought from Alfa Aesar in 98 % purity and used directly in the reactions.

Pentane: Pentane was bought from Roth in 25 L metal cans and destilled in a rotary evaporator before use.

2-Propanol (*i*PrOH): *i*PrOH was bought in 10 L plastic cans and used as received.

Pyridine: Pyridine was purchased from Merck-Schuchardt and used as received.

Tetrahydrofuran (THF): THF was distilled on a rotary evaporator to remove the stabilisers and stored over KOH in brown glass bottles to bind formed peroxides.

THF was dried at reflux temperature under argon atmosphere over sodium and benzophenone until ketyl radical indicated dryness by the appearance of a deep blue color. Dry THF was distilled and stored over 4 Å molecular sieves in a brown glass bottle under argon atmosphere.

Toluene: Toluene was bought from Sigma-Aldrich in 2.5 L glass bottles and used as received.

Dry Toluene was prepared by filtering through an alox-column (Pure Solv by Innovative Technology) and it was stored over 4 Å molecular sieves in brown glass bottles under argon.

7.3 Analytical Methods[24]

7.3.1 Nuclear magnetic resonance

NMR spectra were recorded on a Bruker Avance III 300 MHz FT NMR spectrometer (300.36 MHz (^{1}H), 75.53 MHz (^{13}C)). Chemical shifts δ [ppm] are referenced to residual protonated solvent signals as internal standard DMSO-d_6: δ = 2.50 ppm (^{1}H); 39.52 ppm (^{13}C), and $CDCl_3$: δ = 7.26 ppm (^{1}H); 77.16 ppm (^{13}C).[122] Signal multiplicities are abbreviated as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), dt (doublet of triplet), q (quadruplet), dq (doublet of quadruplet), sept (septet), m (multiplet) with the prefix b in case of broad signals. Superscript abbreviations are used as follows: HPy (pyridyl), HAr (phenyl), HBPin (boronic acid pinacol ester) and HPhth (phthalimide); abbreviation Cq is used for quaternary carbon atoms. ^{1}H NMR resonances were assigned by 2D-COSY experiments and ^{13}C NMR resonances by APT and 2D-HSQC experiments. Chemical shifts are stated in ppm (part per millions) and the coupling

constants in Hz (Hertz). To reduce the number of signals all ^{13}C and APT NMR spectra were ^{1}H decoupled.

7.3.2 Gas chromatography

For analytical gas chromatography two different instruments were used. GC-MS measurements were performed on an Agilent Technologies 7890A (G3440A) GC system equipped with an Agilent Technologies J&W GC-column HP-5MS ((5%-phenyl) methylpolysiloxane; length: 30 m; inner-diameter: 0.250 mm; film: 0.25 µm) at a constant helium flow rate with He 5.0 as carrier gas. The sample was injected in split mode using an Agilent Technologies 7683 Series autosampler and an Agilent Technologies 7683B Series injector. The GC was coupled to a 5975C inert mass sensitive detector with triple-axis detector (MSD, EI, 70 eV; transfer line: 300°C; MS source: 240°C; MS quad: 180°C). Different temperature programs were used.

MT_50_XS: 50°C 1 min, ramp: 10°C·min^{-1} linear to 150°C, 150°C 2 min, ramp: 40°C·min^{-1} linear to 300°C, solvent delay: 3.0 min

MT-50_35S: 50°C 1 min, ramp: 40°C·min^{-1} linear to 300°C, 300°C 5 min, solvent delay: 3.5 min

MT_50_S: 50°C 1 min, ramp: 40°C·min^{-1} linear to 300°C, 300°C 5 min, solvent delay: 4.0 min

MT_100_L: 100°C 1 min, ramp: 50°C·min^{-1} linear to 300°C, 300°C 12 min, solvent delay: 3.0 min

GC-FID measurements were performed employing an Agilent Technologies 6890N GC system with an Agilent Technologies J&W GC-column DB-1701 ((14%-cyanopropylphenyl)methylpolysiloxane; length: 30 m; inner-diameter: 0.250 mm; film: 0.25 µm). The injection was executed by an Agilent Technologies 7683 Series autosampler in split mode. Nitrogen 5.0 was used as carrier gas and for detection a flame ionization detector (FID) with Hydrogen 5.0 and air as detector gases were used. One method was used.

MT_FID: 80°C 1 min, ramp: 30°C·min^{-1} linear to 280°C, 280°C 3 min

When GC was used for reaction monitoring, the samples were prepared using a microscale workup. Therefore an aliquot was taken from the reaction mixture, quenched with ~1 mL aqueous solution and extracted with ~1 mL DCM. After proper mixing and phase separation, the organic layer was collected, dried over $MgSO_4$ and filtered through cotton in a Pasteur-pipette. Samples from reaction mixtures containing transition metals were prepared by filtering

through a short pad of silica gel (~1 cm) over cotton in a Pasteur-pipette (eluted with EtOAc or MeOH).

7.3.3 High-performance liquid chromatography (HPLC)

Analytical HPLC analysis was performed on a Shimadzu Nexera Liquid Chromatograph with a tempered column oven. The separation was performed on a C-18-Reversed-Phase column of the type „Poroshell® 120 SB-C18, 3.0 x 100 mm, 2.7 µm“ by Agilent Technologies. For detection a Shimadzu SPD-M20A Prominence Diode Array Detector at a wavelength of λ = 210 nm and a mass selective detector Shimadzu LCMS-2020 Liquid Chromatograph Mass Spectrometer in ESI positive and ESI negative mode were used.

MT_general: 0.0 – 4.5 min, linear, 10 % CH_3CN to 100 % CH_3CN (90 % to 0 % H_2O + 0.01 % HCOOH); 4.5 – 5 min, isocratic, 100 % CH_3CN, T = 40 °C, flow rate: 0.7 mL/min

MT_60to100: 0.0 – 4.5 min, linear, 60 % CH_3CN to 100 % CH_3CN (40 % to 0 % H_2O + 0.01 % HCOOH); 4.5 – 5 min, isocratic, 100 % CH_3CN, T = 40 °C, flow rate: 0.7 mL/min

7.3.4 Semi-preparative HPLC

For semi-preparative HPLC a Thermo Scientific Dionex Ulti Mate 3000 Instrument was used. Semi-preparative HPLC was carried out utilizing a Macherey-Nagel VP 125/21 Nucleodur 100-5 C18 ec column.

Prep_80to90: 0.0 – 2.5 min, isocratic, 80 % CH_3CN, 2.5 – 17.5 min, linear, 80 % CH_3CN to 90 % CH_3CN (20 % to 10 % H_2O + 0.01 % HCOOH); 17.5 – 18 min, linear, 90 % CH_3CN to 100 % CH_3CN (10 % to 0 % H_2O + 0.01 % HCOOH); 18 – 20 min, isocratic, 100 % CH_3CN, T = 30 °C, flow rate: 15 mL/min

For analytical and semi-preparative HPLC, demineralized water was additionally purified by filtering through a 0.2 µm cellulose nitrate membrane filter.

7.3.5 Thin layer chromatography (TLC)

For thin layer chromatography silica gel plates from Merck (silica gel 60 F_{254} aluminium sheets 20x20) were used. As detection methods UV–detection and staining with subsequent developing by hot air stream were used. The UV–detection was carried out at λ=254 and 366 nm. Different staining reagents were used depending on the different functional groups.

CAM: 50 g Ammonium molybdate, 2.0 g solid $Ce(SO_4)_2$ and 50 mL concentrated sulphuric acid were dissolved in 400 mL distilled water.

Ninhydrin: 1.5 g ninhydrin were dissolved in 100 mL n-butanol and then 3.0 mL acetic acid were added.

$KMnO_4$: 1.5 g of $KMnO_4$ and 10 g K_2CO_3 were dissolved in 200 mL water and 1.25 mL 10% NaOH were added.

Vanillin: 15 g vanillin were dissolved in 250 mL ethanol and 2.5 mL concentrated sulphuric acid.

$FeCl_3$: 5 g $FeCl_3$ were dissolved in 100 mL 0.1 M HCl.

7.3.6 Flash column chromatography

For preparative flash column chromatography silica gel from Acros Organics (silica gel, for chromatography 0.035 – 0.070 mm, 60 Å, nitrogen flushed) was used. The amount of silica depends on the specific separation problem and was in general the 20 to 100 fold amount of crude product. The column diameter was chosen to give a filling level between 15 and 25 cm. As fraction size, typically one third or half of the volume of the used silica gel volume was chosen. The eluent was selected to result in a R_f-value between 0.2 and 0.3 of the to-be-isolated substance. If the crude product was not soluble in the eluent, the sample was dissolved in a proper solvent (DCM or EtOAc) and the 2.5 fold amount of Celite®545 (particle size 0.02-0.1 mm) was added, followed by removing the solvent using a rotary evaporator and drying in vacuum.

7.3.7 High resolution mass spectroscopy (HRMS)

HRMS measurements were performed on a Waters GCT Premier-system, after ionisation by an EI ionisation source with a potential of E = 70 eV. The measured sample was directly injected as solution. Measurements were perfomred at the ICTM by Prof. Dr. Robert Saf and his working group. The reported value is for a given species, is stated as mass to charge ratio and accompanied by the corresponding calculated value.

7.3.8 Melting point

All stated melting points were determined by using the melting point apparatus “Mel-Temp®” by Electrothermal. For better visibility the apparatus was equipped with a microscope attachment. The reported values are the mean of a duplicate determination and are given uncorrected.

7.3.9 Hydrogenation

High pressure hydrogenation experiments were performed, utilizing an H-Cube™ continuous hydrogenation unit (HC-2.SS) from Thales Nanotechnology Inc. with a Knauer Smartline pump 100, equipped with a 10 mL ceramic pump head. As hydrogenation catalyst a 10% palladium on carbon powder cartridge (Thales Nanotechnology Inc., THS 01111, 10% Pd/C CatCart™), or a Raney-Nickel cartridge (Thales Nanotechnology Inc., THS 01112, Raney-Nickel CatCart™) was used.

The workup of batch hydrogenation experiments utilizing metal catalysts was performed by filtering off the catalyst using a pad of SiO_2 under inert conditions and eluted with MeOH. The hydrogenation catalyst was washed with H_2O under inert gas and then stored in a glass bottle covered with water.

7.4 Experimental Procedures

7.4.1 Titration of Alkyl-Li solution

A flame dried Schlenk-flask was charged with 2.0 mL absolute THF and 300 mg diphenylacetic acid. The alkyl-Li solution was added dropwise under inert conditions. The equivalence point was indicated by a colour change from colourless to yellow. To ensure a precise titration a triple determination was performed. The titration was carried out before every use of the *tert*-BuLi solution.

7.4.2 General procedure for titration of GRIGNARD-reagent solutions

A flame dried Schlenk-flask was charged with 200.0 mL absolute, degassed toluene and 20.0 mL absolute 2-butanol. This stock solution was stored under an atmosphere of argon over 3 Å molecular sieves (stable over months). The concentration of this stock solution (c = 0.86 M) was used as reference for the titration of GRIGNARD-reagent solutions and was determined by NMR.

In a flame dried and argon flushed 10 mL Schlenk-tube 1 mg *o*-phenantroline was dissolved in 2 mL anhydrous toluene and 0.5 mL of the GRIGNARD-reagent to be titrated were added under inert conditions. The solution was titrated with a standard solution (0.86 M) of butan-2-ol in toluene under inert conditions. The equivalence point was indicated by a colour change from purple to yellow. The added moles of butan-2-ol are equal to the moles GRIGNARD-reagent in the given aliquot. To ensure a precise titration a triple determination was performed. The titration was carried out before every use of the GRIGNARD solution.[123]

7.4.3 Synthesis of Core Units

7.4.3.1 Representative procedure for the iodination of phenol derivatives A

In a one-neck round-bottom flask 1.0 eq of the corresponding phenol derivative was dissolved in acetic acid (~0.75 M) and 1.0 eq iodine monochloride (ICl) was added at RT. In some cases additional ICl was added to ensure quantitative conversion. The reaction mixture was quenched by the addition of 100 mL 0.5 M $NaHCO_3$ solution and the aqueous phase was extracted with DCM (3 x 50 mL). The combined organic layers were washed with $Na_2S_2O_3$ solution (25%, 3 x 100 mL), followed by saturated NaCl solution (1 x 100 mL). After drying over $MgSO_4$ and filtering the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography.[80,80,85]

7.4.3.2 Representative procedure for the iodination of phenol derivatives B

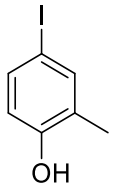
In a one-neck round-bottom flask 1.0 eq iodine monochloride (ICl) was dissolved in DCM (~1 M) and cooled to 0 °C. 1.0 eq of the corresponding phenol derivative dissolved in DCM (~1 M) was added. The reaction was warmed to RT and stirred until full conversion was observed. In some cases additional ICl was added to ensure quantitative conversion. The reaction mixture was diluted with 100 mL DCM and washed with $Na_2S_2O_3$ solution (25%, 2 x 100 mL). The aqueous phase was extracted with DCM (3 x 50 mL) and the organic layer was then washed with saturated NaCl solution (1 x 200 mL). After drying over Na_2SO_4 and filtering, the solvent was removed under reduced pressure, and the crude product was purified via flash column chromatography or recrystallization.[80,89]

7.4.3.3 Representative procedure for the synthesis of the triflate derivatives from the corresponding phenols

In a one-neck round-bottom flask 1.0 eq of the corresponding phenol derivative was dissolved in pyridine (~1 M). After cooling the solution to 0 °C trifluoromethanesulfonic anhydride (Tf_2O) was carefully added. After stirring 5 min at 0 °C, the solution was allowed to warm to RT and stirred until quantitative conversion was detected by TLC. 60 mL Et_2O were added and the organic phase was washed with H_2O (3 x 30 mL), followed by extracting the combined aqueous layers with Et_2O (2 x 30 mL). The combined organic lyers were washed with 1 M HCl (2 x 60 mL) and saturated NaCl solution (1 x 60 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified via flash column chromatography.[80,86]

7.4.3.4 Synthesis of Alanine building block

7.4.3.4.1 4-Iodo-2-methylphenol (1b)



1b

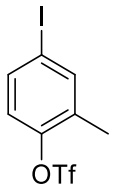
Compound **1b** was prepared according to procedure 1.4.1.1 from 2.00 g *o*-cresole (**1c**) (18.5 mmol, 1.0 eq) in 25 mL acetic acid and 1.11 mL ICl (3.60 g, 22.2 mmol, 1.2 eq). After 24 h again 250 µL ICl (810 mg, 4.99 mmol, 0.3 eq) were added and quantitative conversion was detected after 27 h. After flash column chromatography (100 g SiO_2, 4.5 x 13.5 cm, eluent: cyclohexane/EtOAc = 10/1, R_f = 0.27, UV and CAM) compound **1b** was isolated as a pale brown powder.[80]

Yield: 4.03 g (93%), pale brown powder, C_7H_7IO [234.03 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (d, ^4J (H,H) = 1.4 Hz, 1 H; H^{Ar}), 7.35 (dd, ^3J (H,H) = 8.4 Hz, ^4J (H,H) = 1.9 Hz, 1 H; H^{Ar}), 6.54 (d, ^3J (H,H) = 8.4 Hz, 1 H; H^{Ar}), 4.78 (s, 1 H; OH), 2.20 (s, 3 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 153.8 (C_q; C^{Ar}), 139.6 (C^{Ar}), 136.0 (C^{Ar}), 126.9 (C_q; C^{Ar}), 117.3 (C^{Ar}), 82.8 (C_q; C^{Ar}), 15.6 (CH_3) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 5.64 min; *m/z* (%): 234 (100) [M^+], 107 (25) [M^+−I]; **TLC**: R_f = 0.27 (cyclohexane/EtOAc = 10/1, UV and CAM); **m.p.**$^{exp.}$ = 65-66°C (m.p.$^{lit.}$ = 65-67°C).[124]

Analytical data are in accordance with those reported.[124]

7.4.3.4.2 4-Iodo-2-methylphenyl trifluoromethanesulfonate (1a)



1a

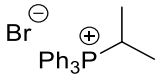
Compound **1a** was prepared according to procedure 1.4.1.2 from 3.26 g phenol derivative **1b** (13.9 mmol, 1.0 eq) in 17 mL pyridine and 4.10 mL Tf_2O (4.80 g, 17.0 mmol, 1.2 eq). Quantitative conversion was detected after 24 h. After flash column chromatography (250 g SiO_2, 8.0 x 12 cm, eluent: cyclohexane, R_f = 0.46, CAM) compound **1a** was isolated as a colourless oil.[80]

Yield: 3.85 g (76%), colourless oil, $C_8H_6F_3IO_3S$ [366.09 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, ^4J (H,H) = 1.5 Hz, 1 H; H^{Ar}), 7.58 (dd, ^3J (H,H) = 8.6 Hz, ^4J (H,H) = 1.8 Hz, 1 H; H^{Ar}), 6.98 (d, ^3J (H,H) = 8.6 Hz, 1 H; H^{Ar}), 2.34 (s, 3 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 148.5 (C_q; C^{Ar}), 141.1 (C^{Ar}), 136.9 (C^{Ar}), 133.5 (C_q; C^{Ar}), 123.2 (C^{Ar}), 118.7 (q, ^1J (C,F) = 320 Hz; CF_3), 93.2 (C_q; C^{Ar}), 16.2 (CH_3) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 5.46 min; *m/z* (%): 366 (73) [M^+], 233 (100) [M^+−CF_3O_2S], 106 (10) [M^+−CF_3IO_2S], **TLC**: R_f = 0.46 (cyclohexane, UV and CAM).

7.4.3.5 Synthesis of Leucine building block

7.4.3.5.1 Isopropyltriphenylphosphonium bromide (2b)



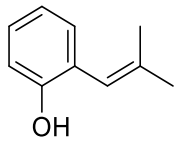
2b

A Teflon®-coated autoclave-flask was charged with 15.0 g triphenylphosphine (PPh_3) (57.2 mmol, 1.0 eq) and 19.0 mL isopropyl bromide (24.9 g, 200 mmol, 3.5 eq). The autoclave was sealed and heated to 150 °C (~12 bar internal pressure). After 23 h the reaction mixture was allowed to cool to RT, and the resulting pale orange solid was subsequently thoroughly washed with THF (4 x 25 mL) and Et_2O (2 x 25 mL). After filtration and drying of the filter cake, compound **2b** was isolated as a colorless powder.[80]
Yield: 20.51 g (93%), colorless solid, $C_{21}H_{22}BrP$ [385.28 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01-7.95 (m, 6 H; H^{Ar}), 7.78-7.65 (m, 9 H; H^{Ar}), 5.62-5.47 (m, 1 H; CH), 1.33 (dd, ^3J (H,P) = 19.0 Hz, ^3J (H,H) = 6.8 Hz, 6 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$): δ = 134.8 (d, ^4J (C,P) = 3 Hz; C^{Ar}), 134.1 (d, ^3J (C,P) = 9 Hz; C^{Ar}), 130.6 (d, ^2J (C,P) = 12 Hz; C^{Ar}), 117.8 (d, ^1J (C,P) = 83 Hz; C^{Ar}), 21.5 (d, ^1J (C,P) = 46 Hz; CH), 16.4 (d, ^2J (C,P) = 2 Hz; CH_3) ppm; **m.p.**$^{exp.}$ = 235-238°C (m.p.$^{lit.}$ = 237-238°C).[125]

Analytical data are in accordance with those reported.[125]

7.4.3.5.2 2-(2-Methylprop-1-en-1-yl)phenol (2c)



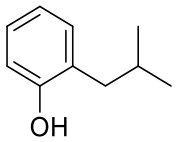
2c

In a flame dried 500 mL three-neck round-bottom flask equipped with reflux condenser and argon-inlet 23.3 g (60.3 mmol, 2.3 eq) phosphonium-salt **2b** were suspended in 175 mL absolute, degassed toluene. In a second flame dried Schlenk-flask 6.88 g (61.1 mmol, 2.3 eq) KO*t*Bu were suspended in 44 mL absolute, degassed THF. This colourless suspension was cannulated to the phosphonium-salt suspension **2b** and stirred for 60 min at 50 °C. After several min the suspension became a dark red solution. In the meanwhile in another flame dried Schlenk-flask 2.80 mL (3.20 g, 26.2 mmol, 1.0 eq) salicylaldehyde were dissolved in 35 mL absolute, degassed toluene. The dark red phosphonium-salt solution **2b** was cooled to -78 °C and the salicylaldehyde (**2d**) solution was added via cannula. During the cannulation the reaction mixture became brighter and a pale yellow precipitate was formed. The suspension was stirred overnight (16 h) at RT and then stirred at 80 °C until complete conversion was detected by GC-MS. The red-brown suspension was quenched by the addition of 60 mL saturated NH_4Cl solution. The phases were separated. The aqueous phase was diluted with 120 mL water and extracted with Et_2O (3 x 120 mL). The combined organic layers were washed with saturated NaCl solution (1 x 300 mL), dried over $MgSO_4$, filtered and concentrated to dryness under reduced pressure. The brown crude product was purified by distillation.[80]
Yield: 2.47 g (64%), yellow oil, $C_{10}H_{12}O$ [148.09 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17 (dt, ^3J (H,H) = 8.0 Hz, ^4J (H,H) = 1.3 Hz, 1 H; H^{Ar}), 7.08-7.05 (m, 1 H; H^{Ar}), 6.92-6.87 (m, 2 H; H^{Ar}), 6.14 (s, 1 H; CH), 5.09 (bs, 1 H; OH), 1.96 (d, ^4J (H,H) = 1.2 Hz, 3 H; CH_3), 1.70 (d, ^4J (H,H) = 1.0 Hz, 3 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$): δ = 152.9 (C_q; C^{Ar}), 140.7 (C_q; CH=*C*$(CH_3)_2$), 130.0 (C^{Ar}), 128.3 (C^{Ar}), 124.8 (C_q; C^{Ar}), 120.3 (C^{Ar}), 118.8 (CH), 115.0 (C^{Ar}), 26.0 (CH_3), 19.6 (CH_3) ppm; **GC-MS** (EI, 70 eV; MP_50_S): t_R = 4.79 min; *m/z* (%): 148 (92) [M^+], 133 (100) [M^+-CH_3], 105 (63) [$M^+-C_3H_8$]; **b.p.**$^{exp.}$ = 45°C, 0.1 torr (**b.p.**$^{lit.}$ = 104°C, 15 torr).[126]

Analytical data are in accordance with those reported.[126]

7.4.3.5.3 2-Isobutylphenol (2e)



2e

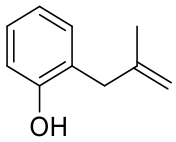
In an argon flushed 250 mL three-neck round-bottom flask equipped with argon-inlet 2.40 g phenol derivative **2c** (16.2 mmol, 1.0 eq) were dissolved in 120 mL MeOH. To this yellow solution 240 mg palladium on activated charcoal (Pd/C) (10 wt%) were added.[1] After ensuring hydrogen atmosphere by evacuating and back-flushing with hydrogen gas (6 x), the reaction mixture was stirred for 3 h at RT with an attached balloon filled with H_2. After filtering off the catalyst (SiO_2, eluent: MeOH) under inert atmosphere and evaporating the solvent using a rotary evaporator, the crude product was purified by distillation.[80]

Yield: 1.85 g (77%), colourless oil, $C_{10}H_{12}O$ [150.22 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13-7.07 (m, 2 H; H^{Ar}), 6.88 (dt, ^3J (H,H) = 7.5 Hz, ^4J (H,H) = 1.1 Hz, 1 H; H^{Ar}), 6.79-6.76 (m, 1 H; H^{Ar}), 4.67 (s, 1 H; OH), 2.50 (d, ^3J (H,H) = 7.2 Hz, 2 H; CH_2), 2.04-1.86 (m, 1 H; CH), 0.95 (d, ^3J (H,H) = 6.6 Hz, 6 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$): δ = 153.7 (C_q; C^{Ar}), 131.4 (C^{Ar}), 127.6 (C_q; C^{Ar}), 127.2 (C^{Ar}), 120.7 (C^{Ar}), 115.4 (C^{Ar}), 39.4 (CH_2), 29.0 (CH), 22.7 (CH_3) ppm; **GC-MS** (EI, 70 eV; MP_50_S): t_R = 4.90 min; *m/z* (%): 150 (39) [M^+], 107 (100) [$M^+-C_3H_8$]; **b.p.**$^{exp.}$ = 45 °C, 0.2 torr, (**b.p.**$^{lit.}$ = 45-50°C, 1 torr).[127]

Analytical data are in accordance with those reported.[127]

7.4.3.5.4 2-(2-Methylallyl)phenol (2f)



2f

A 15 mL "Ace pressure tube®, back seal" (Aldrich Z181064) with a "Duro-Silicone O-ring" was charged with 4.0 mL methallyl phenyl ether (**2g**) (3.85 g, 26.0 mmol, 1.0 eq) and 15 mL of *N*,*N*-dimethylacetamide. The flask was sealed, and the mixture was stirred at 190 °C for 5 d. When conversion stops (~95 % according to GC-MS) the reaction was cooled to RT and 100 mL *n*-pentane were added. The organic phase was extracted with 2 M NaOH (4 x 100 mL). The aqueous phase was acidified with 70 mL conc. HCl (pH 2-3) and extracted with Et_2O (4 x 100

[1] Palladium on activated charcoal, moistened with water, 5% Pd basis (based on dry substance), Aldrich 75992.

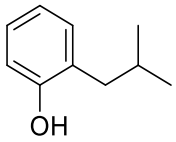
mL). The combined organic layers were washed with saturated NaCl solution (1 x 200 mL), dried over Na_2SO_4 and filtered. The solvent was removed in vacuo and the crude product was used without further purification.

Yield: 3.58 g (93%), brown oil, $C_{10}H_{12}O$ [148.21 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.18-7.09 (m, 2 H; H^{Ar}), 6.92-6.83 (m, 2 H; H^{Ar}), 5.29 (s, 1 H; OH), 4.93 (s, 1 H; CH_2), 4.86 (s, 1 H; CH_2), 3.39 (s, 2 H; CH_2), 1.75 (s, 3 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$): δ = 154.8 (C_q; C^{Ar}), 144.8 (C_q;C^{Ar}), 131.1 (C^{Ar}), 128.1 (C^{Ar}), 125.0 (C_q), 120.9 (C^{Ar}), 116.2 (C^{Ar}), 112.4 (CH_2), 40.0 (CH_2), 22.2 (CH_3) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 4.68 min; *m/z* (%): 148 (83) [M^+], 133 (100) [M^+-CH_3]; **TLC**: R_f = 0.52 (cyclohexane/EtOAc = 5/1, UV and CAM).

Analytical data are in accordance with those reported.[128]

7.4.3.5.5 2-Isobutylphenol (2e)



2e

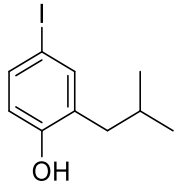
Hydrogenation was performed utilizing an H-Cube™ at a pressure of 60 bar at 60°C with a Raney-Ni powder cartridge (THS 01112). A solution of 3.50 g phenol derivative **2f** (23.6 mmol, 1.0 eq) in 250 mL MeOH (~0.1 M) was used in continuous flow mode of 1.0 mL/min. The hydrogenation was run in a loop until full conversion was detected by GC-MS (24 h). After removing the solvent under reduced pressure, compound **2e** was isolated as colourless oil. An analytical sample was purified by distillation.

Yield: 3.51 g (99%), colourless oil, $C_{10}H_{12}O$ [150.22 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13-7.07 (m, 2 H; H^{Ar}), 6.88 (dt, ^3J (H,H) = 7.5 Hz, ^4J (H,H) = 1.1 Hz, 1 H; H^{Ar}), 6.79-6.76 (m, 1 H; H^{Ar}), 4.67 (s, 1 H; OH), 2.50 (d, ^3J (H,H) = 7.2 Hz, 2 H; CH_2), 2.04-1.86 (m, 1 H; CH), 0.95 (d, ^3J (H,H) = 6.6 Hz, 6 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$): δ = 153.7 (C_q; C^{Ar}), 131.4 (C^{Ar}), 127.6 (C_q; C^{Ar}), 127.2 (C^{Ar}), 120.7 (C^{Ar}), 115.4 (C^{Ar}), 39.4 (CH_2), 29.0 (CH), 22.7 (CH_3) ppm; **GC-MS** (EI, 70 eV; MP_50_S): t_R = 4.90 min; *m/z* (%): 150 (39) [M^+], 107 (100) [$M^+-C_3H_8$]; **b.p.**$^{exp.}$ = 45 °C, 0.3 mbar, (**b.p.**$^{lit.}$ = 45-50°C, 1.3 mbar).[127]

Analytical data are in accordance with those reported.[127]

7.4.3.5.6 4-Iodo-2-isobutylphenol (2g)



2g

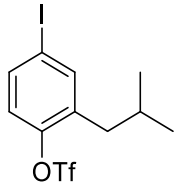
Compound **2g** was prepared according to procedure 1.4.1.1 from 1.50 g phenol derivative **2e** (10.0 mmol, 1.0 eq) in 14 mL acetic acid and 500 µL ICl (1.62 g, 10.0 mmol, 1.0 eq). After 24 h 200 µL ICl (648 mg, 3.99 mmol, 0.4 eq) were additionally added and quantitative conversion was detected after further 24 h. After flash column chromatography (140 g SiO_2, 4.0 x 28 cm, eluent: cyclohexane/EtOAc = 12/1, R_f = 0.20, UV and CAM), compound **2g** was isolated as a pale orange powder.[80]

Yield: 2.35 g (85%), pale orange powder, $C_{10}H_{13}IO$ [276.11 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38-7.33 (m, 2 H; H^{Ar}), 6.54 (d, ^3J (H,H) = 8.2 Hz, 1 H; H^{Ar}), 4.71 (bs, 1 H; OH), 2.41 (d, ^3J (H,H) = 7.2 Hz, 2 H; CH_2), 1.97-1.83 (m, 1 H; CH), 0.92 (d, ^3J (H,H) = 6.6 Hz, 6 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$): δ = 153.7 (C_q; C^{Ar}), 139.8 (C^{Ar}), 135.9 (C^{Ar}), 130.6 (C_q; C^{Ar}), 117.7 (C^{Ar}), 82.8 (C_q; C^{Ar}), 39.0 (CH_2), 29.0 (CH), 22.6 (CH_3) ppm; **GC-MS** (EI, 70 eV; MP_50_S): t_R = 6.26 min; *m/z* (%): 276 (73) [M^+], 233 (100) [$M^+-C_3H_8$], 107 (17) [$M^+-C_3H_8I$]; **TLC**: R_f = 0.20 (cyclohexane/EtOAc = 12/1, UV and CAM); **m.p.**$^{exp.}$ = 62-63°C.

Analytical data are in accordance with those reported.[85]

7.4.3.5.7 4-Iodo-2-isobutylphenyl trifluoromethanesulfonate (2a)



2a

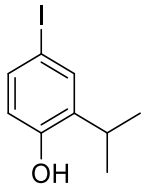
Compound **2a** was prepared according to procedure 1.4.1.2 from 2.20 g phenol derivative **2g** (7.97 mmol, 1.0 eq) in 9 mL pyridine and 2.10 mL Tf_2O (2.47 g, 8.76 mmol, 1.1 eq). Quantitative conversion was detected after 24 h. After flash column chromatography (200 g SiO_2, 4.0 x 34 cm, eluent: cyclohexane, R_f = 0.50, UV and CAM), compound **2a** was isolated as a pale yellow oil.[80]

Yield: 2.97 g (91%), pale yellow oil, $C_{11}H_{12}F_3IO_3S$ [408.18 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63-7.57 (m, 2 H; H^{Ar}), 6.99 (d, ^{3}J (H,H) = 8.6 Hz, 1 H; H^{Ar}), 2.52 (d, ^{3}J (H,H) = 7.3 Hz, 2 H; CH_2), 2.01-1.83 (m, 1 H; CH), 0.92 (d, ^{3}J (H,H) = 6.6 Hz, 6 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$): δ = 148.3 (C_q; C^{Ar}), 141.0 (C^{Ar}), 137.0 (C_q; C^{Ar}), 136.9 (C^{Ar}), 123.2 (C^{Ar}), 118.7 (q, ^{1}J (C,F) = 320 Hz; CF_3), 93.2 (C_q; C^{Ar}), 39.1 (CH_2), 29.3 (CH), 22.4 (CH_3) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 5.98 min; *m/z* (%): 408 (59) [M^+], 233 (100) [M^+−$C_4H_8F_3O_2S$]; **TLC**: R_f = 0.50 (cyclohexane, UV and CAM); **HRMS** (EI): calcd for [M^+]: 407.9504; found: 407.9510.

7.4.3.6 Synthesis of Valine building block

7.4.3.6.1 4-Iodo-2-isopropylphenol (3b)



3b

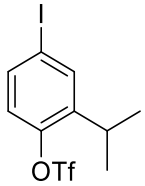
Compound **3b** was prepared according to procedure 1.4.1.1 from 2.00 g 2-isopropylphenol (**3c**) (14.7 mmol, 1.0 eq) in 20 mL acetic acid and 884 µL ICl (2.86 g, 17.6 mmol, 1.2 eq). After 24 h 125 µL ICl (405 mg, 2.49 mmol, 0.2 eq) were additionally added and quantitative conversion was detected after 27 h. After flash column chromatography (100 g SiO_2, 4.5 x 13 cm, eluent: cyclohexane/EtOAc = 12/1, R_f = 0.23, UV and CAM) compound **3b** was isolated as a dark yellow oil.[80]

Yield: 3.38 g (88%), dark yellow oil, $C_9H_{11}IO$ [262.09 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 (d, ^{4}J (H,H) = 2.1 Hz, 1 H; H^{Ar}), 7.34 (dd, ^{3}J (H,H) = 8.4 Hz, ^{4}J (H,H) = 2.2 Hz, 1 H; H^{Ar}), 6.52 (d, ^{3}J (H,H) = 8.4 Hz, 1 H; H^{Ar}), 4.73 (bs, 1 H; OH), 3.14 (sept, ^{3}J (H,H) = 6.9 Hz, 1 H; CH), 1.23 (d, ^{3}J (H,H) = 6.9 Hz, 6 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 152.8 (C_q; C^{Ar}), 137.5 (C_q; C^{Ar}), 135.6 (C^{Ar}), 135.6 (C^{Ar}), 117.7 (C^{Ar}), 83.5 (C_q; C^{Ar}), 27.2 (CH), 22.5 (CH_3) ppm; **GC-MS** (EI, 70 eV; MP_50_S): t_R = 6.04 min; *m/z* (%): 262 (97) [M^+], 247 (100) [M^+−CH_3], 120 (45) [M^+−CH_3I]; **TLC**: R_f = 0.23 (cyclohexane/EtOAc = 12/1, UV and CAM).

Analytical data are in accordance with those reported.[129]

7.4.3.6.2 4-Iodo-2-isopropylphenyl trifluoromethanesulfonate (3a)



3a

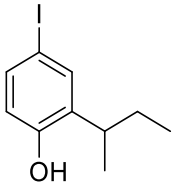
Compound **3a** was prepared according to procedure 1.4.1.2 from 2.58 g phenol derivative **3b** (9.84 mmol, 1.0 eq) in 12 mL pyridine and 2.61 mL Tf_2O (3.06 g, 10.8 mmol, 1.1 eq). Quantitative conversion was detected after 3 h. After flash column chromatography (325 g SiO_2, 8.0 x 16 cm, eluent: cyclohexane, R_f = 0.49, UV and CAM) compound **3a** was isolated as a colourless oil.[80]

Yield: 2.59 g (67%), colourless oil, $C_{10}H_{10}F_3IO_3S$ [394.15 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, ^4J (H,H) = 2.2 Hz, 1 H; H^{Ar}), 7.57 (dd, ^3J (H,H) = 8.6 Hz, ^4J (H,H) = 2.2 Hz, 1 H; H^{Ar}), 6.97 (d, ^3J (H,H) = 8.6 Hz, 1 H; H^{Ar}), 3.22 (sept, ^3J (H,H) = 6.8 Hz, 1 H; CH), 1.25 (d, ^3J (H,H) = 6.9 Hz, 6 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 147.1 (C_q; C^{Ar}), 143.8 (C_q; C^{Ar}), 137.3 (C^{Ar}), 136.7 (C^{Ar}), 123.2 (C^{Ar}), 118.7 (q, ^1J (C,F) = 320 Hz; CF_3), 93.8 (C_q; C^{Ar}), 27.3 (CH), 23.1 (CH_3) ppm; **GC-MS** (EI, 70 eV; MP_50_S): t_R = 5.71 min; *m/z* (%): 394 (85) [M^+], 134 (100) [$M^+-CF_3IO_2S$], 119 (14) [$M^+-C_2H_3F_3IO_2S$]; **TLC**: R_f = 0.49 (cyclohexane, UV and CAM); **HRMS** (EI): calcd for [M^+]: 393.9348; found: 393.9339.

7.4.3.7 Synthesis of Isoleucine building block

7.4.3.7.1 2-*sec*-Butyl-4-iodophenol (4b)



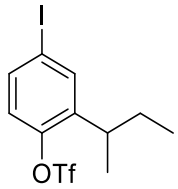
4b

Compound **4b** was prepared according to procedure 1.4.1.1 from 2.00 g 2-*sec*-butylphenol (**4c**) (13.4 mmol, 1.0 eq) in 20 mL acetic acid and 806 µL ICl (2.61 g, 16.1 mmol, 1.2 eq). After 24 h again 200 µL ICl (648 mg, 3.99 mmol, 0.3 eq) were added and quantitative conversion was detected after 27 h. After flash column chromatography (80 g SiO_2, 4.0 x 15 cm, eluent: cyclohexane/EtOAc = 12/1, R_f = 0.11, UV and CAM) compound **4b** was isolated as a pale brown oil.[80]

Yield: 2.80 g (76%), pale brown oil, $C_{10}H_{13}IO$ [276.12 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41 (d, ^4J (H,H) = 2.1 Hz, 1 H; H^{Ar}), 7.33 (dd, ^3J (H,H) = 8.4 Hz, ^4J (H,H) = 2.2 Hz, 1 H; H^{Ar}), 6.53 (d, ^3J (H,H) = 8.4 Hz, 1 H; H^{Ar}), 4.76 (bs, 1 H; OH), 2.95-2.83 (m, 1 H; CH), 1.66-1.52 (m, 2 H; CH_2), 1.21 (d, ^3J (H,H) = 6.9 Hz, 3 H; CH_3), 0.86 (t, ^3J (H,H) = 7.4 Hz, 3 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 153.1 (C_q; C^{Ar}), 136.4 (C_q; C^{Ar}), 136.2 (C^{Ar}), 135.5 (C^{Ar}), 117.7 (C^{Ar}), 83.5 (C_q; C^{Ar}), 34.1 (CH), 29.8 (CH_2), 20.4 (CH_3), 12.2 (CH_3) ppm; **GC-MS** (EI, 70 eV; MP_50_S): t_R = 6.27 min; *m/z* (%): 276 (58) [M^+], 247 (100) [$M^+-C_2H_5$], 120 (45) [$M^+-C_2H_5I$]; **TLC**: R_f = 0.11 (cyclohexane/EtOAc = 12/1, UV and CAM); **HRMS** (EI): calcd for [M^+]: 276.0011; found: 276.0019.

7.4.3.7.2 2-(*sec*-Butyl)-4-iodophenyl trifluoromethanesulfonate (4a)



4a

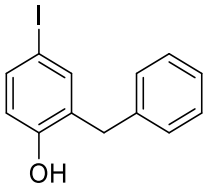
Compound **4a** was prepared according to procedure 1.4.1.2 from 2.80 g phenol derivative **4b** (10.1 mmol, 1.0 eq) in 12 mL pyridine and 2.70 mL Tf_2O (3.15 g, 11.2 mmol, 1.1 eq). Quantitative conversion was detected after 3 h. After flash column chromatography (100 g SiO_2, 4.5 x 13 cm, eluent: cyclohexane, R_f = 0.68, UV and CAM) compound **4a** was isolated as a colourless oil.[80]

Yield: 3.23 g (78%); colourless oil, $C_{11}H_{12}F_3IO_3S$ [408.17 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, ^4J (H,H) = 2.2 Hz, 1 H; H^{Ar}), 7.57 (dd, ^3J (H,H) = 8.6 Hz, ^4J (H,H) = 2.2 Hz, 1 H; H^{Ar}), 6.98 (d, ^3J (H,H) = 8.6 Hz, 1 H; H^{Ar}), 3.02-2.90 (m, 1 H; CH), 1.65-1.57 (m, 2 H; CH_2), 1.23 (d, ^3J (H,H) = 6.9 Hz, 3 H; CH_3), 0.85 (t, ^3J (H,H) = 7.4 Hz, 3 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 147.6 (C_q; C^{Ar}), 142.9 (C_q; C^{Ar}), 137.6 (C^{Ar}), 136.6 (C^{Ar}), 123.2 (C^{Ar}), 118.7 (q, ^1J (C,F) = 320 Hz; CF_3), 93.8 (C_q; C^{Ar}), 34.2 (CH), 30.6 (CH_2), 21.0 (CH_3), 12.1 (CH_3) ppm; **GC-MS** (EI, 70 eV; MP_50_S): t_R = 5.93 min; *m/z* (%): 408 (68) [M^+], 379 (21) [$M^+-C_2H_5$], 246 (23) [$M^+-C_3H_5F_3O_2S$]; **TLC**: R_f = 0.68 (cyclohexane, UV and CAM); **HRMS** (EI): calcd for [M^+]: 407.9504; found: 407.9530.

7.4.3.8 Synthesis of Phenylalanine building block

7.4.3.8.1 2-Benzyl-4-iodophenol (5b)



5b

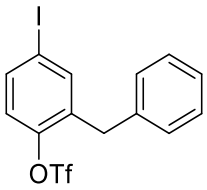
Compound **5a** was prepared according to procedure 1.4.1.1 from 2.00 g 2-benzylphenol (**5c**) (19.0 mmol, 1.0 eq) in 12 mL acetic acid and 1.14 mL ICl (3.70 g, 22.8 mmol, 1.0 eq). After 24 h 191 µL ICl (620 mg, 3.80 mmol, 0.2 eq) were additionally added and quantitative conversion was detected after 27 h. After flash column chromatography (100 g SiO_2, 4.5 x 13 cm, eluent: cyclohexane/EtOAc = 8/1, R_f = 0.31,UV and CAM) compound **5b** was isolated as a brown powder.[80]

Yield: 4.70 g (80%); brown powder, $C_{13}H_{11}IO$ [310.13 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26-7.23 (m, 2 H; H^{Ar}, overlapping), 7.18-7.12 (m, 2 H; H^{Phe}), 7.10-7.04 (m, 3H; H^{Phe}), 6.40 (d, ^3J (H,H) = 8.1 Hz, 1 H; H^{Ar}), 4.63 (bs, 1 H; OH), 3.77 (s, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 153.8 (C_q; C^{Ar}), 139.5 (C^{Ar}), 139.1 (C_q; C^{Phe}), 136.7 (C^{Ar}), 130.0 (C_q; C^{Ar}), 128.9 (C^{Phe}), 128.8 (C^{Phe}), 126.8 (C^{Phe}), 118.2 (C^{Ar}), 83.1 (C_q; C^{Ar}), 36.2 (CH_2) ppm; **GC-MS** (EI, 70 eV; MP_50_S): t_R = 7.47 min; *m/z* (%): 310 (100) [M^+], 232 (31) [$M^+-C_6H_5$], 183 (13) [M^+-I]; **TLC**: R_f = 0.31 (cyclohexane/EtOAc = 8/1, UV and CAM); **m.p.**$^{exp.}$ = 35-37°C.

