A Flexible and Modular Approach for the Synthesis of Teraryls: α-Helical Peptidomimetics as Potential Inhibitors in Protein-Protein-Interactions

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“Liebt einander oder geht zugrunde”

Dienstags bei Morrie: Die Lehre eines Lebens

Mitch Albom

Meiner Familie

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2 Abstract

Protein-protein-interactions (PPIs) are recognized as one of the main factor in controlling protein function in living cells. The number of different PPIs in human cells is estimated to be ~65,000.[1] Typically, PPI domains comprise ~35-150 amino acids[2] and dozens of binding domains are known. Beside PTB- (Phospho-Tyr binding),[3] PDZ- (one of the most frequently encountered domains),[4] SH3- (proline rich binding)[5] or WW-domains (proline rich binding),[6] the motif of an α-helical interaction of one protein with the surface of the second one is the most common one.[7] For the study and pharmaceutical intervention of PPIs tool compounds are needed, which allow the control of the particular interaction of a specific target protein. HAMILTON and coworkers have presented a quite general approach of mimicking α-helices by suitable positioning of amino acid side chains around a terphenylic scaffold (compound **1**, Figure 2.1).[8] They could demonstrate that for several examples selective terphenylic inhibitors with an affinity in the nanomolar range can be developed using this design approach.[9] Due to the challenging aspect of poor solubility of terphenyls under physiological conditions, more polar heteroaryl-based helical emulators have been developed, such as pyrimidine-,[10] pyridazine-[11] or pyrrolopyrimidine-based scaffolds.[12] In addition also pyridine-based teraryls are known, but its synthesis turns out to be of little flexibility[13] and the linear synthesis makes this work very time consuming.[14]

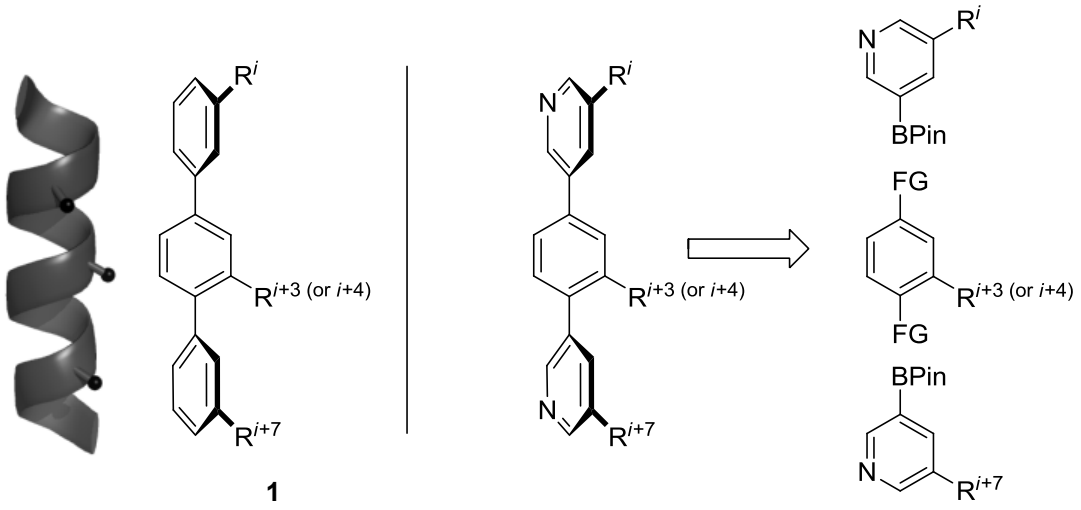


Figure 2.1: Schematic depiction of a terphenyl mimicking an α-helix (left). Retrosynthesis of hetaryl-based teraryls, suitable for mimicking the *i*, *i*+3 (or *i*+4) and *i*+7 positions of an α-helix (right).

In this thesis, not only an efficient synthetic access to amino acid surrogate hetaryl boronic acid building blocks is described, also a new convergent assembly strategy is presented as an universal and flexible approach for the synthesis of hetero-teraryl-based α-helical mimetics (Figure 2.1).

3 Kurzfassung

Einer der wichtigsten Faktoren in der Kontrolle von Proteinfunktionen in lebenden Zellen ist die Protein-Protein-Wechselwirkung. Die Anzahl der unterschiedlichen Wechselwirkungen in menschlichen Zellen werden dabei auf ca. 65.000 geschätzt.[1] Typische Wechselwirkungsareale weisen sich durch eine ~35-150 Aminosäure lange Domäne aus[2] und verschiedenste Bindungsphänotypen sind bekannt.[3-7] Eines der am häufigsten auftretenden Motive ist die Wechselwirkung einer α-helikalen Untereinheit des einen Proteins mit der Oberfläche des anderen Proteins.

Für die Untersuchung der pharmakologischen Beeinflussung von Protein-Wechselwirkungen müssen neue molekulare Strukturtypen entwickelt werden, die es erlauben die Funktionsweise von Proteinen und deren Wechselwirkungen näher zu untersuchen. Lineare Terphenyle **1**, welche mit Aminosäure-Seitenresten substituiert sind, stellen solch einen Strukturtyp dar, welche erstmals von HAMILTON beschrieben wurden (Abbildung 3.1).[8]

Es konnte gezeigt werden, dass Terphenyle in der Lage sind α-helikale Untereinheiten nachzubilden und dabei mit einer Affinität im nanomolaren Bereich als Inhibitoren von Protein-Wechselwirkungen zu agieren.[9] Ein Hindernis bei den phenyl-basierten Substraten ist die schlechte Löslichkeit unter physiologischen Bedingungen, daher wurden auch heteroaryl-basierte Systeme entwickelt und untersucht.[10-14]

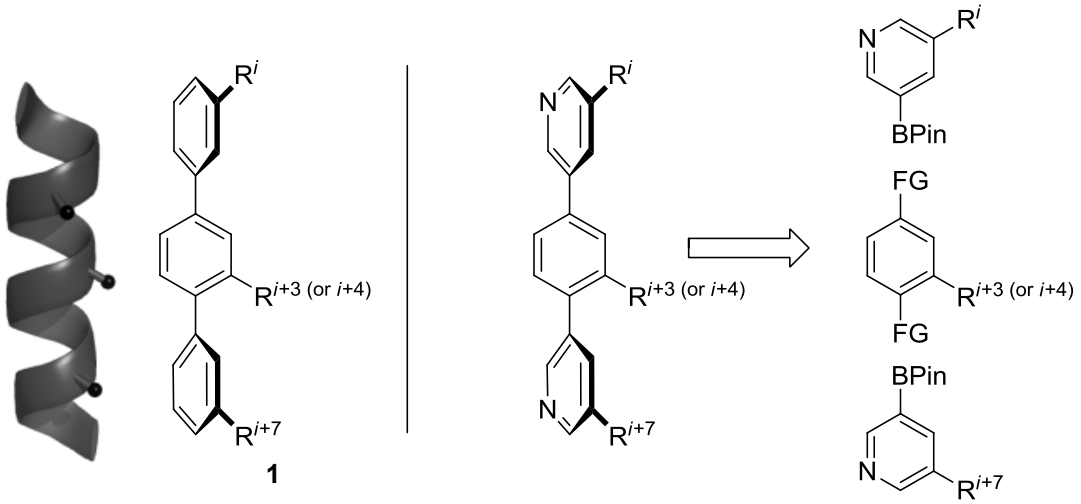


Abbildung 3.1: Darstellung von terarylischen Peptidomimetika.

In dieser Arbeit wird nicht nur ein effizienter Zugang zu heteroaryl-basierten Boronsäurestern, welche mit verschiedenen Aminosäure-Seitenketten substituiert sind, beschrieben, sondern es wird auch eine konvergente Strategie vorgestellt, welche einen universellen und flexiblen Ansatz für die Synthese von heteroaryl-basierten helikalen Peptidomimetika darstellt (Abbildung 3.1).

4 Introduction

The beginning of drug discovery derives from the empirical observations of effects of natural extracts or isolated natural products. For more than 5000 years the extracts of natural plants or drugs have been the most important source of remedy products. Early examples are for instance cocaine or digitalis.[15]

The work of PARACELSUS (Theophrastus Bombastus von Hohenheim, 1493/4-1541) can be seen as the first modern pharmaceutical investigation in history and during the following centuries the pharmaceutical research has evolved from random studies to a more rational one.

However, it took almost 300 years until early examples of synthetic drugs like chloralhydrat (1832) or phenacetin (1887) were applied.[15]

The early years of the 20th century were characterized by the discovery of vitamins and by the development of further drugs. In the late 1920s FLEMING found the germ-killing effect of the strain Penicillium notatum[16] and a stable form of penicillin was isolated by FLOREY and CHAIN.[17] Today infectious diseases like malaria, tuberculosis, typhus or pox are under control or even eradicated.

The second milestone in the history of medicinal drugs has been the determination of the structure of the DNA double helix by WATSON and CRICK in the 50s of the last century.[18]

The combination of the advances in computational proceedings and the raising understanding in human biology has created an enormous amount of knowledge and the 20th century has seen remarkable progresses in the medical sciences resulting in a multibillion-dollar industry.

Today new technologies like combinatoric chemistry, high-throughput screenings, genetics, protein-crystallography, computational chemistry or *de-novo* prediction of proteins are well established and belong to the daily business in pharmaceutical industry.

Nevertheless, due to the decreasing NCEs (new chemical entries) during the last decades; 70-100 (1960-1969), 60-70 (1970-1989), ~50 (1980-1989) and 40-45 in the 1990s the pharmaceutical industry is searching for potentially new therapeutic applications.[15]

One new concept with promising outlook is the intervention of protein-protein-interactions. PPIs are playing an essential role in a wide range of biological processes and offer potentially rewarding targets for therapeutic intervention and drug development. It could be demonstrated that numerous proteins which are involved in signal transduction pathways, such as Ras and Rho, are responsible for different types of cancer or neurological disorders and many inhibitors of proteins are considered as potential drugs.[19]

5 Theoretical Background

Established targets in drug discovery are defined by addressing the active site of enzymes, which can be characterized as a pocket with typically solvent-shielded and hydrophobic and/or hydrophilic binding regions.[8d]

A different concept of addressing new targets in drug discovery is to interfere the formation of protein-complexes. Today it is commonly assumed that proteins fulfill their biological functions as participants of protein-complexes instead of acting in isolation.[20]

The contact areas could thereby be higher than 1000 $Å^2$, essentially defined by less rugged surfaces, which makes the design of small molecules for disrupting therapeutically relevant interactions very complicated.[21] Nevertheless, the intervention of such PPIs by small molecules would offer new opportunities for the treatment of human diseases.[22]

The specific exchange of amino acids at the contact area, e.g., by Ala-scan, has shown that only a few amino acids have an outstanding impact on the binding affinity of the protein-complex.[8d] Such "hotspots" of binding free energy seem to be rather prevalent in PPIs.[22-23] Statistic analysis of the amino acids which are involved in the complexation process gave a significant higher value for hydrophobic and aromatic amino acids such as phenylalanine, leucine, valine, tryptophan and tyrosine.[24]

5.1 Small Molecules as α-Helical Peptidomimetics

The shape and structure of proteins is rather complicated and already in the early 50s of the last century the three-dimensional structure of the polypeptide chains have been assigned into secondary subunits. Two main types (α-helices and β-strands) were first proposed by PAULING and COREY, later β-turns and Ω-loops were additionally verified.[25]

Approximately 40% of all secondary structures are α-helices and many of them were found to be involved in the binding motif of protein-complexes.[8c] Typically α-helices can be built up from a minimum of ten residues, whereby three amino acids resulting in one normally right-handed turn of the helix. If an α-helix is associated in a binding motif of a PPI the comprising amino acids must face one side of the helix, whereby the *i*, *i*+4 and *i*+7 positions are predominantly involved as it is depicted in Figure 5.1.[24]

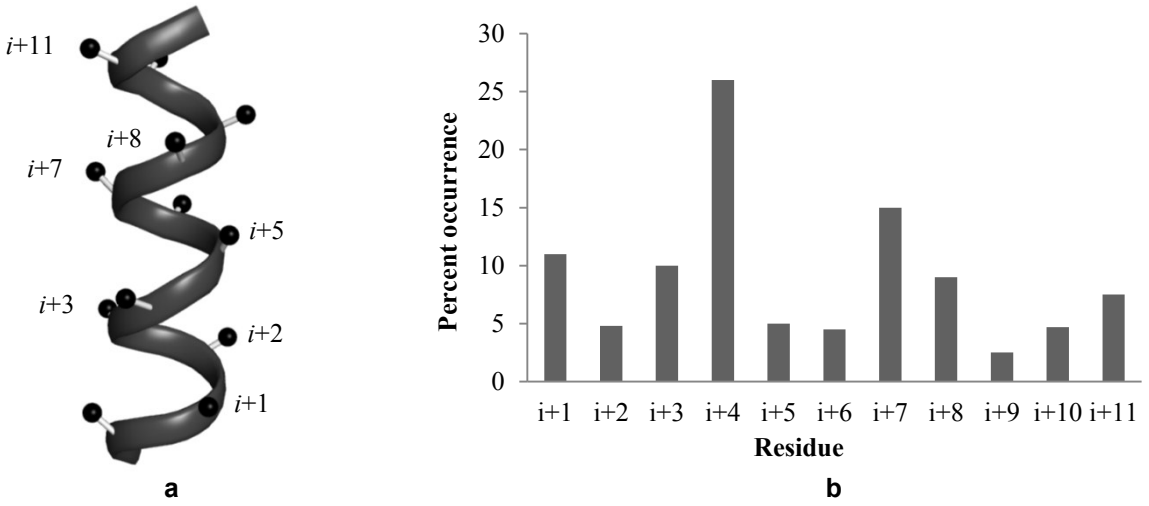
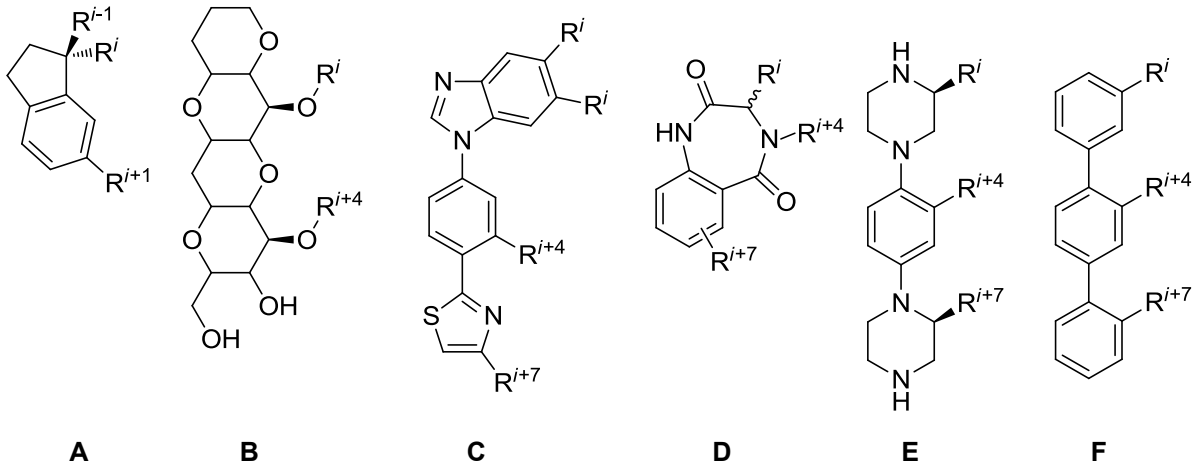


Figure 5.1: Schematic depiction of residues at an α-helix from position *i* to *i*+11 (**a**). Percent occurrence of residues as a function of helical position (**b**).[24]

Due to the percent occurrence of helical subunits in PPIs a lot of investigations were performed to develop non-peptidic small molecules which are capable to mimic the functional structure of α-helices and a large number of different scaffolds have been reported including indanes (**A**), polycyclic ether (**B**), trisubstituted imidazoles (**C**), benzodiazepinediones (**D**), dipiperazino benzenes (**E**), terarylic mimetics (**F**) and many more (Scheme 5.1).[8d]



Scheme 5.1: α-Helix mimetics suitable to emulate amino acid side chains which are facing one side of the helix.[8d]

One of the earliest examples of emulating α-helices by 1,6-disubstituted[26] or 1,1,6-trisubstituted indanes[27] (compound **A**, Scheme 5.1) were published by RATCLIFFE and coworkers in the 90s. Molecular modeling calculations proposed that the two substituents at the chiral carbon atom of the indane moiety are able to mimic the *i*−1 and *i* amino acid, whereby the substituent at the aromatic backbone represents the *i*+1 residue. Further examinations confirmed that only the *S*-isomer is able to mimic an α-helix.[8d] These early

findings by RATCLIFFE demonstrated that the idea of non-peptidic, low molecular weight structures are prone to emulate α-helices.

The distance between the two residues in the polycyclic ether (compound **B**, Scheme 5.1) was found to be 4.8 Å, while the distance between the *i* and *i*+4 residues of an α-helix is determined to be ~5.0 Å.[28]

The predominant drawback of many small molecules mimicking an α-helix is their hydrophobic core structure. The 5,6,5 imidazole-phenyl-thiazole derivative (compound **C**, (Scheme 5.1) is derived from a classical terphenyl by substitution of two hydrophobic benzene rings with two more water soluble five-membered aromatic moieties (imidazole and thiazole), thereby the log P value can be decreased by more than three times.[29]

Tri- and tetrasubstituted benzodiazepinediones (compound **D**, Scheme 5.1) have been proven to serve as α-helical mimetics by representing the *i*, *i*+4 and *i*+7 residues.[30]

KÖNIG and coworkers increased the solubility by 1,4-dipiperazino benzene derivatives (compound **E**, Scheme 5.1) and also for these kinds of mimetics the residues at the dipiperazino benzene scaffold are correlating with the three-dimensional orientation of the *i*, *i*+4 and *i*+7 amino acids side chains.[31]

The best known example to emulate α-helices so far is depicted as compound **F** in Scheme 5.1. HAMILTON and coworkers impressively demonstrated that linear terphenylic structures are able to emulate the shape of an α-helix by substituting the aromatic backbone with suitable amino acid side chains. Crystal structures and computer-based investigations indicated that the *i*, *i*+4 and *i*+7 positions can be mimicked by a 2,3',3''-trisubstituted linear terphenyl.[8b] In the next chapter one early example of teraryl-based application by inhibiting PPIs is explained in more detail.

5.2 Bcl-x_L/Bak Protein-Complex

The B-cell lymphoma-2 protein family (Bcl-2) is involved in the regulation of apoptosis (programmed cell death) and can be divided into two subfamilies: the anti-apoptotic proteins (Bcl-2, Bcl-x_L and Bcl-w) and the pro-apoptotic proteins (Bax, Bak, Bad, Bid and Bok).[32]

The apoptosis of cells is regulated by the equilibrium of the pro- and the anti-apoptotic Bcl-2 proteins.[33] All of the pro-apoptotic proteins have one similar domain; the BH3 domain which is important for their antagonistic role.[8c]

The Bcl-x_L protein, which prevents the apoptosis of a cell, is regulated by the Bak protein as an pro-apoptotic factor. Further investigations recommended that overexpressed

Bcl-x_L protein can block the apoptotic pathway and hamper the function of many anticancer agents.[32b,33]

The binding motif of the Bak protein is an α-helix which interacts with a sustained groove at the surface of the Bcl-x_L protein (Figure 5.2b).[34]

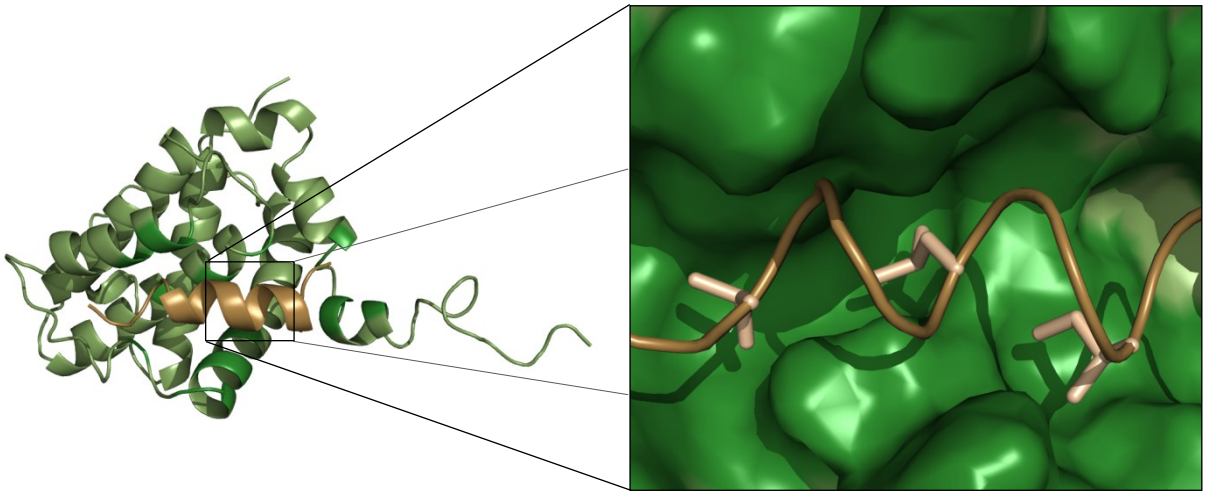
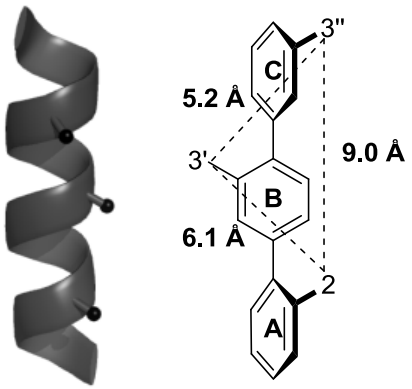


Figure 5.2: Bcl-x_L/Bak protein-complex. The BH3 domain of Bak protein is colored in sand and the Bcl-x_L protein in green (**a**). Only few amino acids; Val-74, Leu-78, Ile-81 (and also Ile-85; not depicted) are mainly responsible for the binding of the protein-complex (PDB file: 1BXL) (**b**).[34]

NMR investigations revealed that the amino acids Val-74, Leu-78, Ile-81 (and also Ile-85) of the Bak protein are involved in the bound form of Bcl-x_L/Bak protein-complex, which are corresponding to the *i*, *i*+4, *i*+7 (and *i*+11) positions.[34]

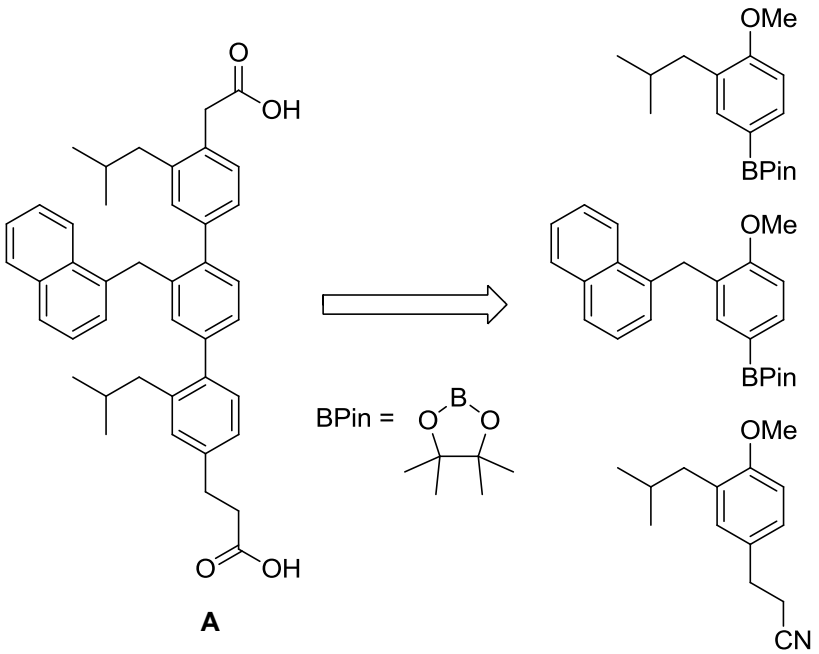
To mimic the three-dimensional shape of the involved amino acids of the Bak protein HAMILTON and coworkers initially calculated the distances of the *i*, *i*+4 and *i*+7 amino acids of the α-helix followed by energy minimization experiments of 2,3',3''-trimethylterphenylene (Scheme 5.2). The distances between the 3',3'' methyl groups (5.2 Å), the 2,3' methyl groups (6.1 Å) and the 2,3'' position (9.0 Å) closely correspond to the distances of the residues at *i*, *i*+4 and *i*+7 positions 5.6 Å, 6.6 Å and 10.1 Å, respectively, of the BH3 domain (Scheme 5.2).[35] In addition the calculation of the torsion angles of the phenyl rings of 56.0° (B-C) and 55.9° (A-B) resulting in a conformation, which is closely in accordance with the orientation of the *i*, *i*+4 and *i*+7 residues in the bound Bak protein (Scheme 5.2).[33]



Scheme 5.2: 2,3',3''-Trimethylterphenylene peptidomimetic with calculated distances.[33]

Due to the matching angles and distances of substituents at a 2,3',3''-trisubstituted terphenylic scaffold, compound **A** (Scheme 5.3) is able to mimic the α-helix of the Bak protein. The ability of emulating α-helices could be thereby of therapeutical relevance for disrupting the protein-complex.[9b]

The retrosynthetic analysis of the most active terphenyl is depicted in Scheme 5.3. The linear synthesis of the terphenyl is an eleven step synthesis starting from 4-iodo-2-isobutyl-1-methoxybenzene.[33] To couple the aromatic rings under chosen Suzuki-conditions the *para*-methoxy functions of the building blocks were at first deprotected by BBr_3 in DCM followed by treatment with triflic anhydride and Hünig´s base (DIEA) in DCM. The resulting triflate derivatives were further coupled under Pd-catalyzed conditions to the biphenylic and later on to the terphenylic scaffold (Scheme 5.3).