Analytical data are in accordance with those reported.[85]

7.4.3.8.2 2-Benzyl-4-iodophenyl trifluoromethanesulfonate (5a)



5a

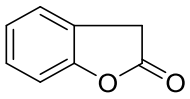
Compound **5a** was prepared according to procedure 1.4.1.2 from 4.60 g phenol derivative **5b** (14.8 mmol, 1.0 eq) in 20 mL pyridine and 4.00 mL Tf_2O (4.68 g, 16.6 mmol, 1.1 eq). Quantitative conversion was detected after 18 h. After flash column chromatography (100 g SiO_2, 4.5 x 13 cm, eluent: cyclohexane, R_f = 0.28, UV and CAM) compound **5a** was isolated as a colourless oil.[80]

Yield: 5.62 g (86%); yellow oil, $C_{14}H_{10}F_3IO_3S$ [442.19 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (dd, ^3J (H,H) = 8.6 Hz, ^4J (H,H) = 2.2 Hz, 1 H; H^{Ar}), 7.32 (d, ^4J (H,H) = 2.1 Hz, 1 H; H^{Ar}), 7.16-7.04 (m, 3 H; H^{Phe}), 6.99-6.96 (m, 2 H; H^{Phe}), 6.83 (d, ^3J (H,H) = 8.6 Hz, 1 H; H^{Ar}), 3.82 (s, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 147.9 (C_q; C^{Ar}), 140.8 (C^{Ar}), 137.7 (C_q; C^{Phe}), 137.5 (C^{Ar}), 136.6 (C_q; C^{Ar}), 129.2 (C^{Phe}), 129.0 (C^{Phe}), 127.1 (C^{Phe}), 123.3 (C^{Ar}), 118.7 (q, ^1J (C,F) = 320 Hz; CF_3), 93.5 (C_q; C^{Ar}), 35.6 (CH_2) ppm; **GC-MS** (EI, 70 eV; MP_50_S): t_R = 7.13 min; *m/z* (%): 442 (100) [M^+], 309 (51) [$M^+-CF_3O_2S$], 181 (23) [$M^+-CF_3IO_2S$]; **TLC**: R_f = 0.28 (cyclohexane, UV and CAM); **HRMS** (EI): calcd for [M^+]: 441.9348; found: 441.9337.

7.4.3.9 Synthesis of Aspartate building block

7.4.3.9.1 Benzofuran-2(3H)-one (6b)



6b

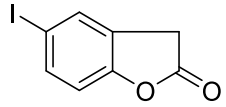
In a 100 mL round-bottom-flask with DEAN-STARK apparatus and reflux condenser 4.40 g 2-hydroxybenzoic acid (**6c**) (28.9 mmol, 1.0 eq) and 2.75 g p-toluenesulfonic acid monohydrate (14.5 mmol, 0.5 eq) were dissolved in 60.0 mL toluene. The colourless suspension was heated under reflux for 4 h. The solid was dissolved at reflux temperature and the colour turned into brown. Full conversion was detected by TLC. When stirring was stopped two phases separated (brown and yellow). The yellow phase was decanted and cooled to RT from which a colourless solid precipitated. After filtration the solid was discarded and the filtrate was concentrated in vacuo. The yellow, oily crude was purified via flash column chromatography (250 g SiO_2, 6.0 x 17 cm, eluent: cyclohexane/EtOAc = 15/1, R_f = 0.11, UV and CAM). The pure product was isolated as a pale yellow solid.

Yield: 3.11 g (80%), pale yellow solid, $C_8H_6O_2$ [134.13 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21-7.19 (m, 2 H; H^{Ar}), 7.07-6.99 (m, 2 H; H^{Ar}), 3.64 (s, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 174.2 (C_q; CO), 154.9 (C_q; C^{Ar}), 129.1 (C^{Ar}), 124.8 (C^{Ar}), 124.3 (C^{Ar}), 123.2 (C_q; C^{Ar}), 111.0 (C^{Ar}), 33.0 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 4.79 min; *m/z* (%): 134 (36) [M^+], 106 (21) [M^+-CO], 78 (100) [$M^+-C_2O_2$]; **TLC**: R_f = 0.11 (cyclohexane/EtOAc = 15/1, UV and CAM); **m.p.**$^{exp.}$ = 27-28°C, (m.p.$^{lit.}$ = 27-28°C).[130]

Analytical data are in accordance with those reported.[130]

7.4.3.9.2 5-Iodobenzofuran-2(3H)-one (6d)

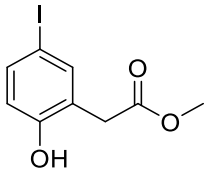


6d

In a flame dried and argon flushed Schlenk-flask 3.00 g benzofuran-2(3H)-one (**6b**) (22.4 mmol, 1.0 eq) were dissolved in 45.0 mL DCM. 3.63 g ICl (22.4 mmol, 1.0 eq) were added. To achieve quantitative conversion, two times 0.5 eq ICl (total: 3.63 g, 22.4 mmol, 1.0 eq) were added every further 24 h. After full conversion (72 h) the reaction was diluted with 100 mL DCM and washed with 0.1 M $Na_2S_2O_3$ solution (3 x 50 mL). The combined aqueous layers were reextracted with DCM (3 x 50 mL). The combined organic layers were washed with saturated NaCl solution (1 x 100 mL), dried over $MgSO_4$, filtered and the solvent was removed in vacuum. The orange, solid crude was recrystallized from DCM/cyclohexane (1/4).
Yield: 3.23 g (55%), pale orange powder, $C_8H_5IO_2$ [260.03 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64-7.61 (m, 2 H; H^{Ar}), 6.89 (d, ^3J (H,H) = 8.1 Hz, 1 H; H^{Ar}), 3.73 (s, 2H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 173.0 (C_q; CO), 154.5 (C_q; C^{Ar}), 138.0 (C^{Ar}), 133.7 (C^{Ar}), 125.7 (C_q; C^{Ar}), 113.0 (C^{Ar}), 86.8 (C_q; C^{Ar}), 32.7 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 6.20 min; *m/z* (%): 260 (4) [M^+], 127 (100) [$M^+-C_8H_5O_2$], 77 (63) [$M^+-C_2O_2I$]; **m.p.**$^{exp.}$ = 134-137°C.

7.4.3.9.3 Methyl 2-(2-hydroxy-5-iodophenyl)acetate (6e)



6e

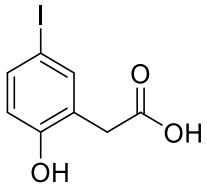
In a flame dried and argon flushed Schlenk-flask 1.00 g 5-iodobenzofuran-2(3H)-one (**6d**) (3.85 mmol, 1.00 eq) were suspended in 15.0 mL MeOH. 2.05 mL conc. H_2SO_4 were added to the pale orange suspension and the solid was dissolved. The orange solution was heated to 50 °C. After full conversion was detected by TLC, the reaction was cooled to RT, neutralized with saturated $NaHCO_3$ solution and the solvent was removed in vacuum. The oily brown residue was diluted with 100 mL H_2O and extracted with ethylacetate (3 x 100 mL). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuum. The crude brown crystals were purified by flash column

chromatography (100 g SiO_2, 4.0 x 15 cm, eluent: cyclohexane/EtOAc = 5/1, R_f = 0.20, UV and CAM) and **6e** was isolated as light yellow crystals.

Yield: 882 mg (79 %), light yellow crystals, $C_9H_9IO_3$ [292.07 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49 (s, 1 H; OH), 7.44-7.41 (m, 1 H; H^{Ar}), 7.38 (d, ^4J (H,H) = 1.8 Hz, 1H; H^{Ar}), 6.67 (d, ^3J (H,H) = 8.4 Hz, 1H; H^{Ar}), 3.74 (s, 3 H; CH_3), 3.60 (s, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 174.1 (C_q; CO), 155.4 (C_q; C^{Ar}), 139.5 (C^{Ar}), 138.2 (C^{Ar}), 123.4 (C_q; C^{Ar}), 120.1 (C^{Ar}), 82.7 (C_q; C^{Ar}), 53.1 (CH_3), 37.4 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 6.52 min; *m/z* (%): 292 (21) [M^+], 260 (100) [M^+−OCH_3], 232 (66) [M^+−$C_2H_3O_2$], 105 (19) [M^+−$C_2H_3O_2I$]; **TLC**: R_f = 0.20 (cyclohexane/EtOAc = 5/1, UV and CAM); **m.p.**$^{exp.}$ = 70-79 °C; **HRMS** (EI): calcd for [M^+]: 291.9597; found: 291.9615.

7.4.3.9.4 2-(2-Hydroxy-5-iodophenyl)acetic acid (6f)



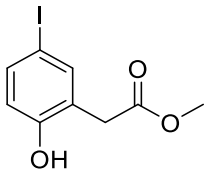
6f

In a 100 mL round-bottom flask 5.34 g ICl (32.9 mmol, 1.0 eq) were dissolved in 40 mL DCM and cooled to 0 °C in an ice bath. 5.00 g 2-Hydroxybenzoic acid (**6c**) (32.9 mmol, 1.0 eq) were added in small portions. After a few min a pale yellow solid starts to precipitate. When full conversion (24 h) was detected by HPLC-MS or TLC the reaction mixture was extracted with half-saturated Na_2SO_3 solution (2 x 100 mL) and the precipitate was dissolved into the aqueous phase. The pH-value was then adjusted with 2 M $KHSO_4$ solution to pH 1. The product precipitated as colourless solid, was collected by filtration and dried in vacuum.

Yield: 8.86 g (97%), colourless powder, $C_8H_7IO_3$ [278.05 g/mol].

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.19 (bs, 1H, COOH), 9.78 (s, 1H, OH) 7.42 (d, ^4J (H,H) = 2.0 Hz, 1 H; H^{Ar}), 7.35 (dd, ^3J (H,H) = 8.4 Hz, ^4J (H,H) = 2.1 Hz, 1 H; H^{Ar}), 6.63 (d, ^3J (H,H) = 8.4 Hz, 1 H; H^{Ar}), 3.44 (s, 2H; CH_2) ppm; **^{13}C NMR** (76 MHz, DMSO-d_6, APT): δ = 172.3 (C_q; CO), 155.5 (C_q; C^{Ar}), 139.2 (C^{Ar}), 136.2 (C^{Ar}), 125.2 (C_q; C^{Ar}), 117.4 (C^{Ar}), 80.5 (C_q; C^{Ar}), 34.8 (CH_2) ppm; **HPLC-MS** (Poroshell, ESI^-, MT_general): t_R = 2.84 min; *m/z*: 277 [M−H^+]; λ_{max} = 234 nm; **TLC**: R_f = 0.45 (cyclohexane/EtOAc/AcOH = 100/200/1, UV and Vanillin); **m.p.**$^{exp.}$ = 171-174°C.

7.4.3.9.5 Methyl 2-(2-hydroxy-5-iodophenyl)acetate (6e)



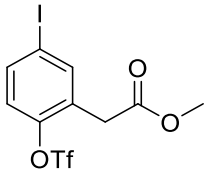
6e

In a 250 mL round-bottom flask with air-condenser 5.00 g 2-(2-hydroxy-5-iodophenyl)acetic acid (**6f**) (18.0 mmol, 1.00 eq) were dissolved in 70.0 mL MeOH and cooled to 0 °C. 10 mL conc. H_2SO_4 were added to the slightly cloudy solution and then the reaction mixture was stirred at 50 °C. After full conversion was detected by TLC, the reaction was cooled to RT, neutralized with 200 mL saturated $NaHCO_3$ solution and the solvent was removed in vacuum. The residual aqueous phase was extracted with ethylacetate (4 x 100 mL). The combined organic layers were washed with saturated NaCl solution (1 x 100 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The crude brown crystals were purified via flash column chromatography (250 g SiO_2, 6.0 x 15 cm, eluent: cyclohexane/EtOAc = 5/1, R_f = 0.20, UV and CAM) and the product was isolated as colourless powder.

Yield: 4.22 g (80 %), colourless powder, $C_9H_9IO_3$ [292.07 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49 (s, 1 H; OH), 7.44-7.41 (m, 1 H; H^{Ar}), 7.38 (d, ^4J (H,H) = 1.8 Hz, 1H; H^{Ar}), 6.67 (d, ^3J (H,H) = 8.4 Hz, 1H; H^{Ar}), 3.74 (s, 3 H; CH_3), 3.60 (s, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 174.1 (C_q; CO), 155.4 (C_q; C^{Ar}), 139.5 (C^{Ar}), 138.2 (C^{Ar}), 123.4 (C_q; C^{Ar}), 120.1 (C^{Ar}), 82.7 (C_q; C^{Ar}), 53.1 (CH_3), 37.4 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 6.52 min; *m/z* (%): 292 (21) [M^+], 260 (100) [M^+-OCH_3], 232 (66) [$M^+-C_2H_3O_2$], 105 (19) [$M^+-C_2H_3O_2I$]; **TLC**: R_f = 0.20 (cyclohexane/EtOAc = 5/1, UV and CAM); **m.p.**$^{exp.}$ = 76-79°C; **HRMS** (EI): calcd for [M^+]: 291.9597; found: 291.9615.

7.4.3.9.6 Methyl 2-(5-iodo-2-(((trifluoromethyl)sulfonyl)oxy)phenyl)acetate (6a)



6a

Compound **6a** was prepared according to procedure 1.4.1.2 from 500 mg phenol derivative **6e** (1.71 mmol, 1.0 eq) in 1.5 mL pyridine and 450 µL Tf_2O (531 mg, 1.88 mmol, 1.1 eq). Quantitative conversion was detected after 2 h. After flash column chromatography (75 g SiO_2,

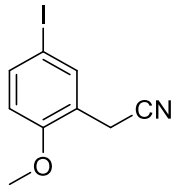
3.0 x 20 cm, eluent: cyclohexane/EtOAc = 20/1, R_f = 0.25, UV and CAM) compound **6a** was isolated as a colourless oil.

Yield: 655 mg (90 %), colourless oil, $C_{10}H_8F_3IO_5S$ [424.13 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, ^4J (H,H) = 2.1 Hz, 1 H; H^{Ar}), 7.67 (dd, ^3J (H,H) = 8.7 Hz, ^4J (H,H) = 2.1 Hz, 1 H; H^{Ar}), 7.04 (d, ^3J (H,H) = 8.4 Hz, 1 H; H^{Ar}), 3.71 (s, 3 H; CH_3), 3.67 (s, 2 H, CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 169.8 (CO), 148.1 (C_q; C^{Ar}), 141.4 (C^{Ar}), 138.6 (C^{Ar}), 128.6 (C_q; C^{Ar}), 123.4 (C^{Ar}), 118.7 (q, ^1J (C,F) = 318 Hz; CF_3), 93.3 (C_q; C^{Ar}), 52.7 (CH_3), 35.3 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 6.36 min; *m/z* (%): 424 (60) [M^+], 365 (31) [$M^+-C_2H_3O_2$], 275 (100) [$M^+-CF_3O_3S$] 164 (60) [$M^+-CF_3IO_2S$]; **TLC**: R_f = 0.25 (cyclohexane/EtOAc = 20/1, UV and CAM); **HRMS** (EI): calcd for [M^+]: 423.9089; found: 423.9132.

7.4.3.10 Synthesis of Asparagine building block

7.4.3.10.1 2-(5-Iodo-2-methoxyphenyl)acetonitrile (7b)



7b

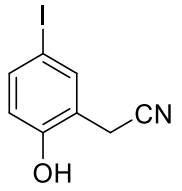
A flame dried and argon flushed Schlenk-flask was charged with 1.00 g 2-(2-methoxyphenyl)-acetonitrile (**7c**) (6.79 mmol, 1.0 eq), 2.41 g Selectfluor® (6.79 mmol, 1.0 eq), and 880 mg iodine (I_2) (3.47 mmol, 0.51 eq). After dissolving the starting material in 65 mL CH_3CN, the brown solution was stirred for 4 h at RT. After quantitative conversion the CH_3CN was removed under reduced pressure using a rotary evaporator. The oily brown residue was dissolved in 100 mL DCM, washed with H_2O (1 x 100 mL) and the aqueous phase was extracted with DCM (3 x 50 mL). The combined organic layers were washed with $Na_2S_2O_3$ solution (25%, 2 x 50 mL) and saturated NaCl solution (1 x 100 mL). After drying over $MgSO_4$ and filtering off the $MgSO_4$, the solvent was removed under reduced pressure. Compound **7b** was isolated as a colourless solid after flash column chromatography (100 g SiO_2, 4.0 x 15 cm, eluent: cyclohexane/EtOAc = 6/1, R_f = 0.28, UV and CAM).[80]

Yield: 1.49 g (80%), colourless crystals, C_9H_8INO [273.07 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63-7.58 (m, 2 H; H^{Ar}), 6.66 (d, ^3J (H,H) = 8.5 Hz, 1 H; H^{Ar}), 3.84 (s, 3 H; CH_3), 3.63 (s, 2H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 156.8

(C_q; C^{Ar}), 138.5 (C^{Ar}), 137.7 (C^{Ar}), 121.3 (C_q; C^{Ar}), 117.5 (C_q; CN), 112.8 (C^{Ar}), 82.6 (C_q; C^{Ar}), 55.8 (CH_3), 18.4 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 6.58 min; *m/z* (%): 273 (100) [M^+], 258 (31) [M^+-CH_3], 233 (11) [$M^+-C_2H_2N$], 146 (9) [M^+-I]; **TLC**: R_f = 0.28 (cyclohexane/EtOAc = 6/1, UV and CAM); **m.p.**$^{exp.}$ = 67-70°C; **HRMS** (EI): calcd for [M^+]: 272.9651; found: 272.9658.

7.4.3.10.2 2-(2-Hydroxy-5-iodophenyl)acetonitrile (7d)

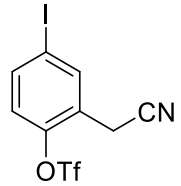


7d

A flame dried and argon flushed Schlenk-flask was charged with 3.66 mL BBr_3 (1 M in DCM) (917 mg, 3.66 mmol, 2.0 eq) and after cooling to 0 °C 500 mg methoxy derivative **7b** (1.83 mmol, 1.0 eq) were carefully added. The brown reaction mixture was stirred for 4 h at 60 °C and after cooling to RT the reaction mixture was diluted with 50 mL DCM and quenched by the addition of 50 mL saturated $NaHCO_3$ solution. The phases were separated and the aqueous phase was extracted with DCM (3 x 50 mL). The combined organic layers were washed with saturated NaCl solution (1 x 100 mL), dried over $MgSO_4$ and filtered. After purification via flash column chromatography (50 g SiO_2, 3.0 x 15 cm, eluent: cyclohexane/EtOAc = 4/1, R_f = 0.22, UV and CAM) compound **7d** was isolated as a pale brown powder.[80]
Yield: 432 mg (91%), pale brown powder, C_8H_6INO [259.04 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, ^4J (H,H) = 1.4 Hz, 1 H, H^{Ar}), 7.48 (dd, ^3J (H,H) = 8.4 Hz, ^4J (H,H) = 1.8 Hz, 1 H, H^{Ar}), 6.59 (d, ^3J (H,H) = 8.4 Hz, 1 H; H^{Ar}), 5.75 (bs, 1 H; OH), 3.67 (s, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 153.3 (C_q; C^{Ar}), 138.5 (C^{Ar}), 138.2 (C^{Ar}), 119.7 (C_q; C^{Ar}), 117.6 (C^{Ar}), 117.5 (C_q; CN), 82.7 (C_q; C^{Ar}), 18.3 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 6.22 min; *m/z* (%): 259 (100) [M^+], 232 (56) [$M^+-C_2H_2N$], 204 (24) [$M^+-C_3H_3O$]; **TLC**: R_f = 0.22 (cyclohexane/EtOAc = 4/1, UV and CAM); **m.p.**$^{exp.}$ = 121°C, decomposition; **HRMS** (EI): calcd for [M^+]: 258.9494; found: 258.9490.

7.4.3.10.3 2-(Cyanomethyl)-4-iodophenyl trifluoromethanesulfonate (7a)



7a

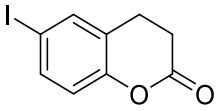
Compound **7a** was prepared according to procedure 7.4.3.3 from 432 mg phenol derivative **7d** (1.67 mmol, 1.0 eq) in 4.0 mL pyridine and 445 µL Tf_2O (518 mg, 1.83 mmol, 1.1 eq). Quantitative conversion was detected after 2 h. After flash column chromatography (60 g SiO_2, 3.0 x 19 cm, eluent: cyclohexane/Et_2O = 10/1, R_f = 0.26, UV and CAM) compound **7a** was isolated as a brown oil.[80]

Yield: 556 mg (85%), brown oil, $C_9H_5F_3INO_3S$ [391.11 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (bs, 1 H; H^{Ar}), 7.79 (dd, ^3J (H,H) = 8.6 Hz, ^4J (H,H) = 1.9 Hz, 1 H; H^{Ar}), 7.10 (d, ^3J (H,H) = 8.7 Hz, 1 H; H^{Ar}), 3.81 (s, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 146.7 (C_q; C^{Ar}), 139.7 (C^{Ar}), 139.5 (C^{Ar}), 125.6 (C_q; C^{Ar}), 123.8 (C^{Ar}), 118.6 (q, ^1J (C,F) = 318 Hz; CF_3), 115.5 (C_q; CN), 93.9 (C_q; C^{Ar}), 18.8 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 6.36 min; *m/z* (%): 391 (51) [M^+], 258 (100) [M^+−CF_3O_2S], 131 (13) [M^+−CF_3IO_2S]; **TLC**: R_f = 0.26 (cyclohexane/EtOAc = 10/1, UV and CAM); **HRMS** (EI): calcd for [M^+]: 390.8987; found: 390.8986.

7.4.3.11 Synthesis of Glutamate building block

7.4.3.11.1 6-Iodochroman-2-one (8b)



8b

In a flame dried and argon flushed 250 mL two-neck round-bottom flask equipped with dropping funnel and argon-inlet 5.00 g dihydrocoumarin (**8c**) (33.8 mmol, 1.0 eq) were dissolved in 35 mL DCM. 5.48 g ICl (33.8 mmol, 1.0 eq) dissolved in 35 mL DCM were added through the dropping funnel within 15 min. After full conversion (20 h) the reaction mixture was diluted with 100 mL DCM and and washed with 0.1 M $Na_2S_2O_3$ solution (2 x 50 mL). The combined aqueous layers were reextracted with DCM (2 x 50 mL). The combined organic layers were washed with saturated NaCl solution (1 x 200 mL), dried over $MgSO_4$, filtered and

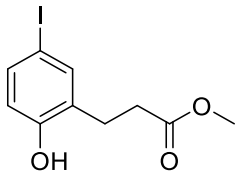
the solvent was removed in vacuum. The yellow, solid crude was recrystallized from DCM/cyclohexane (1/4).

Yield: 8.28 g (90%), colourless powder, $C_9H_7IO_2$ [274.06 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56-7.53 (m, 2 H; H^{Ar}), 6.81 (d, ^2J (H,H) = 8.1 Hz, 1 H; H^{Ar}), 2.97 (t, ^2J (H,H) = 7.2 Hz, 2H; CH_2), 2.76 (t, ^2J (H,H) = 7.1 Hz, 2H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 167.8 (C_q; CO), 152.1 (C_q; C^{Ar}), 137.4 (C^{Ar}), 136.9 (C^{Ar}), 125.2 (C_q; C^{Ar}), 119.2 (C^{Ar}), 87.6 (C_q; C^{Ar}), 28.9 (CH_2), 23.5 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 6.71 min; *m/z* (%): 145 (31) [M^+], 118 (100) [M^+−CN], 51 (7) [M^+−C_6H_5O]; **m.p.**$^{exp.}$ = 134-136°C, (m.p.$^{lit.}$ = 133-134°C).[99]

Analytical data are in accordance with those reported.[99]

7.4.3.11.2 Methyl 3-(2-hydroxy-5-iodophenyl)propanoate (8d)



8d

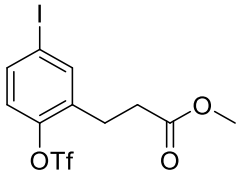
In a flame dried and argon flushed Schlenk-flask 2.00 g 6-iodochroman-2-one (**8b**) (7.30 mmol, 1.00 eq) were suspended in 140 mL MeOH. 1.95 mL H_2SO_4 were added to this colourless suspension. The suspension dissolved and the colourless solution was warmed to 55 °C and stirred overnight at this temperature. After full conversion (24 h) was detected by GC-MS the brown solution was neutralized by adding 50 mL saturated $NaHCO_3$ solution and the solvent was removed in vacuum. The brown residue was diluted with 100 mL H_2O, and extracted with DCM (3 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuum. The crude product was purified via flash column chromatography (250 g SiO_2, 6.0 x 17 cm, eluent: cyclohexane/EtOAc = 5/1, R_f = 0.18, UV and CAM) and **8d** was isolated as a light yellow oil.

Yield: 1.70 g (76 %), light yellow oil, $C_{10}H_{11}IO_3$ [306.10 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39-7.35 (m, 3 H; H^{Ar}, OH), 6.65-6.62 (m, 1 H; H^{Ar}), 3.66 (s, 3H; CH_3), 2.82 (t, ^2J (H,H) = 5.9 Hz, 2H; CH_2), 2.69 (t, ^2J (H,H) = 5.9 Hz, 2H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 176.2 (C_q; CO), 154.6 (C_q; C^{Ar}), 139.2 (C^{Ar}), 137.0 (C^{Ar}), 130.4 (C_q; C^{Ar}), 119.9 (C^{Ar}), 82.9 (C_q; C^{Ar}), 52.6 (CH_3), 35.0 (CH_2), 24.5 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 6.92 min; *m/z* (%): 306 (17) [M^+], 274 (100) [M^+−OCH_3],

246 (64) [M^+−$C_2H_3O_2$], 91 (0.31) [M^+−$C_4H_7O_2I$]; **TLC**: R_f = 0.18 (cyclohexane/EtOAc = 5/1, UV and CAM); **HRMS** (EI): calcd for [M^+]: 305.9753; found: 305.9766.

7.4.3.11.3 Methyl 3-(5-iodo-2-(((trifluoromethyl)sulfonyl)oxy)phenyl)propanoate (8a)



8a

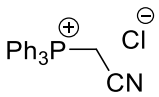
Compound **8a** was prepared according to procedure 7.4.3.3 from 800 mg phenol derivative **8d** (2.61 mmol, 1.0 eq) in 3.30 mL pyridine and 693 µL Tf_2O (811 mg, 2.87 µmol, 1.1 eq). Quantitative conversion was detected after 2 h. After flash column chromatography (100 g, SiO_2, 5.0 x 10 cm, eluent: cyclohexane/EtOAc = 20/1, R_f = 0.26, UV and CAM) compound **8a** was isolated as a colourless oil.

Yield: 966 mg (84%), colourless oil, $C_{11}H_{10}F_3IO_5S$ [438.16 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, ^4J (H,H) = 2.1 Hz, 1 H; H^{Ar}), 7.62 (dd, ^3J (H,H) = 8.7 Hz, ^4J (H,H) = 2.1 Hz, 1 H; H^{Ar}), 7.01 (d, ^3J (H,H) = 8.7 Hz, 1 H; H^{Ar}), 3.69 (s, 3 H; CH_3), 2.99 (t, ^3J (H,H) = 7.7 Hz, 2 H, CH_2), 2.65 (t, ^3J (H,H) = 7.7 Hz, 2 H, CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 172.3 (C_q; C^{Ar}), 147.9 (C_q; C^{Ar}), 140.3 (C^{Ar}), 137.6 (C^{Ar}), 135.8 (C_q; C^{Ar}), 123.4 (C^{Ar}), 118.7 (q, ^1J (C,F) = 318 Hz; CF_3), 93.4 (C_q; CN), 52.0 (CH_3), 33.7 (CH_2), 25.0 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 6.65 min; *m/z* (%): 438 (4) [M^+], 407 (11) [M^+−OCH_3], 289 (100) [M^+−CF_3O_3S] 91 (34) [M^+−$C_5H_3F_3IO_4S$]; **TLC**: R_f = 0.26 (cyclohexane/EtOAc = 20/1, UV and CAM); **HRMS** (EI): calcd for [M^+]: 437.9246; found: 437.9276.

7.4.3.12 Synthesis of Glutamine building block

7.4.3.12.1 (Cyanomethyl)triphenylphosphonium chloride (9b)



9b

In a flame dried and argon flushed Schlenk-flask 9.00 g PPh_3 (34.4 mmol, 1.0 eq) were dissolved in 50 mL absolute, degassed toluene. 4.35 mL 2-chloroacetonitrile (5.18 g, 58.6 mmol, 2.0 eq) were added to the colourless solution. The reaction mixture was heated under reflux for 24 h during which a colourless precipitate was formed. The suspension was

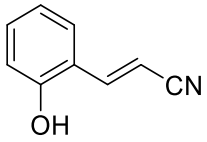
cooled to RT and the precipitate was collected by filtration and washed with Et_2O (2 x 10 mL).[80]

Yield: 11.5 g (99%), colourless powder, $C_{20}H_{17}ClNP$ [337.78 g/mol].

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.01-7.81 (m, 15 H; H^{Ar}), 6.20 (d, ^2J (H,P) = 15.9 Hz, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, DMSO-d_6, APT): δ = 135.9 (d, ^4J (C,P) = 3 Hz; C^{Ar}), 133.8 (d, ^3J (C,P) = 11 Hz; C^{Ar}), 130.5 (d, ^2J (C,P) = 13 Hz; C^{Ar}), 116.3 (d, ^1J (C,P) = 89 Hz; C^{Ar}), 112.9 (d, ^2J (C,P) = 9 Hz; CN), 14.3 (d, ^1J (C,P) = 55 Hz; CH_2) ppm; **m.p.**$^{exp.}$ = 263°C, decomposition (m.p.$^{lit.}$ = 265-267°C, decomposition).[131]

Analytical data are in accordance with those reported.[131]

7.4.3.12.2 3-(2-Hydroxyphenyl)acrylonitrile (9c)



9c

In a flame dried and argon flushed 500 mL three-neck round-bottom flask equipped with reflux condenser, and two argon-inlets 12.5 g phosphonium-salt **9b** (36.9 mmol, 1.5 eq) were suspended in 120 mL absolute THF. After cooling the suspension to 0 °C, 4.13 g KO*t*Bu (36.9 mmol, 1.5 eq) were added. The pale yellow reaction mixture was stirred at 50 °C for 60 min. After cooling the suspension to 0 °C 2.61 mL salicylaldehyde (**2d**) (3.00 g, 24.6 mmol, 1.0 eq) were added and the brown suspension was heated to 80 °C. After quantitative conversion (20 h) the reaction mixture was cooled to RT and quenched by the addition of 120 mL saturated NH_4Cl solution. The aqueous phase was extracted with DCM (3 x 100 mL) and the combined organic layers were washed with saturated NaCl solution (1 x 200 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the brown, oily crude product was purified via flash column chromatography (250 g SiO_2, 7.5 x 11 cm, eluent: cyclohexane/EtOAc = 3/1, R_f = 0.22, UV and CAM).[80]

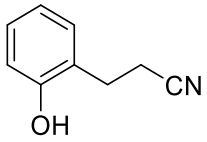
Yield: 3.43 g (96%), orange powder, C_9H_7NO [145.16 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63 (d, ^3J (H,H) = 16.8 Hz, 1 H; CH), 7.35 (dd, ^3J (H,H) = 7.8 Hz, ^4J (H,H) = 1.2 Hz 1 H; C^{Ar}), 7.29 (dt, ^3J (H,H) = 8.1 Hz, ^4J (H,H) = 1.6 Hz, 1 H; C^{Ar}), 6.95 (dt, ^3J (H,H) = 7.7 Hz, ^4J (H,H) = 0.6 Hz, 1 H; C^{Ar}), 6.86 (d, ^3J (H,H) = 8.1 Hz, 1 H; C^{Ar}), 6.30 (s, 1 H; OH), 6.17 (d, ^3J (H,H) = 16.8 Hz, 1H; CH) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 155.4 (C_q; C^{Ar}), 147.3 (CH), 132.4 (C^{Ar}), 129.6 (C^{Ar}), 121.1 (C^{Ar}), 121.1 (C_q; C^{Ar}),

119.2 (C_q; CN), 116.6 (C^{Ar}), 96.8 (CH) ppm; **GC-MS** (EI, 70 eV; MP_50_S): t_R = 6.20 min; *m/z* (%): 145 (31) [M^+], 118 (100) [M^+−CN], 51 (7) [M^+−C_6H_5O]; **TLC**: R_f = 0.22 (cyclohexane/EtOAc = 3/1, UV and CAM); **m.p.**$^{exp.}$ = 124-128°C.

Analytical data are in accordance with those reported.[132]

7.4.3.12.3 3-(2-Hydroxyphenyl)propanenitrile (9d)



9d

An argon flushed 500 mL three-neck round-bottom flask, equipped with argon-inlet, was charged with 3.40 g (23.4 mmol, 1.0 eq) phenol derivative **9c** and dissolved in 190 mL MeOH. 680 mg palladium(II) hydroxide on activated charcoal ($Pd(OH)_2$/C) (20 wt%) were added to the orange reaction mixture.[2] After ensuring hydrogen atmosphere by evacuating and back-flushing with hydrogen gas (6 x), the reaction mixture was stirred for 24 h at RT under an atmosphere of H_2 (balloon present). After filtering off the catalyst (5x3 cm SiO_2, eluent: MeOH) and evaporating the solvent using a rotary evaporator, the crude product was purified via flash column chromatography (200 g SiO_2, 5.5 x 12 cm, eluent: cyclohexane/EtOAc = 5/1, R_f = 0.13, UV and CAM).[80]

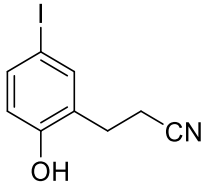
Yield: 2.30 g (67%), pale brown oil, C_9H_9NO [147.17 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17-7.11 (m, 2 H; H^{Ar}), 6.89 (dt, ^3J (H,H) = 7.5 Hz, ^4J (H,H) = 1.0 Hz, 1 H; H^{Ar}), 6.75 (d, ^3J (H,H) = 7.9 Hz, 1 H; H^{Ar}), 5.59 (bs, 1 H; OH), 2.98 (t, ^3J (H,H) = 7.4 Hz, 2 H; CH_2), 2.69 (t, ^3J (H,H) = 7.3 Hz, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 153.9 (C_q; C^{Ar}), 130.7 (C^{Ar}), 128.7 (C^{Ar}), 124.7 (C_q; C^{Ar}), 121.0 (C^{Ar}), 119.8 (C_q; CN), 115.5 (C^{Ar}), 26.9 (CH_2), 17.5 (CH_2) ppm; **GC-MS** (EI, 70 eV; MP_50_S): t_R = 5.82 min; *m/z* (%): 147 (29) [M^+], 107 (100) [M^+−C_2H_2N], 91 (9) [M^+−C_2H_3NO]; **TLC**: R_f = 0.13 (cyclohexane/EtOAc = 5/1, UV and CAM).

Analytical data are in accordance with those reported.[133]

[2] Palladium hydroxide on activated charcoal, moistened with water, 15-20% Pd basis (based on dry substance), Fluka 76063.

7.4.3.12.4 3-(2-Hydroxy-5-iodophenyl)propanenitrile (9e)



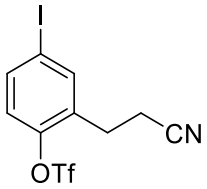
9e

Compound **9e** was prepared according to procedure 2.1.1 from 1.00 g 3-(2-hydroxyphenyl)-propanenitrile (**9d**) (6.79 mmol, 1.0 eq) in 10 mL acetic acid and 1.10 g ICl (6.79 mmol, 1.0 eq). After 24 h quantitative conversion was detected by GC-MS. Compound **9e** was used in the next step without further purification[3].[80]

Yield: 1.25 g (67%), brown oil, C_9H_8INO [273.07 g/mol].

GC-MS (EI, 70 eV; MP_50_S): t_R = 7.13 min; *m/z* (%): 272 (80) [M^+], 233 (100) [$M^+-C_2H_2N$], 146 (13) [M^+-I], 106 (17) [$M^+-C_2H_2IN$]; **TLC**: R_f = 0.15 (cyclohexane/EtOAc = 5/1, CAM); **HRMS** (EI): calcd for [M^+]: 272.9651; found: 272.9670.

7.4.3.12.5 2-(2-Cyanoethyl)-4-iodophenyl trifluoromethanesulfonate (9f)



9f

Compound **9f** was prepared according to procedure 2.1.2 from 870 mg phenol derivative **9e** (3.19 mmol, 1.0 eq) in 4 mL pyridine and 845 µL Tf_2O (989 mg, 3.50 mmol, 1.1 eq). Quantitative conversion was detected after 2 h. After flash column chromatography (100 g SiO_2, 4.0 x 19 cm, eluent: cyclohexane/Et_2O = 10/1, R_f = 0.20, CAM) compound **9f** was isolated as a pale yellow solid.[80]

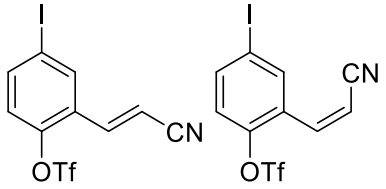
Yield: 893 mg (69%), pale yellow solid, $C_{10}H_7F_3INO_3S$ [405.13 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75-7.69 (m, 2 H; H^{Ar}), 7.06 (d, ^3J (H,H) = 8.6 Hz, 1 H; H^{Ar}), 3.02 (t, ^3J (H,H) = 7.3 Hz, 2 H; CH_2), 2.69 (t, ^3J (H,H) = 7.3 Hz, 2H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$): δ = 147.5 (C_q; C^{Ar}), 140.3 (C^{Ar}), 138.8 (C^{Ar}), 133.1 (C_q; C^{Ar}), 123.7 (C^{Ar}), 118.6 (q, ^1J (C,F) = 320 Hz; CF_3), 118.0 (C_q; CN), 93.8 (C_q; C^{Ar}), 25.9 (CH_2), 17.7 (CH_2) ppm; **GC-MS** (EI, 70 eV; MP_50_S): t_R = 6.65 min; *m/z* (%): 405 (47) [M^+], 272 (53) [$M^+-CF_3O_2S$],

[3] During flash column chromatography, deiodination of compound **17f** was observed.

145 (100) [M^+−CF_3IO_2S]; **TLC**: R_f = 0.20 (cyclohexane/EtOAc = 10/1, UV and CAM); **m.p.**$^{exp.}$ = 46-50°C; **HRMS** (EI): calcd for [M^+]: 404.9143; found: 404.9145.

7.4.3.12.6 2-(2-Cyanovinyl)-4-iodophenyl trifluoromethanesulfonate (9g)



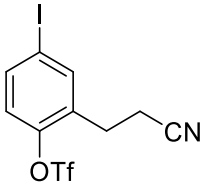
9g

In a flame dried and argon flushed Schlenk-flask 1.33 g phosphonium-salt **9b** (3.95 mmol, 1.5 eq) were suspended in 20 mL absolute THF. After cooling the suspension to 0 °C 413 mg KO*t*Bu (3.68 mmol, 1.4 eq) were added. The yellow reaction mixture was stirred at 50 °C and after 60 min the suspension was cooled again to 0 °C. 1.00 g aldehyde **10c** (2.63 mmol, 1.0 eq) was added and the red suspension was heated to 50 °C. After quantitative conversion (2 h) the reaction mixture was cooled to RT and quenched by the addition of 40 mL saturated NH_4Cl solution. The phases were separated. The aqueous phase was diluted with 100 mL H_2O and extracted with DCM (3 x 100 mL). The combined organic layers were washed with saturated NaCl solution (1 x 200 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the brown, oily crude product was purified via flash column chromatography (150 g SiO_2, 5.0 x 20 cm, eluent: cyclohexane/EtOAc = 20/1, R_f = 0.20, UV and CAM). The received mixture stereoisomers was directly used in the following reduction without further purification.

Yield: 1.06 g (E/Z=1:1.7, 99%), colourless powder, $C_{10}H_5F_3INO_3S$ [403.11 g/mol].

GC-MS (EI, 70 eV; MT_50_S): t_{R1} = 6.56 min, t_{R2} = 6.81 min; *m/z* (%): 403 (30) [M^+], 143 (100) [M^+−CF_3IO_2S]; **TLC**: R_f = 0.20 (cyclohexane/EtOAc = 20/1, UV and CAM); **m.p.**$^{exp.}$ = 79-83°C; **HRMS** (EI): calcd for [M^+]: 402.8987; found: 402.8987.

7.4.3.12.7 2-(2-Cyanoethyl)-4-iodophenyl trifluoromethanesulfonate (9f)



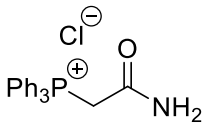
9f

An argon flushed 250 mL two-neck round-bottom flask, equipped with argon-inlet and reflux-condenser, was charged with 1.00 g **9g** (2.48 mmol, 1.0 eq) and dissolved in 20 mL THF. 2.77 g

p-tosylhydrazide (14.9 mmol, 6.0 eq) and 2.03 g NaOAc.3H_2O (14.9 mmol, 6.0 eq) were added and the yellow suspension was stirred at 70 °C. The reaction mixture was cooled to RT after quantitative conversion (18 h) was detected by GC-MS. 100 mL water were added and the phases were separated. The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organic layers were dried over Na_2SO_4. The Na_2SO_4 was filtered off and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography (100 g SiO_2, 4.0 x 20 cm, eluent: cyclohexane/EtOAc = 10/1, R_f = 0.20, CAM). **Yield**: 1.24 g (56%), pale yellow solid, $C_{10}H_7F_3INO_3S$ [405.13 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75-7.69 (m, 2 H; H^{Ar}), 7.06 (d, ^3J (H,H) = 8.6 Hz, 1 H; H^{Ar}), 3.02 (t, ^3J (H,H) = 7.3 Hz, 2 H; CH_2), 2.69 (t, ^3J (H,H) = 7.3 Hz, 2H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$): δ = 147.5 (C_q; C^{Ar}), 140.3 (C^{Ar}), 138.8 (C^{Ar}), 133.1 (C_q; C^{Ar}), 123.7 (C^{Ar}), 118.6 (q, ^1J (C,F) = 320 Hz; CF_3), 118.0 (C_q; CN), 93.8 (C_q; C^{Ar}), 25.9 (CH_2), 17.7 (CH_2) ppm; **GC-MS** (EI, 70 eV; MP_50_S): t_R = 6.65 min; *m/z* (%): 405 (47) [M^+], 272 (53) [$M^+-CF_3O_2S$], 145 (100) [$M^+-CF_3IO_2S$]; **TLC**: R_f = 0.20 (cyclohexane/EtOAc = 10/1, UV and CAM); **m.p.**$^{exp.}$ = 46-50°C; **HRMS** (EI): calcd for [M^+]: 404.9143; found: 404.9145.

7.4.3.12.8 (2-Amino-2-oxoethyl)triphenylphosphonium chloride (9h)



9h

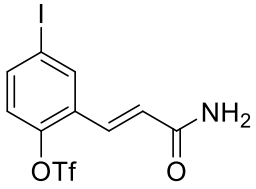
In a flame dried Schlenk-flask 7.86 g PPh_3 (30.0 mmol, 1.05 eq) and 2.67 g 2-chloroacetamide (28.6 mmol, 1.0 eq) were suspended in 30 mL nitromethane. The mixture was stirred for 19 h at 105°C. The pale brown solution was allowed to cool to RT, and the formed colourless precipitate was isolated by filtration, washed with EtOAc (2x10 mL), Et_2O (1x15 mL) and dried in vacuum.[134]

Yield: 10.1 g (99%), colourless powder, $C_{20}H_{19}ClNOP$ [355.80 g/mol].

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.43 (bs, 1 H; $CONH_2$), 7.89-7.74 (m, 15 H; H^{Ar}), 7.62 (bs, 1 H; $CONH_2$), 5.12 (d, ^2J (H,P) = 14.8 Hz, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, DMSO-d_6): δ = 165.0 (d, ^2J (C,P) = 5 Hz; $CONH_2$), 134.7 (d, ^4J (C,P) = 3 Hz; C^{Ar}), 133.8 (d, ^3J (C,P) = 11 Hz; C^{Ar}), 129.9 (d, ^2J (C,P) = 13 Hz; C^{Ar}), 119.1 (d, ^1J (C,P) = 89 Hz; C^{Ar}), 31.2 (d, ^1J (C,P) = 59 Hz; CH_2) ppm; **m.p.**$^{exp.}$ = 219-221°C (m.p.$^{lit.}$ = 227-229°C).[135]

Analytical data are in accordance with those reported.[134]

7.4.3.12.9 2-(3-Amino-3-oxoprop-1-en-1-yl)-4-iodophenyl trifluoromethanesulfonate (9i)



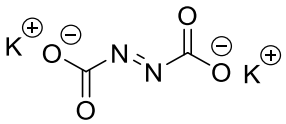
9i

In a flame dried and argon flushed Schlenk-flask 983 mg phosphonium-salt **9h** (2.76 mmol, 1.05 eq) were suspended in 20 mL absolute MeOH. After cooling the suspension to 0 °C, 310 mg KO*t*Bu (2.76 mmol, 1.05 eq) were added. The yellow reaction mixture was stirred at 0 °C for 10 min. 1.00 g **10c** (2.63 mmol, 1.0 eq) was added and the orange solution was stirred at RT until full conversion of the starting material was observed. After quantitative conversion (16 h) the solvent was removed under reduced pressure and the orange crude product was purified via flash column chromatography (250 g SiO_2, 7.5 x 11 cm, eluent: cyclohexane/EtOAc = 1/1, R_f = 0.21, UV and CAM).

Yield: 616 mg (55%), pale yellow crystals, $C_{10}H_7F_3INO_4S$ [421.13 g/mol].

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.16 (bs, 1 H; $CONH_2$), 7.91 (d, ^3J (H,H) = 8.6 Hz, 1 H; H^{Ar}), 7.59 (bs, 1 H; $CONH_2$), 7.44-7.31 (m, 3 H; H^{Ar}, CH), 6.81 (d, ^3J (H,H) = 15.7 Hz, 1 H; CH) ppm; **^{13}C NMR** (76 MHz, DMSO-d_6, APT): δ = 165.3 (CONH2), 146.8 (C_q; C^{Ar}), 139.8 (CH), 136.5 (C^{Ar}), 130.4 (C_q; C^{Ar}), 128.8 (C^{Ar}), 128.4 (C^{Ar}), 124.2 (C^{Ar}), 118.0 (q, ^1J (C,F) = 321 Hz; CF_3), 95.3 (C_q; C^{Ar}) ppm; **HPLC-MS** (Poroshell, ESI$^+$, MT_general): t_R = 3.67 min; *m/z*: 422 [M+H$^+$], 444 [M+Na$^+$]; λ_{max} = 239 nm; **TLC**: R_f = 0.21 (cyclohexane/EtOAc = 1/1, UV and CAM); **m.p.**$^{exp.}$ = 115-117°C; **HRMS** (EI): calcd for [M^+]: 420.9093; found: 420.9094.

7.4.3.12.10 Dipotassium Azodicarboxylate (PADA) (9j)



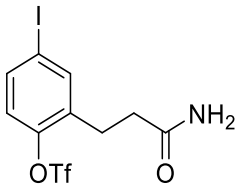
9j

In a 100 mL round-bottom flask 18.3 mL KOH solution (7 M) were cooled to -10 °C by a cryostat. 5.84 g Azodicarbonamide (50.3 mmol, 1.0 eq) were added in small portions. The yellow-orange suspension was stirred at -10 °C for 60 min. Then the yellow precipitate was collected by filtration and washed with cold MeOH (3 x 50mL). The yellow powder was dried in vacuum.[136]

Yield: 9.34 g (96%), yellow powder, $C_2K_2N_2O_4$ [194.23 g/mol].

m.p.$^{exp.}$ = 186°C (decomposition).

7.4.3.12.11 2-(3-Amino-3-oxopropyl)-4-iodophenyl trifluoromethanesulfonate (9a)



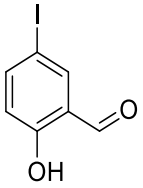
9a

In a 25 mL round-bottom flask equipped with reflux condenser 280 mg **9i** (665 µmol, 1.0 eq) were dissolved in 4.5 mL 1,2-DME. 387 mg PADA (**9j**) (1.99 mmol, 3.0 eq) were added. 114 µL AcOH (120 mg, 1.99 mmol, 3.0 eq) were added to the yellow suspension and the reaction-mixture was heated to 50 °C. When full conversion (3 d) was achieved the reaction was cooled to RT and unreacted PADA was removed by filtration. The solution was concentrated in vacuum. The brown, solid crude was purified via flash column chromatography (30 g SiO_2, 2.5 x 17 cm, eluent: cyclohexane/EtOAc = 1/1, R_f = 0.23, CAM).
Yield: 258 mg (92%), colourless powder, $C_{10}H_9F_3INO_4S$ [423.14 g/mol].

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.84 (s, 1 H; H^{Ar}), 7.75 (dd, ^3J (H,H) = 8.6 Hz, ^4J (H,H) = 1.9 Hz, 1 H; H^{Ar}), 7.34 (bs, 1 H; $CONH_2$), 7.18 (d, ^3J (H,H) = 8.6 Hz, 1H; H^{Ar}), 6.85 (bs, 1 H; $CONH_2$), 2.83 (t, ^3J (H,H) = 7.5 Hz, 2H; CH_2), 2.41 (t, ^3J (H,H) = 7.5 Hz, 2H; CH_2) ppm; **^{13}C NMR** (76 MHz, DMSO-d_6, APT): δ = 172.4 ($CONH_2$), 147.4 (C_q; C^{Ar}), 139.7 (C^{Ar}), 137.2 (C^{Ar}), 136.4 (C_q; C^{Ar}), 123.3 (C^{Ar}), 118.0 (q, ^1J (C,F) = 320 Hz; CF_3), 94.8 (C_q; C^{Ar}), 34.1 (CH_2), 24.8 (CH_2) ppm; **HPLC-MS** (Poroshell, ESI$^+$, MT_general): t_R = 3.65 min; *m/z*: 424 [M+H^+], 446 [M+Na^+]; λ_{max} = 239 nm; **TLC**: R_f = 0.23 (cyclohexane/EtOAc = 1/1, UV and CAM); **m.p.**$^{exp.}$ = 115-118°C; **HRMS** (EI): calcd for [M^+]: 422.9249; found: 422.9258.

7.4.3.13 Synthesis of Serine building block

7.4.3.13.1 2-Hydroxy-5-iodobenzaldehyde (10b)



10b

Compound **10b** was prepared according to procedure 7.4.3.2 from 16.1 g ICl (99.1 mmol, 1.0 eq) in 100 mL DCM and 10.0 mL salicylaldehyde (**2d**) (12.1 g, 99.1 mmol, 1.0 eq) in 37

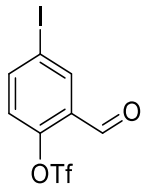
mL DCM. Quantitative conversion was detected after 24 h. The crude product was recrystallized from cyclohexane.[89]

Yield: 16.7 g (68%); pale yellow powder, $C_7H_5IO_2$ [248.02 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.94 (s, 1 H; CHO), 9.83 (s, 1 H; OH), 7.84 (d, ^4J (H,H) = 2.2 Hz, 1 H; H^{Ar}), 7.76 (dd, ^3J (H,H) = 8.8 Hz, ^4J (H,H) = 2.2 Hz, 1 H; H^{Ar}), 6.80 (d, ^3J (H,H) = 8.8 Hz, 1 H; H^{Ar}) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 195.5 (CHO), 161.3 (C_q; C^{Ar}), 145.4 (C^{Ar}), 142.0 (C^{Ar}), 122.7 (C_q; C^{Ar}), 120.3 (C^{Ar}), 80.5 (C_q; C^{Ar}) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 5.48 min; *m/z* (%): 248 (100) [M^+], 219 (6) [M^+−CHO], 202 (3) [M^+−CH_2O_2]; **TLC**: R_f = 0.30 (cyclohexane/EtOAc = 25/1, UV and CAM) **m.p.**$^{exp.}$ = 97-99°C (m.p.$^{lit.}$ = 97-98°C).[89]

Analytical data are in accordance with those reported.[89]

7.4.3.13.2 2-Formyl-4-iodophenyl trifluoromethanesulfonate (10c)



10c

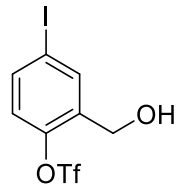
In a flame dried and argon flushed two-neck round-bottom flask equipped with argon-inlet 13.5 g phenol derivative **10b** (54.4 mmol, 1.0 eq) were dissolved in 110 mL DCM and 6.60 mL pyridine (6.46 g, 81.7 mmol, 1.5 eq). The pale yellow solution was cooled to 0 °C and 18.3 mL Tf_2O (30.7 g, 109 mmol, 2.0 eq) were added. After 5 min the orange suspension was allowed to warm to RT. When quantitative conversion (4 h) was achieved the reaction mixture was washed with 200 mL H_2O. The aqueous phase was extracted with DCM (6 x 100 mL) and the combined organic layers were washed with saturated NaCl solution (1 x 100 mL), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The brown, oily crude product was purified via flash column chromatography (500 g SiO_2, 7.5 x 18 cm, eluent: cyclohexane/EtOAc = 40/1, R_f = 0.28 UV and CAM).[80]

Yield: 19.2 g (93%), yellow oil, $C_8H_4F_3IO_3S$ [380.08 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.18 (s, 1 H; CHO), 8.29 (d, ^4J (H,H) = 2.2 Hz, 1 H; H^{Ar}), 8.02 (dd, ^3J (H,H) = 8.6 Hz, ^4J (H,H) = 2.2 Hz, 1 H; H^{Ar}), 7.16 (d, ^3J (H,H) = 8.7 Hz, 1 H; H^{Ar}) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$): δ = 185.1 (CHO), 149.8 (C_q; C^{Ar}), 144.7 (C^{Ar}), 139.6 (C^{Ar}), 129.8 (C_q; C^{Ar}), 124.4 (C^{Ar}), 118.7 (q, ^1J (C,F) = 321 Hz; CF_3), 93.7 (C_q; C^{Ar}) ppm;

GC-MS (EI, 70 eV; MT_50_S): t_R = 5.98 min; *m/z* (%): 380 (100) [M^+], 247 (54) [M^+−CF_3O_2S], 219 (24) [M^+−$C_2HF_3O_3S$], **TLC**: R_f = 0.28 (cyclohexane/EtOAc = 40/1, UV and CAM).

7.4.3.13.3 2-(Hydroxymethyl)-4-iodophenyl trifluoromethanesulfonate (10d)

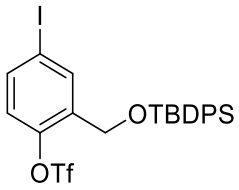


10d

In a flame dried and argon flushed Schlenk-flask 5.00 g aldehyde **10c** (13.2 mmol, 1.0 eq) were dissolved in 20.0 mL absolute DCM. This solution was cooled to -78 °C and 26.3 mL diiso-butylaluminium hydride (DIBALH) (1.0 M in toluene) (3.74 g, 26.3 mmol, 2.0 eq) were slowly added via a dropping funnel. After stirring for 2 h at -78 °C the bright yellow solution was quenched by the addition of 17 mL MeOH and 60 mL saturated Rochelle-salt solution. A yellow emulsion was formed and stirred overnight until phase separation occurs. The phases were separated and the aqueous phase was extracted with DCM (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The yellow, oily crude product was purified via flash column chromatography (250 g SiO_2, 5.5 x 18 cm, eluent: cyclohexane/EtOAc = 5/1, R_f = 0.37, UV and CAM).[80]
Yield: 4.19 mg (83%), pale yellow powder, $C_8H_6F_3IO_4S$ [382.10 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97 (d, ^4J (H,H) = 2.2 Hz, 1 H; H^{Ar}), 7.70 (dd, ^3J (H,H) = 8.6 Hz, ^4J (H,H) = 2.2 Hz, 1 H; H^{Ar}), 7.01 (d, ^3J (H,H) = 8.6 Hz, 1 H; H^{Ar}), 4.76 (s, 2 H; CH_2), 1.96 (bs, 1 H; OH) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$): δ = 146.7 (C_q; C^{Ar}), 138.9 (C^{Ar}), 138.5 (C^{Ar}), 135.9 (C_q; C^{Ar}), 123.2 (C^{Ar}), 118.7 (q, ^1J (C,F) = 320 Hz; CF_3), 93.7 (C_q; C^{Ar}), 59.1 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 6.24 min; *m/z* (%): 382 (49) [M^+], 249 (14) [M^+−CF_3O_2S], 122 (11) [M^+−CF_3IO_2S]; **TLC**: R_f = 0.37 (cyclohexane/EtOAc = 5/1, UV and CAM); **m.p.**$^{exp.}$ = 28-30°C (m.p.$^{lit.}$ = 97-98°C); **HRMS** (EI): calcd for [M^+]: 381.8984; found: 381.8989.

7.4.3.13.4 2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-4-iodophenyl trifluoromethanesulfonate (10a)



10a

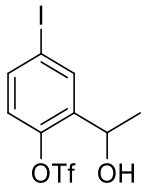
A 500 mL round-bottom flask with drying-tube was charged with 6.28 g (16.4 mmol, 1.00 eq) 2-(hydroxymethyl)-4-iodphenyltrifluormethansulfonate (**10d**) dissolved in 75 mL DCM. 2.95 g (43.4 mmol, 2.64 eq) Imidazole and 6.5 mL (6.87 g, 25.0 mmol, 1.52 eq) *tert*-butyldiphenylchlorsilane (TBDPSCl) were added via syringe. When the whole amount of TBDPSCl was added a colourless solid started to precipitate. The reaction was stirred overnight (16 h) at 22 °C. When quantitative conversion was detected by TLC (Cyclohexan/EtOAc = 5/1, UV and CAM) the reaction was quenched by the addition of 120 mL 3 M NaOH and transferred to a separation funnel. After phase separating the aqueous phase was extracted with DCM (3 x 120 mL). The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The yellow, oily crude product was purified via flash column chromatography (250 g SiO_2, 7.0 x 17 cm, eluent: cyclohexane/EtOAc = 100/1, R_f = 0.34, UV and CAM).

Yield: 8.07 mg (79 %), colourless oil, $C_{24}H_{24}F_3IO_4SSi$ [620.50 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (m, 1 H; H^{Ar}), 7.70 – 7.64 (m, 5 H; H^{Ar}), 7.50 – 7.39 (m, 6 H; H^{Ar}), 6.98 (d, ^{3}J (H,H) = 8.6 Hz, 1 H; H^{Ar}), 4.79 (s, 2 H; CH_2), 1.14 (s, 9 H; 3 x CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 146.3 (C_q; C^{Ar}), 138.3 (C^{Ar}), 137.8 (C^{Ar}), 136.0 (C_q; C^{Ar}), 135.6 (C^{Ar}), 132.7 (C_q; C^{Ar}), 130.2 (C^{Ar}), 128.0 (C^{Ar}), 122.8 (C^{Ar}), 118.6 (q, ^1J (C,F) = 320 Hz; CF_3), 93.5 (C_q; C^{Ar}), 59.9 (CH_2), 27.0 (CH_3), 19.4 (C_q) ppm; **TLC:** R_f = 0.19 (Cyclohexan, UV), 0.34 (Cyclohexan/EtOAc 100/1 (v/v), UV); **HRMS (EI):** calcd for [M^+−C_4H_9]: 562.9457; found: 562.9446.

7.4.3.14 Synthesis of Threonine building block

7.4.3.14.1 2-(1-Hydroxyethyl)-4-iodophenyl trifluoromethanesulfonate (11b)



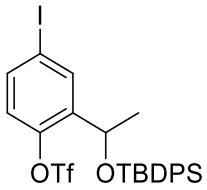
11b

In a flame dried and argon flushed Schlenk-flask 69.1 mg Mg turnings (2.84 mmol, 1.2 eq) were stirred for 20 min without solvent. Then the turnings were suspended in 5 mL Et_2O and 180 µL iodmethane (403 mg, 2.84 mmol, 1.2 eq) dissolved in 5 mL Et_2O were added. The reaction mixture was heated under reflux until the whole Mg was dissolved (30 min). The colourless suspension was added dropwise to a solution of 900 mg aldehyde **10c** (2.37 mmol, 1.0 eq) in 10 mL Et_2O. The pale yellow suspension kept stirring until quantitative conversion was detected by TLC. After 5 h the reaction was diluted with 100 mL Et_2O and washed with 1 M HCl (1 x 100 mL), saturated $NaHCO_3$ solution (1 x 100 mL) and saturated NaCl solution. The organic layer was dried over $MgSO_4$, filtered and the solvent was removed in vacuum. The yellow, oily crude product was purified via flash column chromatography (100 g SiO_2, 3.5 x 22 cm, eluent: cyclohexane/EtOAc = 10/1, R_f = 0.21, CAM).[80]

Yield: 882 mg (94%), pale yellow solid, $C_9H_8F_3IO_4S$ [396.12 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, ^4J (H,H) = 2.1 Hz, 1 H; H^{Ar}), 7.67 (dd, ^3J (H,H) = 8.6 Hz, ^4J (H,H) = 2.3 Hz, 1 H; H^{Ar}), 6.98 (d, ^3J (H,H) = 8.4 Hz, 1 H; H^{Ar}), 5.16 (q, ^3J (H,H) = 6.4 Hz, 1 H; CH), 2.04 (bs, 1 H; OH), 1.50 (d, ^3J (H,H) = 6.6 Hz, 3 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$): δ = 145.9 (C_q; C^{Ar}), 140.8 (C_q; C^{Ar}), 138.3 (C^{Ar}), 137.2 (C^{Ar}), 123.1 (C^{Ar}), 118.6 (q, ^1J (C,F) = 322 Hz; CF_3), 94.0 (C_q; C^{Ar}), 64.1 (CH), 24.2 (CH_3) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 6.24; *m/z* (%): 382 (49) [M^+], 249 (14) [$M^+-CF_3O_2S$], 122 (11) [$M^+-CF_3IO_2S$]; **TLC**: R_f = 0.21 (cyclohexane/EtOAc = 10/1, UV and CAM); **m.p.**$^{exp.}$ = 37-40°C; **HRMS** (EI): calcd for [M^+]: 395.9140; found: 395.9135.

7.4.3.14.2 2-(1-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-4-iodophenyl trifluoromethanesulfonate (11a)



11a

In a 250 mL round-bottom flask 8.24 g crude 2-(1-hydroxethyl)-4-iodophenyl trifluoromethanesulfonate (**11b**) (20.7 mmol, 1.0 eq) from 7.4.3.14.1 were dissolved in 95 mL DCM and 3.52 g imidazole (51.8 mmol, 2.7 eq) were added. Then 5.4 mL *tert*-butylchlorodiphenylsilane (6.28 g, 20.8 mmol, 1.0 eq) were added to the yellow solution and a white precipitate formed. After the reaction was stirred for 16 h at RT additional 540 µL *tert*-butylchlorodiphenylsilane (572 mg, 2.1 mmol, 0.1 eq) were added because of incomplete conversion detected by TLC (Cyclohexane/EtOAc = 10/1, UV and CAM). After additional stirring of the reaction for 5 h the reaction was diluted with 20 mL DCM and was washed with 3 M NaOH (1x150 mL). The aqueous layer was reextracted with DCM (1 x 150 mL). The combined organic layers were again washed with saturated NaCl solution (1 x 200 mL), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to give a yellow oil. The crude product was purified via flash column chromatography (350 g SiO_2, 7.5 x 16 cm, eluent: cyclohexane to cyclohexane/EtOAc = 50/1, R_f = 0.38 (cyclohexane/EtOAc = 100 /1, UV and CAM)).

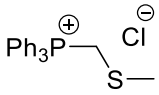
Yield: 9.86 g (75%), clear colourless oil, $C_{25}H_{26}F_3IO_4SSi$ [634.52 g/mol]

^{1}H NMR: (300 MHz , $CDCl_3$): δ = 8.10 (d, ^{4}J (H,H)= 2.0 Hz, 1 H; H^{Ar}), 7.62 (d, ^{3}J (H,H)= 6.3 Hz, 2 H; H^{Ar}), 7.53 (dd, ^{3}J (H,H)= 8.6 Hz, ^{4}J (H,H)= 2.2 Hz, 1 H, H^{Ar}), 7.44 (d, ^{3}J (H,H)= 6.6 Hz, 2 H; H^{Ar}), 7.35 (m, 4 H; H^{Ar}), 7.23 (m, 2 H; H^{Ar}), 6.79 (d, ^{3}J (H,H)= 8.6 Hz, 1 H; H^{Ar}), 5.03 (m, 1 H; CH), 1.32-1.30 (d, ^{3}J (H,H)= 6.2 Hz, 3 H; CH_3), 1.04 (s, 9 H, 3x CH_3) ppm; **^{13}C NMR:** (75 MHz, $CDCl_3$, APT): δ 145.0 (C_q, C^{Ar}), 141.3 (C_q, C^{Ar}), 137.9 (C^{Ar}), 137.6 (C^{Ar}), 135.8 (C^{Ar}), 135.8 (C^{Ar}), 133.6 (C_q, C^{Ar}), 132.9 (C_q, C^{Ar}), 130.0 (C^{Ar}), 129.9 (C^{Ar}), 127.8 (C^{Ar}), 127.8 (C^{Ar}), 122.5 (C^{Ar}), 118.4 (q, ^{1}J (H,H)=320.2 Hz; CF_3), 93.4 (C_q, C^{Ar}), 65.6 (CH), 27.1 (CH_3), 25.7 (CH_3), 19.5 (C_q) ppm; **GC-MS:** (EI, 70 eV; MT_50_S) t_R = 8.467 min; m/z (%): 485 (45) [M^+-CF_3O_3S]; **TLC:** R_f = 0.38 (Cyclohexane/EtOAc = 100/1, UV and CAM)

HRMS: (EI): calcd for [M^+-C_4H_9]: 576.9614; found: 576.9585.

7.4.3.15 Synthesis of Methionine building block

7.4.3.15.1 ((Methylthio)methyl)triphenylphosphonium chloride (12b)



12b

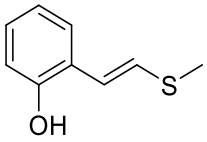
In a flame dried and argon flushed Schlenk-flask 20.0 g PPh_3 (76.3 mmol, 1.0 eq) were dissolved in 40 mL absolute toluene. 6.40 mL Chloromethyl methyl sulfide (7.36 g, 76.3 mmol, 1.0 eq) were added to the colourless solution. The solution turned yellow. The reaction mixture was stirred at 100 °C and within 24 h a colourless precipitate was formed. The suspension was cooled to 0 °C and the precipitate was collected by filtration and washed with toluene (3 x 5 mL).

Yield: 18.7 g (68%), colourless powder, $C_{20}H_{20}ClPS$ [358.86 g/mol].

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.92-7.75 (m, 15 H; H^{Ar}), 5.11 (d, ^2J (H,P) = 9.0 Hz, 2 H; CH_2), 1.90 (s, 3 H; CH_3) ppm; **^{13}C NMR** (76 MHz, DMSO-d_6, APT): δ = 135.1 (d, ^4J (C,P) = 3 Hz; C^{Ar}), 134.0 (d, ^3J (C,P) = 10 Hz; C^{Ar}), 130.1 (d, ^2J (C,P) = 12 Hz; C^{Ar}), 118.2 (d, ^1J (C,P) = 87 Hz; C_q; C^{Ar}), 23.8 (d, ^1J (C,P) = 51 Hz; CH_2), 17.2 (d, ^3J (C,P) = 3 Hz; CH_3) ppm; **m.p.**$^{exp.}$ = 225-227 °C (m.p.$^{lit.}$ = 213-214°C).[137]

Analytical data are in accordance with those reported.[137]

7.4.3.15.2 2-(2-(Methylthio)vinyl)phenol (12c)



12c

In a flame dried and argon flushed 250 mL three-neck round-bottom flask equipped with reflux condenser and an argon-inlet 4.41 g phosphonium-salt **12b** (12.3 mmol, 1.5 eq) were suspended in 40 mL absolute THF. After cooling the suspension to 0 °C, 1.38 g KO*t*Bu (12.3 mmol, 1.5 eq) were added. The yellow reaction mixture was stirred at 50 °C for 60 min. The suspension was cooled to 0 °C, 870 µL salicylaldehyde (**2d**) (1.00 g, 8.19 mmol, 1.0 eq) were added and the orange suspension was heated to 80 °C. After quantitative conversion (20 h) the reaction mixture was cooled to RT and quenched by the addition of 40 mL saturated NH_4Cl solution. The phases were separated and the aqueous phase was diluted with 50 mL H_2O. The aqueous phase was extracted with DCM (3 x 50 mL) and the combined organic layers were washed with saturated NaCl solution (1 x 100 mL), dried over Na_2SO_4 and filtered. The solvent was removed

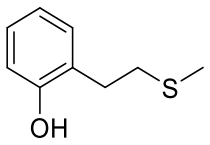
under reduced pressure and the yellow, oily crude product was purified via flash column chromatography (250 g SiO_2, 5.5 x 16 cm, eluent: cyclohexane/EtOAc = 10/1, R_f = 0.11, UV and CAM).

Yield: 1.29 g (95%), pale yellow oil, $C_9H_{10}OS$ [166.24 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, ^3J (H,H) = 7.6 Hz, 1 H; CH), 7.48 (dt, ^3J (H,H) = 7.5 Hz, ^4J (H,H) = 1.4 Hz, 1 H; H^{Ar}), 7.32-7-27 (m, 2 H; H^{Ar}), 7.16 (d, ^3J (H,H) = 8.0 Hz, 1 H; H^{Ar}), 6.91 (d, ^3J (H,H) = 15.5 Hz, 1 H; CH), 2.79 (s, 3 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 152.1 (C_q; C^{Ar}), 127.9 (C^{Ar}), 127.8 (CH), 127.1 (C^{Ar}), 124.8 (C_q; C^{Ar}), 121.3 (C^{Ar}), 119.4 (CH), 116.0 (C^{Ar}), 15.0 (CH_3) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 6.23 min; *m/z* (%): 166 (60) [M^+], 151 (6) [M^+-CH_3], 119 (66) [M^+-CH_3S]; **TLC**: R_f = 0.11 (cyclohexane/EtOAc = 10/1, UV and CAM).

Analytical data are in accordance with those reported.[138]

7.4.3.15.3 2-(2-(Methylthio)ethyl)phenol (12d)



12d

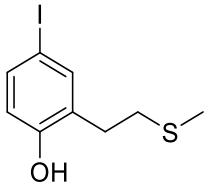
An argon flushed 250 mL two-neck round-bottom flask, equipped with argon-inlet and reflux-condenser, was charged with 2.45 g (15.0 mmol, 1.0 eq) phenol derivative **12c** dissolved in 150 mL THF. 16.8 g (90.2 mmol, 6.0 eq) p-tosylhydrazide and 12.3 g (90.2 mmol, 6.0 eq) $NaOAc.3H_2O$ were added and the yellow suspension was heated at 70°C. The reaction mixture was cooled to RT after quantitative conversion (18 h) was detected by GC-MS. 100 mL water were added and the phases were separated. The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organic layers were dried over Na_2SO_4. The Na_2SO_4 was filtered off and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography (250 g SiO_2, 6.0 x 17 cm, eluent: cyclohexane/EtOAc = 10/1, R_f = 0.17, UV and CAM).

Yield: 2.53 g (93%), pale yellow oil, $C_9H_{12}OS$ [168.25 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13-7.08 (m, 2 H; H^{Ar}), 6.87 (t, ^3J (H,H) = 7.4 Hz, 1 H; H^{Ar}), 6.79 (d, ^3J (H,H) = 7.7 Hz, 1 H; H^{Ar}), 5.48 (bs, 1 H; OH), 2.93 (t, ^3J (H,H) = 7.1 Hz, 2 H; CH_2), 2.77 (t, ^3J (H,H) = 7.2 Hz, 2 H; CH_2), 2.13 (s, 3 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 154.0 (C_q; C^{Ar}), 130.9 (C^{Ar}), 128.0 (C^{Ar}), 127.4 (C_q; C^{Ar}), 121.2 (C^{Ar}), 116.3 (C^{Ar}),

35.0 (CH_2), 31.1 (CH_2), 16.0 (CH_3) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 5.89 min; *m/z* (%): 168 (50) [M^+], 120 (47) [M^+−CH_3S], 107 (100) [M^+−C_2H_5S]; **TLC**: R_f = 0.17 (cyclohexane/EtOAc = 10/1, UV and CAM); **HRMS** (EI): calcd for [M^+]: 168.0609; found: 168.0607.

7.4.3.15.4 4-Iodo-2-(2-(methylthio)ethyl)phenol (12e)



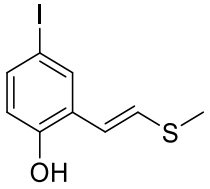
12e

Compound **12e** was prepared according to procedure 7.4.3.2 from 1.93 g ICl (11.9 mmol, 1.0 eq) in 12 mL DCM and 2.00 g **12d** (11.9 mmol, 1.0 eq) in 3.5 mL DCM. After 5 d again 400 µL ICl (1.55 g, 9.52 mmol, 0.8 eq) were added and quantitative conversion was detected after 10 d. After flash column chromatography (125 g SiO_2, 5.0 x 12 cm, eluent: cyclohexane/EtOAc = 10/1, R_f = 0.24, UV and CAM) compound **12e** was isolated as a pale brown oil.

Yield: 2.54 g (73%), pale brown oil, $C_9H_{11}IOS$ [294.15 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40-7.35 (m, 2 H; H^{Ar}), 6.57 (d, ^3J (H,H) = 8.3 Hz, 1 H; H^{Ar}), 5.73 (s, 1 H; H^{Ar}), 2.86 (t, ^3J (H,H) = 6.8 Hz, 2 H; CH_2), 2.73 (t, ^3J (H,H) = 6.7 Hz, 2H; CH_2), 2.12 (s, 3 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$): δ = 154.1 (C_q; C^{Ar}), 139.4 (C^{Ar}), 136.8 (C^{Ar}), 130.4 (C_q; C^{Ar}), 118.7 (C^{Ar}), 83.2 (C_q; C^{Ar}), 34.8 (CH_2), 30.9 (CH_2), 16.1 (CH_3) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 7.14 min; *m/z* (%): 294 (56) [M^+], 246 (100) [M^+−CH_3S], 233 (49) [M^+−C_2H_5S]; **TLC**: R_f = 0.24 (cyclohexane/EtOAc = 10/1, UV and CAM); **HRMS** (EI): calcd for [M^+]: 293.9576; found: 293.9582.

7.4.3.15.5 4-Iodo-2-(2-(methylthio)vinyl)phenol (12f)



12f

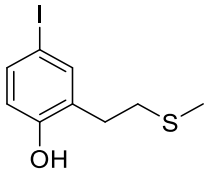
In a flame dried and argon flushed Schlenk-flask 1.30 g phosphonium-salt **12b** (3.63 mmol, 1.5 eq) were suspended in 12 mL THF. 407 mg KO*t*Bu (3.63 mmol, 1.5 eq) were added. The yellow reaction mixture was stirred at 50 °C for 60 min. The suspension was cooled to 0 °C.

600 mg **10b** (2.42 mmol, 1.0 eq) were added and the orange suspension was heated to 70 °C. After quantitative conversion (2 h) the reaction mixture was cooled to RT and quenched by the addition of 60 mL saturated NH_4Cl solution. The phases were separated and the aqueous phase was diluted with 50 mL H_2O. The aqueous phase was extracted with DCM (3 x 50 mL) and the combined organic layers were washed with saturated NaCl solution (1 x 100 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the yellow, oily crude product was purified via flash column chromatography (150 g SiO_2, 4.0 x 25 cm, eluent: cyclohexane/EtOAc = 10/1, R_f = 0.11, UV and CAM).

Yield: 444 mg (63%), pale yellow powder, C_9H_9IOS [292.13 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (d, ^4J (H,H) = 1.8 Hz, 1 H; H^{Ar}), 7.31 (dd, ^3J (H,H) = 8.4 Hz, ^4J (H,H) = 2.0 Hz, 1 H; H^{Ar}), 6.85 (d, ^3J (H,H) = 15.5 Hz, 1 H; CH), 6.52 (d, ^3J (H,H) = 8.4 Hz, 1 H; H^{Ar}), 6.33 (d, ^3J (H,H) = 15.5 Hz, 1 H; CH), 4.95 (s, 1 H; OH), 2.37 (s, 3 H, CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 151.9 (C_q; C^{Ar}), 136.3 (C^{Ar}), 135.6 (C^{Ar}), 129.6 (CH), 127.5 (C_q; C^{Ar}), 118.2 (CH), 117.5 (C^{Ar}), 83.5 (C_q; C^{Ar}), 15.0 (CH_3) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 7.39 min; *m/z* (%): 292 (50) [M^+], 245 (33) [M^+−CH_3S], 118 (100) [M^+−CH_3IS]. **TLC**: R_f = 0.11 (cyclohexane/EtOAc = 10/1, UV and CAM); **m.p.**$^{exp.}$ = 73-76°C; **HRMS** (EI): calcd for [M^+]: 291.9419; found: 292.9415.

7.4.3.15.6 4-Iodo-2-(2-(methylthio)ethyl)phenol (12e)



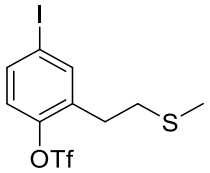
12e

A 25 mL round-bottom flask, equipped with reflux-condenser, was charged with 350 mg **12f** (1.20 mmol, 1.0 eq) and dissolved in 12 mL THF. 1.34 g p-tosylhydrazide (7.19 mmol, 6.0 eq) and 580 mg NaOAc.3H_2O (7.19 mmol, 6.0 eq) were added and the pale yellow suspension was stirred at 70 °C until quantitative conversion (16 h) was detected by GC-MS. The reaction mixture was cooled to RT and 50 mL water were added. The phases were separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography (30 g SiO_2, 2.5 x 17 cm, eluent: cyclohexane/EtOAc = 10/1, R_f = 0.17, UV and CAM).

Yield: 322 mg (91%), pale yellow powder, $C_9H_{11}IOS$ [294.15 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40-7.35 (m, 2 H; H^{Ar}), 6.57 (d, ^{3}J (H,H) = 8.3 Hz, 1 H; H^{Ar}), 5.73 (s, 1 H; H^{Ar}), 2.86 (t, ^{3}J (H,H) = 6.8 Hz, 2 H; CH_2), 2.73 (t, ^{3}J (H,H) = 6.7 Hz, 2H; CH_2), 2.12 (s, 3 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 154.1 (C_q; C^{Ar}), 139.4 (C^{Ar}), 136.8 (C^{Ar}), 130.4 (C_q; C^{Ar}), 118.7 (C^{Ar}), 83.2 (C_q; C^{Ar}), 34.8 (CH_2), 30.9 (CH_2), 16.1 (CH_3) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 7.14 min; *m/z* (%): 294 (56) [M^+], 246 (100) [M^+-CH_3S], 233 (49) [$M^+-C_2H_5S$]; **TLC**: R_f = 0.17 (cyclohexane/EtOAc = 10/1, UV and CAM); **m.p.**$^{exp.}$ = 52-54°C; **HRMS** (EI): calcd for [M^+]: 293.9576; found: 293.9582.

7.4.3.15.7 4-Iodo-2-(2-(methylthio)ethyl)phenyl trifluoromethanesulfonate (12a)



12a

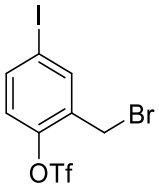
In a 50 mL round-bottom flask 2.00 g **12e** (6.80 mmol, 1.0 eq) were dissolved in 10 mL DCM. After cooling the solution to 0 °C 2.07 mL Et_3N (1.51 g, 15.0 mmol, 2.2 eq) and 1.26 mL trifluoromethanesulfonic anhydride (Tf_2O) (2.11 g, 7.48 mmol, 1.1 eq) were carefully added. After stirring 5 min at 0 °C, the solution was allowed to warm to RT and stirred until quantitative conversion was detected by GC-MS (2 h). 100 mL H_2O were added and the aqueous phase was extracted with DCM (3 x 100 mL). The combined organic phases were washed with saturated NaCl solution (1 x 60 mL), dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified via flash column chromatography (60 g SiO_2, 3.0 x 16 cm, eluent: cyclohexane/EtOAc = 200/1, R_f = 0.23, UV and CAM).

Yield: 2.61 g (90%), colourless solid, $C_{10}H_{10}IO_3S$ [426.21 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68 (d, ^{4}J (H,H) = 1.9 Hz, 1 H; H^{Ar}), 7.61 (dd, ^{3}J (H,H) = 8.6 Hz, ^{4}J (H,H) = 2.1 Hz, 1 H; H^{Ar}), 6.99 (d, ^{3}J (H,H) = 8.6 Hz, 1 H; H^{Ar}), 2.93 (t, ^{3}J (H,H) = 7.7 Hz, 2 H; CH_2), 2.72 (t, ^{3}J (H,H) = 7.6 Hz, 2H; CH_2), 2.13 (s, 3 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 148.0 (C_q; C^{Ar}), 140.6 (C^{Ar}), 137.7 (C^{Ar}), 135.8 (C_q; C^{Ar}), 123.4 (C^{Ar}), 118.7 (q, ^{1}J (C,F) = 320 Hz; CF_3), 93.5 (C_q; C^{Ar}), 34.0 (CH_2), 30.1 (CH_2), 15.7 (CH_3) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 6.80 min; *m/z* (%): 426 (2) [M^+], 277 (100) [$M^+-CF_3O_3S$], 262 (11) [$M^+-C_2H_3F_3O_3S$]; **TLC**: R_f = 0.23 (cyclohexane/EtOAc = 200/1, UV and CAM); **m.p.**$^{exp.}$ = 42-44 °C; **HRMS** (EI): calcd for [M^+]: 425.9088; found: 225.9060.

7.4.3.16 Synthesis of Cysteine building block

7.4.3.16.1 2-(Bromomethyl)-4-iodophenyl trifluoromethanesulfonate (13b)



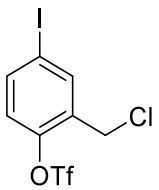
13b

In an argon flushed 250 two-neck round-bottom flask equipped with argon inlet 700 mg alcohol **10d** (1.83 mmol, 1.0 eq) were dissolved in 100 mL DCM. A drop of DMF was added as catalyst. 215 µL thionylbromide (571 mg, 2.75 mmol, 1.5 eq) were added dropwise. The brownish solution was stirred for 16 h and after full conversion the reaction mixture was diluted with 50 mL DCM, washed with saturated $NaHCO_3$ solution (1 x 100 mL) and saturated NaCl solution (1 x 100 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed in vacuum. The oily crude product was purified via flash column chromatography (25 g SiO_2, 2.0 x 17 cm, eluent: cyclohexane, R_f = 0.36, UV and CAM).

Yield: 339 mg (42%), pale yellow oil, $C_8H_5BrF_3IO_3S$ [444.99 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (d, ^4J (H,H) = 2.1 Hz, 1 H; H^{Ar}), 7.72 (dd, ^3J (H,H) = 8.7 Hz, ^4J (H,H) = 2.1 Hz, 1 H; H^{Ar}), 7.06 (d, ^3J (H,H) = 8.4 Hz, 1 H; H^{Ar}), 4.43 (s, 2 H; CH_2), ppm; **^{13}C NMR** (76 MHz, $CDCl_3$): δ = 147.1 (C_q; C^{Ar}), 141.1 (C^{Ar}), 139.6 (C^{Ar}), 133.0 (C_q; C^{Ar}), 123.6 (C^{Ar}), 118.7 (q, ^1J (C,F) = 327 Hz; CF_3), 93.3 (C_q; C^{Ar}), 24.5 (CH_2) ppm; **GC-MS** (EI, 70 eV; MP_50_S): t_R = 6.30; *m/z* (%): 444 (20) [M^+], 365 (100) [M^+−Br], 311 (17) [M^+−CF_3O_2S], 332 (24) [M^+−$CBrF_3O_2S$]; **TLC**: R_f = 0.36 (cyclohexane, UV and CAM); **HRMS** (EI): calcd for [M^+]: 443.8140; found: 443.8143.

7.4.3.16.2 2-(Chloromethyl)-4-iodophenyl trifluoromethansulfonate (13c)



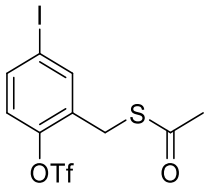
13c

A 50 mL round bottom flask equipped with reflux condenser was charged with 2.12 g alcohol **10d** (5.2 mmol, 1eq) and 20 mL thionylchloride. The pale yellow solution was heated to 95 °C for 24 h. When full conversion was detected by GC-MS the remaining thionylchloride was

removed in vacuum. The brown, oily crude product was purified via flash column chromatography (200 g SiO_2, 5.5 x 12 cm, eluent: cyclohexane, R_f = 0.30, UV and CAM).
Yield: 1.44g (69 %), colourless oil, $C_8H_5ClF_3IO_3S$ [400.53 g/mol]

^{1}H NMR: (300 MHz, $CDCl_3$): δ = 7.91 (s, 1 H; H^{Ar}), 7,74 (dd, ^3J (H,H) = 3Hz, ^4J (H,H) = 3Hz, 1H, H^{Ar}); 7.07 (d, ^3J (H,H) = 9Hz, 1H, H^{Ar}); 4.58(s, 2H, CH2); **^{13}C NMR**: (76 MHz, $CDCl_3$): δ = 147.1 (C_q; C^{Ar}), 140.7(C^{Ar}), 139.7 (C^{Ar}), 132.7 (C_q; C^{Ar}), 132.6 (C^{Ar}), 123.6 (C^{Ar}), 118.6 (q, ^1J (C,F) = 322 Hz; CF_3), 93.4 (C_q; C^{Ar}) ppm; **GC-MS**: (EI, 70 eV; MT_50_S): t_R = 6.08; *m/z* (%): 400 (75) [M^+], 267 (100) [M^+−CF_3O_2S], 365 (6) [M^+−Cl]; **HRMS**: (EI): calcd for [M^+]: 399.8645; found: 399.8626.