Scheme 5.3: Retrosynthesis of HAMILTON´S terphenyl strategy which exhibits good *in vitro* affinity with a K_i value of 114 nM.[33]

The additional carboxyl groups were attached in order to mimic the Asp-83 residue of the Bak protein along with increasing polarity.

Structure-activity studies had verified that the terphenyl **A** (Scheme 5.3) recognizes the Bak-binding site through specific binding and inhibit the Bcl-x_L/Bak interaction with a K_i of 0.114 μM.[33]

Apart from terphenylic mimetics[33] also other mimetics like terephthalamide-based[36] or oligoamide-foldamers[37] have been designed for intervening the Bcl-x_L/Bak PPI.

5.3 Rho GTPase and ROCK

Rho GTPases as members of the Ras superfamily are responsible for a wide range of cellular processes like cell morphology,[38] cell migration,[39] gene transcription, G1 cell cycle progression, inflammation, vesicular trafficking, secretion or cancer cell invasion.[19,40]

As a GTP dependent protein two different states are known, the active (GTP bound) and the inactive form (GDP bound) which are found in all types of GTPases. The GTP/GDP exchange is regulated by three types of effectors; the GEFs (guanine-nucleotide-exchange factors), the GAPs (GTPases-activating proteins) and the GDIs (guanine-nucleotide-dissociation inhibitors) and many of them are kinases.[41]

One of the best characterized kinases are the Rho associated kinases (ROCKs) which binds the RhoA in its active form.[42]

Beside the ROCKI the second isoform ROCKII is identified. Both structures are rather similar and all ROCKs consist of a kinase domain at the *N*-terminus, a coiled-coil forming region and a pleckstrin-homology domain (PH) followed by a cysteine-rich domain (CRD) at the *C*-terminus (Figure 5.3). The Rho-binding domain (RBD) is located at the *C*-terminal coiled-coil region and is characterized by a high structural similarity between ROCKI and ROCKII.[43]

Figure 5.3: Schematic depiction[43c] of the ROCKI domain architecture with a kinase domain at the *N*-terminus, a coiled-coil forming region and a pleckstrin-homology domain (PH) followed by a cysteine-rich domain (CRD). The Rho-binding domain (RBD) is located at the *C*-terminal coiled-coil region at the *C*-terminus (picture taken from ref. [43c]).

5.4 Structure of RhoA/ROCKI Protein-Complex

The structure of the binding domain between RhoA and ROCKI was explored by DVORSKY and AHMADIAN in 2004.[43c] The unit cell of the crystal structure of the RhoA/ROCKI protein-complex is defined by an α-helical coiled-coil ROCKI dimer and two RhoA

molecules (Figure 5.4b and c). The α-helical coiled-coil structure of the ROCKI dimer is important for the binding affinity to the active RhoA protein.[44] The at least 13 amino acid long RBD domain at the *C*-terminus creates a Rho-interacting motif of ROCKI forming a parallel coiled-coil dimer (Figure 5.4d; box). The interface between the helical ROCKI dimer and one of the RhoA molecules involves the residues of ROCKI Leu-998, Gln-1001 and Lys-1005 that represent positions *i*, *i*+3 and *i*+7. These residues are facing one side of the helix and interacting with the surface of one RhoA molecule (Figure 5.4e).

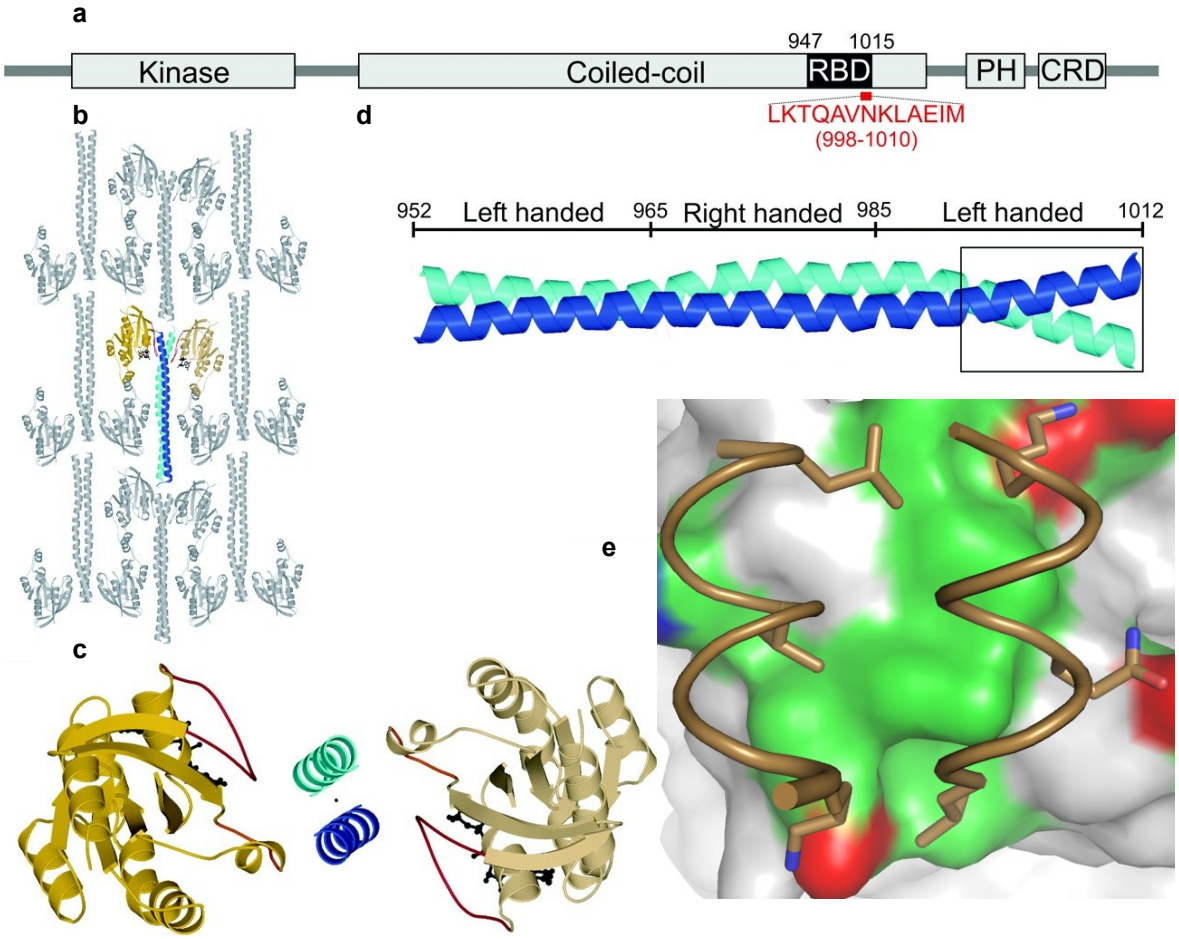


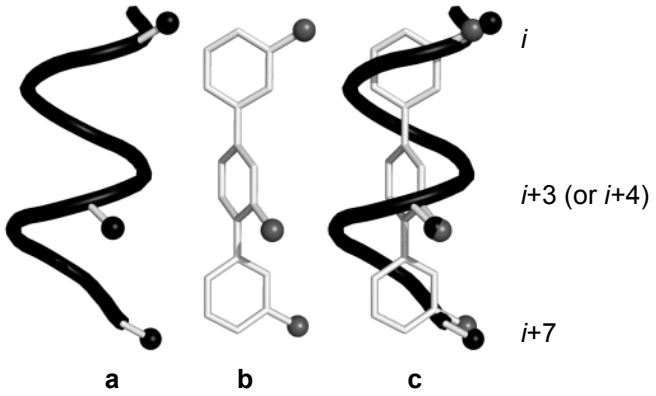
Figure 5.4: Schematic depiction[43c] of the ROCKI domain architecture (see also Figure 5.3). The Rho-interacting motif at the *C*-terminus of the RBD-(998-1010) is depicted in red (**a**). The crystal-packing diagram[43c] shows an α-helical coiled-coil of two ROCKI (blue and cyan) and two RhoA molecules (gold and beige) (**b**). Top view between two RhoA molecules (gold and beige) and the RBD domain (blue and cyan) (**c**). The box at the *C*-terminus shows the minimal Rho-binding motif and the twist of the coiled-coil is specified above (**d**). Residues which are facing one side of the helix and interacting with the surface of one RhoA molecule; ROCKI dimer is depicted as cartoon loop (sand) (**e**) (PDB file: 1S1C; picture taken from ref. [43c]).

6 Aim of this Work

The interaction of small molecules with biologically active targets is the central focus of drug discovery. In the last decades the field of protein-protein-interactions has become one of the big challenges of exploring new drug targets and the area of research is still at its beginning.

One of the most common motifs in protein-protein-interaction is the α-helical interaction of one protein with the surface of a second one and a lot of literature has been published focusing on the inhibition of these kinds of interactions.[9b,45]

HAMILTON and coworkers have presented a quite general approach of mimicking α-helices by suitably positioning amino acid side chains around a terphenylic or hetaryl-based scaffold (Scheme 6.1).[8-9,46]



Scheme 6.1: Schematic representation of an α-helical subunit with its *i*, *i*+3 (or *i*+4) and *i*+7 amino acid residues (**a**). Terphenylic scaffolds with 2',3,3''-substitution pattern (**b**). Terphenyls can mimic the three-dimensional shape of an α-helix (**c**).

The amino acid residues in *i*, *i*+3 (or *i*+4) and *i*+7 positions of an α-helix can be mimicked if these side chains are positioned at the 2',3,3''-position of a terphenylic scaffold.

This work is focused on developing a general approach to mimic the α-helices as they are found in the interaction of the protein-complex of human ROCKI and human RhoA (Figure 6.1).

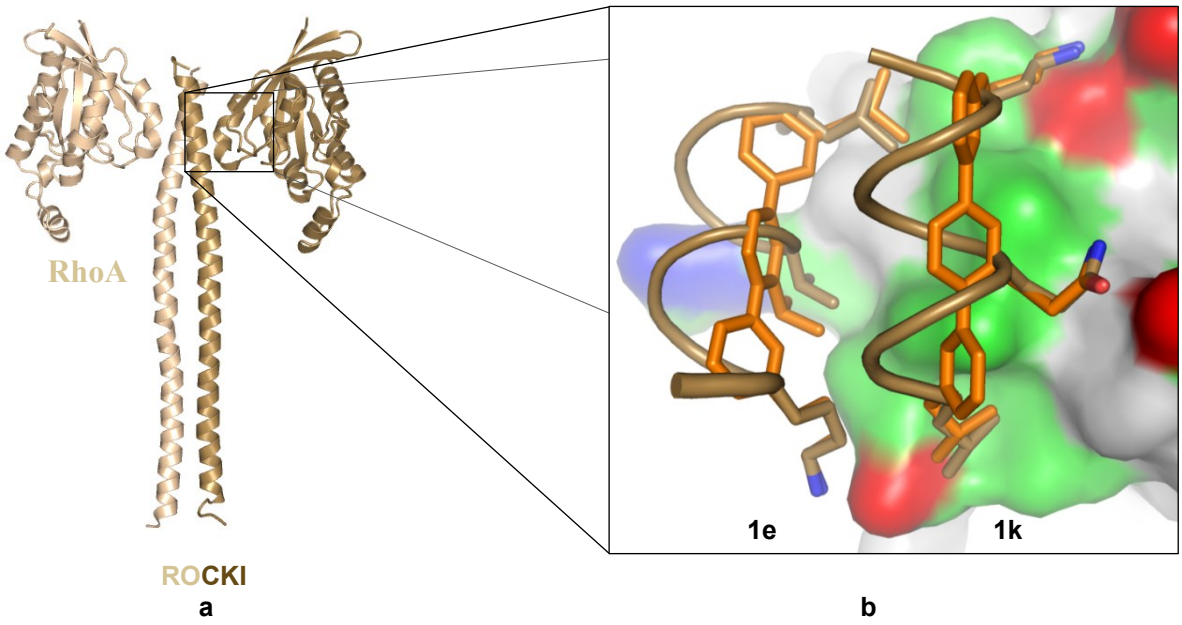
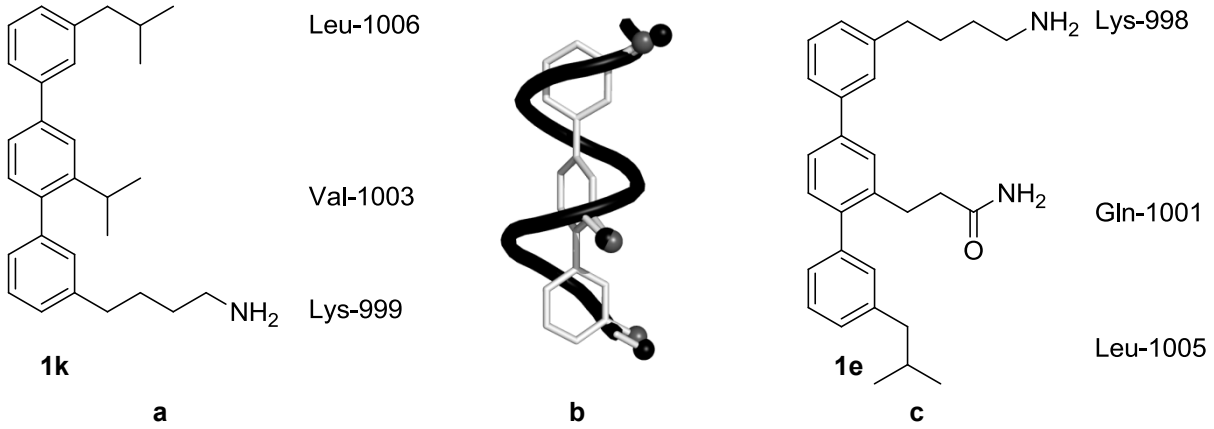


Figure 6.1: Dimeric protein-complex of human ROCKI and human RhoA depicted as cartoon (**a**). The "hotspot" of interaction surface and the computer modeled lead-structures **1k** and **1e** mimicking the α-helix of ROCK (**b**); calculations were performed by DVORSKY (PDB file: 1S1C).[43c,47] The two 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).

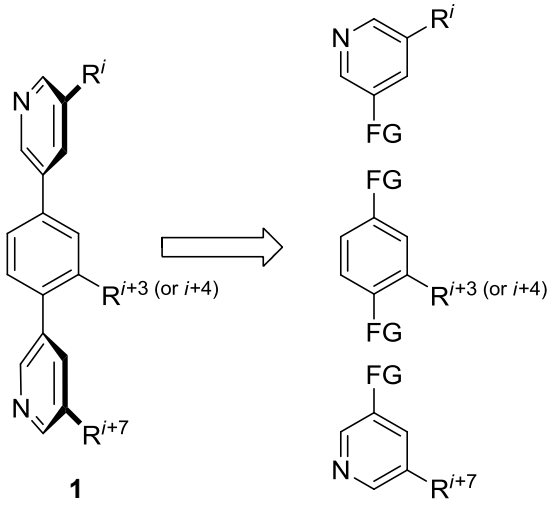
The binding motif of ROCKI and RhoA has been determined by X-ray diffraction, which allowed to consider the α-helical peptidomimetics **1e** and **1k**, which are structurally comparable to the binding motifs of the protein-complex (Scheme 6.2).



Scheme 6.2: Terphenylic peptidomimetics for the two interaction hotspots of human ROCKI and human RhoA (**a**, **c**). Schematic depiction of terphenyls mimicking the secondary structure of an α-helix (**b**); calculations were performed by DVORSKY (PDB-file: 1S1C).[43c,47]

An efficient synthetic access to the peptidomimetic lead-structures **1e** and **1k** and its application in the inhibition of protein-protein-interaction of human ROCKI and human RhoA had to be developed during the course of this thesis.

One of the challenging aspects of this benzene-based strategy is the poor solubility of terphenyls under physiological conditions. In literature pyrrolopyrimidine-,[12] pyrimidine-,[10] or pyridazine-based[11] mimetics have been reported to show improved solubility characteristics.[8] In the present state the assembly of hetaryl-based teraryls is achieved by a linear design of synthesizing these kinds of PPI inhibitors. In few literature reports a convergent strategy has been presented, but its synthesis turns out to be of little flexibility.[13]
In the course of this work the development of a generally applicable convergent and flexible strategy for synthesizing hetaryl-based teraryl libraries should be accomplished.
To increase the polarity of the aromatic backbone *N*-heterocycles like pyridines should improve the solubility of teraryls under physiological conditions. For that reason a general approach for the synthesis of pyridine-based building blocks substituted with appropriate amino acid side chains had to be developed (Scheme 6.3).



Scheme 6.3: Basic concept for a convergent and flexible assembly of pyridine-based teraryls.

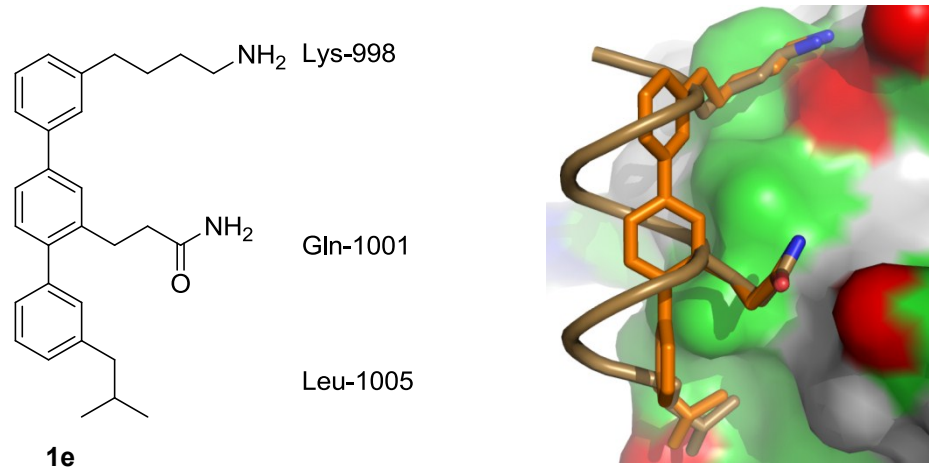
In this work, an efficient synthetic access to amino acid surrogate pyridine boronic acid building blocks and its use in a convergent two-step-one-pot synthesis should be developed.

7 Results and Discussion

7.1 Synthesis of Teraryls using the Linear Approach

Terphenylic or terhetarylic scaffolds are bioinspired motifs for the inhibition of protein-protein-interactions. HAMILTON and coworkers have presented a general approach to emulate α-helices by suitable positioning of amino acid side chains at the terphenylic scaffold.[8b,8e,9a,46] In addition, the intrinsically helical structure of terphenyls has advantageous effects in mimicking peptidic α-helical subunits.[8c,8d,9b]

The terphenyl-based lead-structure **1e** is the first computer modeled compound for inhibition of the PPI between the surface of Rho GTPase and the α-helical protein ROCK (Scheme 7.1). The three side chains (aminobutyl, amidoethyl and isobutyl) of lead-structure **1e** are mimicking the amino acid side chains of lysine-998, glutamine-1001 and leucine-1005, which represent the main binding motif of human RhoA and human ROCKI as it is depicted in Scheme 7.1.[43c,47]



Scheme 7.1: Lead-structure **1e** (left) and the computer modeled docking experiment after binding at the surface of RhoA (right); calculations were performed by DVORSKY (PDB-file: 1S1C).[43c,47] The α-helix of human ROCKI is shown as cartoon loop (sand), lead-structure **1e** is illustrated as sticks (orange) and human RhoA is given as surface (green, red, blue and grey).*

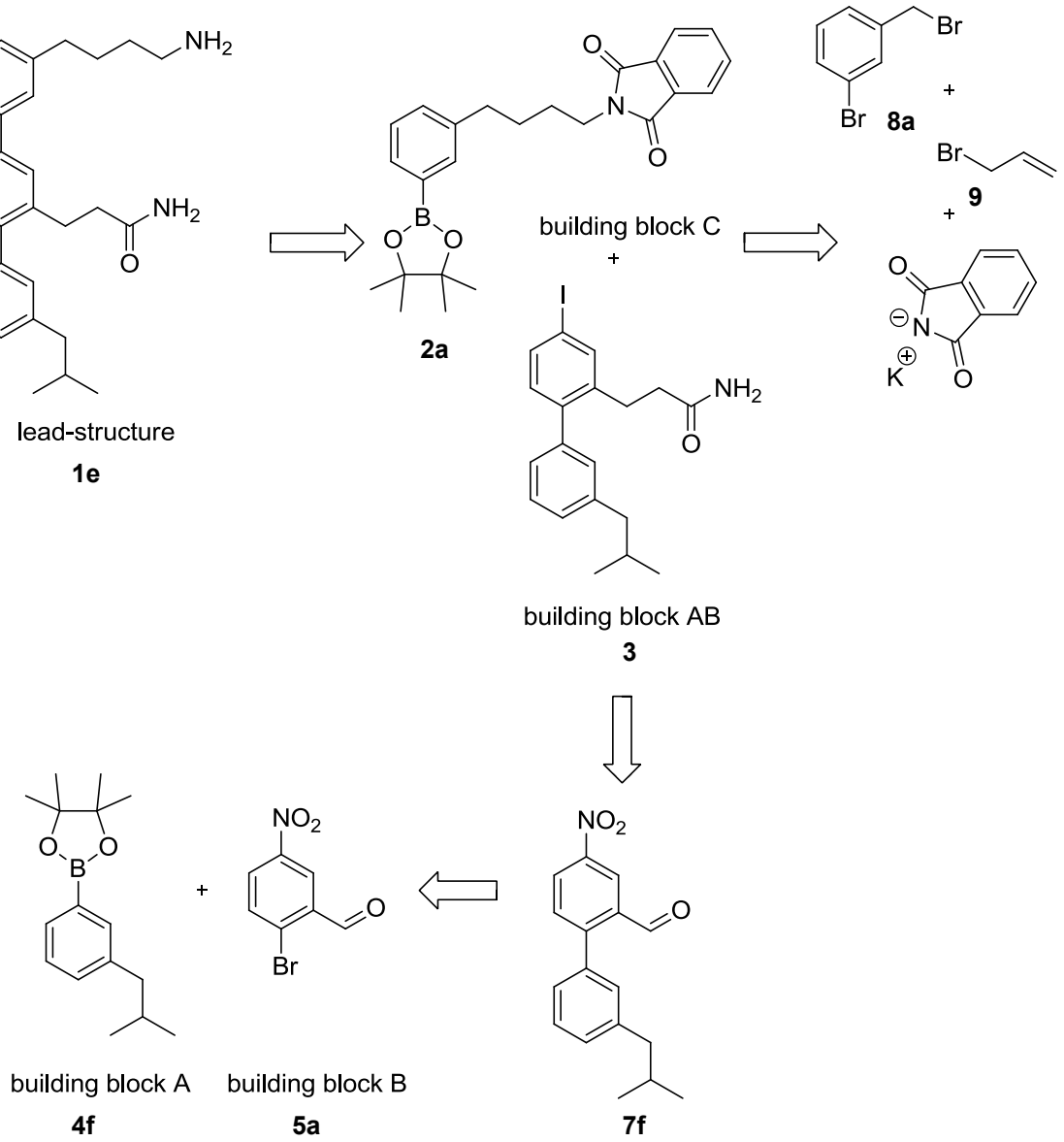
7.1.1 Retrosynthesis

The disconnection in the retrosynthetic analysis of lead-structure **1e** occurs at the C-C bond between the upper "lysine-part" **2a** (building block C) and the biphenylic moiety **3** (building block AB) (Scheme 7.2). The lower "leucine-part" **4f** (building block A) should be derived from a 1-bromo-3-alkylbenzene derivative after borylation. The core unit **5a** (building

* For the sake of clarity only the monomeric form is shown.

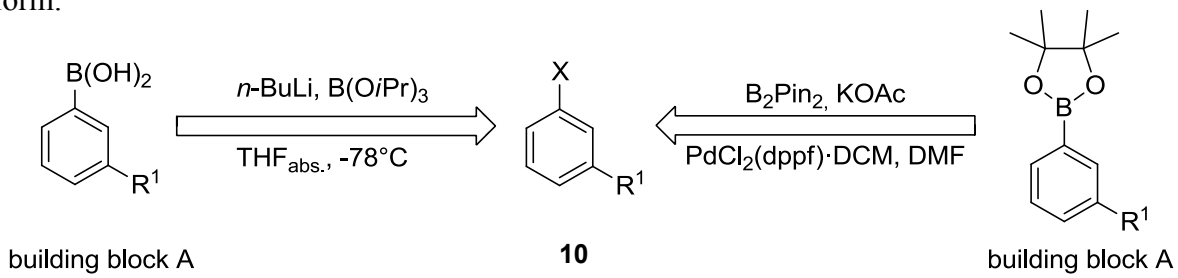
block B) might be introduced after nitration of 2-bromo-benzaldehyde (**6a**) to form 2-bromo-5-nitrobenzaldehyde (**5a**).

The biphenylic precursor **7f** could be synthesized under Suzuki-conditions by formation of the first aryl-aryl bond. Starting from 3-bromo-benzylbromide (**8a**) and potassium phthalimide (KNPhth) building block C might be obtained after modification of the alkyl-chain over several steps using allyl bromide (**9**) under Grignard-conditions (Scheme 7.2). The protection of the amine of the lysine side chain in its latent form of a phthalimide appeared to be necessary for a successful coupling of building block AB and C under intended Suzuki-conditions.[19a,48]



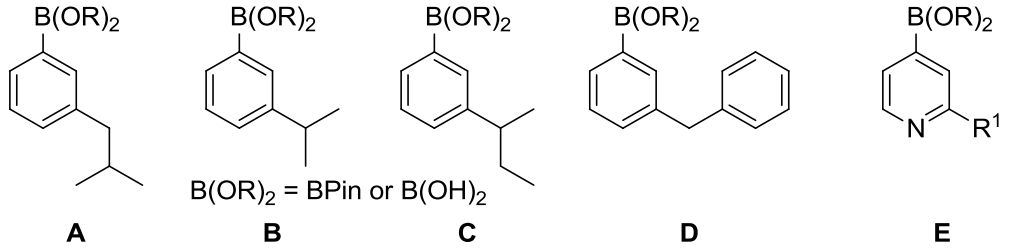
Scheme 7.2: Retrosynthesis of lead-structure **1e**. The key steps are the two Suzuki-coupling reactions between building block A and B and of the resulting building block AB and compound **2a**.

For the borylation of haloaryl derivatives **10** two different reaction conditions might be utilized to generate building block A (Scheme 7.3). On the one hand the free boronic acid could be introduced after lithiation of the corresponding halobenzene derivative followed by quenching with triisopropyl borate ($B(OiPr)_3$). On the other hand a Pd-catalyzed borylation should also be possible by employing bis(pinacolato)diboron (B_2Pin_2) as borylation agent. According to literature, no negative effects are expected regarding the reactivity of building block A in the Suzuki-coupling, neither as in its boronic acid form nor in its pinacol ester form.[49]



Scheme 7.3: Two different borylation methods for halobenzene derivatives **10** are feasible for synthesizing boronic acid derivatives of building block A.

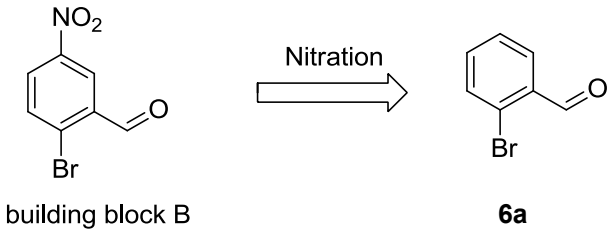
Building block A additionally can be varied by permutation with other side chains such as isopropyl (mimicking valine) or *sec*-butyl (isoleucine side chain), which might be of interest for binding studies of lead-structure **1e** (Scheme 7.4).



Scheme 7.4: Not only mimicking the leucine side chain (**A**) could be important for the inhibition of RhoA and ROCKI interaction, also isopropyl (**B**), *sec*-butyl (**C**) or benzylic side chains (**D**) could be of interest. More polar building blocks like pyridine-based derivatives (**E**) might be suitable to increase the solubility under physiological conditions.

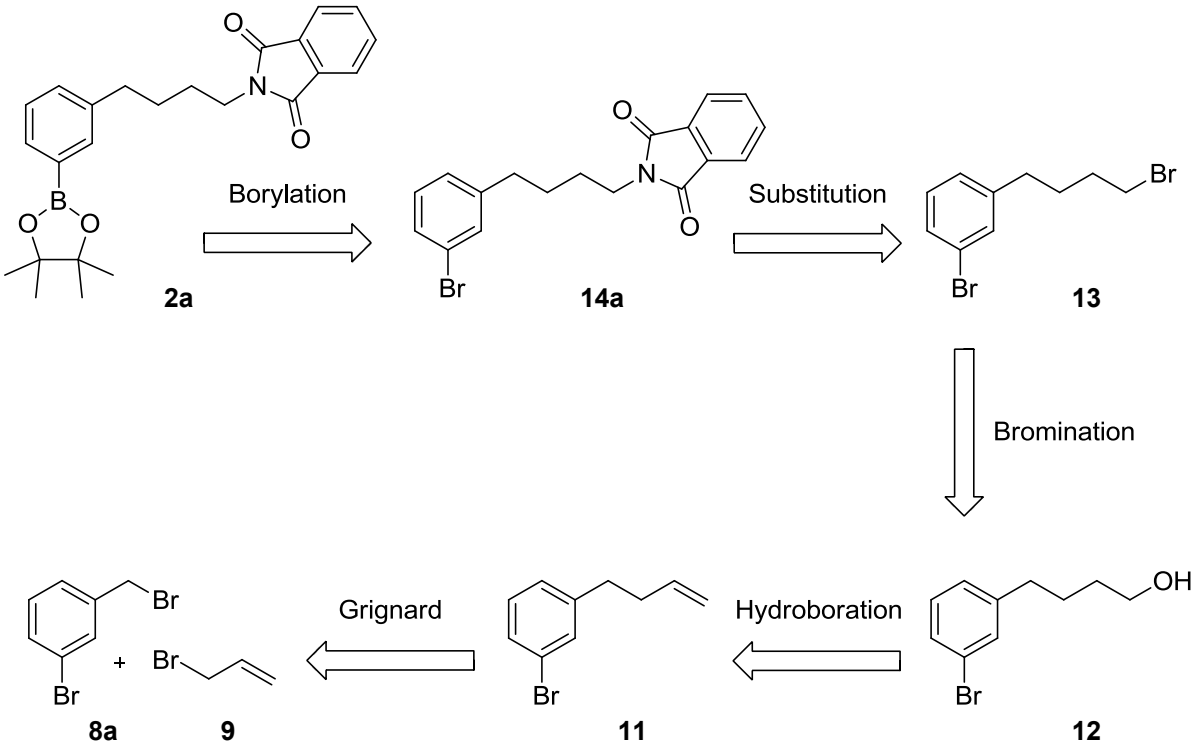
Taking into account that the binding affinity is proportional to the lipophilic contact area and the affinity of hydrophobic interaction is mainly based on the displacement of water molecules (-50 to -200 J/mol per $Å^2$ of lipophilic contact surface), it might be highly desirable to investigate the binding affinity of a benzylic side chain emulating phenylalanine (Scheme 7.4, **D**).[15] However, the intrinsically poor solubility of the benzene-based building blocks A might make the use of more polar *N*-heterocycles necessary (Scheme 7.4, **E**).

Building block B can be easily prepared by nitration of 2-bromo-benzaldehyde (**6a**) (Scheme 7.5).[19a,48]



Scheme 7.5: Retrosynthesis of building block B starting from 2-bromo-benzaldehyde (**6a**).

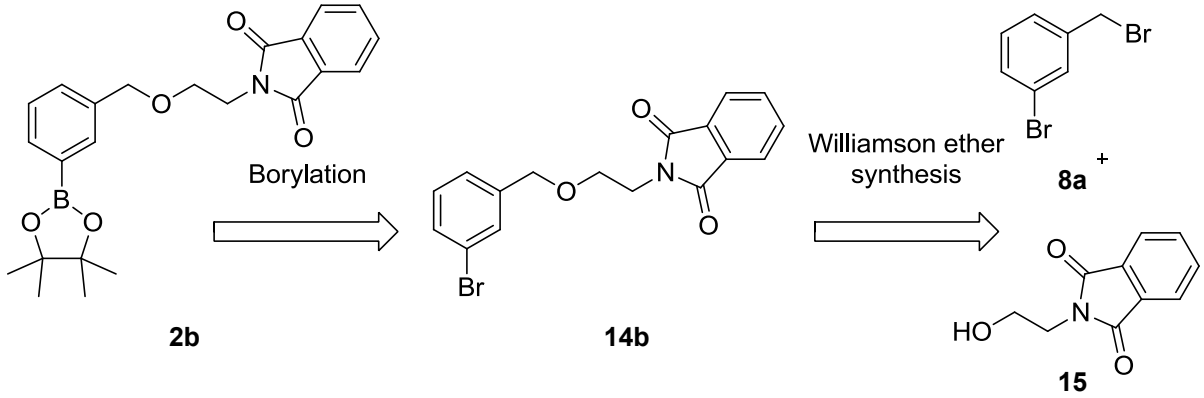
The retrosynthetic analysis of the upper "lysine part" **2a** is shown in Scheme 7.6. Starting from 3-bromo-benzylbromide (**8a**), the modification of the alkyl side chain should be introduced under Grignard-conditions using allyl bromide (**9**). After regioselective hydroboration of the terminal olefin **11** the corresponding primary alcohol **12** can be brominated by tribromophosphine (PBr_3) to afford alkyl bromide **13**. The protected amine function in its latent form of a phthalimide can be prepared by converting bromine **13** into the corresponding phthalimide **14a** under nucleophilic substitution conditions. The 3-substituted bromobenzene derivative **14a** finally can be borylated according to the previously described procedure by Pd-catalyzed borylation using B_2Pin_2 (Scheme 7.3).



Scheme 7.6: Retrosynthetic analysis of building block **2a** starting from 3-bromo-benzylbromide (**8a**).

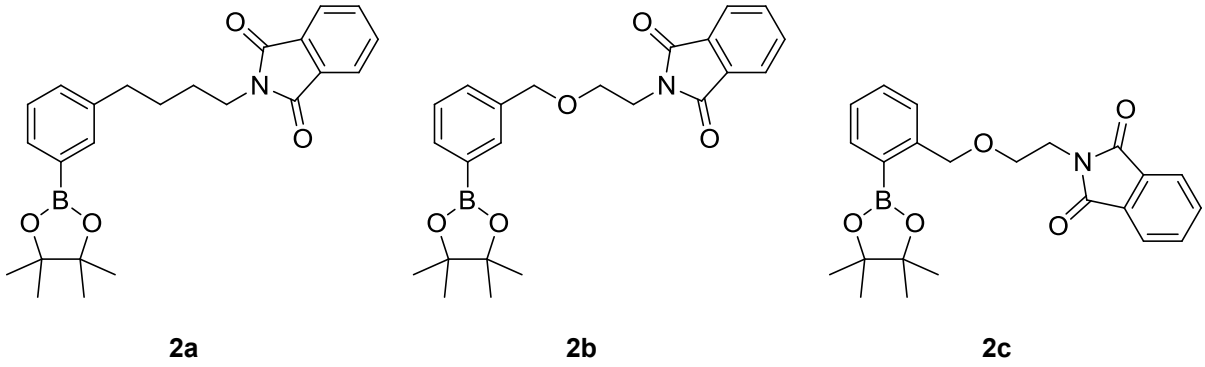
As an alternative to the five step synthesis of building block C in Scheme 7.6, a more pragmatic synthetic approach of the "lysine-part" is also feasible (Scheme 7.7).[19a,48]

Introducing the phthalimide protected side chain by a Williamson ether synthesis of benzyl bromide **8a** and *N*-(2-hydroxyethyl)phthalimide (**15**) furnish the ether bridged derivative **14b**. After borylation by a Pd-catalyzed procedure, a more polar and readily accessible derivative of building block C can be obtained.[19a,48]



Scheme 7.7: Retrosynthetic analysis of an alternative building block C by introducing the phthalimide protected lysine side chain under nucleophilic substitution conditions.

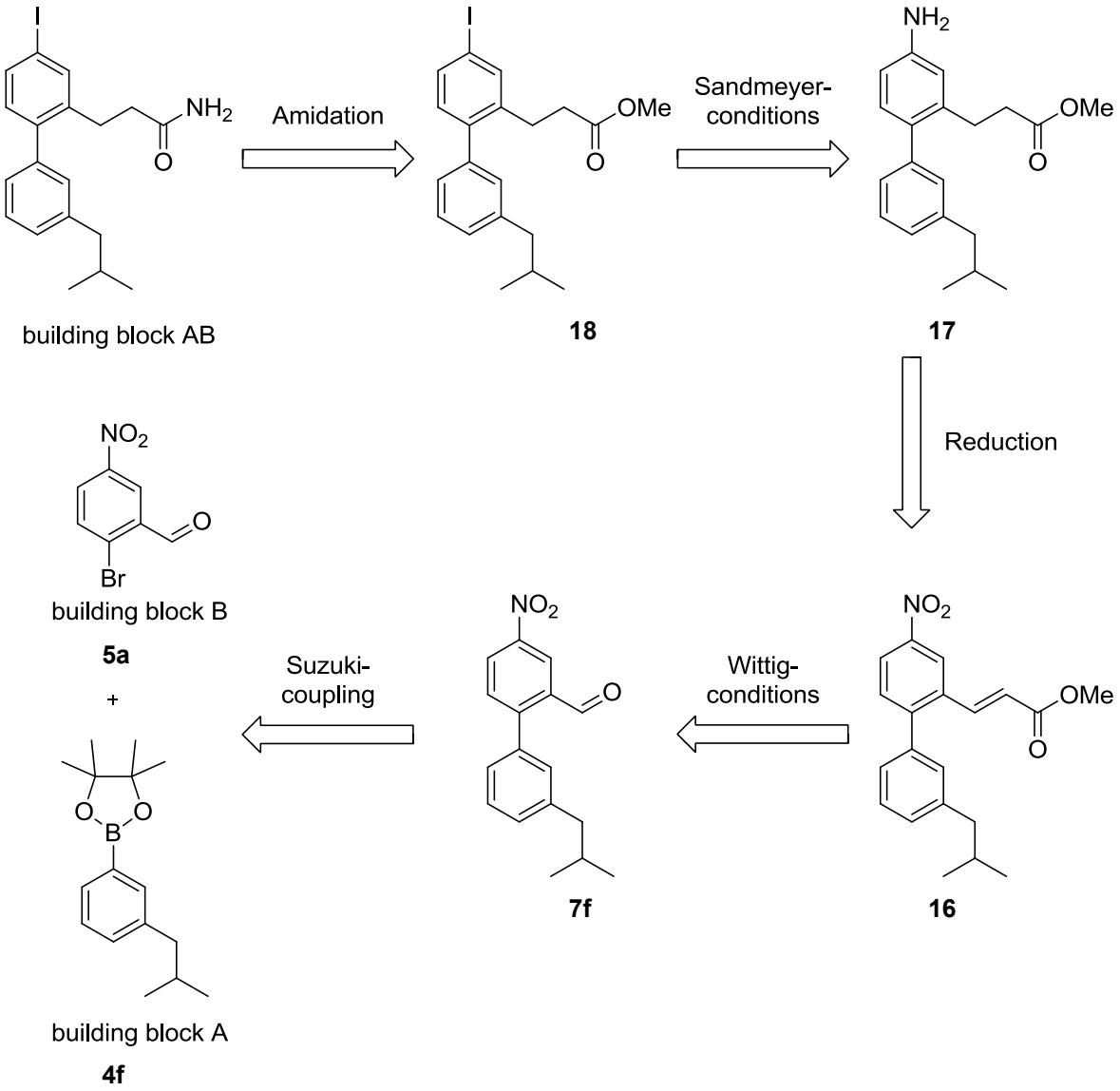
For the variation of the upper "lysine-part" **2a** not only a 1,3-substitution pattern might be of interest, also an *ortho*-substitution would be of importance to study the binding angle of the lysine side chain on the surface of RhoA (Scheme 7.8). The derivative **2c** should be synthesized according to the same procedure as described for the *meta*-derivative **2b** (Scheme 7.7).



Scheme 7.8: Building block **2a** and its modifications derived from lead-structure **1e**. A more convenient access to an ether bridged side chain (compound **2b**), or a variation of the substitution pattern (compound **2c**) are conceivable.

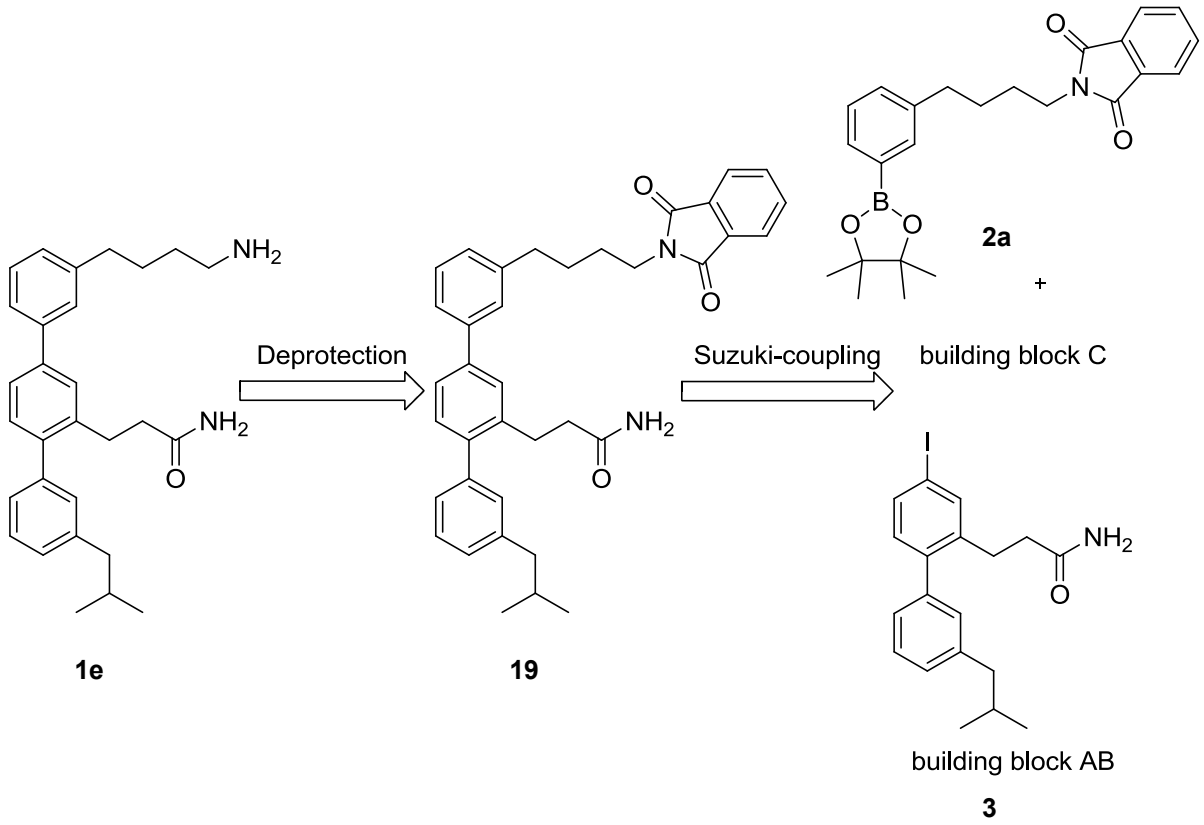
The retrosynthesis of the building block AB derived from the first Suzuki-coupling of building block A and B furnishes the biphenylic nitrobenzaldehyde derivative **7f** (Scheme 7.9). The side chain can be introduced under Wittig-conditions resulting in the α,β-unsaturated methylester **16**, which can easily be reduced to its saturated form. Simultaneously, the nitro group can be reduced affording amine **17**, subsequently followed by

a modified Sandmeyer reaction leading to iodine **18**. Finally, the methylester **18** can be amidated to the desired building block AB.[19a,48]



Scheme 7.9: Retrosynthesis of building block AB starting from the first Suzuki-coupling of building block A and B.