7.4.3.16.3 S-5-Iodo-2-(((trifluoromethyl)sulfonyl)oxy)benzyl ethanethioate (13a)



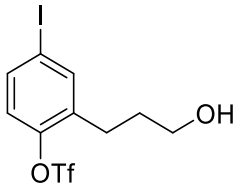
13a

In a flame dried and argon flushed Schlenk-flask 300 mg bromo-derivative **13b** (674 µmol, 1.0 eq) were dissolved in 2 mL absolute THF. 205 mg K_2CO_3 (1.28 mmol, 2.2 eq) and 57.8 µL thioacetic acid (61.6 mg, 809 µmol, 1.2 eq) were added. The colourless suspension was stirred at RT until full conversion was detected by GC-MS after 60 min. Then the reaction mixture was neutralized with HCl (1 M, 1 mL) and diluted with 20 mL H_2O. The aqueous phase was extracted with DCM (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuum. The oily crude product was purified via flash column chromatography (30 g SiO_2, 2.0 x 27 cm, eluent: cyclohexane/EtOAc = 50/1, R_f = 0.27, UV and CAM).
Yield: 245 mg (82%), colourless oil, $C_{10}H_8F_3IO_4S_2$ [440.20 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, ^4J (H,H) = 1.8 Hz, 1 H; H^{Ar}), 7.65 (dd, ^3J (H,H) = 8.7 Hz, ^4J (H,H) = 2.1 Hz, 1 H; H^{Ar}), 7.01 (d, ^3J (H,H) = 8.7 Hz, 1 H; H^{Ar}), 4.11 (s, 2 H; CH_2), 2.38 (s, 3 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$): δ = 194.1 (C_q; COOMe) 147.5 (C_q; C^{Ar}), 140.8 (C^{Ar}), 138.5 (C^{Ar}), 133.3 (C_q; C^{Ar}), 123.2 (C^{Ar}), 118.6 (q, ^1J (C,F) = 318 Hz; CF_3), 93.3 (C_q; C^{Ar}), 30.4 (CH_3), 27.1 (CH_2) ppm; **GC-MS** (EI, 70 eV; MP_50_S): t_R = 6.84; *m/z* (%): 440 (57) [M^+], 397 (24) [M^+−C_2H_3O], 291 (91) [M^+−CF_3O_3S]; **TLC**: R_f = 0.27 (cyclohexane/EtOAc = 50/1, UV and CAM); **HRMS** (EI): calcd for [M^+]: 439.8861; found: 439.8857.

7.4.3.17 Synthesis of Arginine building block

7.4.3.17.1 2-(3-Hydroxypropyl)-4-iodophenyl trifluoromethanesulfonate (14b)



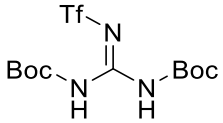
14b

In a flame dried and argon flushed Schlenk-flask 2.00 g ester **8a** (4.56 mmol, 1.0 eq) were dissolved in 7.0 mL DCM (dried over P_4O_{10}). This solution was cooled to -78°C and 9.20 mL diisobutylaluminium hydride (DIBALH) (1.0 M in toluene) (1.30 g, 9.13 mmol, 2.0 eq) were slowly added via a dropping funnel. The colourless solution was warmed up to RT. After stirring for 2 h the solution was cooled again to -78°C and quenched by the addition of 6 mL MeOH. 20 mL saturated Rochelle-salt solution were added and the emulsion was stirred until phase separation occurred (overnight). The phases were separated and the aqueous phase was extracted with DCM (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The colourless, oily crude product was purified via flash column chromatography (75 g SiO_2, 3.0 x 20 cm, eluent: cyclohexane/EtOAc = 5/1, R_f = 0.22, UV and CAM).

Yield: 1.83 g (98%), colourless oil, $C_{10}H_{10}F_3IO_4S$ [410.15 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, ^4J (H,H) = 1.9 Hz, 1 H; H^{Ar}), 7.59 (dd, ^3J (H,H) = 8.6 Hz, ^4J (H,H) = 2.1 Hz, 1 H; H^{Ar}), 6.99 (d, ^3J (H,H) = 8.6 Hz, 1 H; H^{Ar}), 3.69 (t, ^3J (H,H) = 6.1 Hz, 1 H; CH_2), 2.77 (t, ^3J (H,H) = 7.8 Hz, 2 H; CH_2), 1.93-1.83 (m, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 148.1 (C_q; C^{Ar}), 140.4 (C^{Ar}), 137.3 (C_q, C^{Ar}), 137.1 (C^{Ar}), 123.3 (C^{Ar}), 118.7 (q, ^1J (C,F) = 320 Hz; CF_3), 93.5 (C_q; C^{Ar}), 61.9 (CH_2), 32.6 (CH_2), 26.3 (CH_2) ppm; **TLC**: R_f = 0.22 (cyclohexane/EtOAc = 5/1, UV and CAM); **HRMS** (EI): calcd for [M^+]: 409.9297; found: 409.9318.

7.4.3.17.2 *N,N´*-Di-Boc-*N´´*-triflylguanidine (14c)



14c

A flame dried and argon flushed Schlenk-flask was charged with 520 mg 1,3-bis(*tert*-butoxycarbonyl)guanidine (**14e**) (2.01 mmol, 1.0 eq) dissolved in 10 mL absolute DCM. The

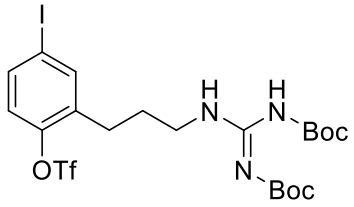
colorless solution was cooled to -78 °C in an acetone/dry ice bath and 293 µL Et_3N (123 mg, 2.11 mmol, 1.05 eq) as well as 355 µL Tf_2O (594 mg, 2.11 mmol, 1.05 eq) were added. The cooling bath was removed after 10 min and the now bright yellow solution was stirred at RT for 2 h. When quantitative conversion was detected by TLC the reaction mixture was transferred to a separation funnel, washed with 2 M $KHSO_4$ solution (2 x 20 mL) and H_2O (1 x 20 mL). The organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The orange crude product was purified via silica gel filtration (20 g SiO_2, 4.0 x 5.0 cm, eluent: DCM, R_f = 0.84, UV and ninhydrin).[101]

Yield: 775 mg (99 %), colourless powder, $C_{12}H_{20}F_3N_3O_6S$ [391.36 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.09 (bs, 2H; NH), 1.53 (s, 18 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 151.5 (C_q, $C^{Carbonyl}$), 119.4 (q, ^1J (C,F) = 320 Hz; CF_3), 86.1 (C_q), 28.0 (CH_3) ppm; **TLC**: R_f = 0.84 (DCM, UV and ninhydrin); **m.p.**$^{exp.}$ = 102-104 °C (m.p.$^{lit.}$ = 114-115 °C).[101]

Analytical data are in accordance with those reported.[101]

7.4.3.17.3 2-(3-(2,3-Bis(*tert*-butoxycarbonyl)guanidino)propyl)-4-iodophenyl trifluoromethanesulfonate (14a)



14a

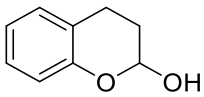
In a 50 mL round-bottom flask 1.3 g compound **14b** (3.17 mmol, 1.0 eq) were dissolved in 15 mL THF (stored over KOH). The colourless solution was cooled to 0 °C and 567 µL DIPEA (410 mg, 3.17 mmol, 1.0 eq), 998 mg PPh_3 (3.80 mmol, 1.2 eq), 756 µL DIAD (777 mg, 3.80 mmol, 1.2 eq) and 820 µL DPPA (1.05 g, 3.80 mmol, 1.2 eq) were added. The pale yellow suspension was stirred for 3 h at RT. When quantitative conversion of the alcohol was detected by TLC 1.08 g PPh_3 (4.12 mmol, 1.3 eq) dissolved in 2.0 mL THF were added and the reaction was stirred overnight at RT. After adding 1.0 mL H_2O the reaction was warmed to 50 °C and stirred until full conversion of the azide-intermediate was detected by GC-MS. The solvent was removed under reduced pressure and the oily residue (amine-intermediate) was dissolved in 16 mL DMF. To this pale yellow solution 986 mg guanylating-reagent **14d** (3.18 mmol, 1.0 eq) were added. The reaction was stirred 4 h at RT. When quantitative conversion of the amine was detected by TLC the reaction was diluted with 100 mL Et_2O and washed with water (2x50 mL).

The organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The pale yellow, oily crude product was purified via flash column chromatography (250 g SiO_2, 5.5 x 18 cm, eluent: cyclohexane/EtOAc = 15/1, R_f = 0.15, UV and CAM).
Yield: 1.14 g (55%), colourless solid, $C_{21}H_{29}F_3IN_3O_7S$ [651.44 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.49 (s, 1H; NH), 8.41 (s, 1H; NH), 7.67 (s, 1 H; H^{Ar}), 7.59 (dd, ^3J (H,H) = 8.6 Hz, ^4J (H,H) = 1.8 Hz, 1 H; H^{Ar}), 6.98 (d, ^3J (H,H) = 8.6 Hz, 1 H; H^{Ar}), 3.59 (q, ^3J (H,H) = 6.6 Hz, 2 H; CH_2), 2.72 (t, ^3J (H,H) = 7.8 Hz, 2 H; CH_2), 1.96-1.86 (m, 2 H; CH_2), 1.50 (s, 9H; CH_3), 1.49 (s, 9H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 163.6 (C_q, CN), 156.4 (C_q, CO), 153.5 (C_q, CO), 1487.9 (C_q; C^{Ar}), 140.2 (C^{Ar}), 137.3 (C^{Ar}), 136.6 (C_q, C^{Ar}), 123.4 (C^{Ar}), 118.7 (q, ^1J (C,F) = 320 Hz; CF_3), 93.5 (C_q; C^{Ar}), 83.4 (C_q), 79.5 (C_q), 40.3 (CH_2), 29.2 (CH_2), 28.4 (CH_3), 28.2 (CH_3), 27.2 (CH_2) ppm; **TLC**: R_f = 0.15 (cyclohexane/EtOAc = 15/1, UV and ninhydrin); **m.p.**$^{exp.}$ = 105-108 °C; **HRMS** (EI): calcd for [M^+]: 651.0723; found: 651.0693.

7.4.3.18 Synthesis of Lysine building block

7.4.3.18.1 Chroman-2-ol (15b)



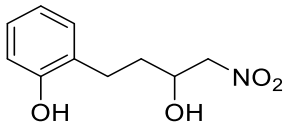
15b

In a flame dried and argon flushed 250 mL three-neck round-bottom flask equipped with argon inlet and dropping funnal 5.00 g dihydrocoumarin (**8c**) (33.7 mmol, 1.0 eq) were dissolved in 100 mL toluene. The solution was cooled to -78 °C and 37.0 mL DIBALH (5.26 g, 37.0 mmol, 1.1 eq) were added dropwise over a period of 60 min. The reaction was stirred until full conversion (2 h) was reached and then quenched by the addition of 20 mL H_2O. The white suspension was warmed to RT and the colourless precipitate was filtered through a pad of Celite®. The phases were separated and the aqueous phase was extracted with Et_2O (1 x 200 mL). The filter cake was stirred with 200 mL Et_2O and filtered again. The combined organic phases were washed with H_2O (1 x 200 mL) and saturated NaCl solution (1 x 200 mL). Then the combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed in vacuum.[139]
Yield: 4.83 g (95%); yellow oil, $C_9H_{10}O_2$ [150.17 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15-7.07 (m, 2 H; H^{Ar}), 6.92-6.82 (m, 2 H; H^{Ar}), 5.62 (t, ^{3}J (H,H) = 3.2 Hz, 1 H; CH), 3.27 (s, 1 H; OH), 3.05-2.94 (m, 1 H; CH_2), 2.76-2.67 (m, 1 H; CH_2), 2.06-1.99 (m, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 152.1 (C_q; C^{Ar}), 129.4 (C^{Ar}), 127.5 (C^{Ar}), 122.2 (C_q; C^{Ar}), 121.0 (C^{Ar}), 117.0 (C^{Ar}), 92.3 (CH), 27.2 (CH_2), 20.4 (CH_2) ppm; **GC-MS** (EI, 70 eV; MP_50_S): t_R = 5.28 min; *m/z* (%): 150 (26) [M^+], 131 (100) [M^+−OH], 107 (23) [M^+−C_2H_2O], 77 (30) [M^+−$C_3H_6O_2$].

Analytical data are in accordance with those reported.[139]

7.4.3.18.2 2-(3-Hydroxy-4-nitrobutyl)phenol (15c)



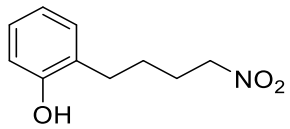
15c

In a flame dried and argon flushed Schlenk-flask 4.00 g lactol **15b** (26.6 mmol, 1.0 eq) were dissolved in 14.5 mL nitromethane. 3.70 mL Et_3N (2.70 g, 26.6 mmol, 1.0 eq) were added to the yellow solution and the reaction mixture was heated to reflux temperature. When quantitative conversion was reached (3 h) the reaction mixture was cooled to RT and 50 mL saturated $NaHCO_3$ solution were added. The aqueous phase was extracted with EtOAc (3 x 50 mL) and the combined organic layers were washed with saturated NaCl solution (1 x 40 mL), dried over $MgSO_4$, filtered and the solvent was removed in vacuum. The crude product was purified via flash column chromatography (500 g SiO_2, 3.0 x 24 cm, eluent: cyclohexane/EtOAc = 10/1, R_f = 0.18, UV and CAM).

Yield: 3.54 g (69%); pale yellow oil, $C_{10}H_{13}NO_4$ [211.21 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13-7.05 (m, 2 H; H^{Ar}), 6.89 (t, ^{3}J (H,H) = 7.4 Hz, 1 H; H^{Ar}), 6.82 (d, ^{3}J (H,H) = 8.1 Hz, 1 H; H^{Ar}), 4.82-4.74 (m, 1 H; CH), 4.71-4.64 (m, 1 H; CH_2), 4.54 (dd, ^{2}J (H,H) = 12.5 Hz, ^{3}J (H,H) = 3.8 Hz, 1 H; CH_2), 3.01-2.78 (m, 2 H; CH_2), 2.15-2.05 (m, 1 H; CH_2), 1.93-1.80 (m, 1 H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 153.4 (C_q; C^{Ar}), 129.6 (C^{Ar}), 127.8 (C^{Ar}), 121.2 (C^{Ar}) 121.0 (C_q; C^{Ar}), 117.1 (C^{Ar}), 78.9 (CH_2), 72.1 (CH), 24.7 (CH_2), 24.0 (CH_2) ppm; **GC-MS** (EI, 70 eV; MP_50_S): t_R = 6.23 min (elimination product); *m/z* (%): 193 (57) [M^+], 146 (36) [M^+−NO_2], 131 (100) [M^+−HNO_3], 107 (37) [M^+−$C_3H_4NO_2$]; **TLC**: R_f = 0.18 (cyclohexane/EtOAc = 10/1, UV and CAM); **HRMS** (EI): calcd for [M−H_2O] $^{+}$: 193.0739; found: 193.0728.

7.4.3.18.3 2-(4-Nitrobutyl)phenol (15d)



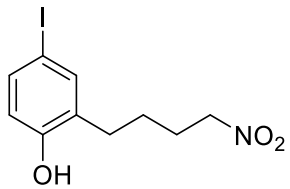
15d

In a flame dried and argon flushed 100 mL three-neck round-bottom flask equipped with argon inlet and reflux condenser 2.21 g phenol derivative **15c** (11.4 mmol, 1.0 eq) were dissolved in 75.0 mL MeOH. 2.27 g $NaBH_3CN$ (36.1 mmol, 3.2 eq) were added to this yellow solution and heated to reflux temperature for 24 h. The reaction was cooled to RT and quenched by the addition of 20 mL HCl (0.1 M). Toxic gases were neutralized by bubbling through a $KMnO_4$ solution. When no more gas is formed MeOH was removed in vacuum. The oily residue was dissolved in 20 mL DCM and washed with H_2O (1 x 20 mL). The aqueous phase was reextracted with DCM (2 x 20 mL) and the combined organic layers were washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered and the solvent was removed in vacuum. The crude product was purified via flash column chromatography (200 g SiO_2, 6.0 x 15 cm, eluent: cyclohexane/EtOAc = 3/1, R_f = 0.31, UV and CAM).

Yield: 1.43 g (64%); yellow oil, $C_{10}H_{13}NO_3$ [195.22 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13-7.07 (m, 2 H; H^{Ar}), 6.88 (t, ^3J (H,H) = 7.4 Hz, 1 H; H^{Ar}), 6.74 (d, ^3J (H,H) = 8.1 Hz, 1 H; H^{Ar}), 4.41 (t, ^3J (H,H) = 6.9 Hz, 2 H; CH_2NO_2), 2.68 (t, ^3J (H,H) = 7.4 Hz, 2 H; CH_2), 2.11-2.01 (m, 2 H; CH_2), 1.77-1.67 (m, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 153.6 (C_q; C^{Ar}), 130.5 (C^{Ar}), 127.6 (C^{Ar}), 127.5 (C_q; C^{Ar}), 121.1 (C^{Ar}), 115.4 (C^{Ar}), 75.7 (CH_2NO_2), 29.2 (CH_2), 27.0 (CH_2), 26.4 (CH_2) ppm; **GC-MS** (EI, 70 eV; MP_50_S): t_R = 6.60 min; *m/z* (%): 195 (13) [M^+], 107 (100) [$M^+-C_3H_6NO_2$], 91 (23) [$M^+-C_3H_7NO_3$], 77 (36) [$M^+-C_4H_9NO_3$]; **TLC**: R_f = 0.31 (cyclohexane/EtOAc = 3/1, UV and CAM); **HRMS** (EI): calcd for [M^+]: 195.0895; found: 195.0898.

7.4.3.18.4 4-Iodo-2-(4-nitrobutyl)phenol (15e)



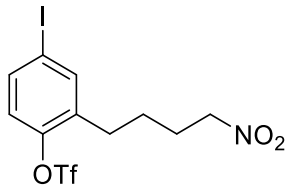
15e

In an argon flushed Schlenk-flask 1.11 g phenol derivative **15d** (5.66 mmol, 1.0 eq) were dissolved in 5 mL acetic acid. 1.16 g ICl (7.14 mmol, 1.3 eq) dissolved in 5 mL acetic acid were added to the yellow solution. The now red-brown solution was heated to 40 °C until full

conversion (4 h) was observed. The reaction mixture was diluted with 50 mL DCM and washed with saturated $NaHCO_3$ solution (1 x 50 mL). The aqueous phase was reextracted with DCM (3 x 50 mL). The combined organic layers were washed with $Na_2S_2O_3$ solution (50%, 2 x 50 mL) and saturated NaCl solution (1 x 100 mL), dried over $MgSO_4$, filtered and the solvent was removed in vacuum. The crude product was purified via flash column chromatography (150 g SiO_2, 5.0 x 21 cm, eluent: cyclohexane/EtOAc = 5/1, R_f = 0.12, UV and CAM).
Yield: 1.38 g (76%); orange oil, $C_{10}H_{12}INO_3$ [321.11 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38-7.34 (m, 2 H; H^{Ar}), 6.52 (d, ^3J (H,H) = 8.1 Hz, 1 H; H^{Ar}), 5.01 (s, 1 H; OH), 4.41 (t, ^3J (H,H) = 6.9 Hz, 2 H; CH_2NO_2), 2.62 (t, ^3J (H,H) = 7.5 Hz, 2 H; CH_2), 2.09-1.99 (m, 2 H; CH_2), 1.74-1.64 (m, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 153.6 (C_q; C^{Ar}), 139.0 (C^{Ar}), 136.3 (C^{Ar}), 130.5 (C_q; C^{Ar}), 117.6 (C^{Ar}), 83.0 (C_q; C^{Ar}), 75.6 (CH_2NO_2), 28.9 (CH_2), 27.0 (CH_2), 26.3 (CH_2) ppm; **GC-MS** (EI, 70 eV; MP_50_S): t_R = 6.60 min; *m/z* (%): 195 (13) [M^+], 107 (100) [$M^+-C_3H_6NO_2$], 91 (23) [$M^+-C_3H_7NO_3$], 77 (36) [$M^+-C_4H_9NO_3$]; **TLC**: R_f = 0.12 (cyclohexane/EtOAc = 5/1, UV and CAM); **HRMS** (EI): calcd for [M^+]: 320.9862; found: 320.9871.

7.4.3.18.5 4-Iodo-2-(4-nitrobutyl)phenyl trifluoromethanesulfonate (15f)



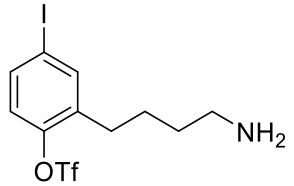
15f

Compound **15f** was prepared according to procedure 2.1.2 from 1.11 mg phenol derivative **15e** (3.47 mmol, 1.0 eq) in 10 mL pyridine and 920 µL Tf_2O (1.08 g, 3.81 mmol, 1.1 eq). Quantitative conversion was detected after 90 min. After flash column chromatography (125 g SiO_2, 4.0 x 24 cm, eluent: cyclohexane/Et_2O = 20/1, R_f = 0.30, UV and CAM) compound **15f** was isolated as yellow oil.
Yield: 1.18 g (75%); yellow oil, $C_{11}H_{11}F_3INO_5S$ [453.17 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65-7.60 (m, 2 H; H^{Ar}), 7.00 (d, ^3J (H,H) = 8.4 Hz, 1 H; H^{Ar}), 4.20 (t, ^3J (H,H) = 6.9 Hz, 2 H; CH_2NO_2), 2.71 (t, ^3J (H,H) = 7.8 Hz, 2 H; CH_2), 2.12-2.02 (m, 2 H; CH_2), 1.78-1.68 (m, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 147.9 (C_q; C^{Ar}), 140.1 (C^{Ar}), 137.5 (C^{Ar}), 136.4 (C_q; C^{Ar}), 123.5 (C^{Ar}), 118.7 (q, ^1J (C,F) = 327 Hz; CF_3), 93.6 (C_q; C^{Ar}), 75.2 (CH_2NO_2), 29.1 (CH_2), 26.9 (CH_2), 26.6 (CH_2) ppm; **GC-MS** (EI, 70 eV; MP_50_S): t_R = 7.41 min; *m/z* (%): 453 (21) [M^+], 365 (26) [$M^+-C_3H_6NO_2$], 131 (87)

[M^+−CF_3INO_5S]; **TLC**: R_f = 0.30 (cyclohexane/EtOAc = 20/1, UV and CAM); **HRMS** (EI): calcd for [M^+]: 452.9355; found: 452.9353.

7.4.3.18.6 2-(4-Aminobutyl)-4-iodophenyl trifluoromethanesulfonate (15g)



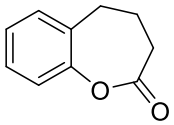
15g

In an argon flushed Schlenk-flask 969 mg **15f** (2.14 mmol, 1.0 eq) and 597 mg Fe-powder (10.7 mmol, 5.0 eq) were suspended in 10 mL HCl (2 M). Quantitative conversion was detected by HPLC-MS after 4.5 h. The reaction mixture was neutralized with NaOH (2 M) and diluted with 20 mL ethylacetate. The formed precipitate was filtered off and the two layers in the filtrate were separated. The aqueous phase was extracted with ethylacetate (2 x 50 mL) and the combined organic layers were washed with saturated NaCl solution (1 x 50 mL), dried over $MgSO_4$, filtered and the solvent was removed in vacuum. The crude product was purified via flash column chromatography (75 g SiO_2, 3.0 x 28 cm, eluent: EtOAc/MeOH/Et_3N = 8/1/1, R_f = 0.24, UV and CAM).

Yield: 325 g (36%); yellow oil, $C_{11}H_{11}F_3INO_3S$ [423.19 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, ^4J (H,H) = 2.1 Hz, 1 H; H^{Ar}), 7.58 (dd, ^3J (H,H) = 8.4 Hz, ^4J (H,H) = 2.1 Hz, 1 H; H^{Ar}), 6.97 (d, ^3J (H,H) = 8.7 Hz, 1 H; H^{Ar}), 3.12 (s, 2 H; NH_2), 2.81-2.63 (m, 4 H; CH_2), 1.67-1.57 (m, 4 H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 148.0 (C_q; C^{Ar}), 140.3 (C^{Ar}), 137.5 (C_q; C^{Ar}), 137.1 (C^{Ar}), 123.3 (C^{Ar}), 118.7 (q, ^1J (C,F) = 327 Hz; CF_3), 93.5 (C_q; C^{Ar}), 41.5 (CH_2NH_2), 32.2 (CH_2), 29.6 (CH_2), 27.1 (CH_2) ppm; **HPLC-MS** (Poroshell, ESI$^+$, MT_general): t_R = 3.23 min; *m/z*: 424 [M+H^+]; λ_{max} = 236 nm; **TLC**: R_f = 0.24 (EtOAc/MeOH/Et_3N = 8/1/1, UV and CAM); **HRMS** (EI): calcd for [M^+]: 422.9613; found: 422.9638.

7.4.3.18.7 4,5-Dihydrobenzo[b]oxepin-2(3*H*)-one (15h)



15h

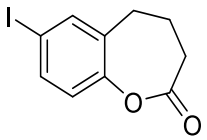
In a 250 mL round-bottom flask 10.0 mL (11.0 g, 75.3 mmol, 1.0 eq) 1-tetralone (**15i**) were dissolved in 200 mL $CHCl_3$. 23.2 g (94.1 mmol, 1.25 eq) mCBPA were added to the resulting pale yellow solution. The yellow suspension was stirred until full conversion was detected by

TLC (48 h). The reaction mixture was washed with 5% $NaHCO_3$ solution (2 x 100 mL) and H_2O (1 x 100 mL). Then the organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography (250 g SiO_2, 6.0 x 18 cm, eluent: cyclohexane/EtOAc = 5/1, R_f = 0.50, UV and CAM).

Yield: 10.9 g (89%), yellow oil, $C_{10}H_{10}O_2$ [162.19 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19 (dt, ^3J (H,H) = 7.9 Hz, ^4J (H,H) = 2.1 Hz, 1 H; H^{Ar}), 7.14−7.03 (m, 2 H; H^{Ar}), 6.99 (d, ^3J (H,H) = 7.9 Hz, 1H; H^{Ar}), 2.73 (t, ^3J (H,H) = 7.3 Hz, 2H; CH_2), 2.38 (t, ^3J (H,H) = 7.2 Hz, 2H; CH_2), 2.09 (p, ^3J (H,H) = 7.1 Hz, 2H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 171.6 (C_q; CO), 151.8 (C_q; C^{Ar}), 130.1 (C_q; C^{Ar}), 129.7 (C^{Ar}), 128.3 (C^{Ar}), 119.2 (C^{Ar}), 125.9 (C^{Ar}), 119.3 (C^{Ar}), 31.1 (CH_2), 28.2 (CH_2), 26.5 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 5.62 min; *m/z* (%): 162 (43) [M^+], 107 (100) [M^+−C_3H_4O], 77 (30) [M^+−$C_4H_6O_2$]; **TLC**: R_f = 0.50 (cyclohexane/EtOAc = 5/1, UV and CAM).

7.4.3.18.8 7-Iodo-4,5-dihydrobenzo[b]oxepin-2(3*H*)-one (15j)



15j

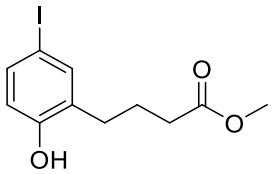
In a 100 mL two-neck round-bottom flask equipped with dropping funnel and argon-inlet 1.5 g **15h** (9.19 mmol, 1.0 eq) were dissolved in 10 mL DCM. 1.5 g ICl (9.19 mmol, 1.0 eq) dissolved in 10 mL DCM were added dropwise. After full conversion (20 h) the reaction was diluted with 100 mL DCM and washed with 0.1 M $Na_2S_2O_3$ solution (2 x 50 mL). The combined aqueous layers were reextracted with DCM (2 x 50 mL). The combined organic layers were washed with saturated NaCl solution (1 x 200 mL), dried over Na_2SO_4 and the solvent was removed in vacuum. The brown, oily crude product was purified via flash column chromatography (150 g SiO_2, 4.5 x 19 cm, eluent: cyclohexane/EtOAc = 10/1, R_f = 0.33, UV and CAM).

Yield: 2.20 g (83%), yellow solid, $C_{10}H_9IO_2$ [288.08 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (dd, ^3J (H,H) = 8.4 Hz, ^4J (H,H) = 2.0 Hz, 1 H; H^{Ar}), 7.54 (d, ^4J (H,H) = 1.8 Hz, 1 H; H^{Ar}), 6.84 (d, ^3J (H,H) = 8.4 Hz, 1 H; H^{Ar}), 2.84 (t, ^3J (H,H) = 7.2 Hz, 2 H; CH_2), 2.48 (t, ^3J (H,H) = 7.2 Hz, 2 H; CH_2), 2.23 (q, ^3J (H,H) = 7.1 Hz, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 170.9 (C_q, CO), 151.9 (C_q, C^{Ar}), 138.5 (C^{Ar}), 137.8 (C^{Ar}), 132.8 (C_q, C^{Ar}) 121.6 (C^{Ar}), 89.6 (C_q, C^{Ar}), 31.1(CH_2), 28.1 (CH_2), 26.4 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 6.86 min; *m/z* (%): 288 (100) [M^+], 233 (64) [M^+−C_2H_4O],

161 (14) [M^+−I]; **TLC**: R_f = 0.33 (cyclohexane/EtOAc = 10/1, UV and CAM); **m.p.**$^{exp.}$ = 74.5-77.5 °C; **HRMS** (EI): calcd for [M^+]: 287.9647; found: 287.9660.

7.4.3.18.9 Methyl 4-(2-hydroxy-5-iodophenyl)butanoate (15k)



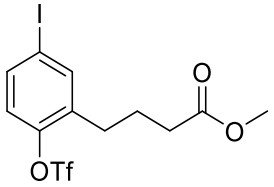
15k

In a Schlenk-flask 4.10 mL H_2SO_4 were added to a colourless suspension of 2.20 g **15j** (7.64 mmol, 1.00 eq) in 30 mL MeOH. The solid dissolved and the pale yellow solution was warmed to 55 °C and stirred overnight at this temperature. After full conversion (24 h) was detected by TLC the brown solution was neutralized with 50 mL saturated $NaHCO_3$ solution and the phases were separated. The aqueous phase was extracted with DCM (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified via flash column chromatography (50 g SiO_2, 4.0 x 10 cm, eluent: cyclohexane/EtOAc = 5/1, R_f = 0.16, UV and CAM).

Yield: 2.42 g (99 %), light brown oil, $C_{11}H_{13}IO_3$ [320.13 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39-736 (m, 2 H; H^{Ar}), 6.75 (bs, 0.8 H; OH), 6.63 (d, ^3J (H,H) = 9.0 Hz, 1 H; H^{Ar}), 3.73 (s, 3 H; CH_3) 2.58 (t, ^3J (H,H) = 7.7 Hz, 2 H; CH_2), 2.40 (t, ^3J (H,H) = 6.6 Hz, 2H; CH_2), 1.86 (q, ^3J (H,H) = 7.1 Hz, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 175.7 (C_q, CO), 154.7 (C_q, C^{Ar}), 138.7 (C^{Ar}), 136.6 (C^{Ar}), 130.1 (C_q, C^{Ar}), 118.5 (C_q, C^{Ar}), 82.2 (C_q, C^{Ar}), 52.2 (CH_3), 32.6 (CH_2), 29.2 (CH_2), 24.9 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 7.22 min; *m/z* (%): 320 (48) [M^+], 288 (100) [M^+−CH_3O], 260 (20) [M^+−$C_2H_3O_2$], 233 (66) [M^+−$C_4H_7O_2$]; **TLC**: R_f = 0.16 (cyclohexane/EtOAc = 5/1, UV and CAM); **HRMS** (EI): calcd for [M^+]: 319.9909; found: 319.9914.

7.4.3.18.10 Methyl 4-(5-iodo-2-(((trifluoromethyl)sulfonyl)oxy)phenyl)butanoate (15l)



15l

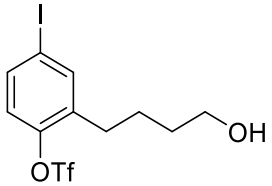
Compound **15l** was prepared according to procedure 7.4.3.3 from 2.40 g phenol derivative **15k** (7.84 mmol, 1.0 eq) in 10 mL pyridine and 2.10 mL Tf_2O (2.43 g, 8.62 mmol, 1.2 eq). Quantitative conversion was detected after 2 h. After flash column chromatography (100 g

SiO_2, 3.5 x 17 cm, eluent: cyclohexane/EtOAc = 20/1, R_f = 0.28, UV and CAM) compound **15l** was isolated as a pale yellow oil.

Yield: 2.68 g (78%), pale yellow oil, $C_{12}H_{12}F_3IO_5S$ [452.18 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, ^4J (H,H) = 7.67 (d, ^4J (H,H) = 1.9 Hz, 1 H; H^{Ar}), 7.59 (dd, ^3J (H,H) = 8.6 Hz, ^4J (H,H) = 2.1 Hz, 1H; H^{Ar}), 6.99 (d, ^3J (H,H) = 8.6 Hz, 1 H; H^{Ar}), 3.67 (s, 3H, CH_3), 2.69 (t, ^3J (H,H) = 7.8 Hz, 2H; CH_2), 2.37 (t, ^3J (H,H) = 7.3 Hz, 2H; CH_2), 1.94 (q, ^3J (H,H) = 7.5 Hz, 2H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 173.3 (C_q, CO) , 147.9 (C_q,C^{Ar}), 140.2 (C^{Ar}), 137.3 (C^{Ar}), 136.7 (C_q, C^{Ar}), 118.6 (q, ^1J (C,F) = 320.2 Hz; CF_3), 123.3 (C^{Ar}), 93.5 (C_q, C^{Ar}), 51.8 (CH_3), 33.3 (CH_2), 29.0 (CH_2), 25.0 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 6.94 min; *m/z* (%): 425 (27) [M^+], 421 (26) [M^+−CH_3O], 378 (25) [M^+−$C_3H_5O_2$], 319 (31) [M M^+−CF_3O_2S]; **TLC**: R_f = 0.28 (cyclohexane/EtOAc = 20/1, UV and CAM); **HRMS** (EI): calcd for [M^+]: 451.9402; found: 451.9423.

7.4.3.18.11 2-(4-Hydroxybutyl)-4-iodophenyl trifluoromethanesulfonate (15m)



15m

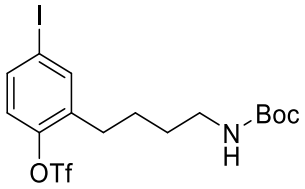
In a flame dried and argon flushed Schlenk-flask 2.60 g **15l** (5.75 mmol, 1.0 eq) were dissolved in 8.0 mL DCM (dried over P_4O_{10}). This solution was cooled to -78 °C and 11.5 mL diisobutyl-aluminium hydride (DIBALH) (1.0 M in DCM) (1.64 g, 11.5 mmol, 2.0 eq) were carefully added via syringe. The colourless solution was warmed up to RT. After quantitative conversion was detected by TLC (2 h) the solution was cooled again to -78°C and quenched by the addition of 8 mL MeOH. 20 mL saturated Rochelle-salt solution were added and the emulsion was stirred until phase separation occured. The phases were separated and the aqueous phase was extracted with DCM (3x50 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The colourless, oily crude product was directly used in the next step without further purification.

Yield: 2.26 g (93%), colourless oil, $C_{11}H_{12}F_3IO_4S$ [424.17 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68 (d, ^4J (H,H) = 1.9 Hz, 1 H; H^{Ar}), 7.59 (dd, ^3J (H,H) = 8.6 Hz, ^4J (H,H) = 2.1 Hz, 1 H; H^{Ar}), 6.98 (d, ^3J (H,H) = 8.6 Hz, 1 H; H^{Ar}), 3.69 (t, ^3J (H,H) = 6.1 Hz, 2 H; CH_2), 2.69 (t, ^3J (H,H) = 7.6 Hz, 2 H; CH_2), 1.73-1.61 (m, 4 H; 2x CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 148.0 (C_q, C^{Ar}), 140.2 (C^{Ar}), 137.6 (CH_2), 137.0 (C^{Ar}),

123.3 (C^{Ar}), 118.7 (d, ^{1}J (C,F) = 320.2 Hz; CF_3), 93.5 (C_q, C^{Ar}), 62.5 (CH_2), 32.3 (CH_2), 29.5 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 6.90 min; *m/z* (%): 424 (31) [M^+], 378 (92) [$M^+-C_2H_5O$]; **TLC**: R_f = 0.23 (cyclohexane/EtOAc = 5/1, UV and CAM); **HRMS** (EI): calcd for [M^+]: 423.9453; found: 451.9423.

7.4.3.18.12 2-(4-((*tert*-Butoxycarbonyl)amino)butyl)-4-iodophenyl trifluoromethanesulfonate (15a)



15a

In a 50 mL round-bottom flask 2.20 g compound **15m** (5.20 mmol, 1.0 eq) were dissolved in 20 mL THF (stored over KOH). The colourless solution was cooled to 0 °C and 930 µL DIPEA (670 mg, 5.20 mmol, 1.0 eq), 1.63 mg PPh_3 (6.23 mmol, 1.2 eq), 1.24 mL DIAD (1.27 mg, 6.23 mmol, 1.2 eq) and 1.34 mL DPPA (1.71 g, 6.23 mmol, 1.2 eq) were added. The pale yellow suspension was stirred for 4 h at RT. When quantitative conversion of the alcohol was detected by TLC, 1.77 g PPh_3 (6.48 mmol, 1.3 eq) dissolved in 4.0 mL THF were added and the reaction was stirred overnight at RT. After adding 2.0 mL H_2O the reaction was warmed to 50 °C and stirred until full conversion of the azide-intermediate was detected by GC-MS. The solvent was removed under reduced pressure and the oily residue (amine-intermediate) was dissolved in 50 mL DCM. To this pale yellow solution 1.13 g Boc_2O (5.20 mmol, 1.0 eq) were added. The reaction was stirred at RT overnight. When quantitative conversion of the amine was detected by TLC the reaction was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The pale yellow, oily crude product was purified via flash column chromatography (200 g SiO_2, 6.0 x 16 cm, eluent: cyclohexane/EtOAc = 15/1, R_f = 0.26, UV and ninhydrin).

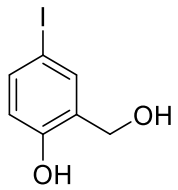
Yield: 1.32 g (49%), yellow oil, $C_{16}H_{21}F_3INO_5S$ [523.31 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, ^{4}J (H,H) = 1.9 Hz, 1 H; H^{Ar}), 7.58 (dd, ^{3}J (H,H) = 8.6 Hz, ^{4}J (H,H)= 2.0 Hz, 1 H; H^{Ar}), 6.58 (d, ^{3}J (H,H) = 8.6 Hz, 1 H; H^{Ar}), 4.54 (bs, 1 H; NH), 3.15 (d, ^{3}J (H,H) = 5.4 Hz, 2 H; CH_2), 2.69-2.63 (m, 2 H; CH_2), 1.67-1.51 (m, 4 H; 2x CH_2), 1.44 (s, 9 H; 3x CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 156.5 (C_q, CO), 147.5 (C_q, C^{Ar}), 141.1 (C^{Ar}), 137.4 (C_q, C^{Ar}), 136.9 (C^{Ar}), 125.1 (C_q, C^{Ar}), 119.0 (d, ^{1}J (C,F) = 320 Hz, CF_3), 93.3 (C_q, C^{Ar}), 79.2 (C_q), 40.1 (CH_2), 29.5 (CH_2), 29.1 (CH_2), 28.1 (3x CH_3), 27.0

(CH_2) ppm; **TLC**: R_f = 0.44 (cyclohexane/EtOAc = 5/1, UV and ninhydrin); **HRMS** (EI): calcd for [M^+]: 523.0137; found: 523.0171.

7.4.3.19 Synthesis of Tryptophan building block

7.4.3.19.1 2-(Hydroxymethyl)-4-iodophenol (16b)



16b

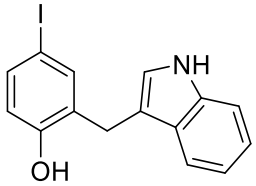
In a 50 mL round-bottom flask 228 mg $NaBH_4$ (6.05 mmol; 0.5 eq) were suspended in 30 mL *i*PrOH. The colourless suspension was cooled to 0 °C and 3.0 g 2-hydroxy-5-iodobenzaldehyde (**10d**) (12.1 mmol, 1.0 eq) were added in small portions. After stirring the yellow suspension for 2 h at RT it turned into a colourless suspension. When full conversion was detected by TLC (4 h) the reaction was cooled again to 0 °C and quenched by the addition of 2 M HCl (12 mL). The colourless solution was diluted with 50 mL saturated NaCl solution and extracted with Et_2O (4 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed in vacuum. The crude product was directly used in the following step without further purification.[102]

Yield: 3.0 g (99%); pale yellow powder, $C_7H_7IO_2$ [250.04 g/mol].

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.66 (s, 1 H; OH), 7.55 (s, 1 H; H^{Ar}), 7.34 (dd, ^3J (H,H) = 8.3 Hz, ^4J (H,H) = 1.6 Hz, 1 H; H^{Ar}), 6.60 (d, ^3J (H,H) = 8.4 Hz, 1 H; H^{Ar}), 5.07 (s, 1 H; OH), 4.42 (s, 2H, CH_2) ppm; **^{13}C NMR** (76 MHz, DMSO-d_6, APT): δ = 154.0 (C_q; C^{Ar}), 135.6 (C^{Ar}), 135.3 (C^{Ar}), 131.9 (C_q, C^{Ar}), 117.2 (C^{Ar}), 80.8 (C^{Ar}), 57.5 (CH_2) ppm; **TLC**: R_f = 0.50 (cyclohexane/EtOAc = 3/1, UV and CAM) **m.p.**$^{exp.}$ = 135-137°C (m.p.$^{lit.}$ = 138 °C).[140]

Analytical data are in accordance with those reported.[141]

7.4.3.19.2 2-((1*H*-Indol-3-yl)methyl)-4-iodophenol (16c)



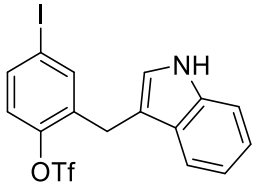
16c

In a flame dried and argon flushed Schlenk-flask 500 mg 2-(hydroxymethyl)-4-iodophenol (**16b**) (2.00 mmol, 1.0 eq) and 235 mg indole (2.00 mmol; 1.0 eq) were dissolved in 2.0 mL DMF. 3 Å molecular sieves were added to this pale yellow solution and the reaction mixture was heated to 150 °C. The mixture turned darker overnight and became finally a dark brown solution. When quantitative conversion was detected by TLC the molecular sieves were removed by filtration and the filter cake was washed with Et_2O (2 x 50 mL) and water (2 x 50 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The brown, oily crude product was purified via flash column chromatography (30 g SiO_2, 2.5 x 14 cm, eluent: cyclohexane/EtOAc = 5/1, R_f = 0.19, UV and ninhydrin).

Yield: 498 mg (71%), orange powder, $C_{15}H_{12}INO_4$ [349.17 g/mol].

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.83 (s, 1 H; NH), 9.76 (s, 1 H; OH), 7.47 (d, ^3J (H,H) = 7.8 Hz, 1 H; H^{Ar}), 7.36-7.25 (m, 3 H, H^{Ar}), 7.14 (s, 1H, H^{Ar}), 7.06 (t, ^3J (H,H) = 7.4 Hz, 1 H; H^{Ar}), 6.94 (t, ^3J (H,H) = 7.2 Hz, 1 H; H^{Ar}), 6.67 (d, ^3J (H,H) = 8.3 Hz, 1 H; H^{Ar}), 3.91 (s, 2 H; CH_2), ppm; **^{13}C NMR** (76 MHz, DMSO-d_6, APT): δ = 154.8 (C_q; C^{Ar}), 137.8 (C^{Ar}), 136.3 (C_q, C^{Ar}), 135.1 (C^{Ar}), 131.3 (C_q, C^{Ar}), 127.0 (C_q, C^{Ar}), 123.4 (C^{Ar}), 120.9 (C^{Ar}), 118.5 (C^{Ar}), 118.3 (C^{Ar}), 117.6 (C^{Ar}), 112.8 (C_q, C^{Ar}), 111.4 (C^{Ar}), 80.8 (C_q, C^{Ar}), 24.2 (CH_2) ppm; **TLC**: R_f = 0.19 (cyclohexane/EtOAc = 5/1, UV and ninhydrin); **m.p.**$^{exp.}$ = 128-130°C; **HRMS** (EI): calcd for [M^+]: 348.9964; found: 348.9971.

7.4.3.19.3 2-((1*H*-Indol-3-yl)methyl)-4-iodophenyl trifluoromethanesulfonate (16a)



16a

A 25 mL round-bottom flask was charged with 1.0 g indole-derivative **16c** (2.86 mmol, 1.0 eq) and 6 mL DCM. The pale yellow solution was cooled to 0 °C in an ice bath and 500 µL 2,6-

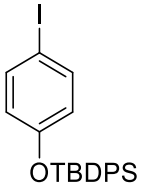
lutidine (460 mg, 4.30 mmol, 1.5 eq) were added. Then 690 µL Tf_2O (808 mg, 2.86 mmol, 1.0 eq) were added and a reddish-brown solution was formed. The reaction was stirred at 0 °C until full conversion was detected by TLC (cyclohexane/EtOAc = 5/1, R_f = 0.35, UV and ninhydrin). Then the reaction mixture was diluted with 50 mL DCM and washed with H_2O (2 x 50 mL) as well as brine (1 x 50 mL). The organic phase was dried over Na_2SO_2, filtered and the solvent was removed under reduced pressure. The brown, oily crude product was purified via flash column chromatography (150 g SiO_2, 4.0 x 23 cm, eluent: cyclohexane/EtOAc = 10/1, R_f = 0.23, UV and ninhydrin).

Yield: 1.09 g (78 %), pale brown oil, $C_{16}H_{11}F_3INO_3S$ [481.23 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 (s, 1 H; NH), 7.60-7.58 (m, 2 H; H^{Ar}), 7.46 (d, ^3J (H,H) = 7.8 Hz, 1 H; H^{Ar}), 7.40 (d, ^3J (H,H) = 8.1 Hz, 1 H; H^{Ar}), 7.23 (dt, ^3J (H,H) = 8.3 Hz, ^4J (H,H) = 1.2 Hz, 2 H; H^{Ar}), 7.15-7.09 (m, 1H, H^{Ar}), 7.06-7.01 (m, 2 H; H^{Ar}), 4.16 (s, 2 H; CH_2), ppm; **^{13}C NMR** (76 MHz, $CDCl_3$), APT): δ = 147.8 (C_q; C^{Ar}), 140.3 (C^{Ar}), 137.1 (C^{Ar}), 136.6 (C_q, C^{Ar}), 136.4 (C_q, C^{Ar}), 127.0 (C_q, C^{Ar}), 123.1 (C^{Ar}), 123.1 (C^{Ar}), 122.4 (C^{Ar}), 118.6 (q, ^1J (C,F) = 320 Hz; CF_3), 119.9 (C^{Ar}), 118.7 (C^{Ar}), 112.0 (C_q; C^{Ar}), 111.3 (C^{Ar}), 93.4 (C_q; C^{Ar}), 25.4 (CH_2) ppm; **TLC**: R_f = 0.23 (cyclohexane/EtOAc = 10/1, UV and ninhydrin).

7.4.3.20 Synthesis of Tyrosine building block

7.4.3.20.1 *tert*-Butyl(4-iodophenoxy)diphenylsilane (17b)



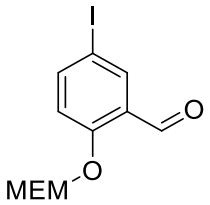
17b

In a 250 mL round-bottom flask equipped with a drying tube 5.00 g *p*-iodophenol (**17f**) (22.7 mmol, 1.0 eq) and 3.87 g imidazole (56.8 mmol, 2.5 eq) were dissolved in 100 mL DCM. 7.10 mL *tert*-butyl diphenyl silylchloride (7.47 g, 27.3 mmol, 1.1 eq) were added to this pale orange solution. A colourless precipitate was formed and the suspension was stirred at RT over night. When complete conversion was detected by GC-MS the reaction mixture was diluted with 50 mL DCM. The organic phase was washed with 1 M HCl (1 x 100 mL), saturated $NaHCO_3$ solution (1 x 100 mL) and saturated NaCl solution (1 x 100 mL). Then the organic layer was dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The yellow, oily crude product was purified via flash column chromatography (200 g SiO_2, 5.5 x 13 cm, eluent: cyclohexane, R_f = 0.47, CAM).

Yield: 9.22 g (89%), colourless oil, $C_{22}H_{23}IOSi$ [458.41 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70-7.67 (m, 4 H; H^{Ar}), 7.46-7.35 (m, 8 H; H^{Ar}), 6.53 (d, ^3J (H,H) = 8.8 Hz, 2 H; H^{Ar}), 1.09 (s, 9 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 155.7 (C_q; C^{Ar}), 139.2 (C^{Ar}), 135.6 (C^{Ar}), 132.6 (C_q; C^{Ar}), 130.2 (C^{Ar}), 128.0 (C^{Ar}), 122.3 (C^{Ar}), 83.6 (C_q; C^{Ar}), 26.6 (CH_3), 19.6 (CH) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 9.28 min; *m/z* (%): 458 (5) [M^+], 401 (100) [M^+−C_4H_9], 273 (49) [M^+−C_4H_9I]; **m.p.**$^{exp.}$ = 37-38°C.

7.4.3.20.2 5-Iodo-2-((2-methoxyethoxy)methoxy)benzaldehyde (17c)



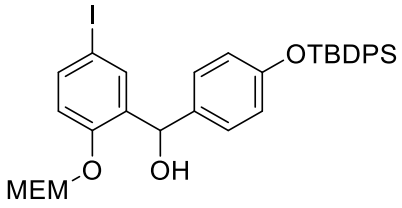
17c

In a 100 mL round-bottom flask 3.0 g 2-hydroxy-5-iodobenzaldehyde (**10d**) (12.1 mmol, 1.0 eq) were dissolved 40 mL DCM. The pale yellow solution was cooled to 0 °C in an ice bath. 2.9 mL DIPEA (2.19 g, 16.9 mmol, 1.4 eq) followed by 1.9 mL MEM-Cl (2.11 g, 16.9 mmol, 1.4 eq) were added. The solution turned intensive yellow and was stirred at RT overnight after complete addition of the reagents. After quantitative conversion was detected by GC-MS the reaction was quenched by the addition of 50 mL saturated NH_4Cl solution. The phases were separated and the aqueous phase was extracted with DCM (3 x 50 mL). The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The orange, oily crude product was purified via flash column chromatography (250 g SiO_2, 4.5 x 30 cm, eluent: cyclohexane/EtOAc = 4/1, R_f = 0.16, UV and CAM).

Yield: 3.43 g (84 %), pale yellow oil, $C_{11}H_{13}IO_4$ [336.13 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.39 (s, 1 H; CHO), 8.13 (d, ^4J (H,H) = 2.2 Hz, 1 H; H^{Ar}), 7.82 (dd, ^3J (H,H) = 8.8 Hz, ^4J (H,H) = 2.3 Hz, 1 H; H^{Ar}), 7.10 (d, ^3J (H,H) = 8.8 Hz, 1 H; H^{Ar}), 5.41 (s, 2 H; CH_2), 3.90-3.87 (m, 2 H; CH_2), 3.60-3.57 (m, 2 H; CH_2), 3.40 (s, 3 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 188.3 (CHO), 159.4 (C_q; C^{Ar}), 144.2 (C^{Ar}), 137.1 (C^{Ar}), 127.2 (C_q; C^{Ar}), 117.7 (C^{Ar}), 93.8 (CH_2), 84.7 (C_q; C^{Ar}), 71.6 (CH_2), 68.5 (CH_2), 59.2 (CH_3) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 7.05 min; *m/z* (%): 336 (1) [M^+], 260 (7) [M^+−$C_3H_7O_2$], 89 (100) [M^+−$C_7H_4IO_2$], 59 (90) [M^+−$C_8H_6IO_3$]; **TLC**: R_f = 0.16 (cyclohexane/EtOAc = 4/1, UV and CAM).

7.4.3.20.3 (4-((*tert*-Butyldiphenylsilyl)oxy)phenyl)(5-iodo-2-((2-methoxyethoxy)methoxy)phenyl)methanol (17d)



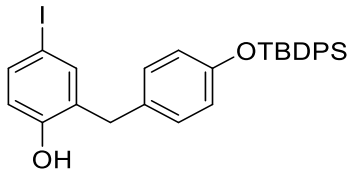
17d

In a flame dried and argon flushed Schlenk-flask 2.0 g **17b** (4.36 mmol, 1.0 eq) were dissolved in 20 mL absolute THF. The colourless solution was cooled to -78 °C and 4.0 mL *tert*-BuLi solution (2.20 M in THF) (559 mg, 8.73 mmol, 2.0 eq) were added. The yellow solution was stirred at -78 °C for 30 min. After quantitative iodine-lithium exchange had been detected by GC-MS, 1.47 g aldehyde **17c** (4.36 mmol, 1.0 eq) were added. The colour turned into orange and the reaction got slightly cloudy. When full conversion was detected by TLC the reaction was quenched by the addition of 50 mL saturated NH_4Cl solution at -78°C. After warming up to RT the phases were separated and the aqueous phase was diluted with 10 mL H_2O. Then the aqueous phase was extracted with DCM (5 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The yellow, oily crude product was purified via flash column chromatography (200 g SiO_2, 4.0 x 27 cm, eluent: cyclohexane/EtOAc = 4/1, R_f = 0.31, UV and CAM).

Yield: 2.43 mg (83 %), colorless, highly viscous oil, $C_{33}H_{37}IO_5Si$ [668.64 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70 (d, ^3J (H,H) = 6.6 Hz, 5 H; H^{Ar}), 7.45-7.33 (m, 7 H, H^{Ar}), 7.06 (d, ^3J (H,H) = 8.5 Hz, 2 H; H^{Ar}), 6.84 (d, ^3J (H,H) = 8.6 Hz, 1 H; H^{Ar}), 6.70 (d, ^3J (H,H) = 8.5 Hz, 2 H; H^{Ar}), 5.87 (s, 1 H; OH), 5.11 (q, ^3J (H,H) = 7.0 Hz, 2 H; CH_2), 3.58-3.36 (m, 4 H; CH_2), 3.30 (s, 3 H,CH_3), 1.09 (s, 9 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 155.2 (C_q; C^{Ar}), 153.9 (C_q, C^{Ar}), 137.4 (C^{Ar}), 136.2 (C^{Ar}), 135.6 (C^{Ar}), 135.5 (C_q; C^{Ar}), 133.0 (C_q, C^{Ar}), 130.1 (C^{Ar}), 127.9 (C^{Ar}), 127.8 (C^{Ar}), 119.6 (C^{Ar}), 116.6 (C^{Ar}), 93.2 (CH_2), 85.0 (C_q, C^{Ar}), 71.6 (CH_2), 71.0 (CH), 67.9 (CH_2), 59.1 (CH_3), 26.7 (CH_3), 19.6 (C_q) ppm; **TLC**: R_f = 0.31 (cyclohexane/EtOAc = 4/1, UV and CAM).

7.4.3.20.4 2-(4-((*tert*-Butyldiphenylsilyl)oxy)benzyl)-4-iodophenol (17e)

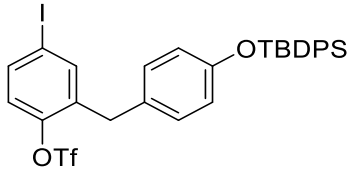


17e

In a 50 mL round-bottom flask 1.90 g **17d** (2.84 mmol, 1.0 eq) were dissolved in 30 mL DCM. 3.60 mL Et_3SiH (2.64 g, 22.7 mmol, 8.0 eq) and 1.30 mL trifluoracetic acid (1.94 g, 17.1 mmol, 6.0 eq) were added to this pale yellow solution. The yellow solution was stirred at RT until full conversion was detected by TLC (3 d). Then the reaction was diluted with 50 mL H_2O and extracted with DCM (4 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The oily crude product was purified via flash column chromatography (100 g SiO_2, 150 g SiO_2, 4.0 x 23 cm, eluent: cyclohexane/EtOAc = 10/1, R_f = 0.23, UV and $FeCl_3$).
Yield: 1.09 g (68 %), orange oil, $C_{29}H_{29}IO_2Si$ [564.54 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72-7.69 (m, 5 H; H^{Ar}), 7.45-7.31 (m, 7 H, H^{Ar}), 6.92 (d, ^3J (H,H) = 8.4 Hz, 2 H; H^{Ar}), 6.70 (d, ^3J (H,H) = 8.4 Hz, 2 H; H^{Ar}), 6.54 (d, ^3J (H,H) = 8.4 Hz, 1 H; H^{Ar}), 5.21 (bs, 1 H; OH), 3.87 (s, 3 H,CH_3), 1.10 (s, 9 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 154.5 (C_q; C^{Ar}), 154.0 (C_q, C^{Ar}), 139.3 (C^{Ar}), 136.5 (C^{Ar}), 135.7 (C^{Ar}), 133.1 (C_q; C^{Ar}), 131.3 (C_q, C^{Ar}), 130.4 (C_q, C^{Ar}), 130.0 (C^{Ar}), 129.6 (C^{Ar}), 127.9 (C^{Ar}), 120.1 (C^{Ar}), 118.1 (C^{Ar}), 82.8 (C_q, C^{Ar}), 35.4 (CH_2), 26.7 (CH_3), 19.6 (C_q) ppm; **TLC**: R_f = 0.23 (cyclohexane/EtOAc = 10/1, UV and $FeCl_3$); **HRMS** (EI): calcd for [M^+]: 564.0981; found: 564.0984.

7.4.3.20.5 2-(4-((*tert*-Butyldiphenylsilyl)oxy)benzyl)-4-iodophenyl trifluoromethanesulfonate (17a)



17a

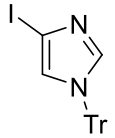
In a 10 mL round-bottom flask 200 mg **17e** (354 µmol, 1.0 eq) were dissolved in 1 mL pyridine and the pale yellow solution was cooled to 0 °C in an ice bath. Then 70 µL Tf_2O (110 mg, 390 µmol, 1.1 eq) were added and the red solution was stirred at RT for 60 min. When quantitative conversion was detected by TLC the reaction mixture was diluted with 40 mL Et_2O. Subsequently the organic phase was washed with H_2O (1 x 20 mL), 1 M HCl (2 x 20 mL) and

brine (1 x 20 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The yellow, oily crude product was purified via flash column chromatography (15 g SiO_2, 2.0 x 16 cm, eluent: cyclohexane/EtOAc = 200/1, R_f = 0.29, CAM). **Yield**: 156 mg (63 %), colorless oil, $C_{30}H_{28}F_3IO_4SSi$ [696.59 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, ^3J (H,H) = 6.4 Hz, 4 H; H^{Ar}), 7.58 (dd, ^3J (H,H) = 8.6 Hz, ^4J (H,H) = 1.8 Hz, 1 H; H^{Ar}) 7.44-7.36 (m, 7 H, H^{Ar}), 6.99 (d, ^3J (H,H) = 8.6 Hz, 1 H; H^{Ar}), 6.88 (d, ^3J (H,H) = 8.4 Hz, 2 H; H^{Ar}), 6.73 (d, ^3J (H,H) = 8.4 Hz, 2 H; H^{Ar}), 3.88 (s, 2 H; CH_2), 1.11 (s, 9 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 154.6 (C_q; C^{Ar}), 147.7 (C_q, C^{Ar}), 146.1 (C_q, C^{Ar}), 140.5 (C^{Ar}), 137.1 (C^{Ar}), 136.9 (C_q; C^{Ar}), 135.6 (C^{Ar}), 132.9 (C_q, C^{Ar}), 129.9 (C^{Ar}), 129.9 (C^{Ar}), 127.8 (C^{Ar}), 123.1 (C^{Ar}), 118.6 (d[4], ^1J (C,F) = 323 Hz; CF_3), 120.1 (C^{Ar}), 93.4 (C_q; C^{Ar}), 34.6 (CH_2), 26.5 (CH_3), 19.5 (C_q) ppm; **TLC**: R_f = 0.29 (cyclohexane/EtOAc = 200/1, UV and CAM); **HRMS** (EI): calcd for [M^+]: 696.0474; found: 696.0477.

7.4.3.21 Synthesis of Histidine building block

7.4.3.21.1 4-Iodo-1-trityl-1*H*-imidazole (18b)



18b

A 50 mL round-bottom flask was charged with 950 mg 4-iodo-1*H*-imidazole (4.90 mmol, 1.0 eq) dissolved in 10 mL DMF. 713 µL Et_3N (520 mg, 5.14 mmol, 1.05 eq) and 1.37 g triphenyl methyl chloride (4.90 mmol, 1.0 eq) were added to this pale brown solution, which became a colourless suspension within 60 min. When quantitative conversion was detected by TLC (24 h) the reaction misxture was poured into 50 mL ice water. The beige precipitate was collected by filtration and dried in an exsiccator with $CaCl_2$. The crude product was suspended in 8 mL Et_2O and stirred for 10 min. The colorless solid was collected by filtration and dried in oil pump vacuo.

Yield: 1.77 g (74 %), colorless solid, $C_{27}H_{17}IN_2$ [436.30 g/mol].

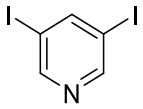
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31-7.34 (m, 10 H; H^{Ar}, H^{Imid}), 7.08-7.11 (m, 6 H; H^{Ar}), 6.90 (s, 1 H; H^{Imid}) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 142.1 (C_q; C^{Ar}), 130.9 (C^{Imid}), 129.9

[4] only doublet observed (signal should give a quadruplet)

(C^{Ar}), 128.5 (C^{Ar}), 128.4 (C^{Ar}), 127.1 (C^{Imid}), 81.6 (C_q; C^{Imid}), 76.0 (C_q) ppm; **TLC**: R_f = 0.55 (cyclohexane/EtOAc = 3/1, UV and vanilline); **m.p.**$^{exp.}$ = 198 °C (decomposition) (m.p.$^{lit.}$ = 224-225 °C).[142]

7.4.4 Synthesis of pyridine boronic acid building blocks

7.4.4.1 3,5-Diiodopyridine (20)



20

In a flame dried 250 mL Schlenk-flask 7.27 g 3,5-dibromopyridine (**19**) (30.7 mmol, 1.0 eq), 585 mg copper(I) iodide (3.1 mmol, 10 mol%) and 18.41 g sodium iodide (0.13 mol, 4.0 eq) were suspended in 50 mL absolute, degassed 1,4-dioxane. After adding 330 µL *N*,*N*'-dimethyl-ethylenediamine (270 mg, 3.07 mmol, 10 mol%), the pale yellow suspension was stirred for ~20 h at 120°C until complete conversion was detected by GC-MS. The reddish brown suspension was quenched by the addition of 50 mL saturated NH_4Cl solution, filtered and the filtercake was washed extensively with DCM (3 x 20 mL). The two phases in the filtrate were separated and the deep blue aqueous phase was extracted with DCM (4 x 70 mL). The combined yellow organic layers were dried over Na_2SO_4, filtered and concentrated to dryness. The crude product was recrystallized from 235 mL EtOH.[58]

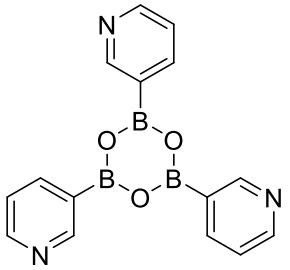
Yield: 8.72 g (86%), pale golden shavings, $C_5H_3I_2N$ [330.89 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.75 (d, ^4J (H,H) = 1.3 Hz, 2 H; H^{Pyr}), 8.35 (t, ^4J (H,H) = 1.8 Hz, 1 H; H^{Pyr}) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$): δ = 154.3 (C^{Pyr}), 151.7 (C^{Py}), 94.0 (C_q; C^{Pyr}) ppm; **GC-MS** (EI, 70 eV; MP_50_S): t_R = 5.66 min; *m/z* (%): 331 (100) [M^+], 204 (46) [M^+−I], 77 (17) [M^+−I_2]; **TLC**: R_f = 0.68 (cyclohexane/EtOAc = 9/1); **m.p.**$^{exp.}$ = 166-168°C (m.p.$^{lit.}$ = 170-172°C).[143]

Analytical data are in accordance with those reported.[143]

7.4.4.2 Synthesis of Glycine pyridine boronic acid ester

7.4.4.2.1 2,4,6-Tri(pyridin-3-yl)-1,3,5,2,4,6-trioxatriborinane (21b)

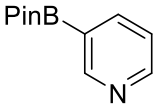


21b

A flame dried and argon flushed Schlenk-flask was charged with 2.0 g 3-bromo pyridine (**21c**) (12.7 mmol, 1.0 eq) and 3.5 mL B(O*i*Pr)$_3$ (2.86 g, 15.2 mmol, 1.2 eq), which were dissolved in 32 mL toluene and 8.0 mL THF. The colourless solution was cooled to -40 °C. When 9.1 mL *n*-BuLi (1.7 M in THF) (973 mg, 15.2 mmol, 1.2 eq) were added the solution turned yellow and after a few min orange. After stirring at -40 °C for 30 min the reaction was warmed to -20 °C and 20 mL 2 M HCl were added. When the reaction mixture reached RT, it was transferred to a separation funnel and the phases were separated. The aqueous phase was neutralized with 7 mL 3 M NaOH (pH 7-8) and saturated with 5 g NaCl. The aqueous phase was extracted with THF (3 x 50 mL) and the combined organic layers were dried over Na_2SO_2. After filtration and removal of the solvent under reduced pressure a yellow powder was obtained. The crude product was suspended in 8 mL CH_3CN and stirred 30 min at 70 °C. Then it was allowed to cool slowly to RT and then to 0 °C in an ice bath. The product was collected by filtration and washed with CH_3CN (3 x 2 mL). [53]

Yield: 1.30 g (98%), colourless powder, $C_{15}H_{12}B_3N_3O_3$ [314.71 g/mol].

7.4.4.2.2 4-Iodo-2-methylphenyl trifluoromethanesulfonate (21a)



21a

A 100 mL round-bottom flask equipped with DEAN-STARK trap and reflux condenser was charged with 1.20 g compound **21b** suspended in 50 mL toluene. 1.71 g Pinacol were added and the suspension was heated to 120 °C until all solids were completely dissolved. The yellow solution was cooled to RT and toluene was removed under reduced pressure. The pale yellow, solid crude was purified by recrystallization from 10 mL cyclohexane.[53]

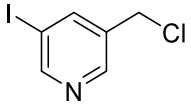
Yield: 2.05 g (86 %), colourless powder, $C_{11}H1_{16}BNO_2$ [205.06 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.87 (s, 1 H; H^{Pyr}), 8.59 (d, ^{4}J (H,H) = 3.4 Hz, 1 H; H^{Ar}), 7.98 (d, ^{3}J (H,H) = 7.5 Hz, 1 H; H^{Pyr}), 7.20 (dd, ^{3}J (H,H) = 6.9 Hz, ^{4}J (H,H) = 5.1 Hz, 1 H; H^{Pyr}), 1.28 (s, 12 H; 4 x CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 155.5 (C^{Ar}), 152.0 (C^{Pyr}), 142.3 (C^{Pyr}), 123.2 (C^{Pyr}), 84.3 (2 x C_q), 25.0 (4 x CH_3) ppm;[5] **GC-MS** (EI, 70 eV; MT_50_S): t_R = 5.51 min; *m/z* (%): 205 (33) [M^+], 190 (100) [M^+-CH_3], 148 (39) [$M^+-C_4H_9$], 148 (39) [$M^+-C_6H_{12}O$]; **m.p.**$^{exp.}$ = 65-66°C (m.p.$^{lit.}$ = 102-105°C).[53]

Analytical data are in accordance with those reported.[53]

7.4.4.3 Synthesis of Alanine pyridine boronic acid ester

7.4.4.3.1 3-(Chloromethyl)-5-iodopyridine (22b)



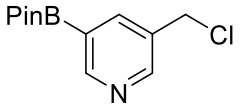
22b

In a 50 mL round-bottom-flask 887 mg (5-iodopyridin-3-yl)methanol (**31c**) (3.7 mmol, 1 eq) were dissolved in 15 mL thionylchloride and the reaction was stirred for 60 min at RT. Evolving acidic gases were neutralized by bubbling through a saturated $NaHCO_3$ solution. After quantitative conversion was detected by TLC (cyclohexane/EtOAc = 1/3, R_f = 0.78, UV) excess thionylchloride was evaporated in vacuum and collected by a cooling trap. The oily residue was dissolved in 50 mL DCM and washed with saturated $NaHCO_3$ solution (1 x 50 mL). The phases were separated and the aqueous phase extracted with DCM (2 x 50 mL). The combined organic phases were washed with brine (1 x 100 mL), dried over Na_2SO_4 and concentrated in vacuum to yield a brown oil. The crude product was purified via flash column chromatography (100 g SiO_2, 3.0 x 27 cm, eluent: cyclohexane/EtOAc = 14/1, R_f = 0.17, UV).[107]
Yield: 839 mg (88 %), colourless powder, C_6H_5ClIN [253.47 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.74 (d, ^{4}J (H,H) = 1.6 Hz, 1 H; H^{Pyr}), 8.51 (d, ^{4}J (H,H) = 1.3 Hz, 1 H; H^{Pyr}), 8.04 (bs, 1 H; C^{Pyr}), 4.48 (s, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 155.8 (C^{Pyr}), 148.1 (C^{Pyr}), 144.4 (C^{Pyr}), 135.2 (C_q; C^{Pyr}), 93.4 (C_q; C^{Pyr}), 42.3 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 5.46 min; *m/z* (%): 253 (100) [M^+], 218 (86) [$M^{++}-Cl$], 126 (29) [M^+-I], 91 (30) [M^+-ClI]; **m.p.**$^{exp.}$ = 63-64 °C; **HRMS** (EI): calcd (*m/z*) for [M^+]: 252.9155; found: 252.9160.

[5] Signal for the quaternary *ipso*-pyridine carbon (C_q; C^{Py}) at the boronic acid pinacol ester function was not observed.

7.4.4.3.2 3-(Chloromethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (22c)



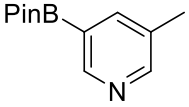
22c

A flame dried and nitrogen flushed Schlenk-flask was charged with 700 mg 3-(chloromethyl)-5-iodopyridine (**22b**) (5.86 mmol, 1 eq) dissolved in 9 mL absolute THF. The reaction mixture was cooled to -78 °C and 2.4 mL *i*PrMgCl·LiCl solution (1.53 M in THF) (3.67 mmol, 1.3 eq) were added dropwise and stirred overnight until complete metal-halogen exchange was detected by GC-MS. After adding 900 µL PinBO*i*Pr (821 mg, 4.41 mmol, 1.6 eq) the reaction mixture was stirred overnight until full conversion was detected by GC-MS. The reaction mixture was quenched by the addition of 20 mL saturated $NaHCO_3$ solution and the aqueous layer was extracted with DCM (5 x 30 mL). The combined organic layers were washed with brine (1 x 150 mL), dried over Na_2SO_4 and concentrated in vacuum. The oily crude product was dissolved in 60 mL cyclohexane/EtOAc = 1/1 and filtrated through a paper filter. The solvent was removed in vacuum to yield a yellow solid.[107]

Yield: 704 mg (99 %), yellow wax like solid, $C_{12}H_{17}BClNO_2$ [253.53 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.92 (bs, 1 H; H^{Pyr}), 8.72 (d, ^4J (H,H) = 2.2 Hz, 1 H; H^{Pyr}), 8.16 (bs, 1 H; H^{Pyr}), 4.62 (s, 2 H; CH_2), 1.38 (s, 12 H; CH_3^{BPin}) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 154.8 (C^{Pyr}), 151.4 (C^{Pyr}), 143.0 (C^{Pyr}), 132.9 (C_q; C^{Pyr}), 93.4 (C_q^{BPin}), 43.2 (CH_2), 25.0 (CH_3^{BPin}) ppm; **GC-MS** (EI, 70 eV; MT_50_35S): t_R = 6.35 min; *m/z* (%): 253 (39) [M^+], 238 (100) [M^+-CH_3], 218 (16) [M^+−Cl], 154 (81) [$M^+-C_6H_{12}O$]; **HRMS** (EI): calcd (*m/z*) for [M^+]: 253.1043; found: 253.1051.

7.4.4.3.3 3-Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (22a)



22a

A 25 mL round bottom flask was charged with 677 mg 3-(chloromethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**22c**) (2.67 mmol, 1 eq) and 523 mg zinc dust (8.01 mmol, 3 eq). The solids were suspended in 40 mL DCM. After addition of 4.0 mL acetic acid (conc.) the reaction mixture was stirred under reflux overnight. After removing excess zinc by filtration through a pad of Celite® 200 mL saturated $NaHCO_3$ solution were added. The phases were separated and the aqueous layer was extracted with DCM (3 x 150 mL). The

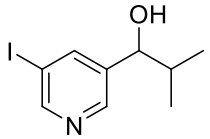
combined organic layers were washed with brine (1 x 200 mL), dried over Na_2SO_4 and concentrated in vacuum to yield a slightly beige solid.[107]

Yield: 335 mg (57 %), beige solid, $C_{12}H_{18}BNO_2$ [219.14 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.74 (s, 1 H; H^{Pyr}), 8.49 (2, 1 H; H^{Pyr}), 7.87 (s, 1 H; H^{Pyr}), 2.31 (s, 3 H; CH_3), 1.34 (s, 12 H; CH_3^{BPin}) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 152.8 (C^{Pyr}), 152.6 (C^{Pyr}), 142.8 (C^{Pyr}), 123.4 (C_q; C^{Pyr}), 84.3 (C_q; C^{Pyr}), 25.0 (CH_3^{BPin}), 18.4 (CH_3) ppm;[6] **GC-MS** (EI, 70 eV; MT_50_35S): t_R = 5.71 min; *m/z* (%): 219 (34) [M^+], 204 (59) [M^+-CH_3], 162 (26) [$M^+-C_4H_{12}$], 120 (100) [$M^+-C_6H_{12}O$]; **m.p.**$^{exp.}$ = 121-123 °C.

7.4.4.4 Synthesis of Leucine pyridine boronic acid ester

7.4.4.4.1 1-(5-Iodopyridin-3-yl)-2-methylpropan-1-ol (23b)



23b

In a flame dried and nitrogen-flushed Schlenk-flask 2.00 g 3,5-diiodopyridine (**20**) (6.04 mmol, 1.0 eq) were dissolved in 30 ml absolute THF. The pale yellow solution was then cooled to -78 °C in an acetone/dry ice bath. 4.04 mL Isopropylmagnesium chloride lithium chloride solution (1.57 M in THF) (1.20 g, 6.35 mmol, 1.05 eq) were added via syringe under stirring at -78 °C under N_2-flow. The reaction mixture was stirred at -78 °C until quantitative conversion of the metal halide exchange was detected via GC-MS (4 h). 610 µL Isobutyraldehyde (480 mg, 6.65 mmol, 1.1 eq) were added and the reaction mixture was then warmed to RT and kept stirring until full conversion (overnight, 16 h) was detected by GC-MS. The reaction mixture was quenched by the addition of 50 ml saturated NH_4Cl solution. Subsequently the aqueous phase was extracted with DCM (5 x 50 ml). The combined organic layers were dried over Na_2SO_4, filtered and then the solvent was removed under reduced pressure to give a yellow, oily crude product. The crude product was purified via flash column chromatography (75 g SiO_2, 3.0 x 20 cm, eluent: CH/EtOAc = 3/1, Rf = 0.20, UV and CAM).[58]

Yield: 1.53 g (92 %), pale yellow oil, $C_9H_{12}INO$ [277.11 g/mol].

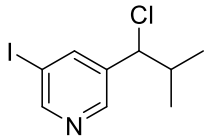
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.69 (d, ^4J (H,H) = 1.9 Hz, 1 H; H^{Pyr}), 8.43 (d, ^4J (H,H) = 1.6 Hz, 1 H; H^{Pyr}), 8.05 (t, ^4J (H,H) = 1.7 Hz, 1 H; H^{Pyr}), 4.41 (d, ^3J (H,H) = 6.3 Hz, 1 H; CH-OH),

[6] Signal for the quaternary *ipso*-pyridine carbon (C_q; C^{Py}) at the boronic acid pinacol ester function was not observed.

2.62 (bs, 1 H; OH), 2.00-1.89 (m, 1 H; CH), 0.96 (d, ^{3}J (H,H) = 6.7 Hz, 3 H; CH_3), 0.86 (d, ^{3}J (H,H) = 6.8 Hz, 3 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$): δ = 154.3 (C^{Pyr}), 146.5 (C^{Pyr}), 143.0 (C^{Pyr}), 141.4 (C_q; C^{Pyr}), 93.5 (C_q; C^{Pyr}), 76.7 (CH-OH), 35.4 (CH), 18.9 (CH_3), 17.7 (CH_3) ppm; **GC-MS** (EI, 70 eV; MT_50_35S): t_R = 6.21 min; *m/z* (%): 277 (39) [M^+], 234 (100) [$M^+-C_3H_7$]; **TLC:** R_f = 0.20 (CH/EtOAc = 3/1, UV and CAM); **HRMS** (EI): calcd (*m*/*z*) for [M^+]: 276.9964; found: 276.9965.

Analytical data are in accordance with those reported.[58]

7.4.4.4.2 3-(1-Chloro-2-methylpropyl)-5-iodopyridine (23c)



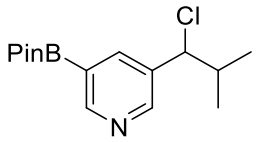
23c

In a 25 ml round-bottom flask 1.20 g **23b** (4.33 mmol, 1.0 eq) were dissolved in 8 ml $SOCl_2$. The reaction mixture was stirred at 80 °C until quantitative conversion was detected by GC-MS (20 h). The remaining $SOCl_2$ was distilled off under reduced pressure. The oily, brown residue was then quenched with 20 ml saturated $NaHCO_3$ solution. The aqueous phase was then extracted with DCM (4 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to give a reddish brown oil. The crude product was purified via flash column chromatography (100 g SiO_2, 3.5 x 25 cm, eluent: CH/EtOAc = 10/1, R_f = 0.24, UV and CAM).[58]
Yield: 1.14 g (89 %), yellow oil, $C_9H_{11}ClIN$ [295.55 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.76 (d, ^{4}J (H,H) = 1.6 Hz, 1 H; H^{Pyr}), 8.50 (d, ^{4}J (H,H) = 1.6 Hz, 1 H; H^{Pyr}), 8.07 (t, ^{4}J (H,H) = 1.8 Hz, 1 H; H^{Pyr}), 4.60 (d, ^{3}J (H,H) = 7.2 Hz, 1 H; CH-Cl), 2.27-2.15 (m, 1 H; CH), 1.08 (d, ^{3}J (H,H) = 6.6 Hz, 3 H; CH_3), 0.92 (d, ^{3}J (H,H) = 6.7 Hz, 3 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$): δ = 155.0 (C^{Pyr}), 146.9 (C^{Pyr}), 143.8 (C^{Pyr}), 138.9 (C_q; C^{Pyr}), 93.3 (C_q; C^{Pyr}), 66.5 (CH-Cl), 36.6 (CH), 20.1 (CH_3), 19.1 (CH_3) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 6.16 min; *m/z* (%): 295 (60) [M^+], 253 (100) [$M^+-C_3H_7$], 218 (13) [$M^+-C_3H_7Cl$]; **TLC:** R_f = 0.24 (CH/EtOAc = 10/1, UV and CAM); **HRMS** (EI): calcd (*m*/*z*) for [M^+]: 294.9625; found: 294.9626.

Analytical data are in accordance with those reported.[58]

7.4.4.4.3 3-(1-Chloro-2-methylpropyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (23d)



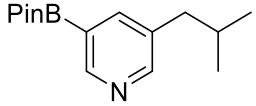
23d

In a flame dried, nitrogen flushed Schlenk-flask 1.14 g **23c** (3.86 mmol, 1.0 eq) were dissolved in 20 ml absolute THF giving a pale yellow solution. After cooling the solution to -78 °C in an acetone/dry ice bath 2.90 ml isopropylmagnesium chloride lithium chloride solution (1.5 M in THF) (612 mg, 4.24 mmol, 1.10 eq) were added under inert conditions and kept stirring at -78 °C until full conversion of the metal halide exchange was detected by GC-MS (2 h). 910 µl PinBO*i*Pr (825 mg, 4.44 mmol, 1.15 eq) were added and then the reaction mixture was warmed to RT. After full conversion (2 h) was detected by GC-MS, the reaction mixture was quenched by the addition of 30 ml saturated NH_4Cl solution. The aqueous phase was then extracted with DCM (5 x 30 mL). The combined organic layers were washed with brine (1 x 50 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the orange oily crude product was used in the next step without further purification.[58]

Yield: 1.14 g (quant.), pale yellow oil, $C_{15}H_{23}BClNO_2$ [295.61 g/mol].

GC-MS (EI, 70 eV; MT_50_S): t_R = 7.00 min; *m/z* (%): 295 (57) [M^+], 280 (100) [M^+-CH_3], 253 (84) [$M^+-C_4H_9$]; **HRMS** (EI): calcd (*m/z*) for [M^+-H]: 295.1513; found: 295.1535.

7.4.4.4.4 3-Isobutyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (23a)



23a

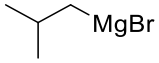
In a Schlenk-flask 1.14 g **23d** (3.86 mmol, 1.0 eq) were dissolved in 100 ml DCM. 5.5 mL AcOH (5.79 g, 96.4 mmol, 25 eq) and 1.26 g zinc dust (19.3 mmol, 5 eq) were added. The grey suspension was stirred at 40 °C overnight until full conversion was detected by GC-MS. After quantitative conversion (16 h) the reaction mixture was quenched by the addition of 30 mL saturated Na_2CO_3 solution. The suspension was filtered through a pad of Celite® and washed with DCM (3 x 20 mL). The phases were separated and subsequently the aqueous phase was extracted with DCM (4 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to give a pale yellow powder. An analytical sample was purified by recrystallization or Kugelrohr-distillation (100°C, $3 \cdot 10^{-2}$ mbar).[58]

Yield: 1.01 g (99 %), pale yellow powder, $C_{15}H_{24}BNO_2$ [261.17 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.77 (d, ^4J (H,H) = 1.3 Hz, 1 H; H^{Pyr}), 8.46 (d, ^4J (H,H) = 2.2 Hz, 1 H; H^{Pyr}), 7.88 (bs, 1 H; H^{Pyr}), 2.48 (d, ^3J (H,H) = 7.2 Hz, 2 H; CH_2), 1.95-1.82 (m, 1 H; CH), 1.35 (s, 12 H; CH_3^{BPin}), 0.91 (d, ^3J (H,H) = 6.6 Hz, 6 H; CH_3) ppm; **^{13}C NMR** (76 MHz, CDCl3): δ = 152.3 (C^{Pyr}), 151.8 (C^{Pyr}), 143.4 (C^{Pyr}), 136.5 (C_q; C^{Pyr}), 84.4 (C_q; C^{BPin}), 42.4 (CH_2), 30.2 (CH), 25.0 (CH_3^{BPin}), 22.4 (CH_3) ppm;[7] **GC-MS** (EI, 70 eV; MT_50_S): t_R = 6.53 min; *m/z* (%): 261 (64) [M^+], 246 (100) [M^+-CH_3], 218 (46) [$M^+-C_3H_7$], 162 (69) [$M^+-C_6H_{12}O$]; **m.p.**$^{exp.}$ = 74-77 °C, (m.p.$^{lit.}$ = 75-77 °C);[58] **HRMS** (EI): calcd (*m/z*) for [M^+]: 261.1903; found: 261.1884.

Analytical data are in accordance with those reported.[58]

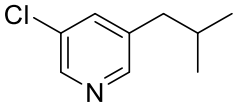
7.4.4.4.5 Isobutylmagnesium bromide (23e)



23e

A three-neck round-bottom flask equipped with reflux condenser, inline oil bubbler (after flame drying), dropping funnel and vacuum adapter with stopcock was charged with 2.00 g Mg turnings (82.3 mmol, 1.0 eq). Then the setup was flame dried and flushed with argon. Under inert conditions 10 mL absolute THF were added and the Mg was activated by adding I_2. A solution of 8.90 mL isobutyl bromide (11.3 g, 82.3 mmol, 1.0 eq) in 20 mL absolute THF were added dropwise via the dropping funnel. After stirring the grey, cloudy reaction mixture for 2 h at 70 °C the Grignard reagent was transferred to a flame dried and argon flushed Schlenk-flask. For determination the actual concentration of the Grignard solution, a titration was done as described in general procedure 7.4.2.

7.4.4.4.6 3-Chloro-5-isobutylpyridine (23f)



23f

A flame dried and argon flushed three-neck round-bottom flask equipped with dropping funnel and vacuum adapter with stopcock was charged with 3.0 g 3,5-dichloropyridine (**23g**) (20.3 mmol, 1.0 eq) and 358 mg $Fe(acac)_2$ (1.01 mmol, 0.05 eq). 120 mL absolute THF and 6.5 mL

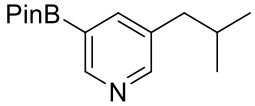
[7] Signal for the quaternary *ipso*-pyridine carbon (C_q; C^{Py}) at the boronic acid pinacol ester function was not observed.

absolute NMP were added and a red-orange solution was formed. The solution was cooled to 0 °C in an ice bath and 6.9 mL isobutylmagnesium bromide (**23e**) (2.95 M in THF) (3.27 g, 20.3 mmol, 1.0 eq) were added dropwise via the dropping funnel. The reaction mixture turned dark brownish purple and was stirred overnight at RT. When quantitative conversion was detected via GC-MS (16 h) the catalyst was removed by filtration through a pad of silica gel (eluted with 150 mL EtOAc) and the solvent of the collected filtrate was removed under reduced pressure to yield a brown, oily crude product, which was purified via flash column chromatography (250 g SiO_2, 6.0 x 16 cm, eluent: cyclohexane/EtOAc = 5/1, R_f = 0.52, UV).
Yield: 2.88 g (84 %), pale yellow oil, $C_9H_{12}ClN$ [169.65 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.38 (d, ^4J (H,H) = 2.1 Hz, 1 H; H^{Pyr}), 8.25 (d, ^4J (H,H) = 1.3 Hz, 1 H; H^{Pyr}), 7.43 (bs, 1 H; CH), 2.44 (d, ^3J (H,H) = 7.2 Hz, 2 H; CH_2), 1.84 (h, ^3J (H,H) = 6.8 Hz, 1 H; CH), 0.89 (d, ^3J (H,H) = 6.6 Hz, 6 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 148.4 (C^{Pyr}), 146.3 (C^{Pyr}), 138.2 (C_q; C^{Pyr}), 136.2 (C^{Pyr}), 131.7 (C_q; C^{Pyr}), 41.9 (CH_2), 30.0 (CH), 22.2 (CH_3) ppm; **GC-MS** (EI, 70 eV; MT_50_XS): t_R = 9.70 min; *m/z* (%): 169 (40) [M^+], 127 (100) [$M^+-C_3H_7$], 92 (16) [$M^+-C_3H_7Cl$]; **TLC:** R_f = 0.52 (CH/EtOAc = 5/1, UV and CAM).