Coupling of building block AB and C to the corresponding terphenylic scaffold should occur under Suzuki-conditions in the final step (Scheme 7.10). The phthalimide masked amine **19** might be deprotected by employing hydrazine in polar solvents like aqueous MeOH.



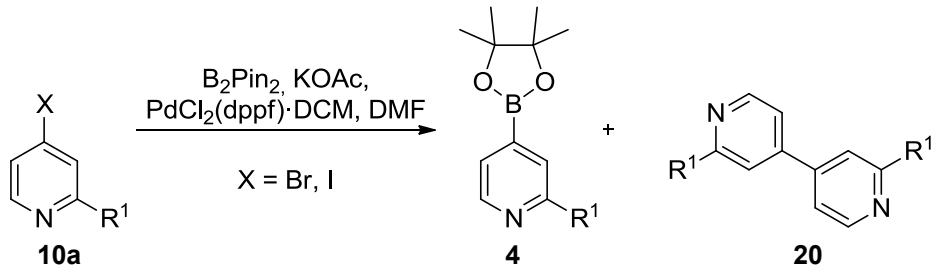
Scheme 7.10: Retrosynthetic analysis of the final lead-structure **1e** starting from the second Suzuki-coupling of building block AB and compound **2a**.

In the following chapters (7.1.2-7.1.6) the syntheses of the different building blocks and the coupling to the final teraryls and its derivatives of lead-structure **1e** are discussed in detail.

7.1.2 Synthesis of Building Blocks A

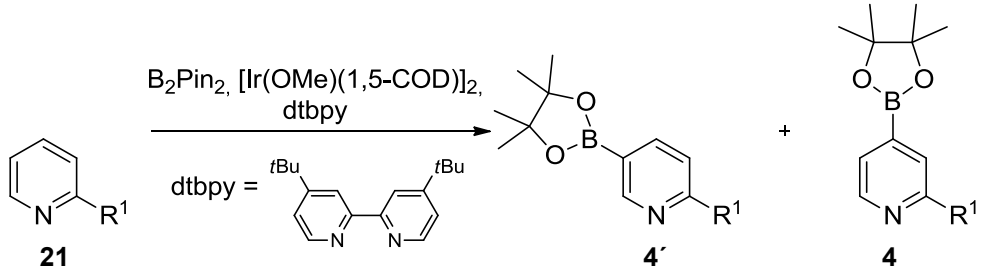
Considering potential solubility problems of phenyl-based lead-structure **1e**, *N*-heterocycles like pyridine might increase the solubility in aqueous solutions. For that purpose, a pyridine-based synthesis of building blocks A was developed.

In a first attempt conditions were investigated to introduce the pinacol ester function in *meta*-position to the residue R^1 (Scheme 7.11). It can be contemplated to use the well-known Miyaura-borylation of 2-substituted 4-haloaryl derivatives (like **10a**) using B_2Pin_2 and $PdCl_2(dppf)\cdot DCM$ in absolute, degassed DMF. But literature evidence insinuated that the competitive formation of homo-coupling by-product **20** could be expected as one of the main products.[50]



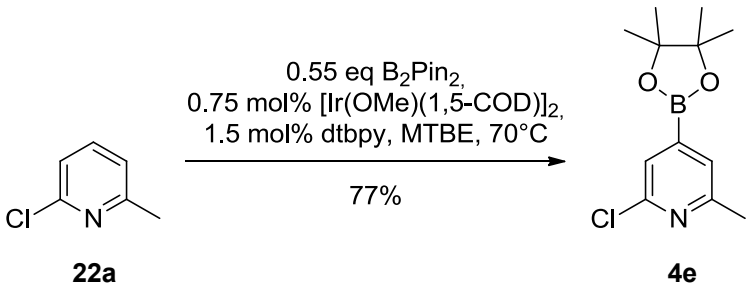
Scheme 7.11: Borylation of *meta*-substituted haloaryl derivative **10a** under Miyaura-conditions with the homo-coupling by-product **20**.[50]

For that reason another strategy for the borylation of heteroarenes had to be developed.[51]
The C-H activated Ir-catalyzed borylation of arenes is regioselective in favor of *meta*-position, which originates from steric interactions with the catalytically active species (Scheme 7.12). Mono-substituted substrates (like compound **21**) give a regioisomeric mixture of 5- and 4-substitued pinacol esters **4´** and **4**, which are difficult to separate.[52]



Scheme 7.12: Example for the *meta*-selective borylation under Ir-catalyzed C-H activation.[52] 2-Substituted pyridines furnish two regioisomers **4´** and **4**.

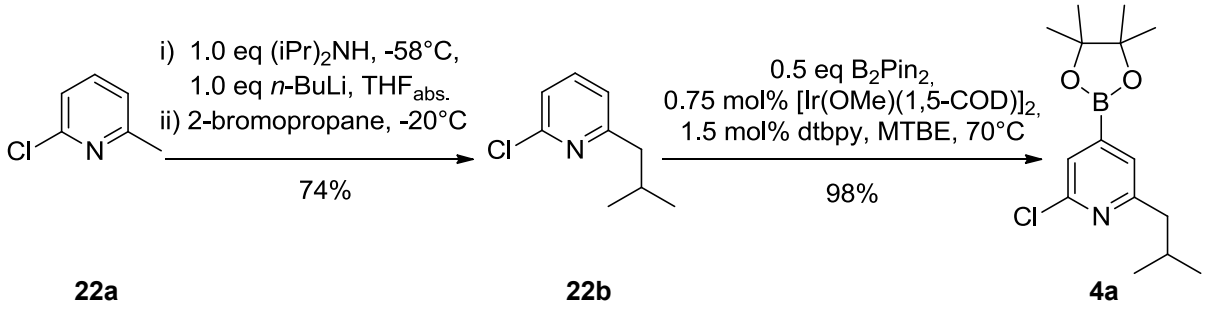
To avoid the formation of two regioisomers, 2-chloro-6-methylpyridine (**22a**) was used in the Ir-catalyzed borylation as shown in Scheme 7.13. Due to the chloride in 2-position only one regioisomer could be formed under the used conditions. Later in the synthetic route the chloride should easily be removed under hydrogenation conditions (e.g., $Pd(OH)_2/C$, H_2).



Scheme 7.13: Synthesis of 2-chloro-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**4e**).

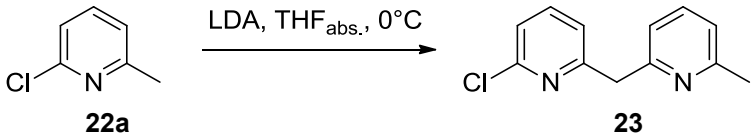
2-Chloro-6-methylpyridine (**22a**) was deprotonated by LDA in absolute THF at -58°C (using a cryostat) followed by quenching with 2-bromopropane at -20°C (Scheme 7.14). After addition of chloro-methylpyridine **22a**, the dark red solution was stirred at -20°C for 30 min

followed by addition of the electrophile 2-bromopropane at the same temperature. The mixture was stirred overnight to give product **22b** in 74% yield after purification *via* flash column chromatography. The precatalyst $[Ir(OMe)(1,5\text{-}COD)]_2$ was applied to ensure high conversion in the borylation towards the desired substituted pyridine derivatives **4a** (98%).



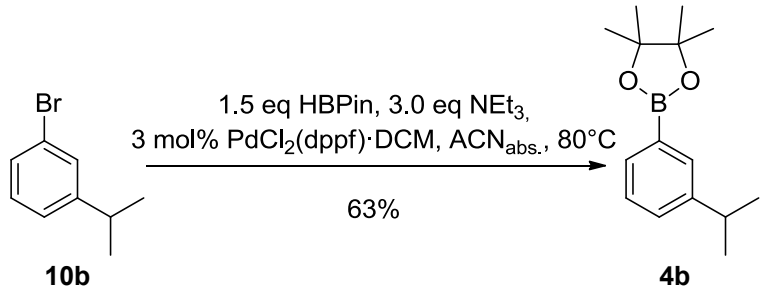
Scheme 7.14: Synthesis of 2-chloro-6-isobutyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-pyridine (**4a**).[19a]

In previous work of TAN the LDA mediated derivatization of compound **22a** was recognized to be highly temperature-sensitive.[19a] If the temperature was too high, the major compound was the undesired dimeric by-product **23** (Scheme 7.15). The benzylic hydrogen of compound **23** is more acidic than the hydrogen of compound **22a**, consequently after addition of 2-bromopropane almost no desired product could be obtained.[19a]



Scheme 7.15: Performing the lithiation of compound **22a** at 0°C resulted in the formation of the dimeric by-product **23**.[19a]

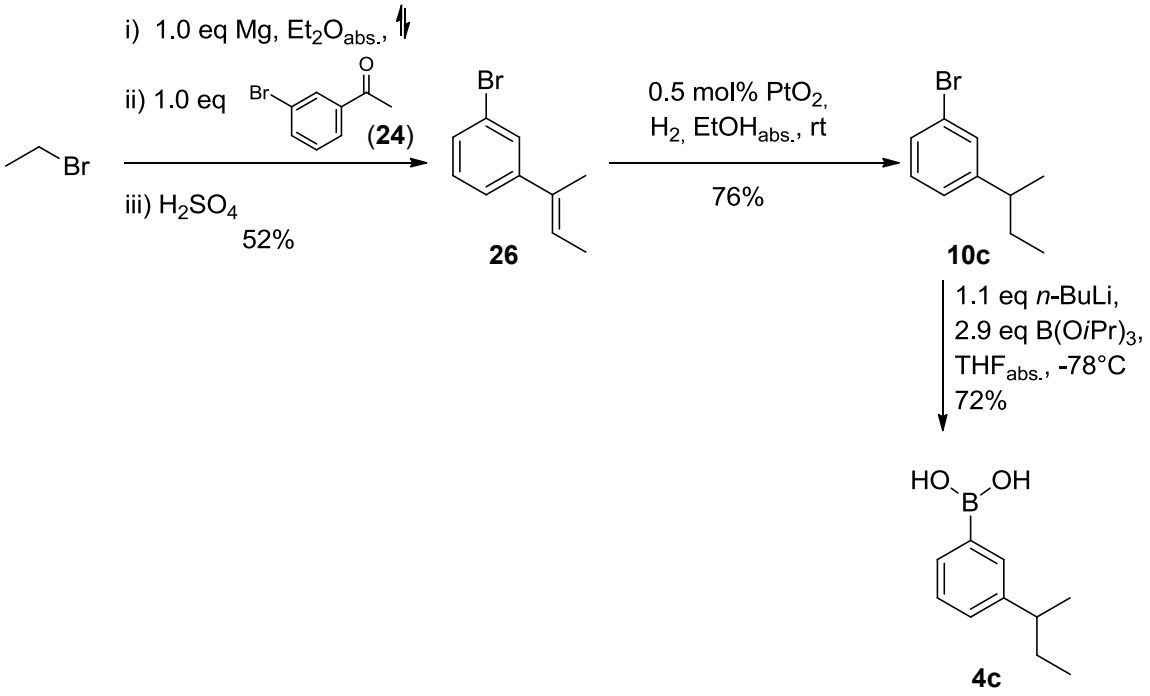
Starting from 1-bromo-3-isopropylbenzene (**10b**) the isopropyl derivative **4b** could be synthesized in one step (Scheme 7.16). The borylation of arene **10b** was performed with 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (HBPin) as borylation agent.[53] HBPin is a less reactive borylation agent compared to the dimer B_2Pin_2 along with lower yields of the final product. But in combination with NEt_3 as base and acetonitrile as solvent more than 77% conversion could be achieved after 23 h (based on GC-MS). Using the same conditions with 1,4-dioxane no conversion was observed at all.



Scheme 7.16: Synthesis of 2-(3-isopropylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**4b**) starting from 1-bromo-3-isopropylbenzene (**10b**).

Building block **4c** bearing a *sec*-butyl moiety was prepared according to the method of MARVEL and coworkers (Scheme 7.17).[54] The *sec*-butyl side chain was introduced under Grignard-conditions utilizing bromoethane and 1-(3-bromophenyl)ethanone (**24**) as electrophile. Due to the instability of the resulting tertiary alcohol, the intermediate **25** was directly converted to the *sec*-butenyl-benzene derivative **26** with sulfuric acid in catalytic amounts resulting in elimination of water. After distillation of compound **26** an inseparable mixture of the *E*- and *Z*-isomer was obtained. At this stage two strategies were contemplated: a) the hydrogenation of the olefinic intermediate **26** or b) first borylation and then hydrogenation of the corresponding boronic species.

Hydrogenation conditions in the presence of an aromatic boronic acid could lead to the hydrocarbon by protodeborylation. In literature palladium black (Pd-black) in alcoholic solution is a common reductive system.[55] To avoid the potential problems of protodeborylation, the strategy was chosen in which intermediate **26** was first reduced under hydrogenation conditions employing 5 mol% platinum(IV) oxide (PtO_2). Although debromination was observed as side reaction, the quantity of the side-product could be suppressed to less than 6% under the used conditions and mainly the desired product **10c** was isolated after flash column chromatography as a colorless liquid.

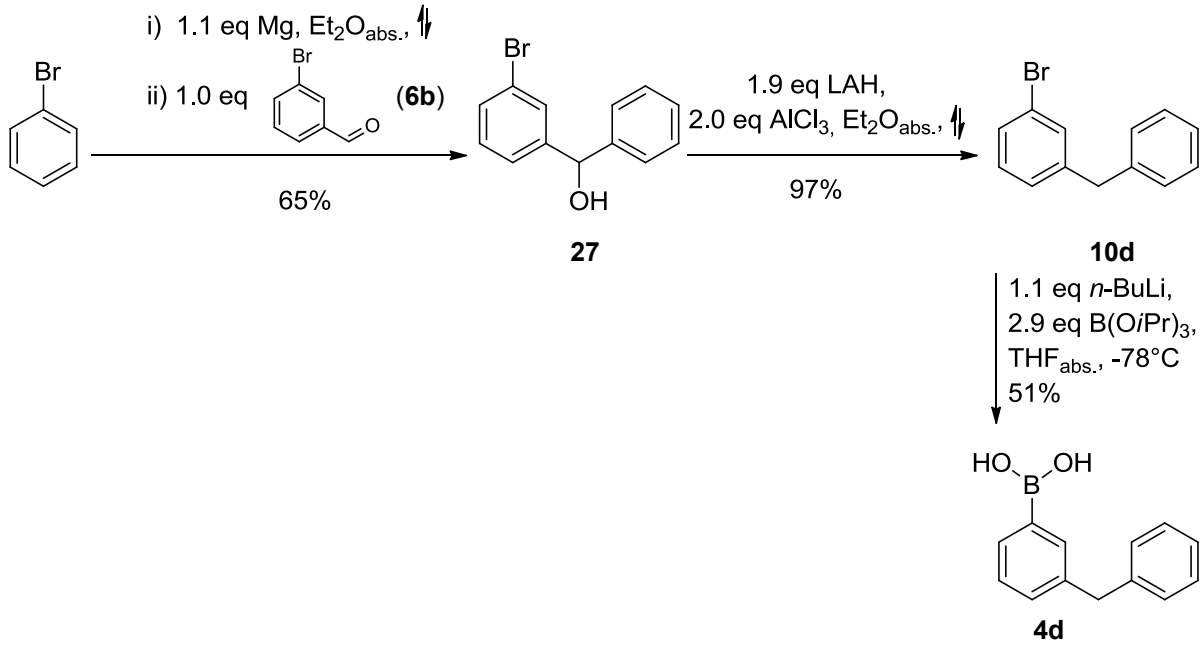


Scheme 7.17: Synthesis of (3-(*sec*-butyl)phenyl)boronic acid (**4c**) starting from 1-(3-bromophenyl)-ethanone (**24**).

In analogy to literature known borylation methods, the boronic acid function was then introduced by lithiation with *n*-BuLi at -78°C followed by quenching with triisopropyl borate ($B(OiPr)_3$).[56]

The synthesis of building block **4d** is shown in Scheme 7.18. The first two steps were performed according to a procedure of IWAMURA and coworkers, starting from 1.1 eq bromobenzene.[57] After formation of the Grignard reagent in absolute Et_2O, the solution was cannulated to a solution of 3-bromobenzaldehyde (**6b**) and after workup with saturated NH_4Cl solution the desired benzyl alcohol **27** was isolated as a colorless oil after flash column chromatography. The deoxygenation was performed with lithium aluminum hydride (LAH) and aluminum chloride ($AlCl_3$) in absolute Et_2O under reflux furnishing 1-benzyl-3-bromo-benzene (**10d**) in 63% yield over two steps. The LAH/$AlCl_3$ combination leaves the bromoarene completely intact.

The borylation of bromide **10d** was achieved as described above using *n*-BuLi and $B(OiPr)_3$ as electrophile (Scheme 7.18). The final boronic acid **4d** was isolated as a colorless solid, which is stable over years in the freezer.

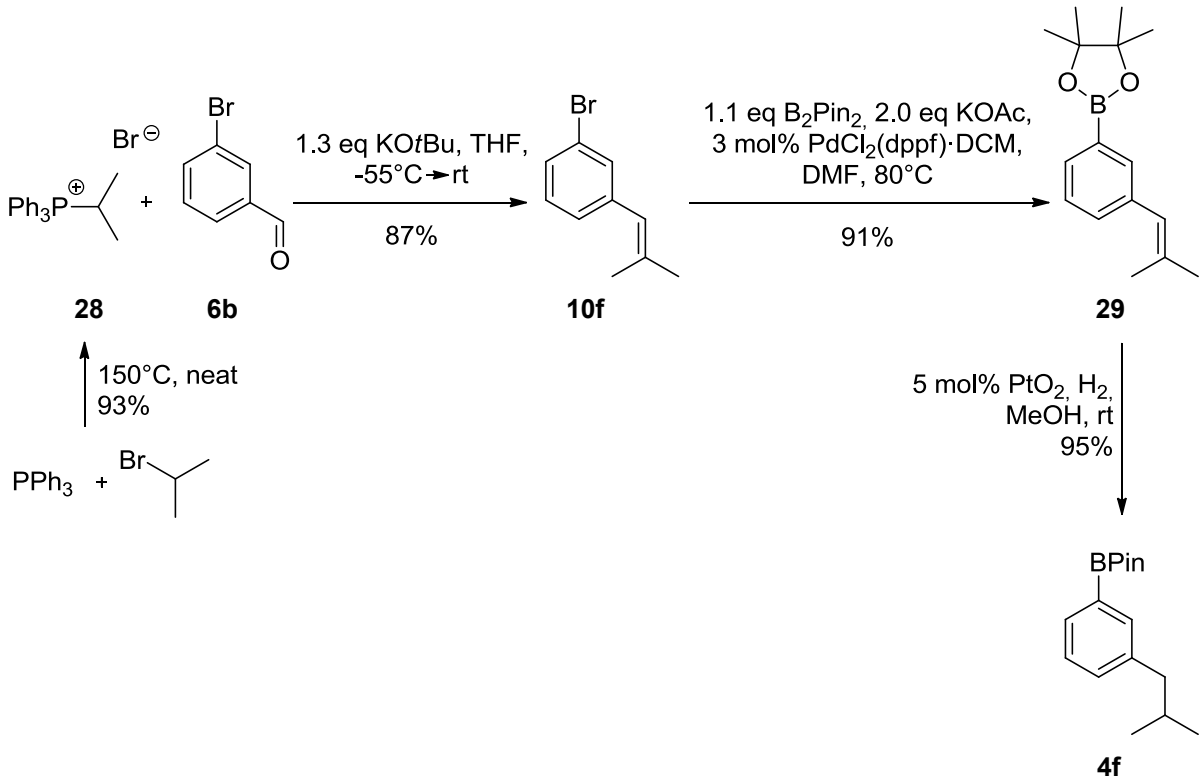


Scheme 7.18: Synthesis of (3-benzylphenyl)boronic acid (**4d**).

For the synthesis of the isobutyl building block **4f** the side chain was introduced by Wittig-salt **28** (Scheme 7.19). The phosphonium-salt was synthesized according to SILVA and coworkers[58] from 3.5 eq isopropyl bromide and 1.0 eq triphenylphosphine (PPh_3) in a Teflon®-coated autoclave-reactor.* In this reaction the isopropyl bromide was used as solvent to facilitate continuous stirring. Employing only 1.0 eq as it is described in literature led to unsustainable stirring during the formation of the Wittig-salt **28**.[58] Due to the instability of the corresponding ylide, the deprotonation of **28** was performed *in situ* utilizing 1.3 eq potassium *tert*-butoxide (KO*t*Bu) as a moderately strong base followed by addition of aldehyde **6b**.

In previous work by KLEINEWEISCHEDE 3-bromobenzaldehyde (**6b**) was converted to the corresponding olefin **10f** in the presence of *n*-BuLi, which represents a considerably stronger base and more difficult to handle than KO*t*Bu.[48]

* During heating to 150°C the pressure in the autoclave was <10 bar.