Analytical data are in accordance with those reported.[144]

7.4.4.4.7 3-Isobutyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (23a)



23a

A flame dried and argon flushed Schlenk-flask was charged with 7.04 g B_2Pin_2 (27.7 mmol, 1.1 eq), 3.28 g KOAc (33.4 mmol, 1.3 eq) 133 mg Pd_2dba_3 (145 µmol, 0.6 mol%) and 207 mg XPhos (434 µmol, 1.7 mol%). A solution of 4.41 g pyridine-derivative **23f** (26.0 mmol, 1.0 eq) in 40 mL absolute, degassed 1,4-dioxane was added and the purple suspension was stirred at 110 °C for 48 h. When full conversion was detected by GC-MS (48 h) the catalyst was removed by filtration through a pad of silica gel (eluted with 900 mL EtOAc) and the solvent was removed under reduced pressure. The product was purified by recrystallization from pentane and HBPin was removed by sublimation in vacuum (50 °C, $8\cdot10^{-2}$ mbar).
Yield: 1.37 g (20 %), colorless powder, $C_{18}H_{26}BNO_2$ [261.17 g/mol].

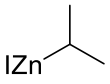
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.77 (bs, 1 H; H^{Pyr}), 8.45 (bs, 1 H; H^{Pyr}), 7.84 (bs, 1 H; H^{Pyr}), 2.46 (d, ^3J (H,H) = 7.1 Hz, 2 H; CH_2), 1,88 (h, ^3J (H,H) = 6.7 Hz, 1 H; CH), 1.34 (s, 12 H;

CH_3^{BPin}), 1.26 (s, 9 H; CH_3^{B2Pin2}) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 152.7 (C^{Pyr}), 152.3 (C^{Pyr}), 142.9 (C^{Pyr}), 136.1 (C_q; C^{Ar}), 84.2 (C_q, C^{BPin}), 92.9 (C_q; C^{B2Pin2}), 42.3 (CH_2), 30.0 (CH), 24.9 (CH_3^{BPin}), 24.6 (CH_3^{B2Pin2}), 22.2 (CH_3) ppm; **GC-MS** (EI, 70 eV; MT_50_XS): t_R = 15.53 min; *m/z* (%): 261 (67) [M^+], 246 (100) [M^+-CH_3], 218 (43) [$M^+-C_3H_7$], 162 (76) [$M^+-C_6H_{12}O$]; **m.p.**$^{exp.}$ = 71-73 °C, (m.p.$^{lit.}$ = 75-77 °C);[58] **HRMS** (EI): calcd (*m/z*) for [*M*+]: 261.1903; found: 261.1884.

Analytical data are in accordance with those reported.[58]

7.4.4.5 Synthesis of Valine pyridine boronic acid ester

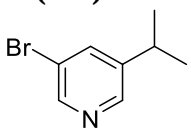
7.4.4.5.1 Isopropylzinc(II) iodide (24b)



24b

A two-neck round-bottom flask was charged with 4.62 g Zn-powder (70.6 mmol, 2.0 eq). Subsequently the flask was evacuated, heated with a heat gun and after cooling to RT back flushed with argon for three times. The Zn was suspended in 10 mL absolute THF and 152 µL 1,2-dibromoethane (332 mg, 1.76 mmol, 0.05 eq) were added. The mixture was heated to reflux temperature and cooled again to RT for three times. After the third cycle 225 µL TMS-Cl (192 mg, 1.76 mmol, 0.05 eq) were added and stirred at RT for 10 min. A solution of 3.50 mL 2-iodpropane (6.0 g, 35.3 mmol, 1.0 eq) in 10 mL absolute THF was added slowly via a dropping funnel. A water bath was used to keep the reaction at RT. When addition was finished the reaction was stirred at RT for another 2 h. The conversion of 2-iodpropane was measured by GC-FID (concentration of *i*PrZnI was not determined).

7.4.4.5.2 3-Bromo-5-isopropylpyridine (24c)



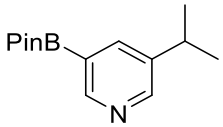
24c

A flame dried and argon flushed Schlenk-flask was charged with 5.33 g 3,5-dibromopyridine (**19**) (22.5 mmol, 1.0 eq), 181 mg $PdCl_2$(dppf) (225 µmol, 0.01 eq) and 20 mL absolute THF. 15 mL isopropylzinc iodide solution (5.30 g, 22.9 mmol, 1.0 eq) were added to this orange suspension and the brown solution was stirred at 70 °C overnight (16 h). At 95 % conversion already 10 % dialkylation was detected and the catalyst was removed by filtration through a pad of silica gel and the product was eluted with EtOAc (3 x 250 mL). The solvent was removed

under reduced pressure and the brown oil was purified via flash column chromatography (200 g SiO_2, 5.0 x 22 cm, eluent: CH/EtOAc = 9/1, Rf = 0.30, UV and CAM).
Yield: 2.34 g (52 %), yellow oil, $C_8H_{10}BrN$ [200.08 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.63 (s, 1 H; H^{Pyr}), 8.42 (d, ^3J (H,H) = 5.0 Hz, 1 H; H^{Pyr}), 7.18 (d, ^3J (H,H) = 5.0 Hz, 1 H; H^{Pyr}), 3.30 (h, ^3J (H,H) = 6.8 Hz, 1 H; CH), 1.24 (d, ^3J (H,H) = 6.9 Hz, 6 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 156.1 (C_q; C^{Pyr}), 152.0 (C^{Pyr}), 148.7 (C^{Pyr}), 123.0 (C_q; C^{Pyr}), 121.9 (C^{Pyr}), 32.7 (CH), 22.0 (CH_3) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 4.72 min; *m/z* (%): 203 (76) [M^+], 201 (77) [M^+], 186 (91) [M^+-CH_3], 184 (93) [M^+-CH_3], 120 (19) [M^+-Br], 104 (100) [M^+-CH_3Br]; **TLC:** R_f = 0.30 (CH/EtOAc = 9/1, UV and CAM); **HRMS** (EI): calcd for [M^+]: 198.9997; found: 199.0001.

7.4.4.5.3 3-Isopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (24a)



24a

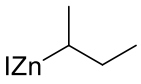
A flame dried and argon flushed Schlenk-flask was charged with 1.67 g 3-bromo-5-isopropylpyridine (**24c**) (8.35 mmol, 1.0 eq) which was dissolved in 20 mL absolute THF. The pale yellow solution was cooled to 0 °C and 6.6 mL iPrMgCl.LiCl (1.51 M in THF) (10.0 mmol, 1.2 eq) were added. The solution was stirred 5 h and the conversion of metal-halogen exchange was monitored by GC-MS (~ 74 %). After adding 2.3 mL PinO*i*Pr (2.10 g, 11.3 mmol, 1.4 eq) the reaction was warmed to RT and stirred overnight. 50 % product were detected by GC-MS and the reaction was quenched by the addition of 50 mL saturated NH_4Cl solution. The phases were separated, the aqueous phase was diluted with 50 mL H_2O and extracted with DCM (5 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified via recrystallization from pentane.
Yield: 482 mg (21 %), colourless powder, $C_{14}H_{22}BNO_2$ [247.15 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.82 (s, 1 H; H^{Pyr}), 8.54 (d, ^3J (H,H) = 5.2 Hz, 1 H; H^{Pyr}), 7.18 (d, ^3J (H,H) = 5.2 Hz, 1 H; H^{Pyr}), 3.62 (h, ^3J (H,H) = 6.8 Hz, 1 H; CH), 1.35 (s, 12 H; CH_3^{BPin}), 1.21 (d, ^3J (H,H) = 6.9 Hz, 6 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 164.4 (C_q; C^{Pyr}), 156.3 (C^{Pyr}), 151.9 (C^{Pyr}), 83.9 (C_q^{BPin}), 31.5 (CH), 24.9 (CH_3^{BPin}), 23.6

(CH_3) ppm;[8] **GC-MS** (EI, 70 eV; MT_50_XS): t_R = 14.91 min; *m/z* (%): 274 (16) [M^+], 232 (16) [M^+−CH_3], 147 (100) [M^+− $C_6H_{12}O$], 132 (29) [M^+−$C_6H_{13}O_2$]; **m.p.**$^{exp.}$ = 81-82 °C; **HRMS** (EI): calcd (*m*/*z*) for [M^+]: 247.1746; found: 247.1751.

7.4.4.6 Synthesis of Isoleucine pyridine boronic acid ester

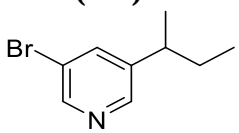
7.4.4.6.1 *sec*-Butylzinc(II) iodide (25b)



25b

A two-neck round-bottom flask was charged with 4.26 g Zn-powder (65.2 mmol, 2.0 eq). Subsequently the flask was evacuated, heated with a heat gun and after cooling to RT back flushed with argon for three times. The Zn was suspended in 10 mL absolute THF and 140 µL 1,2-dibromoethane (306 mg, 1.63 mmol, 0.05 eq) were added. The mixture was heated to reflux temperature and cooled again to RT for three times. After the third cycle 207 µL TMS-Cl (177 mg, 1.63 mmol, 0.05 eq) were added and stirred at RT for 10 min. A solution of 3.80 mL 2-iodbutane (6.0 g, 32.6 mmol, 1.0 eq) in 8 mL absolute THF was added slowly via a dropping funnel to avoid high temperatures. When addition was finished the reaction was stirred at RT for another 60 min. The conversion of 2-iodbutane was measured by GC-FID (concentration of *sec*BuZnI was not determined).

7.4.4.6.2 3-Bromo-5-(sec-butyl)pyridine (25c)



25c

A flame dried and argon flushed Schlenk-flask was charged with 6.44 g 3,5-dibromopyridine (**19**) (27.2 mmol, 1.0 eq), 219 mg $PdCl_2$(dppf) (272 µmol, 0.01 eq) and 20 mL absolute THF. 20 mL *sec*-butylzinc iodide solution (**25b**) (6.78 g, 27.2 mmol, 1.0 eq) were added to this orange suspension and the brown solution was stirred at 70 °C overnight. The reaction was stopped at 98 % conversion since already by-products were detected. The catalyst was removed by filtration through a pad of silica gel and the product was eluted with EtOAc (3 x 250 mL). The solvent was removed under reduced pressure and the brown crude oil was purified via flash

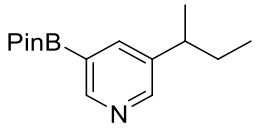
[8] Signal for the quaternary *ipso*-pyridine carbon (C_q; C^{Py}) at the boronic acid pinacol ester function was not observed.

column chromatography (250 g SiO_2, 7.0 x 17 cm, eluent: CH/EtOAc = 9/1, Rf = 0.30, UV and CAM).

Yield: 3.00 g (51 %), yellow oil (contains ~10 % *n*-isomer), $C_9H_{12}BrN$ [214.11 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.65 (s, 1 H; H^{Pyr}), 8.41 (d, ^3J (H,H) = 4.6 Hz, 1 H; H^{Pyr}), 7.13 (d, ^3J (H,H) = 5.0 Hz, 1 H; H^{Pyr}), 3.17-3.05 (m, 1 H; CH), 1.71-1.53 (m, 2 H; CH_2), 1.21 (d, ^3J (H,H) = 6.9 Hz, 3 H; CH_3), 0.87 (t, ^3J (H,H) = 7.4 Hz, 3 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 155.3 (C_q; C^{Pyr}), 152.1 (C^{Pyr}), 148.5 (C^{Pyr}), 122.5 (C^{Pyr}), 120.9 (C_q; C^{Pyr}), 39.4 (CH), 29.5 (CH_2), 20.0 (CH_3), 11.9 (CH_3) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 5.04 min; *m/z* (%): 215 (71) [M^+], 201 (73) [M^+], 186 (96) [$M^+-C_2H_5$], 184 (97) [$M^+-C_2H_5$], 134 (21) [M^+-Br], 104 (100) [$M^+-C_2H_5Br$]; **TLC:** R_f = 0.30 (CH/EtOAc = 9/1, UV and CAM).

7.4.4.6.3 3-(*sec*-Butyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (25a)



25a

A flame dried and argon flushed Schlenk-flask was charged with 2.39 g 3-bromo-5-(sec-butyl)pyridine (**25c**) (11.2 mmol, 1.0 eq), which was dissolved in 20 mL absolute THF. The pale yellow solution was cooled to 0 °C and 9.0 mL *i*PrMgCl.LiCl (1.51 M in THF) (13.6 mmol, 1.2 eq) were added. The solution was stirred 5 h and the conversion of metal-halogen exchange was monitored by GC-MS (~ 84 %). After adding 2.7 mL PinO*i*Pr (2.46 g, 13.2 mmol, 1.2 eq) the reaction was warmed to RT and stirred overnight. 88 % product were detected by GC-MS and the reaction was quenched by the addition of 50 mL saturated NH_4Cl solution. The phases were separated, the aqueous phase was diluted with 50 mL H_2O and extracted with DCM (5 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by recrystallization from pentane.

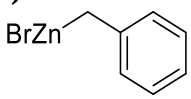
Yield: 967 mg (32 %), colourless powder, $C_{15}H_{24}BNO_2$ [261.17 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.82 (s, 1 H; H^{Pyr}), 8.53 (d, ^3J (H,H) = 5.3 Hz, 1 H; H^{Pyr}), 7.14 (d, ^3J (H,H) = 5.2 Hz, 1 H; H^{Pyr}), 3.46-3.34 (m, 1 H; CH), 1.64-1.47 (m, 2 H; CH_2), 1.34 (s, 12 H; CH_3^{BPin}), 1.20 (d, ^3J (H,H) = 6.9 Hz, 3 H; CH_3), 0.82 (t, ^3J (H,H) = 7.4 Hz, 3 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 163.5 (C_q; C^{Pyr}), 156.3 (C^{Pyr}), 151.5 (C^{Pyr}), 120.5 (C^{Pyr}), 83.9 (C_q^{BPin}), 38.2 (CH), 31.3 (CH_2), 25.0 (CH_3^{BPin}), 24.9 (CH_3^{BPin}), 20.9 (CH_3),

12.1 (CH_3) ppm;[9] **GC-MS** (EI, 70 eV; MT_50_S): t_R = 6.29 min; *m/z* (%): 246 (14) [M^+], 177 (17) [M^+−C_6H_{12}], 161 (100) [M^+− $C_6H_{12}O$]; **m.p.**$^{exp.}$ = 83-84 °C; **HRMS** (EI): calcd (*m*/*z*) for [M^+]: 261.1903; found: 261.1914.

7.4.4.7 Synthesis of Phenylalanine boronic acid ester

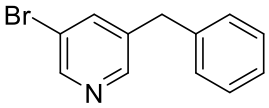
7.4.4.7.1 Benzylzinc(II) bromide (26b)



X

A Schlenk flask was charged with 1.15 g Zn-powder (17.5 mmol, 2.0 eq). Subsequently the flask was evacuated, heated with a heat gun and after cooling to RT back flushed with argon for three times. The Zn was suspended in 3 mL absolute THF and 76 µL 1,2-dibromoethane (165 mg, 877 µmol, 0.1 eq) were added. The mixture was heated to reflux temperature and cooled again to RT for three times. After the third cycle 112 µL TMS-Cl (95.3 mg, 877 µmol, 0.1 eq) were added and stirred at RT for 10 min. A solution of 1.00 mL benzylbromide (1.50 g, 8.77 mmol, 1.0 eq) in 2 mL absolute THF was added via a dropping funnel. A smooth reflux was maintained by the addition rate of benzylbromide. When addition was finished the reaction was stirred at 40 °C for another 3 h. The conversion of benzylbromide was measured by GC-FID and the amount of Zn-reagent was estimated by integral areas (25 % Wurtz-coupling was detected).

7.4.4.7.2 3-Benzyl-5-bromopyridine (26c)



26c

A flame dried and argon flushed Schlenk-flask was charged with 950 mg 3,5-dibromo pyridine (**19**) (4.01 mmol, 1.0 eq), 32.3 mg $PdCl_2$(dppf) (40.1 µmol, 0.01 eq) and 5 mL absolute THF. To this orange suspension 2.5 mL benzyl zinc bromide solution (**26b**) (948 mg, 4.01 mmol, 1.0 eq) were added and the brown solution was stirred for 2 h at 70 °C. At 93 % conversion already 5 % dibenzylation was detected and the catalyst was removed by filtration over a pad of silica gel and the product was eluted with 100 mL EtOAc. The solvent was removed under reduced pressure and the brown oil was purified via flash column chromatography (100 g SiO_2, 2.5 x

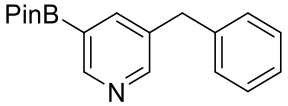
[9] Signal for the quaternary *ipso*-pyridine carbon (C_q; C^{Py}) at the boronic acid pinacol ester function was not observed.

20 cm, eluent: CH/EtOAc = 10/1 changing to CH/EtOAc = 5/1 when product starts eluting, R_f = 0.40, UV and CAM).

Yield: 620 mg (61 %), colourless oil, $C_{12}H_{10}BrN$ [248.12 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.56 (d, ^4J (H,H) = 1.9 Hz, 1 H; H^{Pyr}), 8.45 (s, 1 H; H^{Pyr}), 7.64 (s, 1 H; H^{Pyr}), 7.39-7.28 (m, 3 H; H^{Ar}), 7.20 (d, ^3J (H,H) = 7.0 Hz, 2 H; H^{Ar}), 3.99 (s, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 148.9 (C^{Pyr}), 148.4 (C^{Pyr}), 139.0 (C_q; C^{Pyr}) 138.9 (C^{Pyr}), 138.5 (C_q; C^{Ar}), 129.0 (C^{Ar}), 126.9 (C^{Ar}), 120.9 (C_q; C^{Pyr}), 38.8 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 6.46 min; *m/z* (%): 247 (100) [M^+], 167 (100) [M^+−Br], 91 (36) [M^+−C_6H_5Br]; **TLC:** R_f = 0.40 (CH/EtOAc = 5/1, UV and CAM).

7.4.4.7.3 3-Benzyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (26a)



26a

A flame dried and argon flushed Schlenk-flask was charged with 860 mg 3-benzyl-5-bromopyridine (**26c**) (3.47 mmol, 1.0 eq), which was dissolved in 10 mL absolute THF. The pale yellow solution was cooled to 0 °C and 1.80 mL *i*PrMgCl.LiCl were added (3.81 mmol, 1.1 eq). The solution was stirred overnight until quantitative metal-halogen exchange was detected by GC-MS. After adding 780 µL PinO*i*Pr (3.81 mmol, 1.1 eq) the reaction was warmed to RT and stirred overnight. Full conversion was detected by GC-MS and the reaction was quenched by the addition of 30 mL saturated NH_4Cl solution. The phases were separated and the aqueous phase was extracted with DCM (4 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by recrystallization from pentane.

Yield: 187 mg (18 %), colourless powder, $C_{18}H1_{22}BNO_2$ [295.19 g/mol].

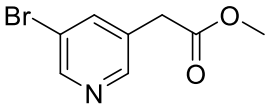
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.80 (d, ^4J (H,H) = 1.3 Hz, 1 H; H^{Py}), 8.53 (d, ^4J (H,H) = 2.3 Hz, 1 H; H^{Py}), 7.99 (bs, 1 H; H^{Py}), 7.33-7.16 (m, 5 H; H^{Ar}), 3.99 (s, 2 H; CH_2), 1.34 (s, 12 H; CH_3^{BPin}) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$): δ = 152.0 (C^{Py}), 150.9 (C^{Py}), 144.0 (C^{Py}), 139.6 (C_q; C^{Ar}), 136.6 (C_q; C^{Py}), 129.0 (C^{Ar}), 128.9 (C^{Ar}), 126.8 (C^{Ar}), 84.6 (C_q; C^{BPin}), 39.2 (CH_2), 25.0 (CH_3^{BPin}) ppm;[10] **GC-MS** (EI, 70 eV; MT_50_S): t_R = 7.53 min; *m/z* (%): 295 (97) [M^+], 280 (100) [M^+−CH_3], 238 (55) [M^+−C_4H_{13}], 194 (80) [M^+−$C_6H_{13}O$]; **TLC**: R_f = 0.08

[10] Signal for the quaternary *ipso*-pyridine carbon (C_q; C^{Py}) at the boronic acid pinacol ester function was not observed.

(EtOAc/NEt_3 = 1/1000, tailing, CAM); **m.p.**$^{exp.}$ = 95-97°C; **b.p.**^{KRD} = 175°C, $7 \cdot 10^{-3}$ mbar; **HRMS** (EI): calcd (*m*/*z*) for [M^+]: 295.1747; found: 295.1749.

7.4.4.8 Synthesis of Aspartate pyridine boronic acid ester

7.4.4.8.1 Methyl 2-(5-bromopyridin-3-yl)acetate (27b)



27b

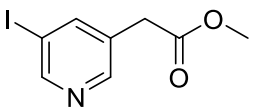
A flame dried, nitrogen flushed Schlenk-flask was charged with 91.7 mg $Pd_2(allyl)_2Cl_2$ (250 µmol, 0.02 eq), 480 mg BINAP (770 µmol, 0.06 eq), 2.97 g potassium 3-methoxy-3-oxopropanoate (19.0 mmol, 1.5 eq), 3.0 g 3,5-dibromopyridine (**19**) (12.7 mmol, 1.0 eq) and 153 mg of DMAP (1.25 mmol, 0.1 eq) under nitrogen counter flow. The Schlenk-flask containing the reagents was evacuated and then nitrogen flushed. Subsequent to repeating this procedure two more times, 30 mL degassed mesitylene were added under inert conditions and the reaction mixture was stirred for 10 min at RT. Then the reaction mixture was heated to 140 °C and kept stirring until quantitative conversion of the starting material was detected by GC-MS. After full conversion (4 d) the brown suspension was brought to RT and directly purified via flash column chromatography (300 g SiO_2, 8.5 x 15 cm, eluent CH/EE=5/2, R_f = 0.26, UV and CAM)

Yield: 1.04 g (37 %), yellow oil, $C_8H_8BrNO_2$ [230.06 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.59 (d, ^4J (H,H) = 2.0 Hz, 1 H; H^{Pyr}), 8.43 (d, ^4J (H,H) = 1.5 Hz, 1 H; H^{Pyr}), 7.80 (s, 1 H; H^{Pyr}), 3.72 (s, 3 H; CH_3), 3.62 (s, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 170.6 (C_q; $C^{Carbonyl}$), 149.9 (C^{Pyr}), 148.6 (C^{Pyr}), 139.6 (C^{Pyr}), 131.4 (C_q; C^{Pyr}), 120.8 (C_q; C^{Pyr}), 52.6 (CH_3), 37.8 (CH_2),; **GC-MS** (EI, 70 eV; MT_50_35S): t_R = 5.50 min; *m/z* (%): 231 (90) [M^+], 229 (93) [M^+], 172 (100) [$M^+-COOCH_3$], 170 (100) [$M^+-COOCH_3$], 91 (44) [$M^+-COOCH_3Br$]; **TLC:** R_f = 0.26 (CH/EtOAc = 5/2, UV and CAM).

Analytical data are in accordance with those reported.[145]

7.4.4.8.2 Methyl 2-(5-iodopyridin-3-yl)acetate (27c)



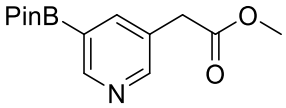
27c

A Schlenk-flask was charged with 1.0 g pyridine-derivative **27b** (4.35 mmol, 1.0 eq) which was dissolved in 10 mL absolute, degassed 1,4-dioxane. 50 µL *N*,*N´*-dimethyl ethylene diamine (38.2 mg, 435 µmol, 0.1 eq), 2.61 g NaI (17.4 mmol, 4.0 eq) and 82.8 mg CuI (435 µmol, 0.1 eq) were added. The green suspension was stirred at 120 °C until full conversion was detected by GC-MS (24 h). Then the reaction was cooled to RT and quenched by the addition of 50 mL saturated NH_4Cl solution. A light brown precipitate was formed which was removed by filtration through a pad of Celite® (eluted with 50 mL DCM). The phases were separated and the dark blue aqueous phase was extracted with DCM (4 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The yellow solid crude was purified via flash column chromatography (100 g SiO_2, 4.5 x 13 cm, eluent: CH/EtOAc = 4/1, Rf = 0.28, UV and CAM).

Yield: 743 mg (62 %), colourless powder, $C_8H_8INO_2$ [277.06 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.73 (d, ^4J (H,H) = 1.4 Hz, 1 H; H^{Pyr}), 8.44 (bs, 1 H; H^{Pyr}), 7.98 (bs, 1 H; H^{Pyr}), 3.72 (s, 3 H; CH_3), 3.58 (s, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 170.6 (C_q; $C^{Carbonyl}$), 154.7 (C^{Ar}), 149.0 (C^{Ar}), 145.1 (C^{Ar}), 131.7 (C_q; C^{Pyr}), 93.4 (C_q; C^{Pyr}), 52.5 (CH_3), 37.8 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 5.95 min; *m/z* (%): 277 (100) [M^+], 218 (57) [M^+−COOCH; **TLC:** R_f = 0.28 (CH/EtOAc = 4/1, UV and CAM); **m.p.**$^{exp.}$ = 41-43 °C.

7.4.4.8.3 Methyl 2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)acetate (27a)



27a

A Schlenk-flask was charged with 500 mg pyridine-derivative **27c** (1.80 mmol, 1.0 eq) dissolved in 10 mL dry THF. The reaction mixture was cooled to -78 °C and 1.32 mL *i*PrMgCl·LiCl solution (1.5 M in THF) (288 mg, 1.99 mmol, 1.2 eq) were added dropwise. When complete metal-halogen exchange was detected by GC-MS (2 h), 425 µL PinBO*i*Pr (386 mg, 2.08 mmol, 1.15 eq) were added to the reaction mixture. The reaction was allowed to warm up in the cooling bath overnight and full conversion was detected by GC-MS (24 h). The reaction mixture was quenched by the addition of 50 mL saturated NH_4Cl solution. The phases were separated and the aqueous layer extracted with DCM (4 x 50 mL). The combined organic layers were washed with brine (1 x 50 mL), dried over Na_2SO_4 and concentrated in vacuum to yield a pale brown oil. Due to the formation of isopropanolate during the reaction, partial trans-

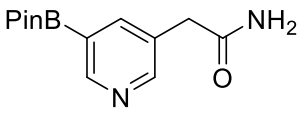
esterification occurred, resulting in an inseparable mixture of desired methyl ester (Me) and the isopropyl ester (*i*Pr) (17/3).

Yield: 498 mg (99 %), colourless oil, $C_{14}H_{20}BNO_4$ [277.13 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.83 (s, 1 H; H^{Py}), 8.56 (d, ^4J (H,H) = 1.8 Hz, 1 H; H^{Py}), 7.98 (s, 1 H; H^{Py}), 5.00 (sept, ^3J (H,H) = 6.3 Hz, 0.2 H; CH^{iPr}), 3.69 (s, 3 H; CH_3^{Me}), 3.62 (s, 2 H; CH_2^{Me}), 3.57 (s, 0.4 H; CH_2^{iPr}), 1.24 (s, 1.3 H; CH_3^{iPr}), 1.22 (s, 12 H; CH_3^{BPin}) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 171.3 (C_q; $C{=}O^{Me}$), 170.3 (C_q; $C{=}O^{iPr}$), 154.0 ($C^{Pyr(Me)}$), 153.9 ($C^{Pyr(iPr)}$), 152.4 ($C^{Pyr(Me)}$), 152.4 ($C^{Pyr(iPr)}$), 143.4 ($C^{Pyr(Me)}$), 143.4 ($C^{Pyr(iPr)}$), 129.5 (C_q; $C^{Py(Me)}$), 129.2 (C_q; $C^{Py(iPr)}$), 84.4 (C_q; C^{BPin}), 68.8 (CH^{iPr}), 52.4 (CH_3^{Me}), 38.9 (CH_2^{iPr}), 38.4 (CH_2^{Me}), 25.0 ($CH_3^{BPin(Me)}$), 24.7 ($CH_3^{BPin(iPr)}$), 21.9 (CH_3^{iPr}) ppm; **GC-MS** (EI, 70 eV; MT_50_S): $t_{R\ Me}$ = 6.82 min; *m/z* (%): 277 (50) [M^+], 262 (64) [M^+-CH_3], 218 (53) [$M^+-COOCH_3$], 178 (100) [$M^+-C_6H_{12}O$], 118 (47)) [$M^+-COOCH_3$]; $t_{R\ iPr}$ = 7.00 min; *m/z* (%): 305 (24) [M^+], 262 (14) [$M^+-C_3H_7$], 218 (100) [$M^+-COOC_3H_7$].

7.4.4.9 Synthesis of Asparagine pyridine boronic acid ester

7.4.4.9.1 2-(5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)acetamide (28a)



28a

A 15 mL "Ace pressure tube®, front seal" (Aldrich Z181099) with a "Duro-Silicone O-ring" was charged with 100 mg of compound mixture **27a** (361 µmol, 1.0 eq), 7.1 mg KCN (108 µmol, 30 mol%) and 5 mL of ammonia solution (7 M in MeOH). The flask was sealed, and the mixture was stirred at 50 °C for 9 d. The solvent was evaporated in vacuo and the brown residue was purified by sublimation (210 °C, $1.4 \cdot 10^{-2}$ mbar).[58]

Yield: 55 mg (61 %), colourless solid, $C_{13}H_{19}BN_2O_3$ [262.11 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.85 (s, 1 H; H^{Pyr}), 8.61 (s, 1 H; H^{Pyr}), 8.03 (s, 1 H; H^{Pyr}), 5.82 (bs, 1 H; $CONH_2$), 5.75 (bs, 1 H; $CONH_2$), 3.57 (s, 2 H; CH_2), 1.34 (s, 12 H; CH_3^{BPin}) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$): δ = 172.0 (C_q; $CONH_2$), 153.6 (C^{Pyr}), 151.9 (C^{Pyr}), 143.9 (C^{Pyr}), 130.4 (C_q; C^{Pyr}), 84.6 (C_q; C^{BPin}), 40.2 (CH_2), 25.0 (CH_3^{BPin}) ppm;[11] **GC-MS** (EI, 70 eV; MT_50_S): t_R = 7.63 min; *m/z* (%): 262 (43) [M^+], 247 (70) [M^+-CH_3], 203 (80) [$M^+-C_2H_5NO$],

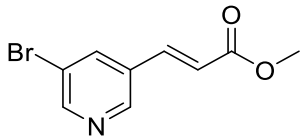
[11] Signal for the quaternary *ipso*-pyridine carbon (C_q; C^{Py}) at the boronic acid pinacol ester function was not observed.

163 (100) [$C_8H_{10}BNO_2^+$], 146 (9) [$C_7H_5BNO_2^+$], 119 (50) [$C_7H_5NO^+$]; **m.p.**$^{exp.}$ = 174-179°C; **HRMS** (EI): calcd (*m*/*z*) for [M^+]: 262.1491; found: 262.1501.

Analytical data are in accordance with those reported.[58]

7.4.4.10 Synthesis of Glutamate pyridine boronic acid ester

7.4.4.10.1 Methyl (*E*)-3-(5-bromopyridin-3-yl)acrylate (29b)

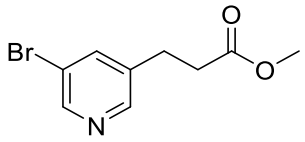


29b

A flame dried and argon flushed Schlenk-flask was charged with 2.0 g 3,5-dibromopyridine (**19**) (8.44 mmol, 1.0 eq), 760 µL methyl acrylate (727 mg, 8.44 mmol, 1.0 eq) and 30 mL degassed DMF. 190 mg $Pd(OAc)_2$ (844 µmol, 0.1 eq) and 1.75 g K_2CO_3 (12.7 mmol, 1.5 eq) were added to this pale yellow solution. The yellow suspension was heated to 100 °C and stirred until full conversion was detected by GC-MS (48 h). The reaction mixture darkened during heating and turned dark brown after 24 h. When the starting material was fully converted the reaction was cooled to RT and diluted with 100 mL EtOAc. 100 mL H_2O were added and the dark brown emulsion was stirred 20 min. A fine dark brown precipitate was formed, which was removed by filtration through a thin pad of Celite®. The phases of the filtrate were separated and the aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (1 x 100 mL), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The brown solid crude was purified via flash column chromatography (250 g SiO_2, 6.0 x 15 cm, eluent: CH/EtOAc = 4/1, Rf = 0.31, UV and $KMnO_4$).
Yield: 1.30 g (71 %), colourless powder, $C_9H_8BrNO_2$ [242.07 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.65 (d, ^4J (H,H) = 4.8 Hz, 2 H; H^{Pyr}), 7.97 (s, 1 H; H^{Pyr}), 7.60 (d, ^3J (H,H) = 16.1 Hz, 1 H; CH), 6.50 (d, ^3J (H,H) = 16.1 Hz, 1 H; CH), 3.81 (s, 3 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 166.4 (C_q; $C^{Carbonyl}$), 152.0 (CH), 147.7 (CH), 139.6 (C^{Pyr}), 136.7 (C^{Pyr}), 131.9 (C_q; C^{Pyr}), 121.6 (C^{Pyr}), 121.3 (C_q; C^{Pyr}), 52.2 (CH_3) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 6.10 min; *m/z* (%): 243 (34) [M^+], 241 (34) [M^+], 212 (100) [M^+−CH_3O], 212 (100) [M^+−CH_3O], 210 (100) [M^+−CH_3O], 184 (31) [M^+−$C_2H_3O_2$], 182 (31) [M^+−$C_2H_3O_2$], 103 (70) [M^+− $C_2H_3O_2Br$]; **TLC:** Rf = 0.31 (CH/EtOAc = 4/1, UV and $KMnO_4$); **m.p.**$^{exp.}$ = 120-121 °C.

7.4.4.10.2 Methyl 3-(5-bromopyridin-3-yl)propanoate (29c)

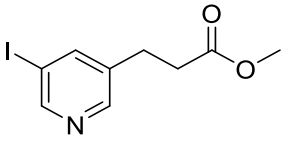


29c

A 50 mL round-bottom flask was charged with 1.10 g pyridine derivative **29b** (4.54 mmol, 1.0 eq), 5.08 g p-tosyl hydrazide (27.3 mmol, 6.0 eq) and 3.71 g NaOAc.3H_2O (27.3 mmol, 60 eq). 30 mL THF were added to give a pale yellow suspension. The suspension was warmed to 70 °C and after 24 h an orange solution was formed. When quantitative conversion was detected by GC-MS the reaction mixture was cooled to RT and diluted with 100 mL DCM. The organic phase was washed with saturated $NaHCO_3$ solution (1 x 60 mL) and the aqueous phase was re-extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine (1 x 100 mL), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The yellow solid crude was purified via flash column chromatography (100 g SiO_2, 5.0 x 20 cm, eluent: CH/EtOAc = 3/1, Rf = 0.27, UV and CAM).
Yield: 988 mg (89 %), colourless powder, $C_9H_{10}BrNO_2$ [244.09 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.52 (d, ^4J (H,H) = 1.3 Hz, 1 H; H^{Pyr}), 8.38 (s, 1 H; H^{Pyr}), 7.68 (s, 1 H; H^{Pyr}), 3.67 (s, 3 H; CH_3), 2.93 (t, ^3J (H,H) = 7.5 Hz, 2 H; CH_2), 2.64 (t, ^3J (H,H) = 7.5 Hz, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 172.5 (C_q; $C^{Carbonyl}$), 149.1 (C^{Pyr}), 148.1 (C^{Pyr}), 138.6 (C^{Pyr}), 137.8 (C_q; C^{Pyr}), 120.8 (C_q; C^{Pyr}), 52.0 (CH_3), 34.9 (CH_2), 27.7 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 5.90 min; *m/z* (%): 245 (20) [M^+], 243 (20) [M^+], 230 (26) [M^+-CH_3], 228 (26) [M^+-CH_3], 215 (93) [M^+-OCH_3], 213 (100) [M^+-OCH_3], 185 (100) [$M^+-COOCH_3$], 183 (100) [$M^+-COOCH_3$]; **TLC:** Rf = 0.27 (CH/EtOAc = 3/1, UV and CAM); **m.p.**$^{exp.}$ = 32-34 °C.

7.4.4.10.3 Methyl 3-(5-iodopyridin-3-yl)propanoate (29d)



29d

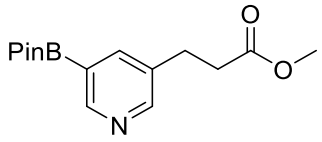
A Schlenk-flask was charged with 675 mg pyridine-derivative **29c** (2.77 mmol, 1.0 eq) which was dissolved in 6 mL degassed 1,4-dioxane. 50 µL *N,N´*-dimethyl ethylene diamine (41 mg, 464 µmol, 0.2 eq), 1.91 g NaI (12.7 mmol,4.6 eq) and 66 mg CuI (347 µmol, 0.1 eq) were added. The green-grey suspension was stirred at 120 °C until full conversion was detected by

GC-MS (24 h). Then the reaction was cooled to RT and quenched by the addition of 10 mL saturated NH_4Cl solution. The dark blue aqueous phase was diluted with 40 mL H_2O and extracted with DCM (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The yellow oily crude was purified by flash column chromatography (75 g SiO_2, 4.0 x 18 cm, eluent: CH/EtOAc = 3/1, R_f = 0.32, UV and CAM).

Yield: 666 mg (83 %), yellow powder, $C_9H_{10}INO_2$ [291.09 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51 (d, ^4J (H,H) = 1.3 Hz, 1 H; H^{Pyr}), 8.38 (bs, 1 H; H^{Pyr}), 7.68 (bs, 1 H; H^{Pyr}), 3.67 (s, 3 H; CH_3), 2.93 (t, ^3J (H,H) = 7.5 Hz, 2 H; CH_2), 2.64 (t, ^3J (H,H) = 7.5 Hz, 2 H; CH_2), ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 172.5 (C_q; $C^{Carbonyl}$), 149.1 (C^{Ar}), 148.1 (C^{Ar}), 138.6 (C^{Ar}), 137.8 (C_q; C^{Pyr}), 120.8 (C_q; C^{Pyr}), 52.0 (CH_3), 34.9 (CH_2), 27.7 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 6.27 min; *m/z* (%): 291 (53) [M^+], 261 (100) [M^+−OCH_3], 231 (67) [M^+−$COOCH_3$]; **TLC:** Rf = 0.32 (CH/EtOAc = 3/1, UV and CAM); **m.p.**$^{exp.}$ = 60-61 °C; **HRMS** (EI): calcd for [M^+]: 290.9756; found: 290.9775.

7.4.4.10.4 Methyl 3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3 yl)propanoate (29a)



29a

A Schlenk flask was charged with 576 mg 3-(5-iodopyridin-3-yl)propanoate (**29d**) (1.98 mmol, 1.0 eq) dissolved in 8 mL dry THF. The reaction mixture was cooled to -78 °C and 1.9 mL *i*PrMgCl·LiCl solution (1.26 M in THF) (2.2 mmol, 1.1 eq) were added dropwise. After 2 h complete metal-halogen exchange was detected by GC-MS and 500 µL PinBO*i*Pr (2.45 mmol, 1.2 eq) were added to the reaction mixture, which was allowed to warm up in the cooling bath overnight. Full conversion was detected by GC-MS (16 h) and the reaction mixture was quenched by adding 30 mL saturated NH_4Cl solution. The phases were separated and the aqueous layer extracted with DCM (5 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum. During the reaction isopropanolate was formed and caused a partial transesterification, resulting in an inseparable mixture of desired methyl ester (Me) and isopropyl ester (*i*Pr) (77/23).

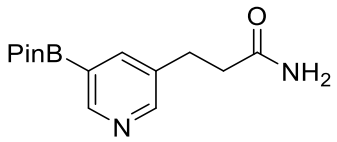
Yield: 1.85 g (99 %), pale yellow oil, $C_{15}H_{22}BNO_4$ [291.15 g/mol].

^{1}H NMR (300 MHz, CDCl3): δ = 8.77 (bs, 1H; H^{Pyr}), 8.51 (bs, 1H; H^{Pyr}), 7.90 (bs, 1H; H^{Pyr}), 4.98 (sep, ^3J (H,H) = 6.2 Hz, 0.5H; CH^{iPr}), 3.66 (s, 1.8 H; CH_3^{Me}), 2.95-2.91 (m, 2 H, CH_2),

2.66-2.57 (m, 2H, CH_2), 1.34 (s, 12H, CH_3^{BPin}), 1.23 (s, undefined signal), 1.19 (d, ^3J (H,H) = 6.2 Hz, 3.6 H; CH_3^{iPr}) ppm; **^{13}C NMR** (76 MHz, CDCl3): 172.9 (Cq, $C^{Carbonyl(Me)}$), 172.0 (Cq, $C^{Carbonyl(iPr)}$), 153.5 ($C^{Pyr(Me)}$), 153.4 ($C^{Pyr(iPr)}$), 152.1 ($C^{Pyr(Me)}$), 152.0 ($C^{Pyr(iPr)}$), 142.3 ($C^{Pyr(Me)}$), 142.2 ($C^{Pyr(iPr)}$), 135.2 ($C^{Pyr(Me)}$), 135.2 ($C^{Pyr(iPr)}$), 84.4 (C_q^{BPin}), 68.1 (CH^{iPr}), 51.9 (CH_3^{Me}), 35.9 (CH_2^{iPr}), 35.3 (CH_2^{Me}), 28.3 (CH_2^{iPr}), 28.2 (CH_2^{Me}), 25.0 (CH_3^{BPin}), 21.9 (CH_3^{iPr}) ppm; **GC-MS** (EI, 70 eV; MT_50_S): $t_{R\ Me}$ = 7.07 min; *m/z* (%): 291 (50) [M^+], 232 (89) [$M^+-COOCH_3$], 192 (100) [$M^+-C_6H_{12}O$], 132 (66) [$M^+-C_8H_{15}O_3$]; $t_{R\ iPr}$ = 7.29 min; *m/z* (%): 319 (11) [M^+], 277 (36) [$M^+-C_3H_7$], 232 (100) [$M^+-COOCH_3$], 132 (47) [$M^+-C_{10}H_{19}O_3$]; **HRMS** (EI): calcd for [M_{Me+}]: 291.1645; found: 291.1647; [M_{iPr+}]: 319.1958; found: 319.1977.

7.4.4.11 Synthesis of Glutamine pyridine boronic acid ester

7.4.4.11.1 3-(5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)propanamide (30a)



30a

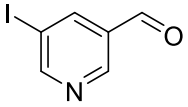
A 45 mL "Ace pressure tube®, front seal" (Aldrich Z568767) with a "Duro-Silicone O-ring" was charged with 407 mg of compound mixture **29a** (1.40 mmol, 1.0 eq), 30 mg KCN (461 µmol, 33 mol%) and 30 mL of ammonia solution (7 M in MeOH). The flask was sealed, and the mixture was stirred at 50 °C for 9 d (77 % conversion, 58 % product). The solvent was evaporated in vacuo.

Yield: 388 mg (crude), brown solid, $C_{14}H_{21}BN_2O_3$ [276.14 g/mol].

GC-MS (EI, 70 eV; MT_50_S): t_R = 7.79 min; *m/z* (%): 276 (86) [M^+], 261 (56) [M^+-NH_2], 177 (84) [$M^+-C_6H_{12}O$], 132 (100) [$M^+-C_7H_{14}NO_2$].

7.4.4.12 Synthesis of Serine pyridine boronic acid ester

7.4.4.12.1 5-Iodonicotinaldehyde (31b)



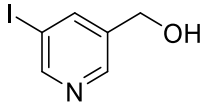
31b

In a flame dried, nitrogen flushed 100 ml Schlenk-flask 1.0 g 3,5-diiodopyridine (**20**) (3.0 mmol, 1.0 eq) was dissolved in 10 ml abs. THF. After cooling to -78 °C in a dry ice/acetone

bath 2.5 mL isopropylmagnesium chloride lithium chloride solution (1.27 M in THF) (3.2 mmol, 1.05 eq) were added under N_2 counter flow and kept stirring at -78 °C until full conversion of the metal-halogen exchange was detected by GC-MS. After full conversion (3.5 h) 460 µL dry DMF (5.9 mmol, 2.0 eq) were added at -78 °C under inert conditions. Subsequently the reaction mixture was brought to RT and stirred overnight (12 h). After quantitative conversion the reaction mixture was quenched by the addition of 10 mL saturated NH_4Cl solution and the aqueous layer was extracted with Et_2O (3 x 20 ml). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to give a pale orange solid. The crude product was purified via flash column chromatography (100 g SiO_2, 4.5 x 15 cm, eluent: CH/EtOAc = 4/1, R_f = 0.21, UV and CAM). **Yield**: 526 mg (78 %), colourless powder, C_6H_4INO [233.01 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.02 (s, 1 H; CHO), 9.05 (d, ^4J (H,H) = 1.8 Hz, 1 H; H^{Pyr}), 9.00 (d, ^4J (H,H) = 1.5 Hz, 1 H; H^{Pyr}), 8.49-8.47 (m, 1 H; H^{Pyr}) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 189.4 ($C^{Carbonyl}$), 160.8 (C^{Pyr}), 150.3 (C^{Pyr}), 144.0 (C^{Pyr}), 132.9 (C_q; C^{Pyr}), 94.0 (C_q; C^{Pyr}) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 5.00 min; *m/z* (%): 233 (100) [M^+], 204 (17) [M^+−CHO], 127 (14) [M^+−C_6H_4NO], 78 (15) [M^+−CHIO]; **TLC:** R_f = 0.21 (CH/EtOAc = 4/1, UV and CAM); **m.p.**$^{exp.}$ = 143-145 °C.

7.4.4.12.2 (5-Iodopyridin-3-yl)methanol (31c)



31c

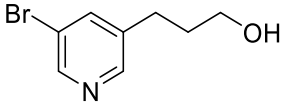
A flame dried and argon flushed 250 mL two-neck round-bottom flask was charged with 1.80 g 5-iodonicotinaldehyde (**31b**) (7.78 g, 1.0 eq) and 50 mL DCM. The pale yellow solution was cooled to -78 °C in an acetone/dry ice bath. 13 mL DIBAL-H (1 M in toluene) (1.84 g, 13.0 mmol, 1.7 eq) were added and the reaction was stirred for 2 h at the indicated temperature. After quantitative conversion was detected by GC-MS the reaction was quenched by the addition of 20 mL MeOH and 50 mL saturated potassium sodium tartrate solution was added. The emulsion was stirred overnight until phase separation occurred. The aqueous phase was diluted with 50 mL H_2O and the phases were separated. The aqueous phase was extracted with DCM (3 x 50 mL) and the combined organic layers were dried over Na_2SO_4. After the solvent was removed under reduced pressure the yellow oil was purified via flash column chromatography (100 g SiO_2, 4.0 x 17 cm, eluent: CH/EtOAc = 1/3, Rf = 0.30, UV and CAM). **Yield**: 1.01 g (55 %), pale yellow powder, C_6H_6BINO [235.02 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.69 (d, ^{4}J (H,H) = 1.4 Hz, 1 H; H^{Pyr}), 8.46 (s, 1 H; H^{Pyr}), 8.07 (s, 1 H; H^{Pyr}), 4.67 (s, 2 H; CH_2), 2.78 (bs, 1 H; OH) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 154.8 (C^{Pyr}), 146.7 (C^{Pyr}), 143.2 (C^{Pyr}), 138.6 (C_q; C^{Pyr}), 93.6 (C_q; C^{Pyr}), 61.9 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_35S): t_R = 5.60 min; *m/z* (%): 235 (100) [M^+], 206 (36) [M^+-CH_2OH], 108 (14) [M^+-I]; **TLC:** R_f = 0.30 (CH/EtOAc = 1/3, UV and CAM); **m.p.**$^{exp.}$ = 63-65°C.

Analytical data are in accordance with those reported.[107]

7.4.4.13 Synthesis of Arginine pyridine boronic acid ester

7.4.4.13.1 3-(5-Bromopyridin-3-yl)propan-1-ol (35b)

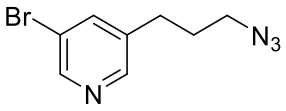


35b

A flame dried and argon flushed two-neck round-bottom flask was charged with 106 mg $LiAlH_4$ (2.79 mmol, 2.0 eq), which was suspended in 2 mL THF. The grey suspension was cooled to -78 °C and 340 mg pyridine-derivative **29c** (1.39 mmol, 1.0 eq) dissolved in 3 mL THF were added via a dropping funnel. When quantitative conversion was detected by GC-MS the reaction was quenched by the addition of 400 µL EtOAc and 106 µL H_2O, 106 µL 15 % NaOH and 320 µL H_2O were added. Then the reaction mixture was warmed to RT and stirred for 60 min. Subsequently the solution was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The orange crude was purified via flash column chromatography (25 g SiO_2, 2.5 x 18 cm, eluent: CH/EtOAc = 1/1, R_f = 0.17, UV and CAM).
Yield: 221 mg (73 %), pale yellow powder, $C_8H_{10}BrNO$ [216.08 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.45 (s, 1 H; H^{Pyr}), 8.33 (s, 1 H; H^{Pyr}), 7.67 (s, 1H; H^{Pyr}), 3.64 (d, ^{3}J (H,H) = 6.2 Hz, 2 H; CH_2), 2.72-2.67 (m, 2 H; CH_2), 1.89-1.80 (m, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 148.3 (C^{Pyr}), 148.0 (C^{Pyr}), 139.4 (C_q; C^{Pyr}), 138.8 (C^{Pyr}), 120.8 (C_q; C^{Pyr}), 61.3 (CH_2), 33.6 (CH_2), 18.9 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 5.87 min; *m/z* (%): 217 (19) [M^+], 215 (20) [M^+], 198 (100) [M^+-OH]; **TLC:** R_f = 0.17 (CH/EtOAc = 1/1, UV and CAM).

7.4.4.13.2 3-(3-Azidopropyl)-5-bromopyridine (35c)

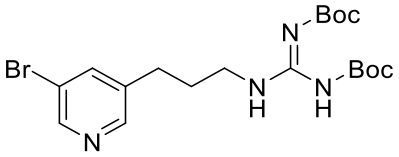


35c

In a 50 mL round-bottom flask 780 mg compound **35b** (3.60 mmol, 1.0 eq) were dissolved in 10 mL THF (stored over KOH). The colourless solution was cooled to 0 °C and 630 µL DIPEA (1.17 g, 9.05 mmol, 2.5 eq), 1.14 g PPh_3 (4.35 mmol, 1.2 eq), 680 µL DIAD (1.71 g, 11.6 mmol, 3.2 eq) and 940 µL DPPA (2.80 g, 10.2 mmol, 2.8 eq) were added. The pale yellow solution was stirred for 24 h at RT. Due to incomplete conversion the solvent was removed under reduced pressure and the azide-intermediate was purified via flash column chromatography (100 g SiO_2, 4.0 x 17 cm, eluent: cyclohexane/EtOAc = 4/1, R_f = 0.29, UV and ninhydrin).
Yield: 280 mg (32 %), colourless solid, $C_8H_9BrN_4$ [241.09 g/mol].

GC-MS (EI, 70 eV; MT_50_S): t_R = 6.13 min; *m/z* (%): 213 (27) [M^+-N_2], 211 (27) [M^+-N_2];
TLC: Rf = 0.29 (CH/EtOAc = 4/1, UV and ninhydrin).

7.4.4.13.3 3-((5-Bromopyridin-3-yl)propyl-*N*,*N´*-di-Boc-guanidine (35d)



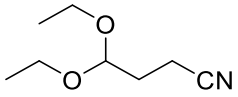
35d

280 mg Azide-intermediate **35c** (1.16 mmol, 1.0 eq) were dissolved in 5 mL THF and 400 mg PPh_3 (1.53 mmol, 1.3 eq) dissolved in 2 mL THF were added and the reaction was stirred overnight at RT. After adding 800 µL H_2O the reaction was warmed to 50 °C and stirred until full conversion of the azide-intermediate was detected by TLC. The solvent was removed under reduced pressure and the oily residue (amine-intermediate) was dissolved in 6 mL DMF. 433 mg guanylating-reagent **14d** (1.39 mmol, 1.2 eq) were added to this pale yellow solution. The reaction was stirred at RT for 3 h. When quantitative conversion of the amine was detected by TLC the reaction was diluted with 70 mL Et_2O and washed with water (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The pale yellow, oily crude product was purified via flash column chromatography (30 g SiO_2, 2.0 x 16 cm, eluent: cyclohexane/EtOAc = 5/1, R_f = 0.11, UV and ninhydrin).
Yield: 521 mg (98 %), colourless solid, $C_{19}H_{29}BrN_4O_4$ [457.37 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.5 (bs, 1H; NH), 8.51 (d, ^{4}J (H,H) = 1.7 Hz, 1 H; H^{Pyr}), 8.37 (s, 1 H; H^{Pyr}), 7.68 (bs, 1 H; H^{Pyr}), 3.47 (q, ^{3}J (H,H) = 6.8 Hz, 2 H; CH_2), 2.67 (t, ^{3}J (H,H) = 7.7 Hz, 2 H; CH_2), 1.96-1.86 (m, 2 H; CH_2), 1.50 (s, 9H; CH_3, overlapping), 1.49 (s, 9H; CH_3, overlapping) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 163.7 (C_q, CN), 156.4 (C_q, CO), 153.5 (C_q, CO), 148.8 (C^{Pyr}), 148.1 (C^{Pyr}), 138.6 (C_q; C^{Pyr}), 138.5 (C^{Pyr}), 120.8 (C_q, C^{Pyr}), 83.4 (C_q), 79.5 (C_q), 40.1 (CH_2), 30.4 (CH_2), 30.0 (CH_2), 28.4 (CH_3), 28.2 (CH_3) ppm; **TLC**: R_f = 0.11 (cyclohexane/EtOAc = 5/1, UV and ninhydrin); **m.p.**$^{exp.}$ = 105-107 °C.

7.4.4.14 Synthesis of Lysine pyridine building block

7.4.4.14.1 4,4-Diethoxybutanenitrile (36b)



36b

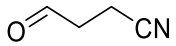
In a 250 ml round-bottom flask 1.33 g NaCN (27.1 mmol, 1.1eq) and 886 mg Bu_4NI (2.40 mmol, 0.1 eq) were suspended in 60 ml DMSO. 4.03 g 3-Chloro-1,1-diethoxypropane (24.2 mmol, 1.0 eq) dissolved in 6 mL DMSO were added to the reaction mixture. The brown suspension was heated under stirring to 50 °C. After quantitative conversion (20 h) monitored by GC-MS the reddish-brown reaction mixture was brought to RT and diluted with 240 mL H_2O. The product was then extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (1 x 150 mL), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to give an orange-brown viscous oil. The crude product was purified via flash column chromatography (200 g SiO_2, 6.0 x 15 cm, eluent: CH/EtOAc = 3/1, R_f = 0.40, UV and CAM).

Yield: 3.03 g (80 %), pale yellow oil, $C_8H_{15}NO_2$ [157.21 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.56 (t, ^{3}J (H,H) = 5.3 Hz, 1 H; CH), 3.72-3.61 (m, 2 H; CH_2), 3.55-3.45 (m, 2 H; CH_2), 2.42 (d, ^{3}J (H,H) = 7.3 Hz, 2 H; CH_2), 1.93 (q, ^{3}J (H,H) = 7.3 Hz, 2 H; CH_2), 1.20 (t, ^{3}J (H,H) = 7.0 Hz, 6 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 119.6 (C_q; CN), 101.0 (CH), 62.5 (CH_2), 29.7 (CH_2), 15.3 (CH_3), 12.6 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_35S): t_R = 4.175 min, *m/z* (%):112 (41) [$M^+-C_2H_5O$], 103 (48) [$M^+-C_3H_4N$], 84 (100) [$M^+-C_4H_9O$], **TLC:** R_f = 0.40 (CH/EtOAc=3/1, UV and CAM).

Analytical data are in accordance with those reported.[113]

7.4.4.14.2 4-Oxobutanenitrile (36c)



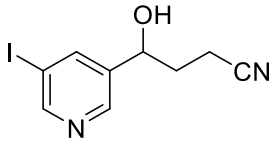
36c

In a 250 mL two-neck round-bottom flask with argon-inlet 3.03 g 4,4-diethoxybutanenitrile (**36b**) (19.3 mmol, 1.0 eq) were dissolved in 125 mL degassed acetone and cooled to -4 °C. 40 mL 6 M HCl were added and the reaction mixture was stirred at the indicated temperature overnight. After the reaction was completed (detected by GC-MS), the acetone was removed in vacuo using a rotary evaporator at 25°C. The aqueous residue (~80 mL) was extracted with DCM (10 × 50 mL), and the combined organic layers were dried over Na_2SO_4 and filtered. The solvent was removed in vacuo using a rotary evaporator to give the crude product as a colourless oil. An analytical sample was purified by distillation (b.p.$^{1.7}$ = 56-58°C).[58]
Yield: 1.92 g (74%), colourless liquid, C_4H_5NO [83.09 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.80 (s, 1 H; CHO), 2.91 (t, ^3J (H,H) = 7.1 Hz, 2 H; CH_2), 2.64 (t, ^3J (H,H) = 7.1 Hz, 2 H; CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_XS): t_R = 4.26 min; *m/z* (%): 82 (4) [M^+−H], 54 (100) [M^+−CHO]; **TLC:** R_f = 0.40 (CH/EtOAc = 1/1, UV and CAM); **b.p.**$^{exp.}$ = 56-58°C, 2.3 mbar (b.p.$^{lit.}$ = 66-68°C, 2.7 mbar).[146]

Analytical data are in accordance with those reported.[147]

7.4.4.14.3 4-Hydroxy-4-(5-iodopyridin-3-yl)butanenitrile (36d)



36d

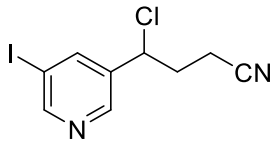
In a flame dried and nitrogen-flushed 100 mL round-bottom flask equipped with a vacuum adapter with stopcock 3.00 g 3,5-diiodopyridine (**20**) (9.07 mmol, 1.0 eq) were dissolved in 35 mL absolute THF. The yellow solution was then cooled to -78 °C in an acetone/dry ice bath. Under stirring at -78 °C 7.5 mL isopropylmagnesium chloride lithium chloride solution (1.27 M in THF) (1.36 g, 9.38 mmol, 1.05 eq) were added via syringe under N_2-flow. The reaction mixture was stirred at -78 °C until quantitative conversion of the metal halide exchange was detected via GC-MS (3.5 h). 829 mg 4-Oxobutanenitrile (**36c**) (9.98 mmol, 1.1 eq) were added at -78 °C under N_2-flow. The reaction mixture was then warmed to RT and was kept stirring until full conversion (overnight, 11 h) was detected by GC-MS. The reaction mixture was quenched by the addition of 15 mL saturated NH_4Cl solution. Subsequently the aqueous phase was extracted with DCM (5 x 20 mL). The pooled organic layers were dried over Na_2SO_4 and

then the solvent was removed under reduced pressure to give an orange, oily crude product. The crude product was purified via flash column chromatography (275 g SiO_2, 6.5 x 20 cm, eluent: CH/EtOAc = 1/1, R_f = 0.20, UV and CAM).

Yield: 2.24 g (86 %), pale yellow, highly viscous oil, C_9H_9INO [288.09 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.71 (d, ^4J (H,H) = 1.9 Hz, 1 H; H^{Pyr}), 8.49 (d, ^4J (H,H) = 1.7 Hz, 1 H; H^{Pyr}), 8.09 (t, ^4J (H,H) = 1.7 Hz, 1 H; H^{Pyr}), 4.84 (t, ^3J (H,H) = 6.6 Hz, 1 H; CH), 3.15 (bs, 1 H; OH), 2.70-2.43 (m, 2 H; CH_2), 2.05-1.98 (m, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$): δ = 155.0 (C^{Pyr}), 145.7 (C^{Pyr}), 142.4 (C^{Pyr}), 141.2 (C_q; C^{Pyr}), 119.3 (C_q; CN), 93.8 (C_q; C^{Pyr}), 69.2 (CH), 34.3 (CH_2), 13.9 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 7.08 min; *m/z* (%): 288 (20) [M^+], 234 (100) [$M^+-C_3H_4N$]; **TLC:** R_f = 0.20 (CH/EtOAc = 1/1, UV and CAM); **HRMS** (EI): calcd (*m*/*z*) for [M^+]: 287.9760; found: 287.9776.

7.4.4.14.4 4-Chloro-4-(5-iodopyridin-3-yl)butanenitrile (36e)



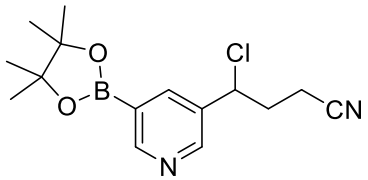
36e

In a 50 mL round-bottom flask 2.24 g **36d** (7.78 mmol, 1.0 eq) were dissolved in 13 mL DCM and 20 mL $SOCl_2$ were added under stirring. The reaction mixture was stirred at RT until quantitative conversion was detected by TLC (20 h). The remaining $SOCl_2$ was distilled off under reduced pressure using a cooling trap. The oily, brown residue was then quenched with 30 mL saturated $NaHCO_3$ solution. The aqueous phase was extracted by the addition of DCM (5 x 20 mL). Subsequently the combined organic layers were washed with brine (1 x 20 mL) and dried over Na_2SO_4. The solvent was then removed under reduced pressure to give a reddish brown oil. The crude product was purified via flash column chromatography (200 g SiO_2, 6.5 x 15 cm, eluent: CH/EtOAc = 3/2, Rf = 0.37, UV and CAM).[58]

Yield: 1.66 g (70 %), reddish brown oil, $C_9H_8ClIN_2$ [306.53 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.82 (d, ^4J (H,H) = 1.7 Hz, 1 H; H^{Pyr}), 8.59 (d, ^4J (H,H) = 1.7 Hz, 1 H; H^{Pyr}), 8.10 (t, ^4J (H,H) = 1.8 Hz, 1 H; H^{Pyr}), 4.95 (dd, ^3J (H,H) = 9.1 Hz, ^4J (H,H) = 5.3 Hz, 1 H; CH), 2.73-2.57 (m, 2 H; CH_2), 2.40-2.32 (m, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$): δ = 156.1 (C^{Pyr}), 146.4 (C^{Pyr}), 143.1 (C^{Pyr}), 137.8 (C_q; C^{Pyr}), 118.0 (C_q; CN), 93.6 (C_q; C^{Pyr}), 57.5 (CH), 35.3 (CH_2), 15.4 (CH_2) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 6.86 min; *m/z* (%): 306 (97) [M^+], 271 (100) [M^+-Cl], 252 (58) [$M^+-C_3H_4N$]; **TLC:** R_f = 0.37 (CH/EtOAc = 3/2, UV and CAM); **HRMS** (EI): calcd (*m*/*z*) for [M^+]: 305.9421; found: 305.9422.

7.4.4.14.5 4-Chloro-4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)-butanenitrile (36f)



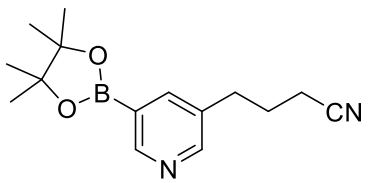
36f

In a flame dried, nitrogen flushed 100 mL round-bottom flask 1.51 g **36e** (4.93 mmol, 1.0 eq) were dissolved in 20 mL absolute THF giving a reddish brown solution. After cooling the solution to -78 °C in an acetone/dry ice bath 2.60 mL isopropylmagnesium chloride lithium chloride solution (2.11M in THF) (797 mg, 5.49 mmol, 1.10 eq) were added under inert conditions and kept stirring at -78 °C until full conversion of the metal halide exchange was detected by GC-MS. After quantitative conversion (3 h) 1.12 mL PinBO*i*Pr (1.02 g, 5.49 mmol, 1.10 eq) were added at -78 °C under N_2-flow and then the reaction mixture was brought to RT. After full conversion (1 h) detected by GC-MS, the reaction mixture was quenched by the addition of 20 mL saturated NH_4Cl solution. The aqueous phase was then extracted with DCM (4 x 25 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure to give an orange oil. The crude product was used in the next step without further purification.

Yield: 1.60 g (quant.), pale yellow oil, $C_{15}H_{20}BClN_2O_2$ [306.60 g/mol].

GC-MS (EI, 70 eV; MT_50_S): t_R = 7.55 min; *m/z* (%): 306 (9) [M^+], 291 (48) [M^+-CH_3], 271 (100) [M^+-Cl], 221 (30) [$M^+-C_6H_{13}$], 207 (68) [$M^+-C_5H_9NO$]; **TLC**: R_f = 0.09 (cyclohexane/EtOAc = 3/7, CAM); **HRMS** (EI): calcd (*m/z*) for [M^+-H]: 304.1264; found: 304.1273.

7.4.4.14.6 4-(5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)butane-nitrile (36a)



36a

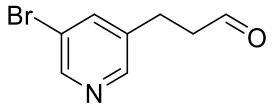
In a 250 ml round-bottom flask 1.60 g of **36f** (5.22 mmol, 1.0 eq) were dissolved in 100 mL DCM. 6 mL AcOH (6.31 g, 105 mmol, 20 eq) and 974 mg zinc dust (14.9 mmol, 3 eq) were added. The reaction mixture was kept stirring at RT until full conversion was detected by GC-MS. After quantitative conversion (5 h) the reaction mixture was quenched by the addition of

25 mL saturated Na_2CO_3 solution. Subsequently the aqueous phase was extracted with DCM (4 x 25 mL). The combined organic layers were washed with brine (1 x 25 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure to give a yellow oil. An analytical sample was purified by Kugelrohr-distillation (150°C, $1 \cdot 10^{-3}$ mbar).
Yield: 1.40 g (99 %), pale brown solid, $C_{15}H_{21}BN_2O_2$ [272.15 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.82 (d, ^4J (H,H) = 1.3 Hz, 1 H; H^{Pyr}), 8.53 (d, ^4J (H,H) = 2.3 Hz, 1 H; H^{Pyr}), 7.93 (bs, 1 H; H^{Pyr}), 2.81-2.76 (m, 2 H; CH_2), 2.36 (t, ^3J (H,H) = 7.1 Hz, 2 H; CH_2), 2.05-1.96 (m, 2 H; CH_2), 1.35 (s, 12 H; CH_3^{BPin}) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$): δ = 153.2 (C^{Pyr}), 151.4 (C^{Pyr}), 142.7 (C^{Pyr}), 134.8 (C_q; C^{Pyr}), 119.1 (C_q; CN), 84.5 (C_q; C^{BPin}), 31.7 (CH_2), 26.8 (CH_2), 25.0 (CH_3^{BPin}), 16.7 (CH_2) ppm;[12] **GC-MS** (EI, 70 eV; MT_50_S): t_R = 7.27 min; *m/z* (%): 272 (28) [M^+], 257 (59) [M^+-CH_3], 187 (41) [$M^+-C_6H_{13}$], 173 (100) [$M^+-C_5H_9NO$]; **TLC**: R_f = 0.11 (EtOAc/MeOH = 4/1, CAM); **m.p.**$^{exp.}$ = 55-57°C; **b.p.**^{KRD} = 150°C, $1 \cdot 10^{-3}$ mbar; **HRMS** (EI): calcd (*m/z*) for [M^+-H]: 271.1620; found: 271.1633.

7.4.4.15 Synthesis of Tryptophan pyridine boronic acid ester

7.4.4.15.1 3-(5-Bromopyridin-3-yl)propanal (37b)



37b

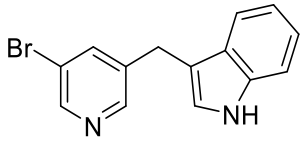
A 50 mL round-bottom flask was charged with 930 mg alcohol **35b** dissolved in 10 mL DCM. 2.01 g DMP (4.70 mmol, 1.1 eq) were added and the colourless suspension was stirred for 3 h at RT. When quantitative conversion was detected by TLC excess DMP was removed by filtering the suspension through a pad of Celite® (eluted with 3 x 50 mL DCM). The solvent was removed under reduced pressure and the crude product was purified via flash column chromatography (100 g SiO_2, 4.0 x 17 cm, eluent: CH/EtOAc = 2/1, Rf = 0.26, UV and CAM).
Yield: 620 mg (67 %), pale yellow oil, C_8H_8BrNO [214.06 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.81 (s, 1 H; CHO), 8.52 (d, ^4J (H,H) = 1.5 Hz, 1 H; H^{Pyr}), 8.38 (s, 1 H; H^{Pyr}), 7.69 (s, 1 H; H^{Pyr}), 2.93 (t, ^3J (H,H) = 7.0 Hz, 2 H; CH_2), 2.83 (t, ^3J (H,H) = 6.9 Hz, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 199.9 (C_q; $C^{Carbonyl}$), 148.8 (C^{Pyr}), 147.9 (C^{Pyr}), 138.7 (C^{Pyr}), 137.8 (C_q; C^{Pyr}), 120.7 (C_q; C^{Pyr}), 44.5 (CH_2), 24.7 (CH_2) ppm;

[12] Signal for the quaternary *ipso*-pyridine carbon (C_q; C^{Py}) at the boronic acid pinacol ester function was not observed.

GC-MS (EI, 70 eV; MT_50_S): t_R = 5.67 min; *m/z* (%): 215 (90) [M^+], 213 (93) [M^+], 173 (100) [M^+−C_2H_3O], 171 (100) [M^+−C_2H_3O]; **TLC:** R_f = 0.26 (CH/EtOAc = 2/1, UV and CAM).

7.4.4.15.2 3-((5-Bromopyridin-3-yl)methyl)-1*H*-indole (37c)



37c

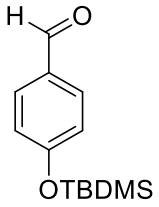
A Schlenk-flask was charged with 100 mg aldehyde **37b** (467 µmol, 1.0 eq) and 52 µL phenyl hydrazine (55.6 mg, 514 µmol, 1.1 eq) dissolved in 2 mL 1,2-DCE. The yellow solution was degassed 10 min by ultra-sonication and bubbling argon through. 32 µL TFA were added and the solution turned orange. The orange solution was stirred at 60 °C until full conversion was detected by TLC (3 h). The reaction mixture was diluted by the addition of 10 mL H_2O and neutralized with 10 mL saturated $NaHCO_3$ solution (pH 8). The aqueous phase was extracted with EtOAc (3 x 20 mL), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The orange, oily crude product was purified via flash column chromatography (20 g SiO_2, 1.5 x 13 cm, eluent: cyclohexane/EtOAc = 3/1, R_f = 0.30, UV and CAM).

Yield: 42 mg (31 %), orange powder, $C_{14}H_{11}BrN_2$ [287.16 g/mol].

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.94 (s, 1H; NH), 8.56 (s, 1H; H^{Pyr}), 8.50 (d, ^4J (H,H) = 1.5 Hz, 1 H; H^{Pyr}), 7.89 (s, 1 H; H^{Pyr}), 7.46 (d, ^3J (H,H) = 7.8 Hz, 1 H; H^{Ind}), 7.36 (d, ^3J (H,H) = 8.0 Hz, 1 H; H^{Ind}), 7.24 (d, ^4J (H,H) = 1.0 Hz, 1 H; H^{Ind}), 7.07 (t, ^3J (H,H) = 7.4 Hz, 1 H; H^{Ind}), 6.95 (t, ^3J (H,H) = 7.3 Hz, 1 H; H^{Ind}), 4.08 (s, 2 H; CH_2) ppm; **^{13}C NMR** (76 MHz, DMSO-d_6, APT): δ = 148.2 (C^{Pyr}), 147.6 (C^{Pyr}), 139.7 (C_q, C^{Pyr}), 138.2 (C^{Pyr}), 136.3 (C_q; C^{Ind}), 126.6 (C_q; C^{Ind}), 123.5 (C^{Ind}), 121.1 (C^{Ind}), 120.0 (C_q; C^{Ind}), 118.5 (C^{Ind}), 118.2 (C^{Ind}), 112.3 (C_q; C^{Pyr}), 111.5 (C^{Ind}), 27.6 (CH_2) ppm; **TLC**: R_f = 0.30 (cyclohexane/EtOAc = 3/1, UV and CAM).

7.4.4.16 Synthesis of Tyrosine pyridine boronic acid ester

7.4.4.16.1 4-((*tert*-Butyldimethylsilyl)oxy)benzaldehyde (38b)



38b

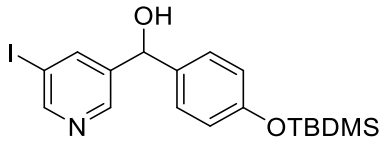
In a 100 mL round-bottom flask 2.00 g 4-hydroxybenzaldehyde (16.4 mmol, 1.0 eq) and 2.79 g imidazole (40.9 mmol, 2.5 eq) were dissolved in 80 mL DCM. 2.96 g *tert*-butylchlorodimethylsilane (19.7 mmol, 1.2 eq) were added to the pale yellow solution and immediately a white precipitate was formed. After the reaction was stirred for 6 h at RT full conversion was detected by GC-MS. The suspension was diluted with 70 mL DCM and washed with H_2O (2 x 100 mL) and brine (1 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The orange oily crude product was purified via silica gel filtration (25 g SiO_2, 7.5 x 5.0 cm, eluent: cyclohexane/EtOAc = 20/1, R_f = 0.29, UV and CAM).

Yield: 3.47 g (90 %), yellow oil, $C_{13}H_{20}O_2Si$ [236.39 g/mol]

^{1}H NMR (300 MHz , $CDCl_3$): δ = 9.88(s, 1 H; CHO), 7.78 (d, ^3J (H,H) = 8.6 Hz, 2 H; H^{Ar}), 6.94 (d, ^3J (H,H) = 8.5 Hz, 2 H; H^{Ar}), 0.99 (s, 9 H; CH_3), 0.24 (s, 6 H; CH_3) ppm; **^{13}C NMR** (75.53 MHz, $CDCl_3$, APT): δ = 191.0 (CHO), 161.6 (C_q; C^{Ar}), 132.0 (C^{Ar}), 130.6 (C_q; C^{Ar}), 120.6 (C^{Ar}), 25.7 (CH_3), 18.4 (C_q), 4.2 (CH_3) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 5.94 min; m/z (%): 236 (11) [M^+], 179 (100) [M^+-C_4H_9], 151 (43) [M^+-C_6H_{15}]; **TLC:** R_f = 0.29(Cyclohexane/EtOAc = 20/1, UV and CAM).

Analytical data are in accordance with those reported.[148]

7.4.4.16.2 (4-((*tert*-Butyldimethylsilyl)oxy)phenyl)(5-iodopyridin-3-yl)methanol (38c)



38c

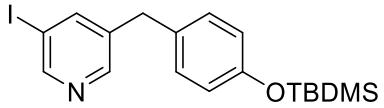
A flame dried and nitrogen-flushed Schlenk-flask was charged with 200 mg 3,5-diiodopyridine (**20**) (604 µmol, 1.0 eq), which was dissolved in 3 mL absolute THF. The yellow solution was then cooled to -78 °C in an acetone/dry ice bath. Under stirring at -78 °C 300 µL isopropylmagnesium chloride lithium chloride solution (2.1 M in THF) (635 µmol, 1.05 eq)

were added via syringe under N_2-flow. The reaction mixture was stirred at -78 °C until quantitative conversion of the metal-halide exchange was detected via GC-MS. After quantitative metal-halide exchange (4 h) 150 mg aldehyde **38b** (635 µmol, 1.05 eq) were added at -78 °C under N_2-flow. The reaction mixture was then warmed to RT and was kept stirring until full conversion (overnight, 16 h) was detected by GC-MS. The reaction mixture was quenched by the addition of 20 ml saturated NH_4Cl solution. Subsequently the aqueous phase was extracted with DCM (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and then the solvent was removed under reduced pressure to give a pale yellow oily crude product. The crude product was purified via flash column chromatography (15 g SiO_2, 2.0 x 16 cm, eluent: CH/EtOAc = 3/1, R_f = 0.30, UV and CAM).

Yield: 198 mg (74 %), pale yellow oil, $C_{18}H_{24}INO_2Si$ [441.38 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.64 (d, ^4J (H,H) = 1.7 Hz, 1H; H^{Pyr}), 8.45 (d, ^4J (H,H) = 1.3 Hz, 1H; H^{Pyr}), 8.06 (bs, 1H; H^{Pyr}), 7.17 (d, ^3J (H,H) = 8.5 Hz, 2H; H^{Ar}), 6.82 (d, ^3J (H,H) = 8.5 Hz, 2H; H^{Ar}), 5.73 (s, 1H; CH), 2.96 (bs, 1H; OH), 0.97 (s, 9H; CH_3), 0.19 (s, 6H, CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$): δ = 155.9 (C_q; C^{Ar}), 154.5 (C^{Pyr}), 146.7 (C^{Pyr}), 142.3 (C^{Pyr}), 141.7 (C_q; C^{Pyr}), 135.4 (C_q; C^{Ar}), 128.1 (C^{Ar}), 120.6 (C^{Ar}), 93.5 (C_q; C^{Pyr}), 73.3 (CH), 25.8 (CH_3), 18.3 (C_q), -4.3 (CH_3) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 9.01 min; m/z (%): 441 (27) [M^+], 384 (100) [M^+-C_4H_9], 234 (40) [M^+-$C_{12}H_{19}OSi$]; **TLC:** R_f = 0.13 (CH/EtOAc = 4/1, UV and CAM); **HRMS** (EI): calcd (*m*/*z*) for [M^+]: 441.0621; found: 441.0633.

7.4.4.16.3 3-(4-((*tert*-Butyldimethylsilyl)oxy)benzyl)-5-iodopyridine (38d)



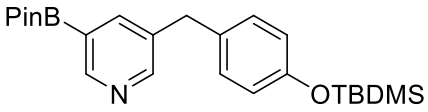
38d

A 25 mL round-bottom-flask equipped with a Schlenk adapter was flushed with nitrogen and charged with 200 mg pyridine derivative **38c** (453 µmol, 1.0 eq) dissolved in 5 mL DCM. After 615 µL triethylsilane (3.85 mmol, 8.5 eq) and 1.1 mL trifluoroacetic acid (14.5 mmol, 32 eq) were added, the yellow solution was stirred at RT overnight. The mixture was quenched by the addition of 150 mL saturated $NaHCO_3$ solution and stirred vigorously for 1 h. The phases were separated and the aqueous layer was extracted with DCM (5 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography (15 g SiO_2, 2.0 x 16 cm, eluent: cyclohexane/EtOAc = 10/1, R_f = 0.34, UV and CAM).[108]

Yield: 145 mg (75 %), yellow oil, $C_{18}H_{24}INOSi$ [425.39 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.66 (bs, 1H; H^{Pyr}), 8.40 (bs, 1H; H^{Pyr}), 7.78 (bs, 1H; H^{Pyr}), 7.01 (d, ^{3}J = 8.4 Hz, 2H; H^{Ar}), 6.78 (d, ^{3}J = 8.4 Hz, 2H; H^{Ar}), 3.85 (s, 2H; CH_2), 0.98 (s, 9H; CH_3), 0.19 (s, 6H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$): δ = 154.6 (C_q; C^{Ar}), 153.6 (C^{Pyr}), 148.7 (C^{Pyr}), 144.6 (C^{Pyr}), 139.3 (C_q; C^{Pyr}), 131.6 (C_q; C^{Ar}), 130.0 (C^{Ar}), 120.5 (C^{Ar}), 93.7 (C_q; C^{Pyr}), 38.0 (CH_2), 25.8 (CH_3), 18.3 (C_q), -4.3 (CH_3) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 8.58 min; *m/z* (%): 425 (24) [M^+], 368 (100) [M^+-C_4H_9]; **R_f** = 0.34 (Cyclohexane/EtOAc = 10/1, UV and CAM); **HRMS** (EI): calcd for [M^+]: 425.0672; found: 425.0680.

7.4.4.16.4 3-(4-((*tert*-Butyldimethylsilyl)oxy)benzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (38a)



38a

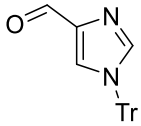
A flame dried and nitrogen flushed Schlenk flask was charged with 150 mg pyridine derivative **38d** (353 µmol, 1.0 eq) dissolved in 1 mL dry THF. After cooling the solution to -78 °C 230 µL *i*PrMgCl·LiCl solution (1.7 M in THF) (391 µmol, 1.1 eq) were added dropwise. After 1 h complete metal-halogen exchange was detected by GC-MS. After adding 100 µL PinBO*i*Pr (490 µmol, 1.4 eq) the reaction mixture was allowed to warm up in the cooling bath overnight. When full conversion was detected by GC-MS the reaction mixture was quenched by the addition of 5 mL saturated NH_4Cl solution. The phases were separated and the aqueous layer was extracted with DCM (4 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure.[108]

Yield: 149 mg (99 %, crude), pale yellow solid, $C_{24}H_{36}BNO_3Si$ [425.45 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.78 (bs, 1H; H^{Pyr}), 8.51 (d, ^{4}J = 2.0 Hz, 1H; H^{Pyr}), 7.86 (bs, 1H; H^{Pyr}), 7.01 (d, ^{3}J = 8.4 Hz, 2H; H^{Ar}), 6.76 (d, ^{3}J = 8.4 Hz, 2H; H^{Ar}), 3.89 (s, 2H; CH_2), 1.34 (s, 12H, CH_3^{BPin}), 0.97 (s, 9H; CH_3), 0.17 (s, 6H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$): δ = 154.3 (C_q; C^{Ar}), 153.3 (C^{Pyr}), 152.5 (C^{Pyr}), 142.7 (C^{Pyr}), 136.2 (C_q; C^{Pyr}), 132.7 (C_q; C^{Ar}), 129.9 (C^{Ar}), 120.3 (C^{Ar}), 84.3 (C_q; C^{Pyr}), 38.4 (CH_2), 25.8 (CH_3), 25.0 (CH_3), 18.3 (C_q), -4.3 (CH_3) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 9.59 min; *m/z* (%): 425 (28) [M^+], 368 (49) [M^+-C_4H_9], 268 (100) [M^+-$C_{10}H_{21}O$]; **m.p.**$^{exp.}$ = 98-99 °C; **HRMS** (EI): calcd for [M^+]: 425.2562; found: 425.2570.

7.4.4.17 Synthesis of Histidine pyridine boronic acid ester

7.4.4.17.1 1-Trityl-1*H*-imidazole-4-carbaldehyde (39b)



39b

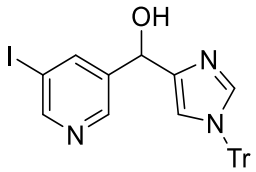
In a 50 mL round-bottom flask 200 mg 1*H*-imidazole-4-carbaldehyde (2.08 mmol, 1.0 eq) were suspended in 7 mL DCM and 346 µL Et_3N (253 mg, 2.50 mmol, 1.2 eq) were added. 698 mg triphenyl methyl chloride (2.50 mmol, 1.2 eq) were added. After 15 h full conversion was detected by TLC and the solvent was removed under reduced pressure. The pale yellow solid crude product was purified via flash column chromatography (15 g SiO_2, 2.0 x 13 cm, eluent: Cyclohexane/EtOAc = 2/1, R_f = 0.29, UV and CAM).[149]

Yield: 272 mg (39 %), colourless powder, $C_{23}H_{18}N_2O$ [338.41 g/mol]

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.72 (s, 1 H; CHO), 7.80 (s, 1 H; H^{Imid}), 7.66 (s, 1 H; H^{Imid}), 7.43 (d, ^3J (H,H)= 6.9 Hz, 9 H; H^{Ar}), 7.13 (d, ^3J (H,H)=7.8, ^{4}J (H,H)= 1.6 Hz, 6 H; H^{Ar}) ppm; **^{13}C NMR** (76 MHz, DMSO-d_6): δ 185.4 (CHO), 141.5 (C_q; C^{Ar}), 140.6 (C_q; C^{Imid}), 129.5 (C^{Imid}), 129.2 (C^{Ar}), 128.5 (C^{Ar}), 128.3 (C^{Imid}) ppm; **HPLC-MS** (Poroshell, ESI$^+$; MT_general): t_R = 4.25 min; *m/z*: 361 [M^++Na]; λ_{max} = 259 nm; **TLC:** R_f = 0.29 (Cyclohexan/EtOAc = 2/1, UV and CAM); **m.p.$^{exp.}$** = 193-196 °C (**m.p.$^{lit.}$** = 193-196 °C).[150]

Analytical data are in accordance with those reported.[151]

7.4.4.17.2 (5-Iodopyridin-3-yl)(1-trityl-1*H*-imidazol-4-yl)methanol (39c)



39c

A flame dried and nitrogen-flushed Schlenk-flask was charged with 1.0 g 3,5-diiodopyridine (**20**) (3.02 mmol, 1.0 eq), which was dissolved in 15 mL absolute THF. The yellow solution was then cooled to -78 °C in an acetone/dry ice bath. Under stirring at -78 °C 1.3 mL isopropylmagnesium chloride lithium chloride solution (2.3 M in THF) (3.02 mmol, 1.0 eq) were added via syringe under N_2-flow. The reaction mixture was stirred at -78 °C until quantitative conversion of the metal-halide exchange was detected via GC-MS (4 h). 1.02 g aldehyde **39b** (3.02 mol, 1.0 eq) were added at -78 °C under N_2-flow, the reaction mixture was

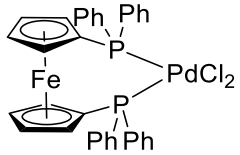
warmed to RT and was kept stirring until full conversion (overnight, 16 h) was detected by GC-MS. The reaction mixture was quenched by the addition of 100 mL saturated NH_4Cl solution. Subsequently the aqueous phase was extracted with DCM (4 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to give yellow crude product. The crude product was purified via flash column chromatography (50 g SiO_2, 4.0 x 12 cm, by-products eluted with EtOAc, product eluted with MeOH, cyclohexane/EtOAc = 1/2, R_f = 0.20, UV and CAM).

Yield: 922 mg (56 %), pale yellow powder, $C_{28}H_{22}IN_3O$ [543.41 g/mol].

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.65 (s, 1H; H^{Pyr}), 8.52 (s, 1H; H^{Pyr}), 8.05 (bs, 1H; H^{Pyr}), 7.41-7.39 (m, 9 H; H^{Ar}), 7.31 (s, 1 H; H^{Imid}), 7.09-7.07 (m, 6 H; H^{Ar}), 6.83 (s, 1H; H^{Imid}), 5.96 (bs, 1H; OH), 5.62 (s, 1 H; CH) ppm; **^{13}C NMR** (76 MHz, DMSO-d_6, APT): δ = 153.4 (C^{Pyr}), 146.9 (C^{Pyr}), 143.6 (C_q; C^{Pyr}), 142.3 (C^{Pyr}), 142.2 (C_q; C^{Imid}), 142.2 (C_q; C^{Ar}), 129.2 (C^{Ar}), 128.2 (C^{Ar}), 128.1 (C^{Ar}), 118.2 (C^{Imid}), 93.8 (C_q; C^{Pyr}), 74.6 (C_q), 67.1 (CH) ppm; **TLC:** R_f = 0.20 (cyclohexane/EtOAc = 1/2, UV and CAM); **m.p.$^{exp.}$** = 153-155 °C.