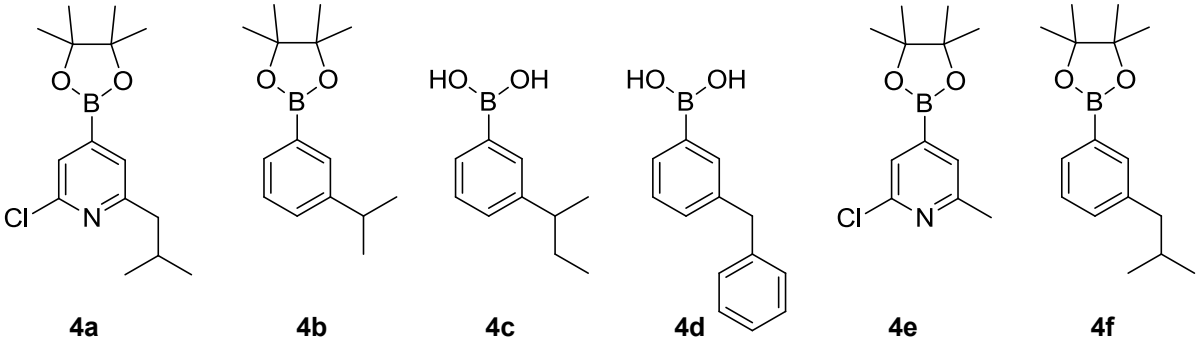


Scheme 7.19: Synthesis of 2-(3-isobutylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**4f**) starting from 3-bromobenzaldeyhde (**6b**).

General borylation methods of arenes under Miyaura-conditions have been reported in literature using inorganic bases such as alkali metal-salts of acetate (e.g., KOAc), carbonates (e.g., K_2CO_3), phosphates (e.g., K_3PO_4) or organic bases like NEt_3 or $EtN(iPr)_2$ in proper solvents like DMSO, DMF, 1,4-dioxane or even water.[59] Typical catalysts are $PdCl_2(dppf)\cdot DCM$, $Pd(PPh_3)_4$, or $Pd(OAc)_2$.

For the borylation of bromide **10f** B_2Pin_2 was used as boron nucleophile and in the presence of $PdCl_2(dppf)\cdot DCM$ as catalyst and KOAc as base. Compound **29** was isolated in very good yields (91%). The strength of the provided base is important, since stronger bases like K_3PO_4 and K_2CO_3 promote the formation of the homo-coupling by-product. Based on the good results obtained in the reduction of compound **26**, the same catalyst was used for the hydrogenation of the *iso*-butenyl derivative **29**; with PtO_2 the protodeborylation could be suppressed to a minimum.

In conclusion, retrosynthetic analysis delivered a convenient strategy to introduce building block A as a boronic acid or as a pinacol ester, suitable for the aryl-aryl coupling under Suzuki-conditions. Therefore not only the isobutyl side chain mimicking the leucine amino acid side chain was prepared, also other building blocks derived from lead-structure **1e** were successfully synthesized (Scheme 7.20).

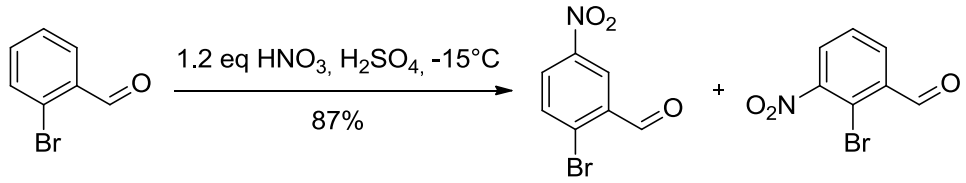


4a 73% **4b** 63% **4c** 28% **4d** 32% **4e** 77% **4f** 70%

Scheme 7.20: Overview of building blocks **4a-f** and their overall yields. The more water-soluble pyridine-based isobutyl building block **4a** and some homologs mimicking amino acid side chain of valine **4b**, isoleucine **4c** or phenylalanine **4d**. Compound **4e** represents a more polar building block to increase the solubility under physiological conditions (emulating alanine).

7.1.3 Synthesis of Building Block B

Building block B was easily be prepared by nitration of 2-bromo-benzaldehyde (**6a**) at a temperature of -15°C.[19a,60] During the reaction with HNO_3 and H_2SO_4 two regioisomers were formed (Scheme 7.21). The ratio of the formed regioisomers **5a** and **5a´** strongly depended on the temperature used within the reaction. At 0°C the formation of the unfavored regioisomer **5a´** increased, due to the electronic effects of the substituents. To ensure a high quantity of isomer **5a** the temperature was kept at -15°C.



6a **5a**:**5a´** ≈ 88:12 **5a** **5a´**

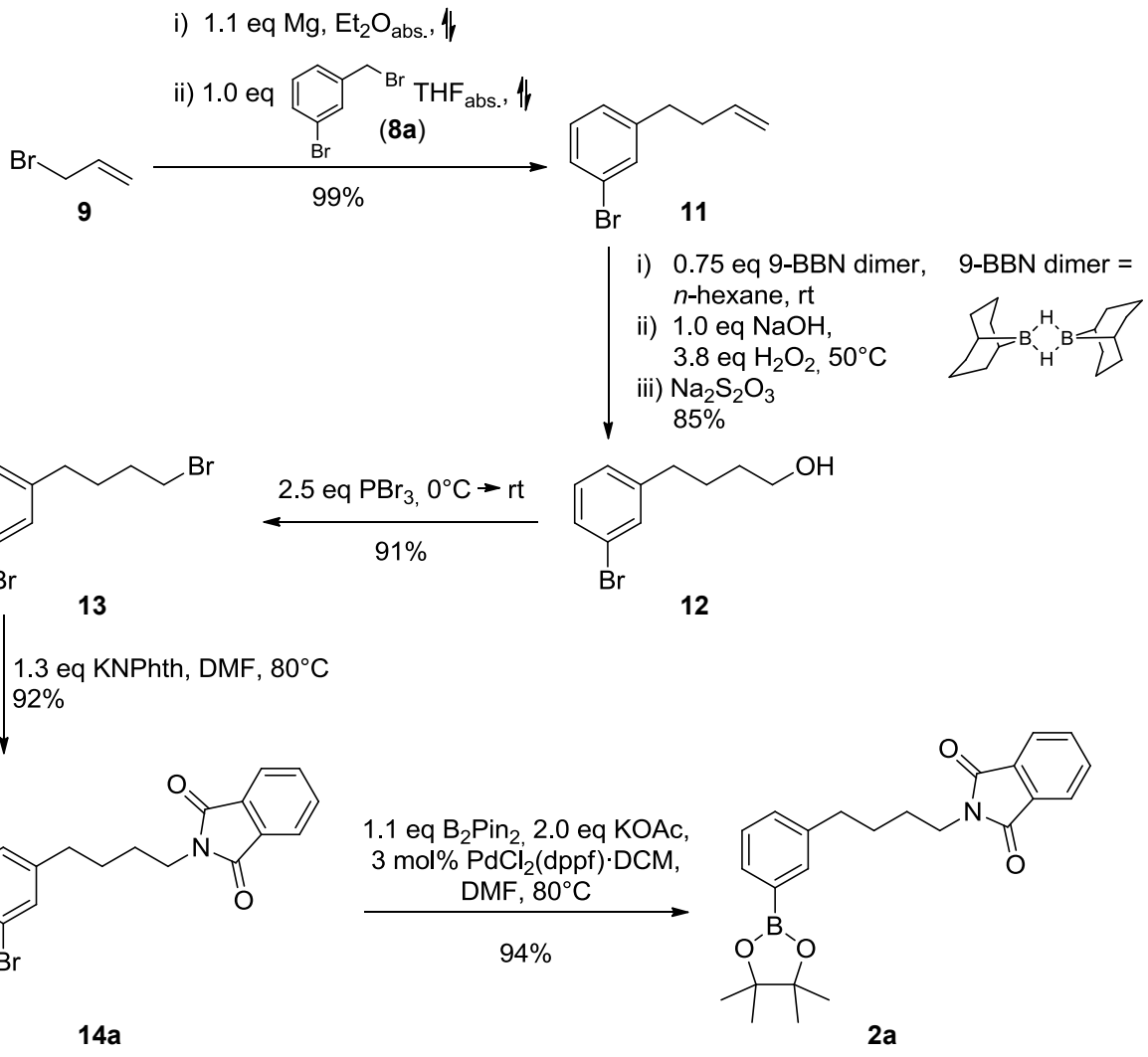
Scheme 7.21: After nitration of 2-bromo-benzaldehyde (**6a**) two regioisomers **5a** and **5a´** were obtained.[19a,60]

Although both regioisomers were formed, **5a** was effectively isolated by recrystallization from MeOH (≥99.5% by GC-MS, 87% yield).

7.1.4 Synthesis of Building Blocks C

The route for the synthesis of building block **2a** is depicted in Scheme 7.22. The elongation of the benzylic side chain of **8a** was performed by a Grignard mediated nucleophilic substitution with allyl bromide (**9**). After the formation of the allylic Grignard, the solution was cooled and cannulated to the benzyl bromide solution **8a** and heated to reflux. The isolated crude product **11** was used in the next step without further purification. Subsequently, a formal anti-Markovnikov addition of water was performed using a standard procedure for hydroboration. Addition of 9-borabicyclo[3.3.1]nonane dimer (9-BBN dimer) formed the

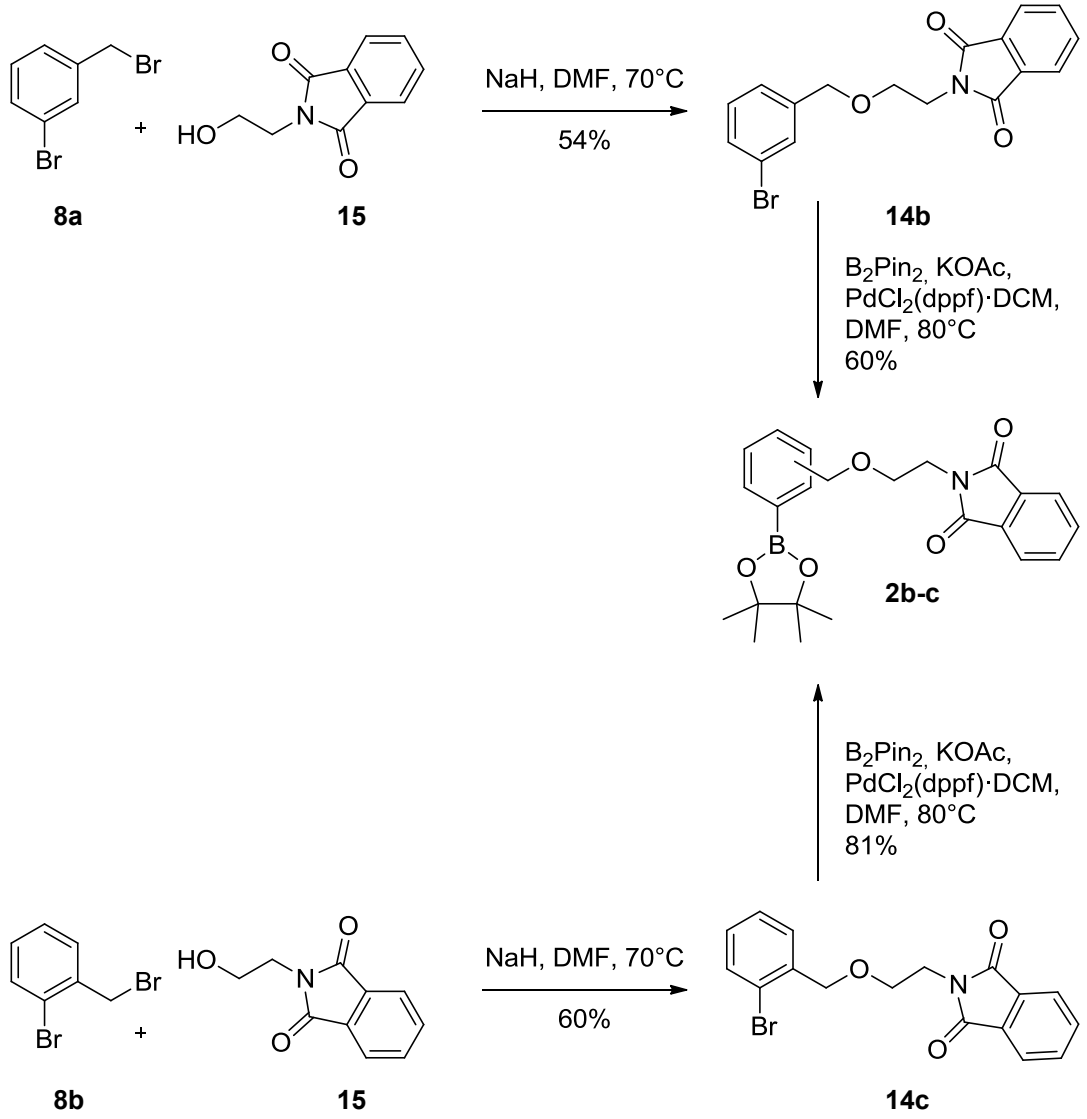
borane intermediate and after addition of 6M NaOH solution and H_2O_2 the anti-Markovnikov product **12** was isolated after workup with $Na_2S_2O_3$ solution. The primary alcohol **12** was easily converted to the primary bromide **13** with PBr_3 under neat conditions. The fast bromination had to be performed at low temperatures due to the increasing by-product formation at higher temperature. Under Gabriel-conditions the amine was introduced using KNPhth as a NH_2^--synthon in absolute DMF resulting in the phthalimide protected amine **14a**. After quantitative nucleophilic substitution, the formed *N*-substituted phthalimide **14a** was borylated according to the previously described method using $PdCl_2$(dppf)·DCM as catalyst and 2.0 eq of KOAc as base (Scheme 7.22).



Scheme 7.22: Synthesis of building block **2a**.

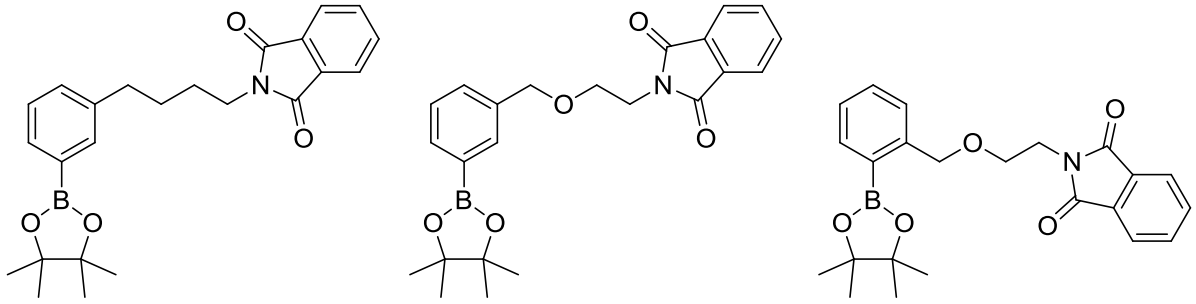
The ether bridged building blocks **2b-c** were prepared according to classic Williamson ether synthesis utilizing benzyl bromides **8a-b** as electrophiles (Scheme 7.23). NaH as a strong base was used for the deprotonation of the *N*-protected aminoethyl alcohol **15** in absolute DMF.[19a] Although by-products of the corresponding benzylic alcohols were

observed, they could be separated from the ether bridged derivatives **14b-c** by flash column chromatography. The borylation of the bromobenzene derivatives **14b-c** were again performed by a Pd-catalyzed coupling. B_2Pin_2 acts as a boron nucleophile and in presence of KOAc the desired building blocks **2b-c** could be isolated. K_2CO_3 promoted the formation of homo-coupling by-product.[19a]



Scheme 7.23: Synthesis of building blocks **2b-c**.

With the variation of the substitution pattern and the ether bridged side chain two major diversifications of building block C have been realized. The *meta*-substituted benzylic ether bridged derivative **2b** was successfully prepared in an overall yield of 32%. The *ortho*-substituted ether bridged derivative **2c** could be obtained in the same manner in an overall yield of 49%. The building block **2a** was synthesized over five steps in excellent yield of 66% (Scheme 7.24).



2a 66%

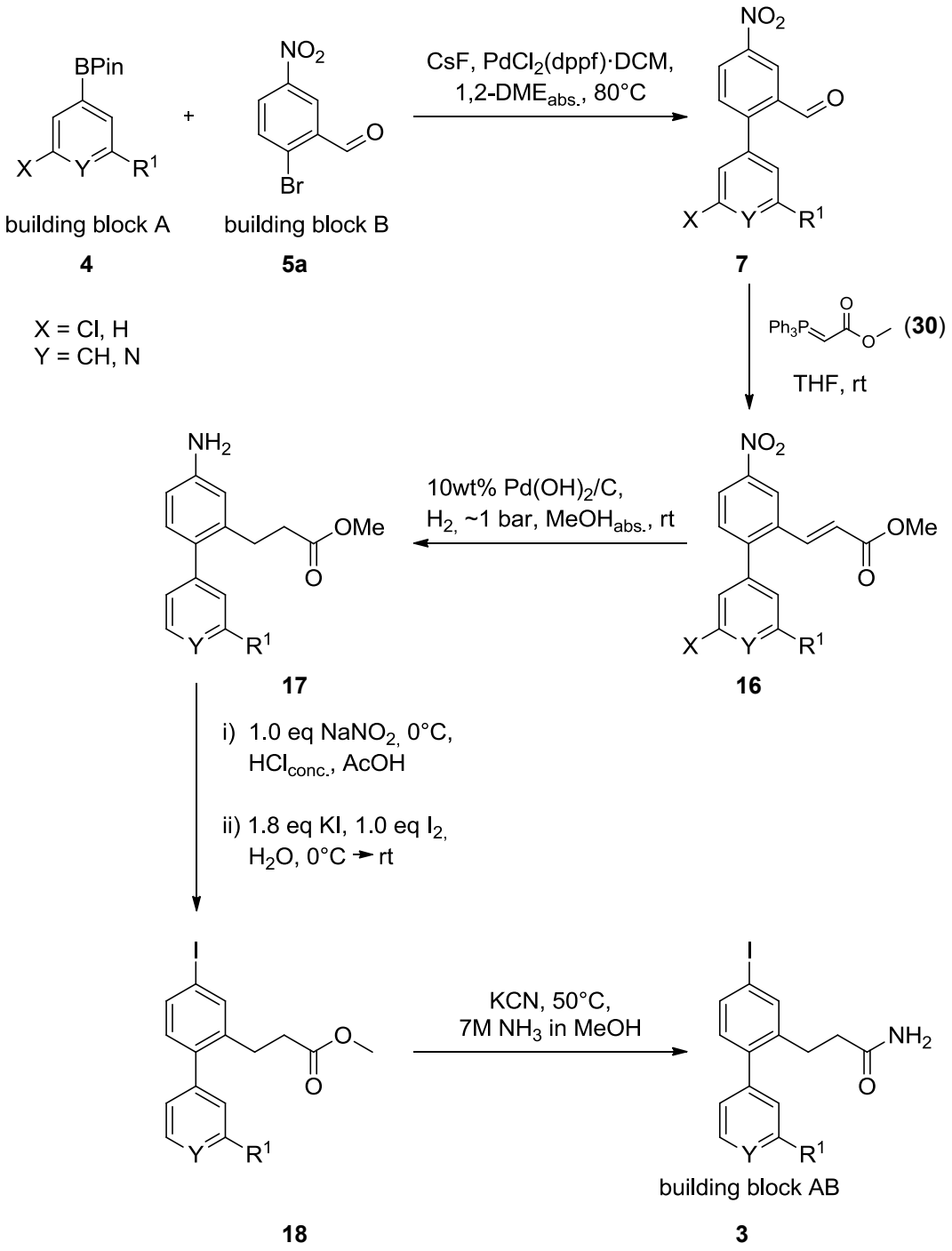
2b 32%

2c 49%

Scheme 7.24: Overview of building blocks C. **2a** with a non-ether bridged *meta*-substitution pattern and building blocks **2b**-**c** with the modified ether moiety in benzyl position.

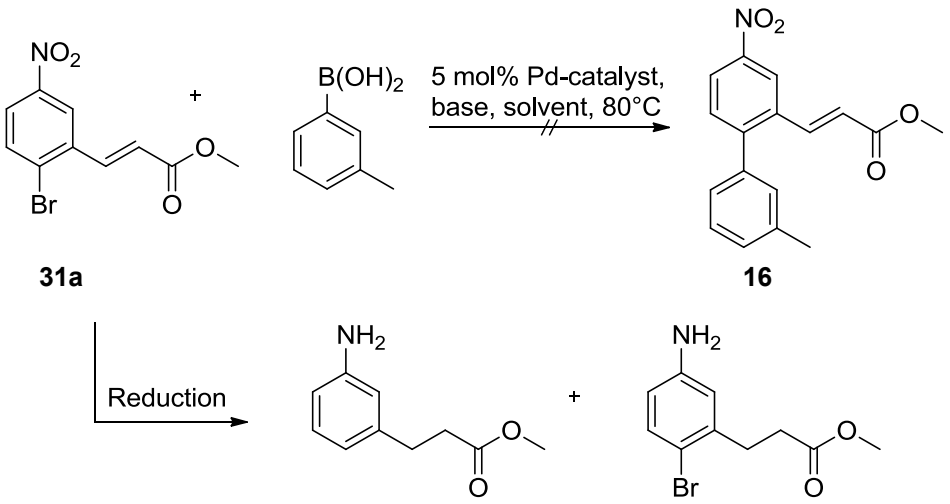
7.1.5 Synthesis of Building Blocks AB

The detailed synthetic route towards building block AB is shown in Scheme 7.25. Starting from 2-bromo-5-nitrobenzaldehyde (**5a**) and building block A the biphenylic derivative **7** could be obtained under Suzuki-conditions. To introduce the glutamine side chain several steps had to be performed. First of all the side chain was elongated by a Wittig reaction with the corresponding methylester ylide **30**. The resulting α,β-unsaturated methylester **16** was reduced under hydrogen atmosphere. Simultaneously, the nitro group of compound **16** was reduced under the used conditions. In case of **4a** and **4e** the chloride in 2-position of the pyridine moiety was also cleaved at the same time. After the iodination of compound **17** under modified Sandmeyer-conditions, the amidation of the resulting iodine-methylester **18** was performed in ammonia solution with catalytic amounts of potassium cyanide (KCN) in MeOH.[19a,48]



Scheme 7.25: Synthetic route for the synthesis of glutamine side chain (Gln) furnishing building block AB.

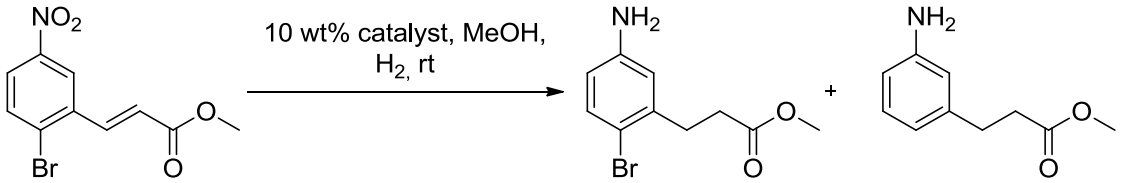
Previous studies had shown that *ortho*-bromo α,β-unsaturated acrylates like **31a** (a possible derivative of building block B) are not suitable for Suzuki-coupling (Scheme 7.26).[48] Apparently the Pd-catalyst forms a π-complex with the acrylate side chain in *ortho*-position under these conditions and thus is inactivated for the catalytic cycle (see also chapter 7.2).