7.4.5 Synthesis of Teraryls

7.4.5.1 [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (40)



40

A 25 mL Erlenmeyer-flask was charged with 354 mg $PdCl_2$ (2.0 mmol, 1.0 eq) and 300 mg LiCl (7.1 mmol, 3.6 eq) suspended in 10 mL EtOH. The red suspension was stirred at 80 °C until a red solution was formed. Meanwhile, a 50 mL two-neck round-bottom flask was charged with 1.11 g dppf (2.0 mmol, 1.0 eq) and the ligand was dissolved in 10 mL degassed toluene. The yellow suspension was stirred at 80 °C until a clear solution was formed. The red Li_2PdCl_4 solution was added and a red solid starts precipitating. The reaction mixture was stirred 30 min at 80 °C and was then cooled to RT. The product was collected by filtration and washed with EtOH (2 x 5 mL) and Et_2O (2 x 5 mL). The orange powder was dried in oil pump vacuum.

Yield: 1.39 g (95 %), orange powder, $C_{34}H_{28}Cl_2FP_2Pd$ [731.71 g/mol].

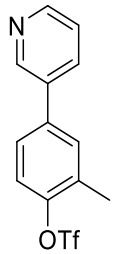
7.4.5.2 Representative procedure for the synthesis of teraryls by consecutive double Suzuki-Coupling (1st step)

A flame dried Schlenk-flask was charged with 1.0 eq of the corresponding boronic acid derivative **21a-39a**, 2.0 eq K_2CO_3 (or CsF), and 4 mol% $PdCl_2$(dppf) (**40**). After drying in vacuo, a solution of 1.0 eq trifluoromethanesulfonate **1a-18a** in absolute, degassed DMF (or 1,2-DME) (~0.2 M) was added. The reaction mixture was stirred at 80 °C until full conversion was detected by GC-MS or TLC. The typically brown suspension was filtered through a pad of SiO_2 (3 x 2 cm, eluents are denoted) and the filtrate was concentrated to dryness using a rotary evaporator. The crude product was purified via flash column chromatography or used in the next step without further purification.

7.4.5.3 Representative procedure for the synthesis of teraryls by consecutive double Suzuki-Coupling (2nd step)

Another flame dried Schlenk-flask was charged with 1.0-1.2 eq of the second boronic acid pinacol ester **21a-39a**, 2.0-3.0 eq caesium carbonate (Cs_2CO_3), and 5 mol% $PdCl_2$(dppf) (**40**). After drying in vacuo, a solution of the previously prepared intermediate (4-(pyridin-3-yl)-phenyl trifluoromethanesulfonate derivative) in absolute, degassed DMF (~0.2 M) was added. The reaction mixture was stirred at 80 °C overnight. The typically black suspension was filtered through a pad of SiO_2 (3 x 2 cm, eluent: 100 mL MeOH) and after concentrating to dryness, the crude product was purified via flash column chromatography. To obtain highly pure substrate, the product was purified via semi-preparative HPLC.

7.4.5.4 2-Methyl-4-(pyridin-3-yl)phenyl trifluoromethanesulfonate (41)



(41)

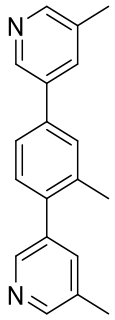
Compound **41** was prepared according to procedure 7.4.5.2 from 1.4 g pyridine boronic acid ester **21a** (6.83 mmol, 1.0 eq), 1.89 g K_2CO_3 (13.7 mmol, 2.0 eq) and 220 mg $PdCl_2$(dppf) (**40**) (273 µmol, 4 mol%) in 50 mL absolute DMF and 2.5 g core building block **1a** (6.83 µmol, 1.0 eq). After quantitative conversion was detected by GC-MS (2 h) the catalyst was removed by filtration through a pad of silica gel (eluted with 400 mL EtOAc). The organic phase was

washed with saturated NH_4Cl solution (2 x 100 mL), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography (200 g SiO_2, 4.5 x 24 cm, eluent: cyclohexane/EtOAc = 3/1, R_f = 0.20, UV and CAM).

Yield: 1.74 g (80 %), yellow oil, $C_{13}H_{10}F_3NO_3S$ [317.28 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.82 (s, 1 H; H^{Ar}), 8.63 (d, ^4J (H,H) = 3.8 Hz, 1 H; H^{Ar}), 7.84 (d, ^3J (H,H) = 7.9 Hz, 1 H; H^{Ar}), 7.50-7.33 (m, 4 H; H^{Ar}) 2.46 (s, 3 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 149.2 (C^{Ar}), 148.5 (C_q; C^{Ar}), 148.3 (C^{Ar}), 138.2 (C^{Ar}), 135.2 (C^{Ar}), 131.8 (C_q; C^{Ar}), 137.0 (C^{Ar}), 126.5 (C^{Ar}), 123.8 (C^{Ar}), 122.1 (C^{Ar}), 118.8 (q, ^1J (C,F) = 320 Hz; CF_3), 16.7 (CH_3) ppm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 6.60 min; *m/z* (%): 317 (17) [M^+], 184 (100) [M^+−CF_3O_2S]; **TLC**: R_f = 0.20 (cyclohexane/EtOAc = 3/1, UV and CAM).

7.4.5.5 5,5'-(2-Methyl-1,4-phenylene)bis(3-methylpyridine) (42)



42

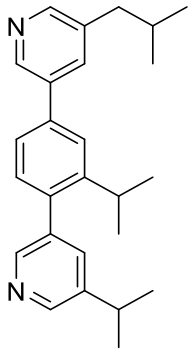
Compound **42** was prepared according to procedure 7.4.5.3 from 374 mg pyridine boronic acid ester **22a** (1.71 mmol, 2.1 eq), 720 mg Cs_2CO_3 (2.63 mmol, 3.0 eq) and 67 mg $PdCl_2$(dppf) (**40**) (82.5 µmol, 10 mol%) in 5 mL 1,2-DME and 312 mg middle building block **1a** (581 µmol, 1.0 eq). After full conversion was detected by GC-MS (48 h) the catalyst was removed by filtration through a pad of silica gel (eluted with 100 mL MeOH) and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography (30 g SiO_2, 2.0 x 21 cm, eluent: cyclohexane/EtOAc = 1/3, R_f = 0.20, UV and CAM) and teraryl **42** was isolated as beige powder.

Yield: 125 mg (56 %), beige powder, $C_{19}H_{18}N_2$ [274.37 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.69 (s, 1 H; H^{Ar}), 8.44 (s, 3 H; H^{Ar}), 7.72 (s, 1 H; H^{Ar}), 7.47 (m, 3 H; H^{Ar}), 7.31 (d, ^3J (H,H) = 7.8 Hz 1 H; H^{Ar}), 2.42 (s, 3 H; CH_3), 2.41 (s, 3 H; CH_3), 2.35 (s, 3 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 138.1 (C_q), 137.8 (C_q), 137.1 (CH),

136.5 (C_q), 135.8 (C_q), 135.1 (CH), 133.2 (C_q), 132.7 (C_q), 130.7 (CH), 129.4 (CH), 124.9 (CH), 20.7 (CH_3), 18.6 (CH_3), 18.6 (CH_3) ppm; **HPLC-MS** (Poroshell, ESI^+, MT_general): t_R = 3.54 min; *m/z*: 275 [M+H^+]; λ_{max} = 277 nm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 8.83 min; *m/z* (%): 274 (100) [M^+], 207 (17) [M^+−C_4H_5N]; **TLC**: R_f = 0.20 (cyclohexane/EtOAc = 1/3, UV and CAM); **m.p.**$^{exp.}$ = 94-95 °C; **HRMS** (DI-EI): calcd (*m/z*) for [M^+]: 274.1470; found: 274.1457.

7.4.5.6 3-Isobutyl-5-(3-isopropyl-4-(5-isopropylpyridin-3-yl)phenyl)pyridine (43)



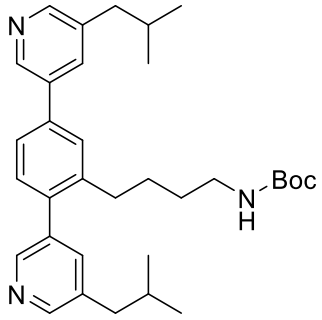
43

Compound **43** was prepared according to procedure 7.4.5.2 with 133 mg pyridine boronic acid ester **23a** (507 µmol, 1.00 eq), 154 mg CsF (1.01 mmol, 2.0 eq) and 20.7 mg $PdCl_2$(dppf) (**40**) (25.3 µmol, 5 mol%) in 5 mL 1,2-DME and 200 mg core building block **3a** (507 µmol, 1.0 eq). To achieve full conversion 10 µL H_2O were added to the reaction mixture after 24 h. When full conversion was detected by GC-MS (48 h, MT_50_S, t_R = 7.61 min) the catalyst was removed by filtration through a pad of silica gel (eluted with 50 mL MeOH) and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography (30 g SiO_2, 2.0 x 20 cm, eluent: cyclohexane/EtOAc = 2/1, R_f = 0.49, UV and CAM) and the corresponding biphenyl was isolated as a brown oil. The second step was performed according to procedure 7.4.5.3 with 56 mg pyridine boronic acid ester **24a** (225 µmol, 1.1 eq), 133 mg Cs_2CO_3 (409 µmol, 2.0 eq) and 8.3 mg $PdCl_2$(dppf) (**40**) (10.2 µmol, 5 mol%) in 2 mL 1,2-DME and biphenyl **43a**. When full conversion was detected by GC-MS (24 h) the catalyst was removed by silica gel filtration (eluted with 100 mL EtOAc) and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography (15 g SiO_2, eluent: cyclohexane/EtOAc = 4/1, R_f = 0.19, UV and CAM) and teraryl **43** was isolated as a pale brown oil. After preparative HPLC (Nucleodur, Prep_80to90) product **43** was isolated as a pale yellow, highly viscous oil.

Yield: 24.2 mg (13 %), pale yellow oil, $C_{26}H_{32}N_2$ [372.56 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.65 (bs, 1 H; H^{Ar}), 8.45 (bs, 1 H; (H^{Ar}), 8.36 (bs, 2 H; H^{Ar}), 7.63 (s, 1 H; H^{Ar}), 7.53 (d, ^4J (H,H) = 1.5 Hz, 1 H; H^{Ar}), 7.46 (bs, 1 H; H^{Ar}), 7.39 (dd, ^3J (H,H) = 7.9 Hz, ^4J (H,H) = 1.7 Hz, 1 H; H^{Ar}), 7.23-7.19 (m, 1 H, H^{Ar}), 2.98-2.93 (m, 2 H, CH), 2.51 (d, ^3J (H,H) = 7.2 Hz, 2 H; CH_2), 1.95-1.81 (m, 1 H, CH), 1.26 (d, ^3J (H,H) = 6.9 Hz, 6 H; CH_3), 1.17 (d, ^3J (H,H) = 6.8 Hz, 6 H; CH_3), 0.90 (d, ^3J (H,H) = 6.6 Hz, 6 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 148.9 (C^{Ar}), 147.7 (C_q; C^{Ar}), 147.0 (C^{Ar}), 146.9 (C^{Ar}), 145.5 (C^{Ar}), 143.5 (C_q; C^{Ar}), 138.2 (C_q; C^{Ar}), 137.2 (C_q; C^{Ar}), 137.1 (C_q; C^{Ar}), 136.9 (C_q; C^{Ar}), 136.4 (C_q; C^{Ar}), 135.5 (C^{Ar}), 135.0 (C^{Ar}), 131.0 (C^{Ar}), 124.8 (C^{Ar}), 124.7 (C^{Ar}),42.5 (CH_2), 31.8 (CH), 30.2 (CH), 29.8 (CH), 24.4 (CH_3), 23.8 (CH_3), 22.4 (CH_3) ppm; **HPLC-MS** (Poroshell, ESI^+, MT_60to100): t_R = 3.68 min; *m/z*: 373 [M+H^+]; λ_{max} = 265 nm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 10.58 min; *m/z* (%): 372 (100) [M^+], 357 (39) [M^+−CH_3], 315 (57) [M^+−C_4H_9]; **TLC**: R_f = 0.19 (cyclohexane/EtOAc = 4/1, UV and CAM); **HRMS** (DI-EI): calcd (*m/z*) for [M^+]: 322.2566; found: 322.2555.

7.4.5.7 *tert*-Butyl (4-(2,5-bis(5-isobutylpyridin-3-yl)phenyl)butyl)carbamate (44)



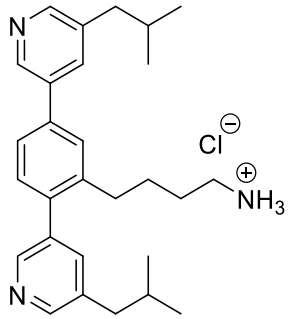
44

Compound **44** was prepared according to procedure 7.4.5.3 from 270 mg pyridine boronic acid ester **23a** (1.03 mmol, 2.0 eq), 672 mg Cs_2CO_3 (2.06 mmol, 4.0 eq) and 42.1 mg $PdCl_2$(dppf) (**40**) (51.6 µmol, 10 mol%) in 5 mL 1,2-DME and 270 mg core building block **15a** (516 µmol, 1.0 eq). When full conversion was detected with HPLC-MS (48 h) the catalyst was removed by filtration through a pad of silica gel (eluted with 100 mL EtOAc) and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography (15 g SiO_2, 1.5 x 20 cm, eluent: cyclohexane/EtOAc = 2/1, R_f = 0.30, UV and CAM) and teraryl **44** was isolated as a brown oil. After preparative HPLC (Nucleodur, Prep_80to90) product **44** was isolated as a pale yellow, highly viscous oil.

Yield: 142 mg (53 %), pale yellow oil, $C_{33}H_{45}N_3O_2$ [515.74 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.64 (bs, 1 H; H^{Ar}), 8.36 (bs, 3 H; (H^{Ar}), 7.63 (bs, 1 H; H^{Ar}), 7.41 (d, ^{3}J (H,H) = 11.2 Hz, 3 H; H^{Ar}), 7.24-7.20 (m, 1 H; H^{Ar}), 4.43 (bs, 1 H; NH), 2.96-2.94 (m, 2 H; CH_2), 2.61-2.55 (m, 2 H; CH_2), 2.52-2.48 (m, 4 H; CH_2), 1.95-1.79 (m, 2 H; CH_2), 1.50-1.40 (m, 2 H; CH_2), 1.34 (s, 9 H; CH_3), 0.91-0.88 (m, 12 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 145.1 (C_q; $C^{Carbonyl}$), 149.1 (C^{Ar}), 148.9 (C^{Ar}), 147.0 (C^{Ar}), 144.5 (C^{Ar}), 141.0 (C_q; C^{Ar}), 137.9 (C_q; C^{Ar}), 137.9 (C_q; C^{Ar}), 137.5 (C^{Ar}), 137.1 (C_q; C^{Ar}), 136.5 (C_q; C^{Ar}), 136.0 (C_q; C^{Ar}), 135.3 (C^{Ar}), 131.1 (C^{Ar}), 128.4 (C^{Ar}), 125.0 (C^{Ar}), 89.2 (C_q), 42.5 (CH_2), 42.3 (CH_2), 40.3 (CH_2), 33.0 (CH_2), 30.2 (CH), 30.1 (CH_2), 28.7 (CH_2), 28.5 (CH_3), 22.4 (CH_3), 22.3 (CH_3) ppm; **HPLC-MS** (Poroshell, ESI^+, MT_60to100): t_R = 4.06 min; *m/z*: 526 [M+H^+], 539 [M+Na^+]; λ_{max} = 269 nm; **TLC**: R_f = 0.30 (cyclohexane/EtOAc = 2/1, UV and CAM); **HRMS** (DI-EI): calcd (*m/z*) for [M^+]: 515.3512; found: 515.3525.

7.4.5.8 4-(2,5-Bis(5-isobutylpyridin-3-yl)phenyl)butan-1-amine hydrochloride (45)



45

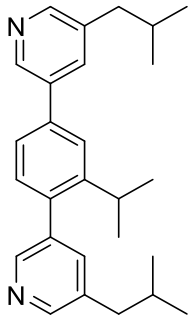
100 mg compound **44** (194 µmol; 1.0 eq) were dissolved in 4 mL DCM in a 10 mL round-bottom flask. The colourless solution was cooled to 0 °C and 390 µL HCl (5 M in iPrOH) (1.94 mmol, 10 eq) were added. The colorless solution was stirred at RT until full conversion of the starting material was detected by HPLC-MS (7 h). The solvent was removed in a N_2-flow and the product was dried in vacuum.

Yield: 81.0 mg (quant.), colorless powder, $C_{28}H_{38}ClN_3$ [452.08 g/mol].

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.28 (s, 1 H; H^{Ar}), 8.92-8.80 (m, 4 H; (H^{Ar}), 8.45 (s, 1 H; H^{Ar}), 8.20 (bs, 3 H; NH_3), 8.09 (s, 1 H; H^{Ar}), 7.93 (d, ^{3}J (H,H) = 7.8 Hz, 1H; H^{Ar}), 7.54 (d, ^{3}J (H,H) = 7.9 Hz, 1H; H^{Ar}), 3.80-3.72 (m, 1 H; CH), 2.77-2.67 (m, 8 H; CH_2), 2.07-1.96 (m, 2 H; CH_2), 1.61-1.50 (m, 4 H; CH_2), 0.92 (d, ^{3}J (H,H) = 6.1 Hz, 12 H; CH_3) ppm; **^{13}C NMR** (76 MHz, DMSO-d_6, APT): δ = 145.3 (C^{Ar}), 143.1 (C^{Ar}), 141.1 (C_q; C^{Ar}), 140.9 (C_q; C^{Ar}), 140.5 (C^{Ar}), 140.4 (C_q; C^{Ar}), 139.6 (C^{Ar}), 138.3 (C_q; C^{Ar}), 137.8 (C^{Ar}), 137.7 (C^{Ar}), 137.5

(C_q; C^{Ar}), 136.1 (C_q; C^{Ar}), 134.6 (C_q; C^{Ar}), 131.3 (C^{Ar}), 128.7 (C^{Ar}), 125.2 (C^{Ar}), 40.5 (CH_2), 38.3 (CH_2), 31.6 (CH_2), 27.1 (CH_2), 26.6 (CH_2), 25.5 (CH), 21.8 (CH_3), 21.7 (CH_3) ppm; **HPLC-MS** (Poroshell, ESI^+, MT_general): t_R = 4.55 min; *m/z*: 416 [M+H^+]; λ_{max} = 269 nm; **HRMS** (DI-EI): calcd (*m*/*z*) for [M^+-HCl]: 415.2987; found: 415.2995.

7.4.5.9 5,5'-(2-Isopropyl-1,4-phenylene)bis(3-isobutylpyridine) (46)



46

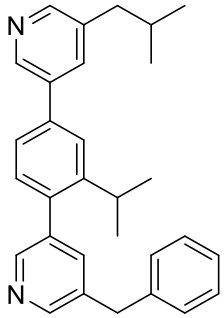
Compound **46** was prepared according to procedure 7.4.5.3 from 265 mg pyridine boronic acid ester **23a** (1.01 mmol, 2.0 eq), 661 mg Cs_2CO_3 (2.03 mmol, 4.0 eq) and 41.4 mg $PdCl_2$(dppf) (**40**) (50.7 µmol, 10 mol%) in 5 mL 1,2-DME and 200 mg core building block **3a** (507 µmol, 1.0 eq). After 48 h (~90 % conversion) the catalyst was removed by filtration through a pad of silica gel (eluted with 100 mL EtOAc) and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography (20 g SiO_2, 2.0 x 20 cm, eluent: cyclohexane/EtOAc = 5/1, R_f = 0.15, UV and CAM) and teraryl **46** was isolated as a brown oil. After preparative HPLC (Nucleodur, Prep_80to90) product **46** was isolated as a colourless, highly viscous oil.

Yield: 74.6 mg (38 %), colourless oil, $C_{27}H_{34}N_2$ [386.58 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.65 (bs, 1 H; H^{Ar}), 8.37 (bs, 3 H; (H^{Ar}), 7.64 (s, 1 H; H^{Ar}), 7.52 (d, ^4J (H,H) = 1.3 Hz, 1 H; H^{Ar}), 7.39-7.37 (m, 2 H; H^{Ar}), 7.20 (d, ^3J (H,H) = 7.7 Hz, 1 H, H^{Ar}), 3.04-2.90 (m, 1 H, CH), 2.53-2.48 (m, 4 H; CH_2), 1.95-1.79 (m, 2 H, CH), 1.16 (d, ^3J (H,H) = 6.8 Hz, 6 H; CH_3), 0.91-0.88 (m, 12 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 148.7 (C^{Ar}), 148.6 (C^{Ar}), 147.6 (C_q; C^{Ar}), 146.8 (C^{Ar}), 145.3 (C^{Ar}), 138.0 (C_q; C^{Ar}), 137.6 (C^{Ar}), 137.1 (C_q; C^{Ar}), 136.6 (C_q; C^{Ar}), 136.4 (C_q; C^{Ar}), 136.4 (C_q; C^{Ar}), 135.4 (C^{Ar}), 130.8 (C^{Ar}), 124.7 (C^{Ar}), 124.5 (C^{Ar}), 42.4 (CH_2), 42.3 (CH_2), 30.1 (CH), 30.1 (CH), 29.7 (CH), 24.2 (CH_3), 22.3 (CH_3), 22.2 (CH_3) ppm; **HPLC-MS** (Poroshell, ESI^+, MT_60to100): t_R = 4.29 min; *m/z*: 387 [M+H^+]; λ_{max} = 264 nm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 11.25 min; *m/z* (%): 386

(100) [M^+], 371 (61) [M^+-CH_3]; **TLC**: R_f = 0.15 (cyclohexane/EtOAc = 5/1, UV and CAM); **HRMS** (DI-EI): calcd (*m*/*z*) for [M^+]: 386.2722; found: 386.2714.

7.4.5.10 3-Benzyl-5-(4-(5-isobutylpyridin-3-yl)-2-isopropylphenyl)pyridine (47)



47

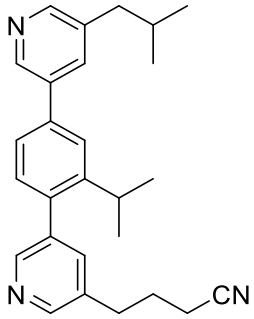
Compound **47** was prepared according to procedure 7.4.5.2 from 72 mg pyridine boronic acid ester **23a** (280 µmol, 1.0 eq), 83 mg CsF (550 µmol, 2.0 eq) and 11 mg $PdCl_2$(dppf) (**40**) (13 µmol, 5 mol%) in 4 mL absolute, degassed 1,2-DME and 108 mg core building block **3a** (270 µmol, 1.0 eq). When full conversion was detected by GC-MS (7 h, MT_50_S, t_R = 7.61 min) the catalyst was removed by filtration through a pad of silica gel (eluted with 100 mL EtOAc) and the solvent was removed under reduced pressure. The crude product was used in the next step without further purification. The second step was performed according to procedure 7.4.5.3 with 85 mg pyridine boronic acid ester **26a** (290 µmol, 1.05 eq), 191 mg Cs_2CO_3 (590 µmol, 2.0 eq) and 11 mg $PdCl_2$(dppf) (**40**) (13 µmol, 5 mol%) in 5 mL absolute, degassed 1,2-DME and biphenyl **47a**. When full conversion was detected by GC-MS (24 h) the catalyst was removed by filtration through a pad of silica gel (eluted with 100 mL MeOH) and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography (15 g SiO_2, 1.5 x 20 cm, eluent: cyclohexane/EtOAc = 4/1, R_f = 0.21, UV and CAM) and teraryl **47** was isolated as a grey, highly viscous oil. After preparative HPLC (Nucleodur) product **47** was isolated as a colourless, highly viscous oil.

Yield: 54 mg (47%), colourless, highly viscous oil, $C_{30}H_{32}N_2$ [420.59 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.74-8.31 (bm, 4 H; H^{Py}), 7.70 (s, 1 H; H^{Py}), 7.59 (s, 1 H; H^{Ar}), 7.45 (bs, 2 H; H^{Ar}, H^{Py}), 7.37-7.24 (m, 6 H; H^{Ar}, H^{Phe}, overlapping), 4.09 (s, 2 H; CH_2^{Phe}), 3.04-2.95 (m, 1 H; CH^{Val}), 2.60 (d, ^3J (H,H) = 7.0 Hz, 2 H; CH_2^{Leu}), 1.99-1.92 (m, 1 H; CH^{Leu}), 1.21 (d, ^3J (H,H) = 6.7 Hz, 6 H; CH_3^{Val}), 0.99 (d, ^3J (H,H) = 6.5 Hz, 6 H; CH_3^{Leu}) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 149.1 (C^{Py}), 148.6 (C^{Py}), 147.6 (C_q; C^{Ar}), 147.6 (C^{Py}), 145.6 (C^{Py}), 139.6 (C_q; C^{Phe}), 138.2 (C_q; C^{Ar}, 2x C_q; C^{Py}), 137.2 (C^{Py}), 137.0 (C_q; C^{Ar}, 2x C_q; C^{Py}), 135.3

(C^{Py}), 130.9 (C^{Ar}), 129.0 (C^{Phe}), 128.9 (C^{Phe}), 126.7 (C^{Phe}), 124.8 (C^{Ar}), 124.6 (C^{Ar}), 42.4 (CH_2^{Leu}), 39.1 (CH_2^{Phe}), 30.2 (CH^{Leu}), 29.7 (CH^{Val}), 24.3 (CH_3^{Val}), 22.4 (CH_3^{Leu}) ppm; **GC-MS** (EI, 70 eV; MT_100_L): t_R = 15.76 min; *m/z* (%): 420 (100) [M^+], 405 (42) [M^+-CH_3], 390 (3) [$M^+-C_2H_6$], 377 (11) [$M^+-C_3H_7$], 362 (5) [$M^+-C_4H_{10}$], 347 (6) [$M^+-C_5H_{13}$]; **HPLC** (Nucleodur, ESI^+): t_R = 13.62 min; *m/z*: 421 [M^++H], 443 [M^++Na]; λ_{max} = 252, 281, 309 nm;[13] **HRMS** (DI-EI): calcd (*m/z*) for [M^+]: 420.2566; found: 420.2557.

7.4.5.11 4-(5-(4-(5-Isobutylpyridin-3-yl)-2-isopropylphenyl)pyridin-3-yl)butanenitrile (48)



48

Compound **48** was prepared according to procedure 7.4.5.2 from 139 mg pyridine boronic acid ester **23a** (533 µmol, 1.05 eq), 154 mg CsF (1.01 mmol, 2.0 eq) and 20.7 mg $PdCl_2$(dppf) (**40**) (25.3 µmol, 5 mol%) in 3 mL 1,2-DME and 200 mg core building block **3a** (507 µmol, 1.0 eq). After 6 d (~86 % conversion according to GC-MS, MT_50_S, t_R = 7.61 min) the catalyst was removed by filtration through a pad of silica gel (eluted with 100 mL EtOAc) and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography (10 g SiO_2, 1.0 x 15 cm, eluent: cyclohexane/EtOAc = 4/1, R_f = 0.18, UV and CAM) and the corresponding biphenyl was isolated as a brown oil. The second step was performed according to procedure 7.4.5.3 from 81.4 mg pyridine boronic acid ester **36a** (299 µmol, 1.20 eq), 243 mg Cs_2CO_3 (747 µmol, 3.0 eq) and 15.3 mg $PdCl_2$(dppf) (**40**) (18.6 µmol, 7.5 mol%) in 3 mL 1,2-DME and biphenyl **48a**. When full conversion was detected by GC-MS (24 h) the catalyst was removed by filtration through a pad of silica gel (eluted with 100 mL MeOH) and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography (10 g SiO_2, 1.0 x 16 cm, eluent:

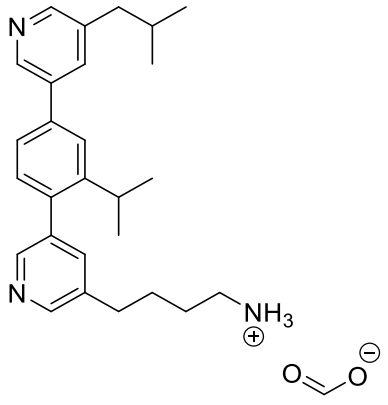
[13] MeOH/water gradient with 1.0% (v/v) HCOOH at a flow rate of 1.0 mL/min: 0.0-1.0 min: 30% MeOH const., 1.0-4.0 min: 40% MeOH lin. gradient, 4.0-10.0 min.: 40% MeOH const., 10.0-10.5 min: 90% MeOH lin. gradient, 10.5-15.0 min: 90% MeOH const., 15.0-15.5 min: 30% MeOH lin. gradient, 15.5-25.0 min: 30% MeOH const.

cyclohexane/EtOAc = 1/2, R_f = 0.20, UV and CAM) and teraryl **48** was isolated as a pale brown oil.[58]

Yield: 95.7 mg (47 %), pale brown oil, $C_{27}H_{31}N_3$ [397.56 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.73-8.27 (m, 4 H; H^{Py}), 7.68 (s, 1 H; H^{Py}), 7.59 (s, 1 H; H^{Ar}), 7.49-7.44 (m, 2 H; H^{Ar}, H^{Py}), 7.25 (d, ^3J (H,H) = 7.0 Hz, 1 H; H^{Ar}, overlapping), 3.05-2.97 (m, 1 H; CH^{Val}), 2.87 (t, ^3J (H,H) = 7.2 Hz, 2 H; CH_2^{Lys}), 2.57 (d, ^3J (H,H) = 6.8 Hz, 2 H; CH_2^{Leu}), 2.42 (t, ^3J (H,H) = 6.6 Hz, 2 H; CH_2^{Lys}), 2.07-2.02 (m, 2 H; CH_2^{Lys}), 1.96-1.91 (m, 1 H; CH^{Leu}), 1.23 (d, ^3J (H,H) = 6.5 Hz, 6 H; CH_3^{Val}), 0.95 (d, ^3J (H,H) = 6.3 Hz, 6 H; CH_3^{Leu}) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 149.3 (C^{Py}), 148.4 (C^{Py}), 148.3 (C^{Py}), 147.5 (C_q; C^{Ar}), 145.8 (C^{Py}), 138.4 (C_q; C^{Ar}, 2x C_q; C^{Py}), 136.7 (C_q; C^{Ar}, 2x C_q; C^{Py}), 136.6 (C^{Py}), 135.1 (C^{Py}), 130.9 (C^{Ar}), 124.8 (C^{Ar}), 124.7 (C^{Ar}), 119.1 (C_q; CN), 42.4 (CH_2^{Leu}), 31.7 (CH_2^{Lys}), 30.2 (CH^{Leu}), 29.8 (CH^{Val}), 26.7 (CH_2^{Lys}), 24.3 (CH_3^{Val}), 22.3 (CH_3^{Leu}), 16.7 (CH_2^{Lys}) ppm; **TLC**: R_f = 0.20 (cyclohexane/EtOAc = 1/2, UV and CAM); **HRMS** (DI-EI): calcd (*m*/*z*) for [M^+]: 397.2518; found: 397.2516.

7.4.5.12 4-(5-(4-(5-Isobutylpyridin-3-yl)-2-isopropylphenyl)pyridin-3-yl)butan-1-ammonium formiate (49)



49

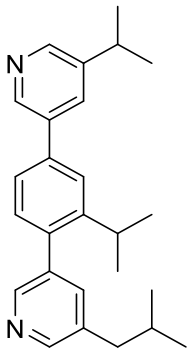
Hydrogenation was performed utilizing an H-Cube™ at a pressure of 80 bar at 70 °C with a Raney-Nickel cartridge (THS 01112). A solution of 55 mg **48** (0.14 mmol, 1.0 eq) in 8 mL MeOH/ammonia solution (35% ammonia in H_2O) (MeOH/ammonia = 125/5) was used in continuous flow mode of 0.5 mL/min (~0.02 M). After removing the solvent under reduced pressure, compound **49** was purified via preparative HPLC (Nucleodur[14]). [58]

[14] MeOH/water gradient with 2.0% (v/v) HCOOH at a flow rate of 13.5 mL/min: 0.0 min: 30% MeOH const., 0.0-8.0 min: 45% MeOH lin. gradient, 8.0-13.0 min: 55% MeOH lin. gradient, 13.0-13.5 min: 100% MeOH lin. gradient, 13.5-19.0 min: 100% MeOH const., 19.0-19.5 min: 30% MeOH lin. gradient, 19.5-25.0 min: 30% MeOH const.

Yield: 54 mg (86%), colourless, highly viscous oil, $C_{28}H_{37}N_3O_2$ [447.61 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.70-8.41 (bm, 5 H; H^{Py}, $HCOO^-$), 8.18 (bs, 3 H; NH_3^+), 7.67 (s, 1 H; H^{Py}), 7.58 (s, 1 H; H^{Ar}), 7.44 (m, 2 H; H^{Py}, H^{Ar}), 7.24 (d, ^3J (H,H) = 7.0 Hz, 1 H; H^{Ar}, overlapping), 2.98 (bs, 3 H; CH^{Val}, CH_2^{Lys}), 2.72 (bs, 2 H; CH_2^{Lys}), 2.56 (d, ^3J (H,H) = 6.9 Hz, 2 H; CH_2^{Leu}), 1.93 (m, 1 H; CH^{Leu}), 1.79 (bs, 4 H; CH_2^{Lys}), 1.21 (d, ^3J (H,H) = 6.4 Hz, 6 H; CH_3^{Val}), 0.96 (d, ^3J (H,H) = 6.5 Hz, 6 H; CH_3^{Leu}) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 149.3 (2x C^{Py}), 147.6 (C_q; C^{Ar}), 145.8 (2x C^{Py}), 138.4 (C_q; C^{Ar}, 2x C_q; C^{Py}), 136.9 (C_q; C^{Ar}, 2x C_q; C^{Py}), 136.8 (C^{Py}), 135.2 (C^{Py}), 131.0 (C^{Ar}), 124.8 (C^{Ar}), 124.7 (C^{Ar}), 42.5 (CH_2^{Leu}), 39.4 (CH_2^{Lys}), 32.5 (CH_2^{Lys}), 30.2 (CH^{Leu}), 29.8 (CH^{Val}), 28.0 (CH_2^{Lys}), 27.7 (CH_2^{Lys}), 24.4 (CH_3^{Val}), 22.4 (CH_3^{Leu}) ppm;[15] **HPLC** (Nucleodur, ESI^+, MT_general): t_R = 4.37 min; *m/z*: 402 [M^++H]; λ_{max} = 252, 281, 313 nm; **HRMS** (MALDI): calcd (*m/z*) for [M^++H]: 402.2909; found: 402.2908.

7.4.5.13 3-Isobutyl-5-(2-isopropyl-4-(5-isopropylpyridin-3-yl)phenyl)pyridine (50)



50

Compound **50** was prepared according to procedure 7.4.5.2 from 125 mg pyridine boronic acid ester **24a** (507 µmol, 1.00 eq), 154 mg CsF (1.01 mmol, 2.0 eq) and 20.7 mg $PdCl_2$(dppf) (**40**) (25.3 µmol, 5 mol%) in 5 mL 1,2-DME and 200 mg middle building block **3a** (507 µmol, 1.0 eq). To achieve full conversion 10 µL H_2O were added to the reaction mixture after 24 h. When full conversion was detected by GC-MS (48 h, MT_50_S, t_R = 7.41 min) the catalyst was removed by filtration through a pad of silica gel (eluted with 50 mL MeOH) and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography (30 g SiO_2, 2.0 x 20 cm, eluent: cyclohexane/EtOAc = 2/1, R_f = 0.59, UV and CAM) and the corresponding biphenyl was isolated as a brown oil. The second step was performed according to procedure 7.4.5.3 with 71 mg pyridine boronic acid ester **23a**

[15] No signal for the carbon atom of the formiate function ($HCOO^-$) was observed.

(273 µmol, 1.1 eq), 162 mg Cs_2CO_3 (499 µmol, 2.0 eq) and 10.1 mg $PdCl_2$(dppf) (**40**) (12.4 µmol, 5 mol%) in 2.5 mL 1,2-DME and biphenyl **50a**. When full conversion was detected by GC-MS (48 h) the catalyst was removed by filtration through a pad of silica gel (eluted with 100 mL EtOAc) and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography (15 g SiO_2, 1.5 x 20 cm, eluent: cyclohexane/EtOAc = 10/1, R_f = 0.16, UV and CAM) and teraryl **50** was isolated as a pale brown oil. After preparative HPLC (Nucleodur, Prep_80to90) product **50** was isolated as a pale yellow, highly viscous oil.

Yield: 88.4 mg (47 %), pale yellow oil, $C_{26}H_{32}N_2$ [372.56 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.63 (bs, 1 H; H^{Ar}), 8.43 (bs, 1 H; (H^{Ar}), 8.36 (bs, 2 H; H^{Ar}), 7.67 (s, 1 H; H^{Ar}), 7.51 (d, ^4J (H,H) = 1.2 Hz, 1 H; H^{Ar}), 7.38 (s, 1 H; H^{Ar}, overlapping), 7.37 (s, 1 H; H^{Ar}, overlapping), 7.20 (d, ^3J (H,H) = 7.8 Hz, 1 H; H^{Ar}), 2.99-2.93 (m, 2 H, CH), 2.48 (d, ^3J (H,H) = 7.1 Hz, 2 H; CH_2), 1.91-1.78 (m, 1 H, CH), 1.27 (d, ^3J (H,H) = 6.9 Hz, 6 H; CH_3), 1.15 (d, ^3J (H,H) = 6.8 Hz, 6 H; CH_3), 0.88 (d, ^3J (H,H) = 6.6 Hz, 6 H; CH_3) ppm; **^{13}C NMR** (76 MHz, $CDCl_3$, APT): δ = 148.8 (C^{Ar}), 147.6 (C_q; C^{Ar}), 147.2 (C^{Ar}), 147.0 (C^{Ar}), 145.7 (C^{Ar}), 143.9 (C_q; C^{Ar}), 138.3 (C_q; C^{Ar}), 137.5 (C^{Ar}) 137.2 (C_q; C^{Ar}), 136.6 (C_q; C^{Ar}), 136.5 (C_q; C^{Ar}), 136.3 (C_q; C^{Ar}), 132.7 (C^{Ar}), 130.9 (C^{Ar}), 134.8 (C^{Ar}), 124.6 (C^{Ar}), 42.3 (CH_2), 31.9 (CH), 30.1 (CH), 29.7 (CH), 24.3 (CH_3), 23.8 (CH_3), 22.3 (CH_3) ppm; **HPLC-MS** (Poroshell, ESI^+, MT_60to100): t_R = 3.74 min; *m/z*: 373 [M+H^+]; λ_{max} = 266 nm; **GC-MS** (EI, 70 eV; MT_50_S): t_R = 10.63 min; *m/z* (%): 372 (100) [M^+], 357 (70) [M^+−CH_3]; **TLC**: R_f = 0.16 (cyclohexane/EtOAc = 10/1, UV and CAM); **HRMS** (DI-EI): calcd (*m/z*) for [M^+]: 322.2566; found: 322.2560.

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9 Abbreviations

9.1 Amino Acid Abbreviation

Ala	Alanine
Arg	Arginine
Asn	Asparagine
Asp	Aspartic acid
Cys	Cysteine
Gln	Glutamine
Glu	Glutamic acid
Gly	Glycine
His	Histidine
Ile	Isoleucine
Leu	Leusine
Lys	Lysine
Phe	Phenylalanine
Met	Methionine
Pro	Proline
Ser	Serine
Thr	Threonine
Trp	Tryptophan
Tyr	Tyrosine
Val	Valine

9.2 Analytical Methods

APT	attached proton test
COSY	correlation spectroscopy
EI	electron impact ionisation
ESI	electronspray ionisation
GC	gaschromatography
GC-MS	gaschromatography-mass spectrometry
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence

NMR	nuclear magnetic resonance
TLC	thin layer chromatography

bs	broad singlet
d	doublet
dd	doublet of doublet
m	multiplet
q	quadrouplet
sept	septet
s	singlet
t	triplet

δ	chemical shift in ppm (parts per million)
Hz	Hertz
J	coupling constant
λ	wave length
MHz	Megahertz
min	minute
M^+	molecular peak
m/z	mass to charge ratio
nm	nanometer
R_f	retardation factor
RT	room temperature
t_R	retention time
UV	ultraviolett
v/v	volume to volume ratio
w/w	mass to mass ratio

9.3 Chemical Formulars

Ac	acetyl
acac	acetylacetone
AcCl	acetyl chloride
AcOH	acetic acid
9-BBN	9-borabicyclo(3.3.1)nonane

B_2Pin_2	bis(pinacolato)diboron
Boc	*tertiär*-Butyloxycarbonyl
Boc_2O	Di-*tert*-butyldicarbonate
CAM	cerammoniummolybdate
COD	1,5-cyclooctadiene
dba	dibenzylideneacetone
DBU	1,8-diazabicycloundec-7-ene
1,2-DCE	1,2-dichloroethane
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMAP	(4-dimethylamino)pyridine
1,2-DME	1,2-dimethoxyethane
DMEDA	*N,N′*-dimethylethylenediamine
DMF	*N*,*N*-dimethylformamide
DMAc	*N*,*N*-dimethylacetamide
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
dtbpy	4,4′-di-*tert*-butyl-2,2′-dipyridyl
Et	Ethyl
Et_2O	diethylether
EtOAc	ethylacetate
EtOH	ethanol
TFA	trifluoroacetic acid
Tf_2O	trifluoromethanesulfonic anhydride
KO*t*Bu	potassium *tert*-butoxide
KSAc	potassium thioacetate
Me	methyl
MeCN	acetonitrile
$MeNO_2$	nitromethane
MeOH	methanol
MIDA	*N*-methyliminodiacetic acid

*n*BuLi	*n*-butyllithium
NBS	*N*-bromsuccinimide
OAc	Acetate
PADA	potassium azodicarboxylate
RaNi	Raney-nickel
RNA	ribonucleic acid
*t*BuLi	tertiär-butyllithium
Tf	triflate
THF	Tetrahydrofuran
TBDMS	tert-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TIPS	triisopropylsilyl
TMS	tetramethylsilyl

9.4 Miscellaneous

Å	Ångström
APC	adenomatous polyposis coli
Bad	Bcl-2-associated death promoter
Bak	Bcl2-antagonist/killer 1
Bcl-x_L	B-cell lymphoma-extra large
b_p	boiling point
calc.	calculated
CaM	calmoduline
CHR	chromate ion transporter
CK1α	casein kinase 1α
c	concentration
d	day
°C	degree Celsius
dest.	distilled
eq	equivalents
et al.	et alii
eV	electronvolt
exp.	experimental
g	gram
GSK3β	glycogen synthase kinase 3β

GTP	guanosine-5'-triphosphate
h	hours
HDM2	human double minute 2
HIV	human immunodeficiency virus
IC_{50}	half minimal inhibitory concentration
K_i	inhibition constant
kJ	kilojoule
M	molar ($mol.L^{-1}$)
µL	microliter
µm	micrometer
mbar	millibar
mg	milligram
mL	milliliter
mmol	millimol
µmol	micromol
m_p	melting point
NHR	nuclear receptor
nm	nanometer
%	percent
PDB	protein data bank
pH	pH-value
PPI	protein-protein-interaction
ppm	parts per million
RDB	Rho-binding domain
ROCK	Rho-associated kinase
RT	room temperature
smMLCK	smooth muscle myosin light chain kinase
TCF	T-cell factor
tert	*tertiary*
Y2H	yeast two hybrid