Scheme 7.26: Model reaction for screening the Suzuki-conditions of coupling *ortho*-bromo α,β-unsaturated acrylate **31a**.[19a]

The easiest way to circumvent this problem would be the reduction of the unsaturated moiety *ortho* to the bromine of compound **31a**. Performing the reaction under different hydrogenation conditions however led to debromination of **31a** (Table 7.1). The best results were obtained using PtS_x/C^* as catalyst. However, an inseparable mixture of unreacted starting material **31a**, product and undesired by-product were obtained, after the catalyst was removed by filtration. When running the reaction to quantitative conversion, the debromination became the main reaction pathway.

Table 7.1: Screening of hydrogenation conditions for the reduction of acrylate **31a**.



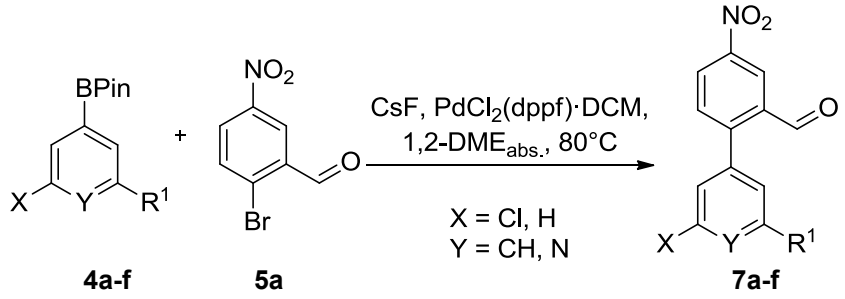
Entry	Catalyst	Conversion[a]	Product[b]	By-Product[b]
1	PtO_2	100% (3 h)	19%	73%
2	Pt/C	100% (3 h)	54%	46%
3	PtS_x/C^*	83% (2.5 h)	67%	16%

[a] Conversion of the starting material and reaction time. [b] Calculated by relative intensities of the GC-MS spectra without internal standard.

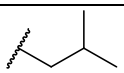
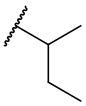
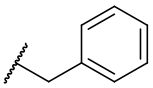
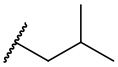
To avoid this problem it was necessary to couple building block A and B prior to the Wittig reaction as it is shown in Scheme 7.25. Table 7.2 gives an overview of the first Suzuki-coupling of the building blocks **4a-g** with compound **5a**.

* Platinum, 3% on activated carbon, sulfided, 50-70% wetted powder.

Table 7.2: Synthesis of biaryl-5-nitrobenzaldehyde derivatives **7a-f**.



4a-f **5a** **7a-f**

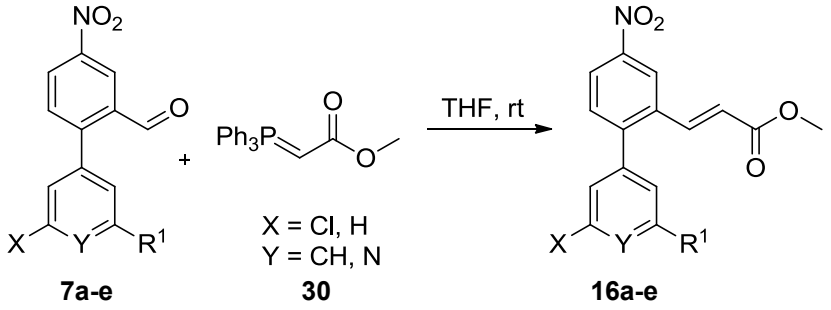
Entry	X	Y	R^1	Compound[a]
1	Cl	N		**7a** (92%)
2	H	CH		**7b** (99%)
3	H	CH		**7c** (97%)
4	H	CH		**7d** (92%)
5	Cl	N		**7e** (72%)
6	H	CH		**7f** (91%)

[a] Isolated yields.

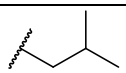
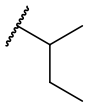
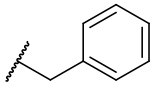
In a typical experiment, 1.1 eq of the corresponding aryl boronic acid derivatives **4a-f**, 1.0 eq 2-bromo-5-nitrobenzaldehyde (**5a**), 2.0-3.0 eq CsF and 3-5 mol% $PdCl_2$(dppf)·DCM in absolute, degassed 1,2-DME were used. With this general procedure good up to excellent yields between 72% and 99% could be obtained (Table 7.2).

Table 7.3 shows the results of the Wittig reaction of methyl acetate ylide **30** and biaryl-5-nitrobenzaldehyde derivatives **7a-e**. The phosphonium precursor was synthesized from 1.0 eq PPh_3 and 1.1 eq methyl 2-bromoacetate in EtOAc.[61] After deprotonation with aqueous NaOH solution the stable methylester ylide **30** was formed in very good yields (90%).[19a] The phosphonium-salt itself can also be used in the Wittig reaction, but an additional base (such as NaOMe or KO*t*Bu) has to be applied by decreasing the isolated yield.

Table 7.3: Synthesis of 3-(phenyl)acrylate derivatives **16a-e**.



7a-e **30** **16a-e**

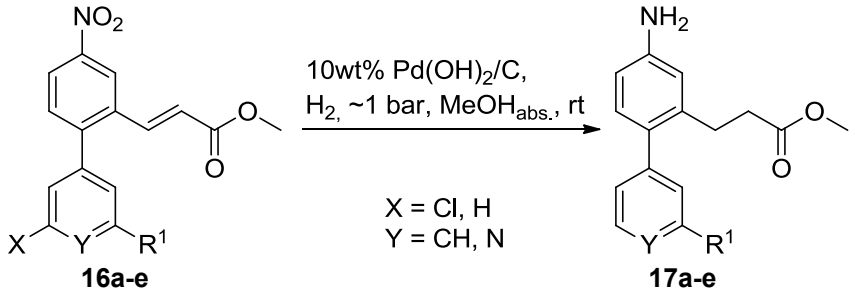
Entry	X	Y	R^1	*E*/*Z* Ratio[a]	Compound[b]
1	Cl	N		100/0	**16a** (98%)
2	H	CH		84/16	**16b** (99%)
3	H	CH		79/21	**16c** (quant.)
4	H	CH		91/9	**16d** (quant.)
5	Cl	N		94/6	**16e** (99%)

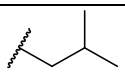
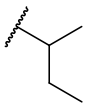
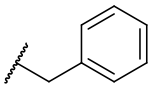
[a] Calculated by relative intensities of the GC-MS spectra without internal standard. [b] Isolated yields.

The reaction was performed using a general procedure: the appropriate aldehydes **7a-e** were dissolved in absolute, degassed THF and after addition of 1.0-1.5 eq of the methylester ylide **30** the resulting mostly colorless suspension was stirred until quantitative conversion was detected by GC-MS. After purification by flash column chromatography the 3-(phenyl)acrylate derivatives **16a-e** were isolated in excellent yields.

To afford the desired biarylic amines **17a-e**, a reduction of the obtained α,β-unsaturated acrylates was performed using palladium(II)hydroxide on activated charcoal ($Pd(OH)_2/C$) as the catalyst (Table 7.4). During this procedure in absolute MeOH under hydrogen atmosphere up to three reactions were performed simultaneously: reduction of the nitro group and the acrylate moiety and a dechlorination in the case of 2-chloropyridine building blocks **4a** and **4e**.

Table 7.4: Synthesis of methyl-propanoate derivatives **17a-e**.



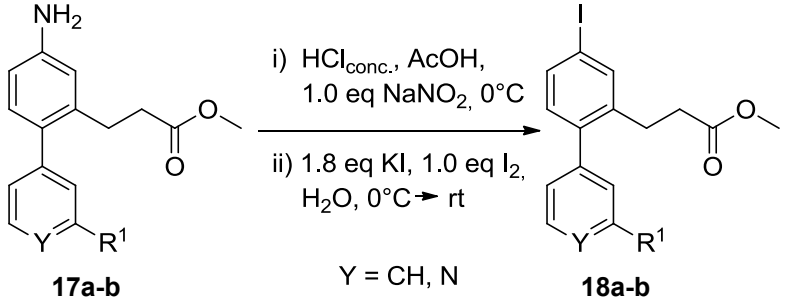
Entry	Y	R^1	Reaction Time[a]	Compound
1	N		45 h (88%)	**17a**
2	CH		3 h (99%)	**17b**
3	CH		3.5 h (quant.)	**17c**
4	CH		3.5 h (quant.)	**17d**
5	N		7.5 h (91%)	**17e**

[a] Isolated yield.

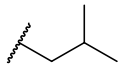
After the catalyst was removed by filtration, the resulting methyl 3-phenylpropanoate derivatives **17a-e** were purified by flash column chromatography.

For the iodination of arylamines **17a-b** a modified Sandmeyer reaction was applied. After dissolving the amines **17a-b** in glacial acetic acid and fuming HCl, an ice cooled aqueous solution of $NaNO_2$ and a KI/I_2 solution were added rapidly (Table 7.5). After stirring the reaction mixture overnight it was quenched with $Na_2S_2O_3$ solution followed by neutralization to finally obtain the desired aryliodides **18a-b**.

Table 7.5: Iodination under modified Sandmeyer-conditions of biarylic amines **17a-b**.



17a-b **18a-b**

Entry	Y	R^1	Yield[a]	Compound
1	N		86%	**18a**
2	CH		64%	**18b**

[a] Isolated yield.

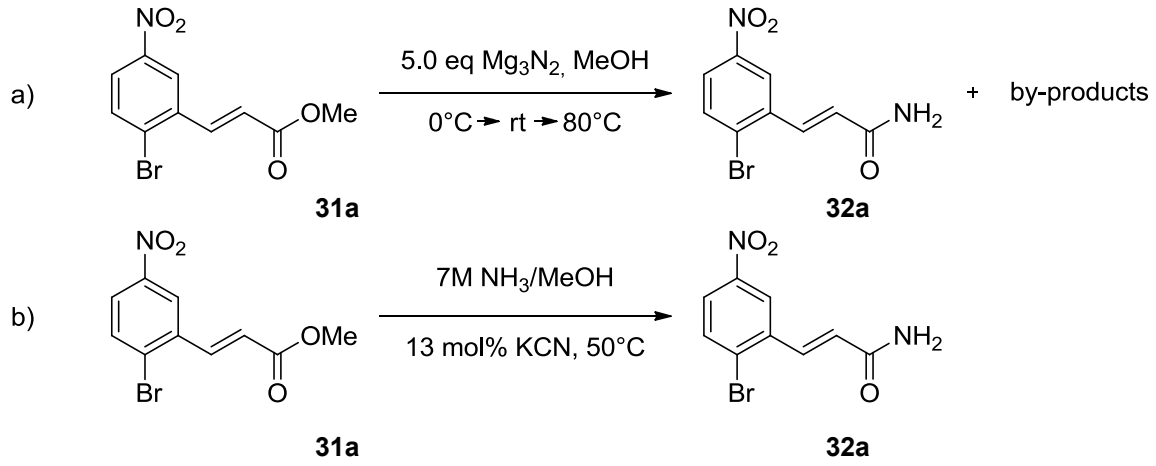
In the last step of synthesizing building block AB the amidation of the corresponding methylesters **18a-b** was performed. For this reaction two different conditions were investigated. On the one hand a magnesium nitride (Mg_3N_2) mediated reaction was examined. In the presence of MeOH the reactive magnesium-salt generates $Mg(OMe)_2$ and ammonia, which should convert the corresponding methylester to the primary amide (Equation 7.1).[62]

$$Mg_3N_2 + 6\ MeOH \longrightarrow 2\ NH_3 + 3\ Mg(OMe)_2$$

Equation 7.1: *In situ* generation of ammonia by dissolving magnesium nitride (Mg_3N_2) in MeOH.[62]

On the other hand a KCN-catalyzed amidation was performed. Both conditions were investigated using the α,β-unsaturated methylester **31a** as model substrate (Scheme 7.27). In the Mg_3N_2 mediated amidation 10 eq of NH_3 were applied (5 eq Mg_3N_2), in the KCN-catalyzed amidation a 7M ammonia/MeOH solution was used.

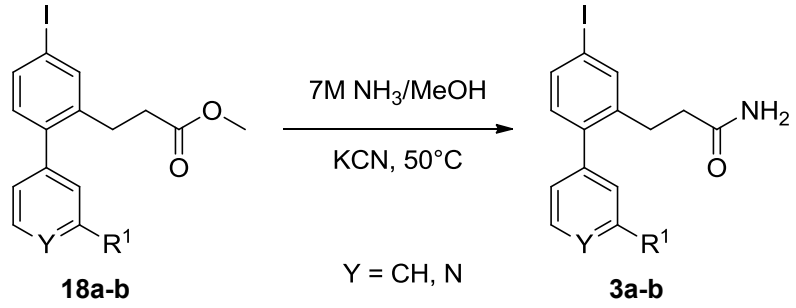
Variant a in Scheme 7.27 gave an inseparable mixture of unreacted starting material **31a** (~80% conversion), product **32a** and not closely defined by-products. Furthermore it has been reported that explosions can occur using Mg_3N_2. The magnesium-salt reacts rapidly and very exothermically with water (ΔH = -165 kcal/mol) to form magnesium hydroxide ($Mg(OH)_2$) and NH_3 so that the reaction had to be performed in absolute MeOH.[63] Variant b has been proven to be more advantageous with quantitative conversion after 8 d stirring at 50°C.

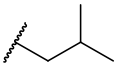


Scheme 7.27: Overview of the two amidation methods; the *in situ* generation of ammonia (a)* and the KCN-catalyzed amidation in an ammonia/MeOH mixture (b).*

Encouraged by the promising results, the last reaction step of building block AB was performed by the KCN-catalyzed amidation method for compounds **18a-b** (Table 7.6).

Table 7.6: KCN-catalyzed amidation of methylesters **18a-b** to the final building blocks **3a-b**.



Entry	Y	R^1	KCN	Time	Yield[a]	Compound
1	N		15 mol%	7 d	84%	**3a**
2	CH		16 mol%	3 d	91%	**3b**

[a] Isolated yields.

The formation of building block AB utilizing catalytic amounts of KCN was performed in an ammonia/MeOH mixture at 50°C in a pressure tube. Although long reaction times up to a week had to be performed, the resulting products **3a-b** were isolated in good to very good yields without significant formation of by-products (84-91%).

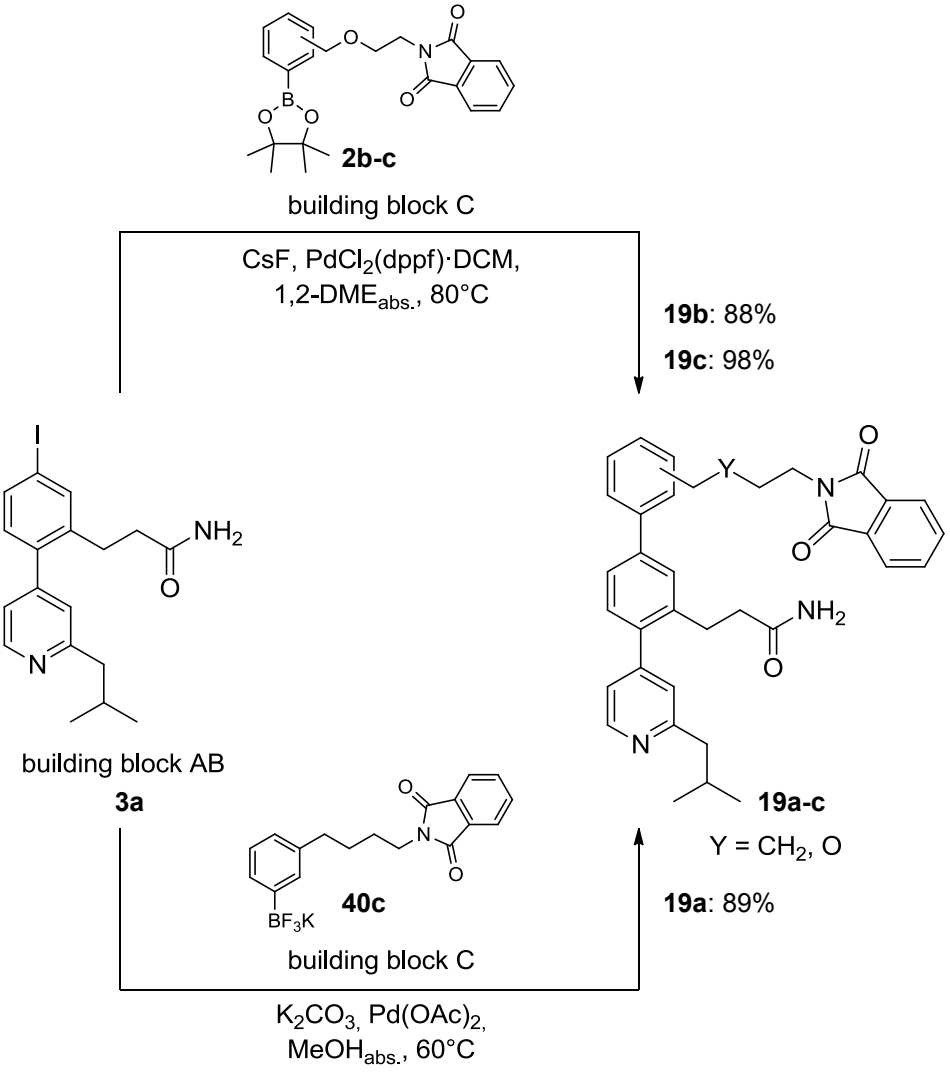
According to Scheme 7.25 two different building blocks AB were successfully synthesized. The five step synthesis was carried out in an overall yield of 57% for both

* Conversion only monitored by GC-MS.

compounds **3a** and **3b**. For the whole synthesis of compounds **3a-b** (including the synthesis of building blocks A and B) a 9 steps synthesis for **3a** (33%) and a 8 steps synthesis for **3b** (28%) were necessary.

7.1.6 Synthesis of Teraryls

The last two steps in the whole synthesis were the Suzuki-coupling (Scheme 7.28) followed by the deprotection of the phthalimide masked primary amine to generate the free lysine side chain (Table 7.7). The coupling of building block AB and **2b-c** was performed according to previously described conditions, utilizing $PdCl_2(dppf)\cdot DCM$ as catalyst and KOAc in absolute, degassed 1,2-DME. In addition, a modified aryl-aryl coupling has been investigated. Compound **19c** was synthesized by coupling building block AB with the potassium-salt **40c** in absolute MeOH using $Pd(OAc)_2$ in catalytic amounts.

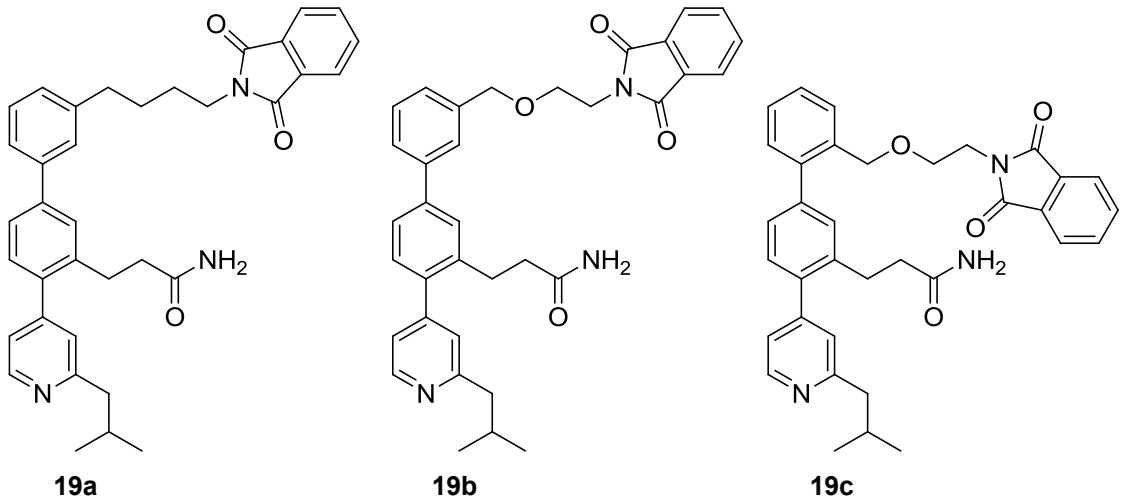


Scheme 7.28: The second aryl-aryl coupling of building block AB and C furnished the final terarylic scaffold.

The BF_3K-salt **40c** was easily prepared by converting pinacol ester **2a** with potassium fluoride (KHF_2) in a water/MeOH mixture (see also page 54).

Comparing these two reaction conditions, only slight differences were observed in reaction time, reactivity and isolated yield.

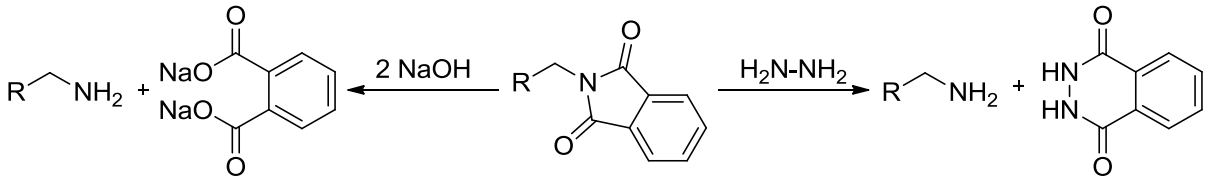
In Scheme 7.29 the synthesized phthalimide protected teraryls **19a-c** are depicted. The lysine side chain of the upper building block C was modified by different substitution pattern and an ether function in benzyl position to increase the polarity of the lysine alkyl chain.



19a **19b** **19c**

Scheme 7.29: Synthesized phthalimide protected teraryls **19a-c**.

In the final step the deprotection under Gabriel-conditions had to be processed. While the hydrolysis of the phthalimide utilizing aqueous NaOH solution required relatively harsh conditions, the conversion with hydrazine monohydrate ($H_2N\text{-}NH_2 \cdot H_2O$) could be performed under much milder conditions (Scheme 7.30).

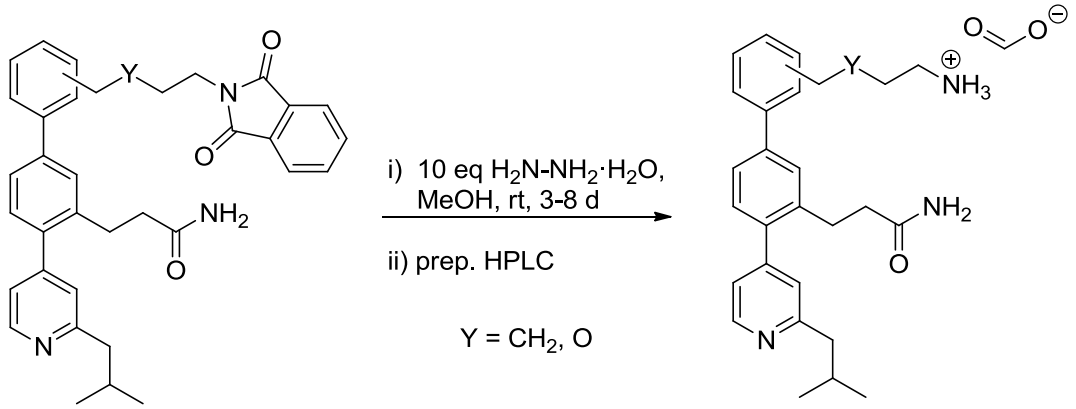


Scheme 7.30: Reaction conditions for the cleavage of a phthalimide protected primary amines.

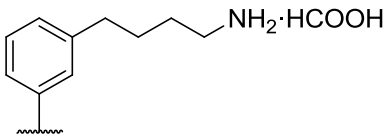
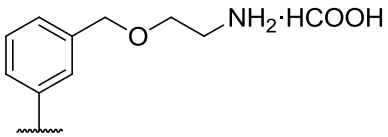
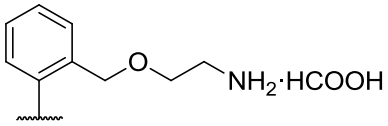
Although the reaction under mild conditions required longer reaction times, higher yields of the final deprotected teraryls **1a-c** were obtained utilizing $H_2N\text{-}NH_2 \cdot H_2O$ (N_2H_4, 64-65%, reagent grade) in MeOH compared to the harsher method applying aqueous NaOH.

The results of the deprotection are summarized in Table 7.7.

Table 7.7: Cleavage of phthalimide protected amines **19a-c** to the final lysine side chain of teraryls **1a-c**.



19a-c **1a-c**

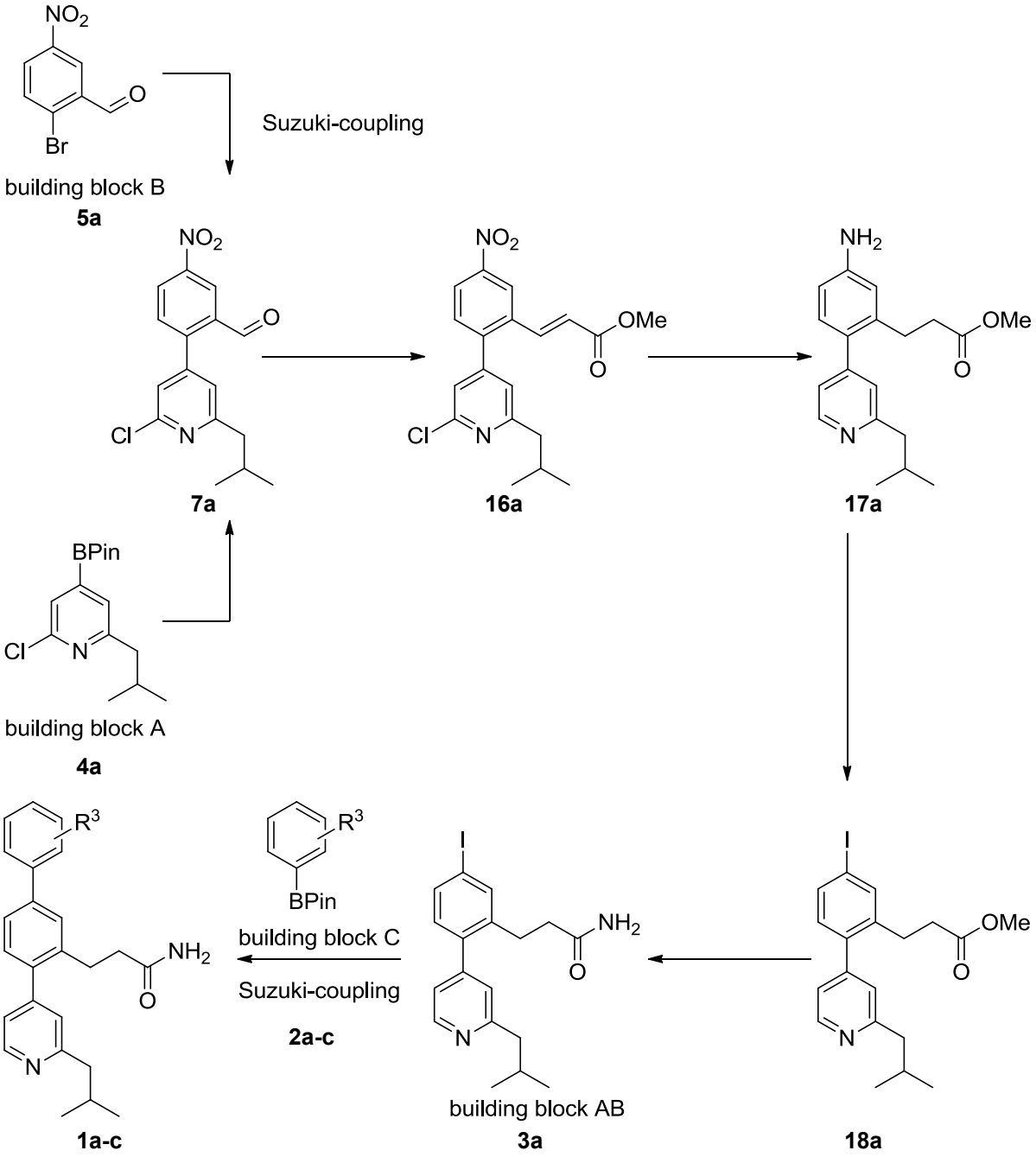
Entry	Lysine Side Chain	Time	Yield[a]	Compound
1		8 d	73%	**1a**
2		6 d	76%	**1b**
3		3 d	77%	**1c**

[a] Isolated yields after preparative HPLC.

To ensure a high purity of the final products **1a-c** the teraryls were purified by preparative HPLC. Due to the fact that the purification was performed in an aqueous formic acid solution, the amine function of the lysine side chain was protonated to its formiate form. This had the advantageous effect, that the isolated products were obtained as salts and in addition the solubility of the teraryls **1a-c** could be increased in aqueous solutions.

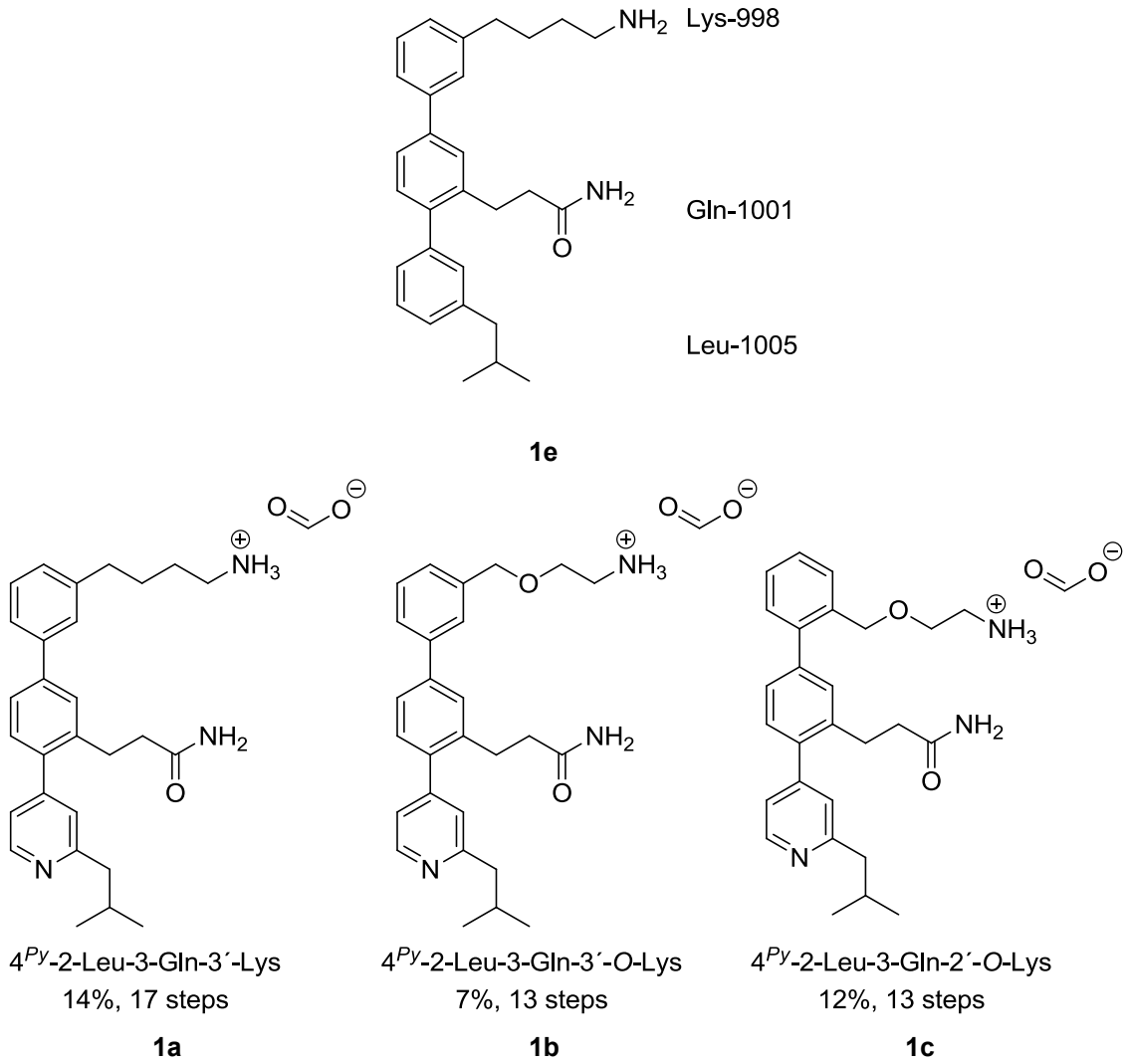
7.1.7 Summary of the Linear Approach

In Scheme 7.31 the entire synthesis of the teraryls **1a-c** is summarized. Starting from building blocks **5a** and **4a** the biarylic aldehyde **7a** was prepared. Introducing the glutamine side chain was realized over four steps. After a Wittig reaction the resulting methyl acrylate **16a** was reduced to its saturated form and after iodination under modified Sandmeyer-conditions the amide function was introduced by a KCN-catalyzed amidation. In the final steps the second Suzuki-coupling leads to the terarylic scaffold and after deprotection of the amine function of the lysine side chain the desired teraryls **1a-c** were obtained.



Scheme 7.31: Synthesis of teraryls **1a-c** using the linear approach. Essential to this synthesis were the two Suzuki-coupling steps for assembling the terarylic scaffold.

Three different teraryls were successfully synthesized by using the linear approach (Scheme 7.32). Based on lead-structure **1e** the teraryl **1a** was prepared in 17 steps with an overall yield of 14%. Teraryl **1b** and **1c** were obtained in 13 steps with an overall yield of 7% for **1b** and 12% for teraryl **1c**.

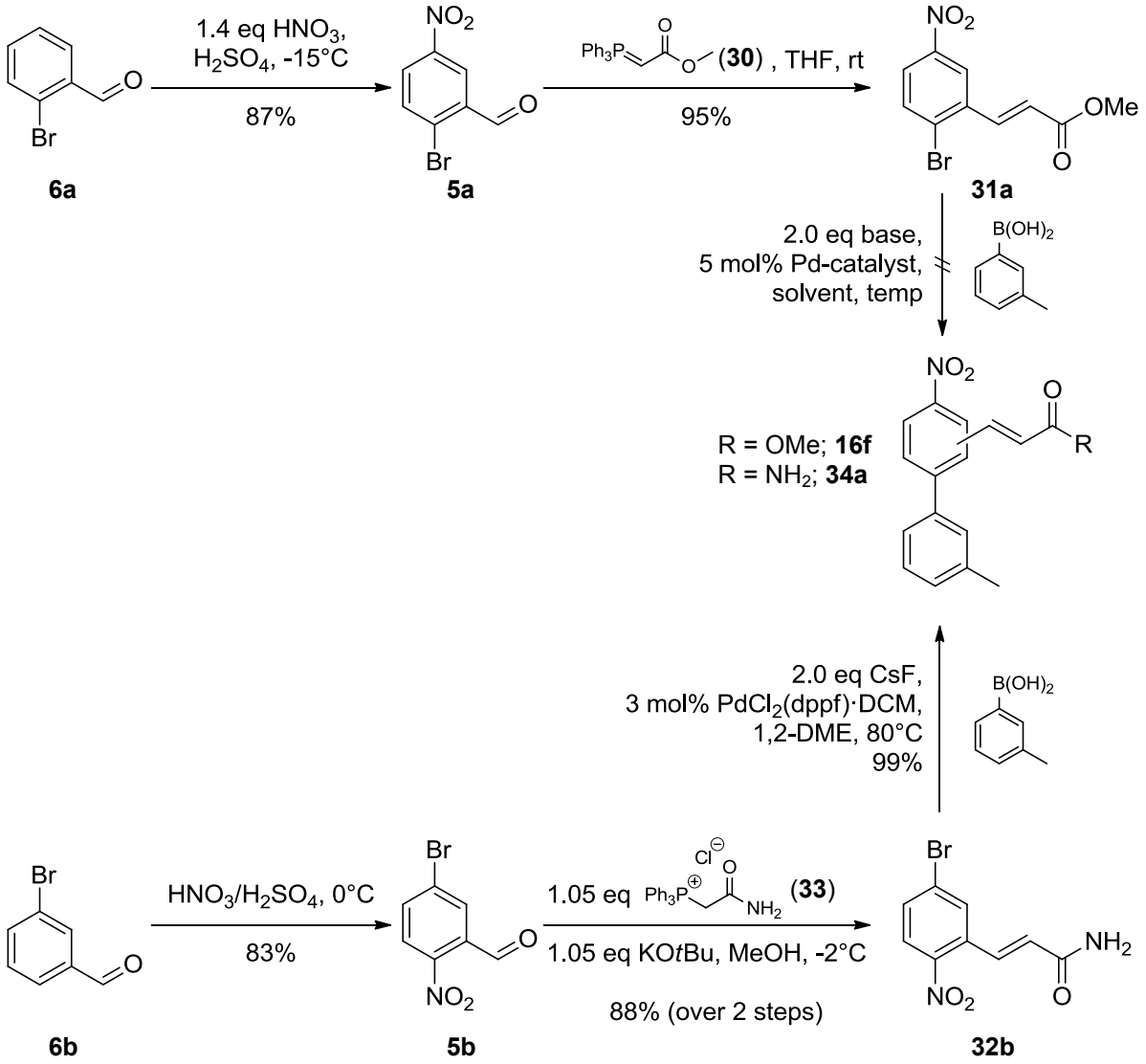


Scheme 7.32: Lead-structure **1e** and overview of the synthesized teraryls **1a-c** with its overall yields.

7.2 Synthesis of Terphenyls using the Diazonium Approach

Taking into account that *ortho*-substituted acrylates like **31a** are not suitable for the chosen aryl-aryl coupling conditions (see also Scheme 7.26) an alternative synthetic strategy was developed (Scheme 7.33).

After nitration of 3-bromobenzaldehyde (**6b**) using HNO_3/H_2SO_4 as solvent mixture, 5-bromo-2-nitrobenzaldehyde (**5b**) was isolated in 83% yield.[64] Similar to the methyl acrylate side chain of compound **31a** the glutamine moiety was introduced under Wittig-conditions utilizing Wittig-salt **33** in the presence of KO*t*Bu. Due to the substitution pattern of the resulting acrylamide **32b** the α,β-unsaturated residue is now in *meta*-position to the halide leaving group (compare Scheme 7.26).

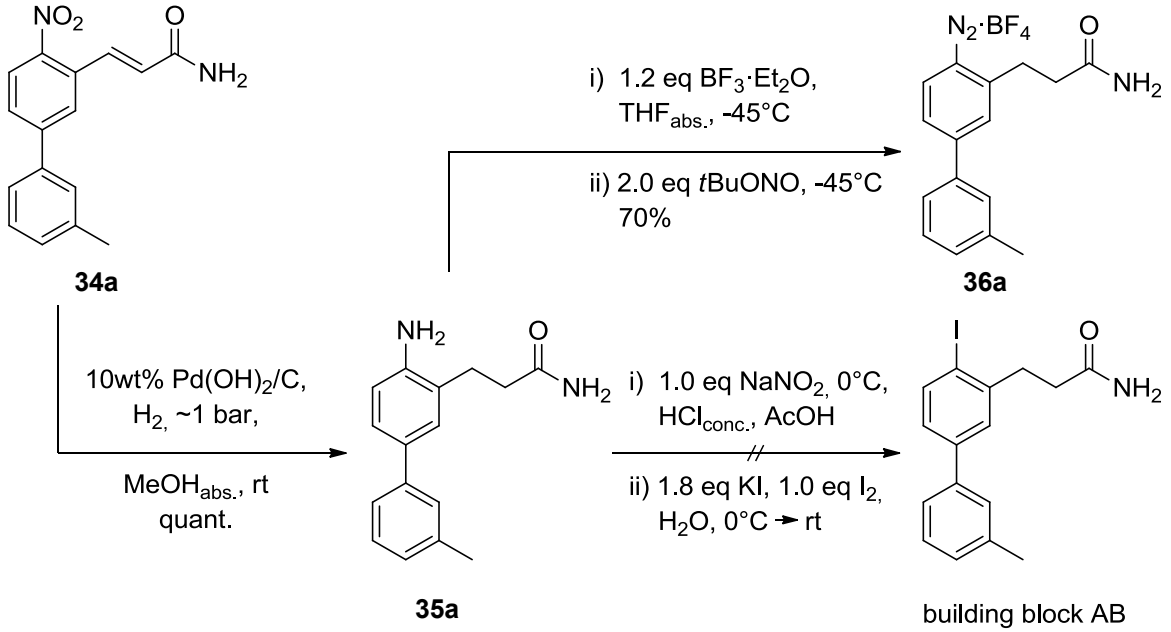


Scheme 7.33: 2,5-Disubstituted phenylacrylamide **32b** in the Suzuki-coupling with *m*-tolylboronic acid as model substrate. The α,β-unsaturated acrylic residue *meta* to the bromide does not interferes the Pd-catalyzed cross-coupling, whereby *ortho*-derivative **31a** gave no desired coupling product at all.

The formation of the previously described π-complex of the involved palladium species should now be suppressed, which might be beneficial for the Suzuki-coupling (see also page 31).

To prove this hypothesis, acrylamide **32b** was coupled under Suzuki-conditions as described above (Scheme 7.33) and excellent yield (99%) could be obtained using *m*-tolylboronic acid as substrate.

After reduction of the formed acrylamide **34a** utilizing $Pd(OH)_2/C$ under hydrogen atmosphere the saturated amine **35a** was isolated in quantitative yield (Scheme 7.34). As it has been mentioned above for the *ortho*-substituted derivatives (see also page 36), iodination was performed in the next step resulting in the final building block AB.



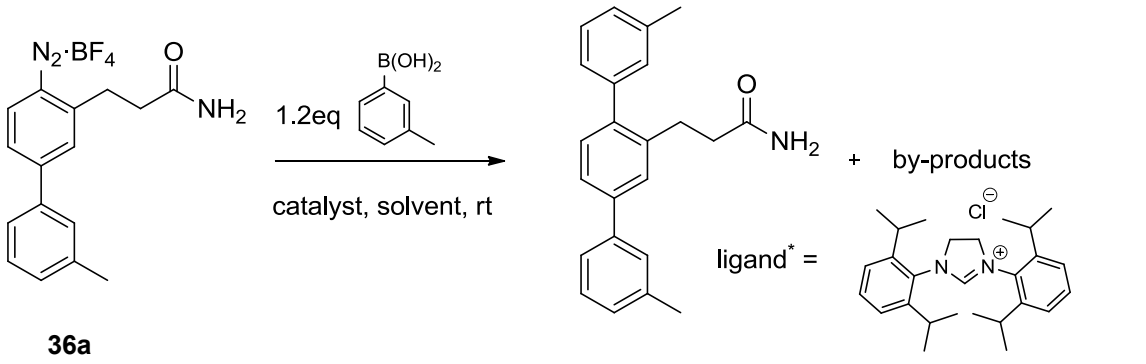
Scheme 7.34: Quantitative hydrogenation of acrylamide **34a** furnishing amine **35a**. The iodination under modified Sandmeyer-conditions however proved to be unsuccessful. The derivatization of the amine function to the diazonium derivative afforded compound **36a** in 70% isolated yield.

From a mechanistic point of view the first step of the modified Sandmeyer reaction is the *in situ* formation of the corresponding diazonium-salt by treatment with $NaNO_2$ under acidic conditions. In the second step, the formed diazo group is converted to the iodine by addition of a KI/I_2 mixture. The formation of the desired iodine in case of amine **35a** however could not be observed under the chosen conditions, while the corresponding methylester derivatives could be iodinated in good to very good yields (compare Table 7.5, page 36).

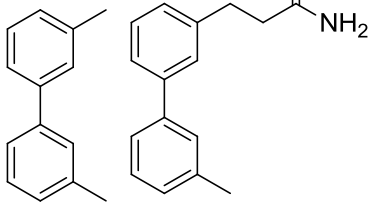
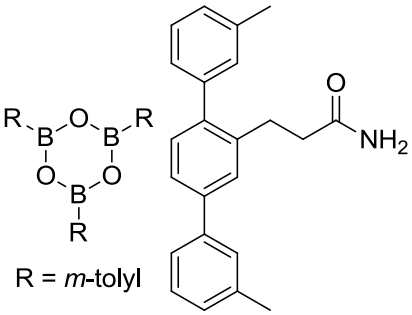
To investigate whether the formation of the diazo group or the iodination step is the limiting fact, amine **35a** was proved to be suitable for the formation of a stable diazonium-salt like trifluoroborate-salts (BF_3K-salts).

During the last decade the diazonium group has received increasing attention as a very reactive leaving group for Pd-catalyzed cross-coupling,[65] for which the sequence of reactivity is known to be in the order -N_2^+, -I, -Br, -OTf, -Cl.[66] For that purpose the diazonium-salt **36a** was tested in the aryl-aryl coupling reaction. First attempts of the aryl-aryl coupling using *m*-tolylboronic acid and diazonium derivative **36a** are summarized in Table 7.8. Best results were obtained by a $Pd(OAc)_2$-catalyzed reaction in absolute MeOH at room temperature. Using the same catalyst in 1,4-dioxane however did not result in terphenylic product (Table 7.8).

Table 7.8: First attempts of diazonium-coupling of compound **36a** and *m*-tolylboronic acid.

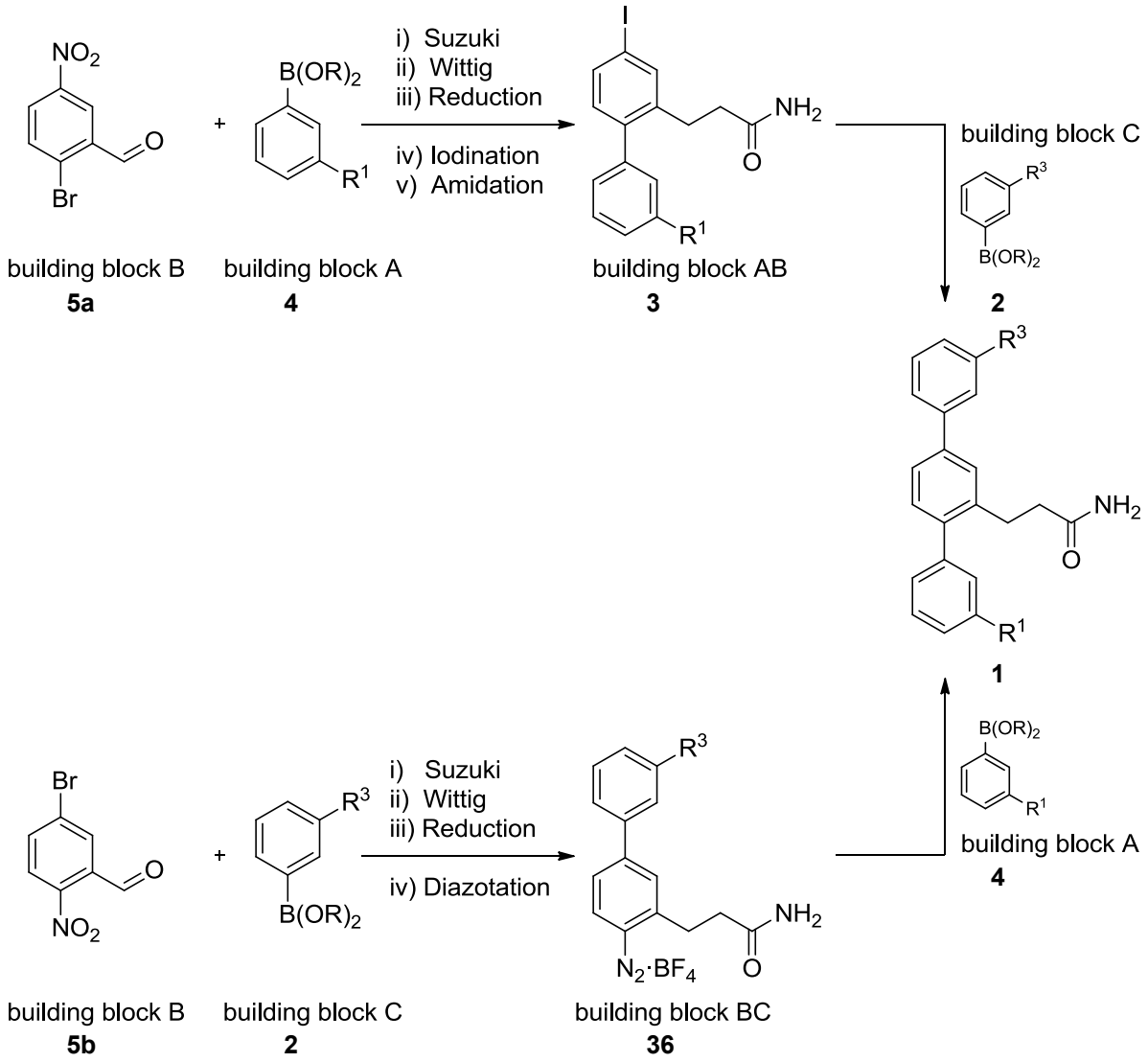


36a

Entry	Conditions[a]	By-Products[b]			Product[b]
					
		A	**B**	**C**	
1	5 mol% $Pd(OAc)_2$, 1,4-dioxane, rt	19%	79%	2%	/
2	5 mol% $Pd(OAc)_2$, MeOH, rt	16%	19%	/	65%
3	5 mol% $Pd(OAc)_2$, 5 mol% ligand*, THF, rt	21%	41%	1%	37%
4	10 wt% Pd/C,[c] MeOH, rt	9%	16%	14%	61%

[a] Absolute, degassed solvents were applied. [b] Calculated by relative intensities of the GC-MS spectra without internal standard. [c] 5% Pd basis (based on dry substance).

Although the glutamine side chain in this reaction sequence is now in *ortho*-position to the upper building block (compound **34a** vs. **16a-e**), the reaction pathway would give a new opportunity to reduce the number of reaction steps and potentially increase the overall yields. But by coupling building block **5b** with one of the building blocks C first, the obtained building block BC (compound **36**) could further be coupled under Suzuki-conditions with building block A to form the desired 2',3,3"-trisubstituted terphenylic scaffold (Scheme 7.35).



Scheme 7.35: Overview for the synthesis of building blocks AB and BC starting from iodine derivative **3** or diazonium derivative **36**. Both reaction pathways led to the desired 2',3,3"-trisubstituted terphenylic scaffold **1**.

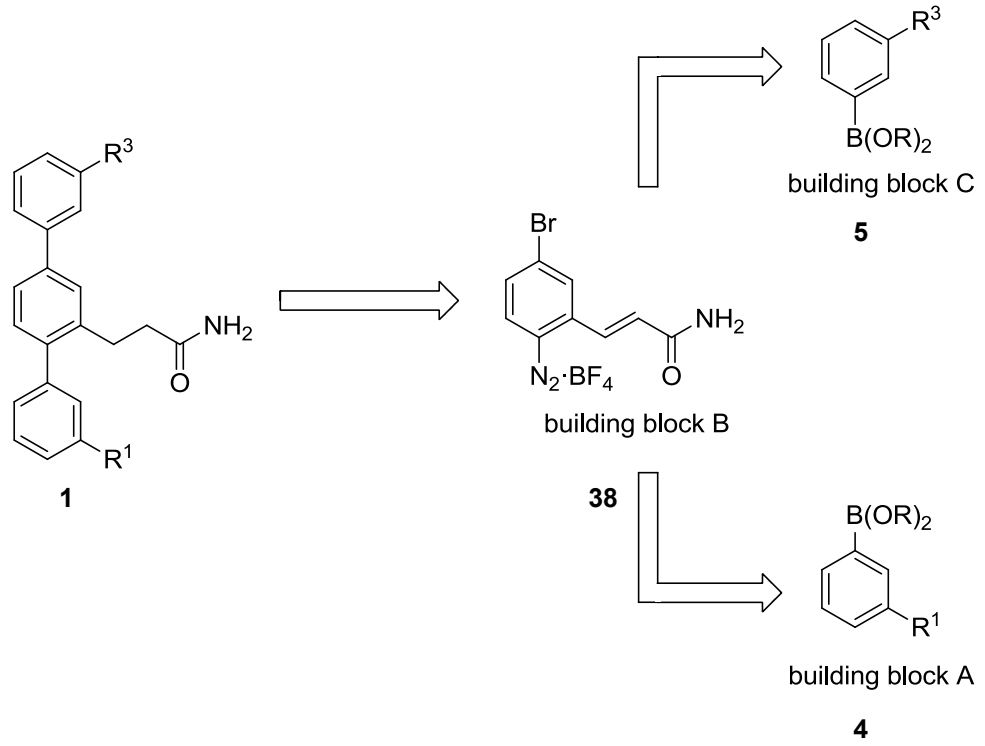
An additional advantage of introducing the side chain by utilizing the amide Wittig-salt **33** (Scheme 7.33) is the time consuming and also poisonous amidation step (KCN, ammonia/MeOH) could know be avoided (compare Table 7.6).

Encouraged by the promising results that the diazonium function could be used for the synthesis of 2',3,3''-trisubstituted terarylic scaffolds, a new diazonium-based retrosynthetic variation was intended.

7.2.1 Retrosynthesis

The formation of lead-structure-based teraryls **1a-c** could be impressively demonstrated using the linear approach (see also chapter 7.1.7). However, a convergent synthetic strategy of a core unit with two differentiated leaving groups in the Pd-catalyzed synthesis seems to be a decent design for a convenient and more flexible approach (Scheme 7.36).

In the retrosynthetic analysis the first disconnection occurs at the C-C bond between building blocks A and B, subsequently followed by the second Pd-catalyzed cross-coupling step of the resulting building block AB and building block C. The two differentiated functional groups in the core unit **38** (diazo and halide function) should ensure the regioselectivity for the consecutive cross-coupling steps.



Scheme 7.36: Synthetic strategy using diazonium core unit **38** with two differentiated leaving groups suitable for regioselective Pd-catalyzed cross-coupling reactions.

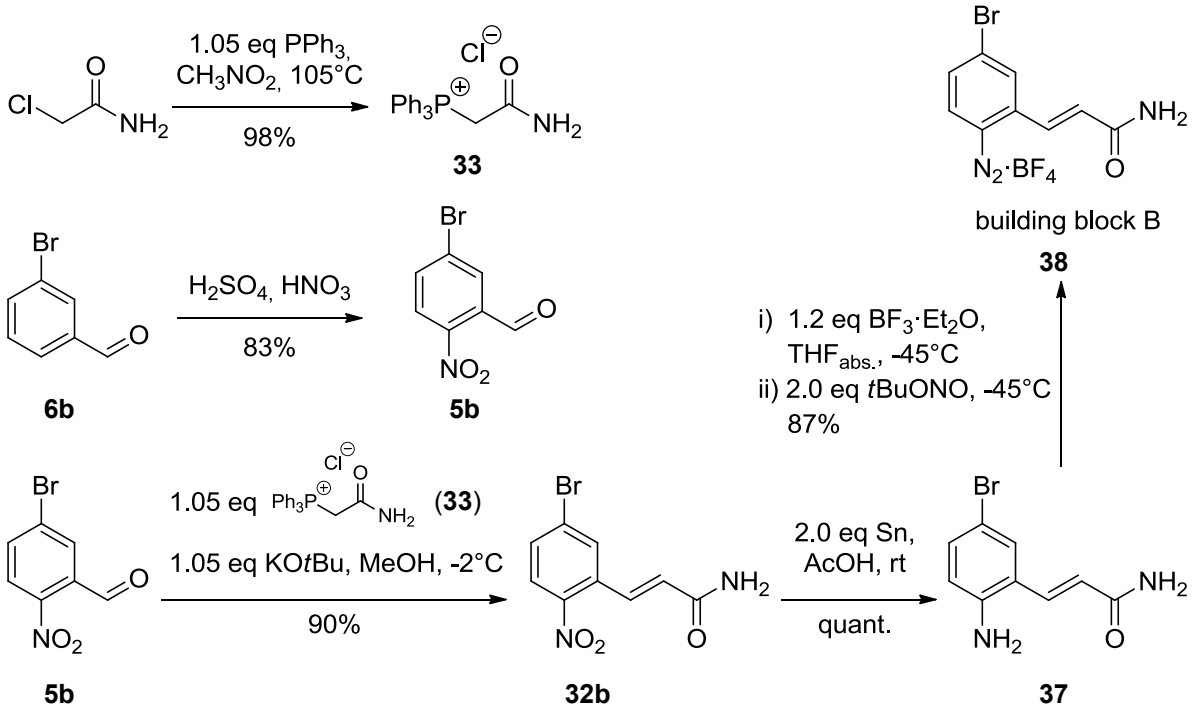
7.2.2 Synthesis of the Diazonium-Based Building Block B

To introduce the glutamine side chain under Wittig-conditions, the phosphonium-salt **33** was synthesized according to a procedure of GUINEY and coworkers (Scheme 7.37).[67]

Under inert conditions 2-chloroacetamide and PPh_3 were stirred under reflux in freshly distilled nitromethane.

The nitration of aldehyde **6b** was performed using a procedure of THUMMEL obtaining isomerically pure compound **5b** as a pale yellow solid.[64a]

For the Wittig reaction 1.05 eq of phosphonium-salt **33** were deprotonated *in situ* employing KO*t*Bu followed by addition of 5-bromo-2-nitrobenzaldehyde (**5b**). Quantitative conversion was detected after less than 40 min resulting in *E*/*Z*-isomers (96/4) of **32b**. The isomers were separated by recrystallization from MeOH/EtOAc (70/25) to finally furnish only the *E*-isomer **32b** in 90% yield.

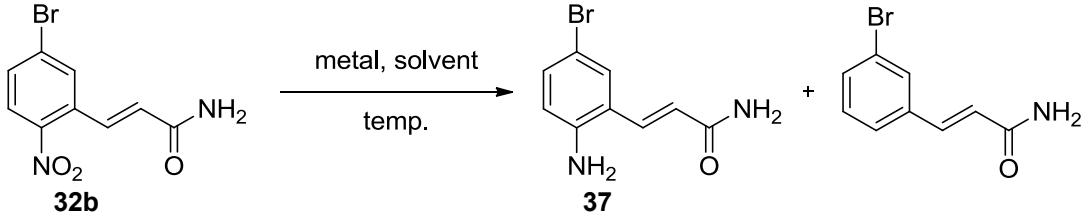


Scheme 7.37: Synthesis of the diazonium core unit **38** with an overall yield of 64% over 5 steps.

Keeping in mind the fact that the reduction of acrylate **31a** (see also Table 7.1, page 32) under hydrogenation conditions led to the formation of the unfavored dehalo by-product, another reaction pathway was investigated for the reduction of compound **32b** (Table 7.9).

Attempts in aqueous HCl under reflux, only resulted in protodeamination. But applying reducing agents like Sn, Zn or Fe in acetic acid at room temperature gave the desired amine **37** as the main product, whereby best results could be obtained using Sn-powder in acetic acid under exclusion of light (Table 7.9, entry 4).

Table 7.9: Screening results of different reduction conditions of compound **32b**.



32b **37**

Entry	Conditions	Conversion[a]	Product[b]	By-Product[b]
1	4.0 eq Sn, HCl/H_2O, 100°C	100% / 2 h	/	100%
2	3.0 eq Zn, HCl/H_2O, 100°C	100% / 3 d	/	100%
3	3.0 eq Fe, HCl/H_2O, 100°C	100% / 3 d	/	100%
4	3.0 eq Sn, AcOH, rt	100% / 22 h	>99%	<1%
5	3.0 eq Zn, AcOH, rt	~73% / 22 h	59%	14%
6	3.0 eq Fe, AcOH, rt	~55% / 22 h	55%	<1%

[a] Conversion and reaction time. [b] Calculated by relative intensities of the GC-MS spectra without internal standard.

The resulting amine **37** was converted to its stable diazonium tetrafluoroborate-salt **38** under inert conditions. At -45°C boron trifluoride ethyl etherate ($BF_3 \cdot Et_2O$) and *tert*-butyl nitrite (*t*BuONO) were added to the amine solution. After stirring for 3.5 h at -15°C and further 11 h at -5°C, the resulting diazonium-salt was precipitated by addition of absolute *n*-hexane. After filtration, the pale yellow-orange diazonium-salt was isolated in 87% yield (Scheme 7.37).[68] The isolated yields strongly depended on the applied temperature. While for temperatures below -20°C only slow conversion was observed, the by-product formation was dramatically increased at temperatures higher than 0°C.

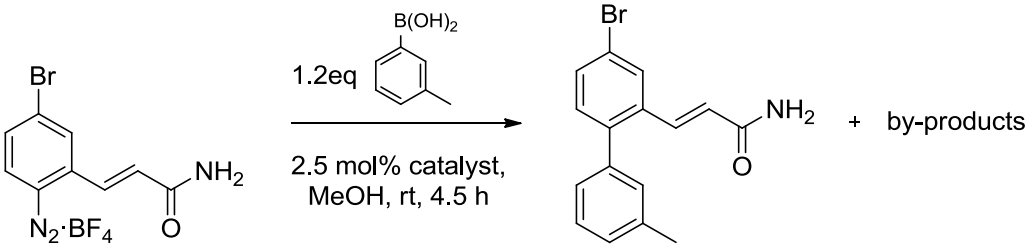
In the following chapter (7.2.3) the screening results of the air stable diazonium-salt **38** are compiled for the Pd-catalyzed aryl-aryl coupling using *m*-tolylboronic acid as model substrate.

7.2.3 Synthesis of Building Blocks AB and BC

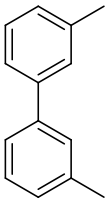
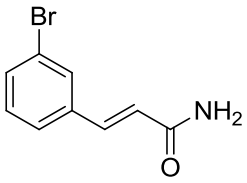
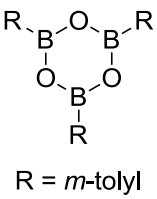
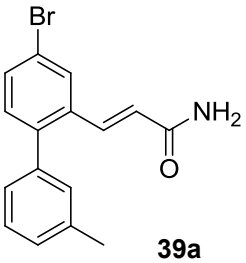
According to the screening results of compound **36a** (Table 7.8, page 45), 1.2 eq *m*-tolylboronic acid and 2.5 mol% catalyst in absolute MeOH were chosen as a starting point (Table 7.10). First of all, different catalysts like $PdCl_2$ or $Pd(OAc)_2$ were tested, but also more sterically demanding catalysts like $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$ were examined. After 4.5 h stirring at room temperature the conversion was quantitative for all mentioned catalysts.

Although the formation of by-product **A** was detected only in the case of $Pd(OAc)_2$, the best catalyst was still the $Pd(OAc)_2$ complex (Table 7.10, entry 1). 51% Product formation of the desired biarylic bromo-acryl derivative **39a** could be detected, with only slight formation of by-product **C**.

Table 7.10: Screening of catalysts for the diazonium-coupling of building block **38** and *m*-tolylboronic acid.



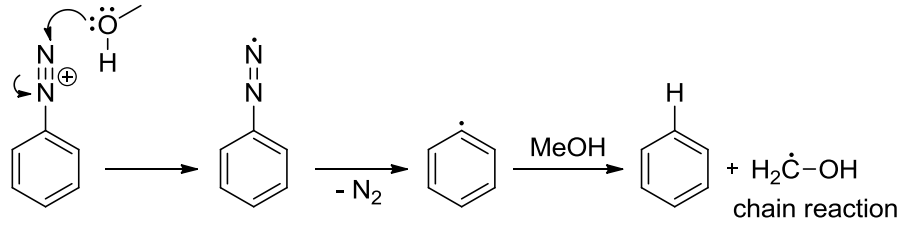
38 **39a**

Entry	Catalyst	By-Products[a]			Product[a]
		 **A**	 **B**	 R = *m*-tolyl **C**	 **39a**
1	$Pd(OAc)_2$	<1%	47%	<2%	51%
2	$PdCl_2$	/	76%	<1%	24%
3	$PdCl_2(PhCN)_2$	/	72%	25%	<4%
4	$PdCl_2(dppf)$	/	77%	22%	<1%
5	$Pd(PPh_3)_4$	/	74%	26%	/
6	$PdCl_2(PPh_3)_2$	/	79%	21%	/

[a] Calculated by relative intensities of the GC-MS spectra without internal standard.

Three different by-products could be formed during the diazonium cross-coupling. The homo-coupling by-product from two molecules *m*-tolylboronic acid (**A**), the protodediazotation by-product (**B**) and the cyclotrimeric anhydride form (**C**) of *m*-tolylboronic acid (boroxine).

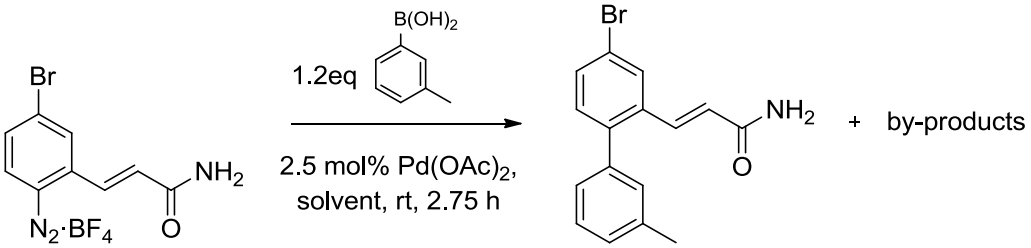
The proposed mechanism of formation by-product **B** is depicted in Scheme 7.38. One electron of the solvent (i.e., MeOH) can be transferred to the diazo function. The resulting aryldiazo radical rapidly decomposes to the corresponding aryl radical under formation of nitrogen. The arylic radical can be quickly quenched by a second solvent molecule under H-abstraction (Scheme 7.38).[69]



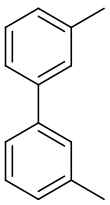
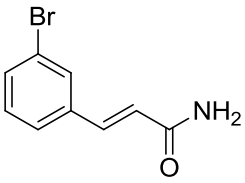
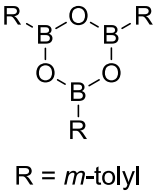
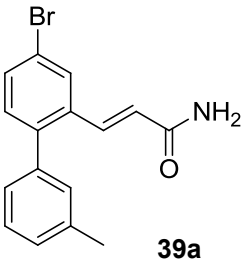
Scheme 7.38: Mechanism of side reaction which can occur in the diazonium cross-coupling chemistry.[69]

In addition the influence of the solvent was also investigated, applying 2.5 mol% $Pd(OAc)_2$ and 1.2 eq *m*-tolylboronic acid. At it is shown in Table 7.11 best results were obtained in THF and MeOH (Table 7.11, entry 2 and 4). The highest by-product formation was detected in solvents like 1,4-dioxane or CF_3CH_2OH (Table 7.11, entry 1 and 8).

Table 7.11: Screening of solvents for the diazonium-coupling of building block **38** and *m*-tolylboronic acid.



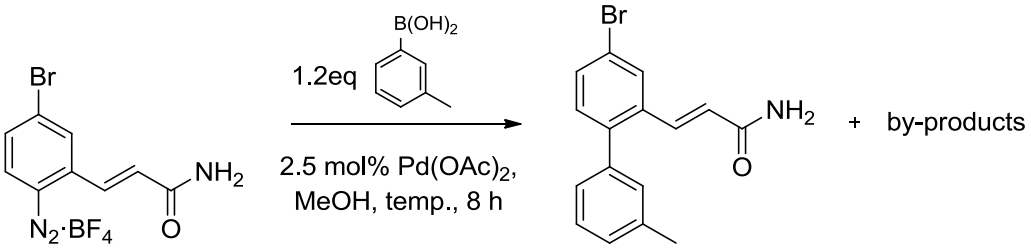
38 **39a**

Entry	Solvent[a]	By-Products[b]			Product[b]
		 **A**	 **B**	 R = *m*-tolyl **C**	 **39a**
1[c]	1,4-dioxane	4%	70%	6%	6%
2	THF	3%	50%	5%	42%
3	ACN	1%	68%	15%	16%
4	MeOH	/	48%	/	52%
5	EtOH	/	58%	4%	38%
6	*i*PrOH	/	58%	13%	29%
7[d]	AcOH	/	67%	27%	/
8	CF_3CH_2OH	4%	86%	7%	3%

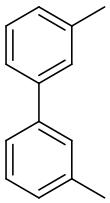
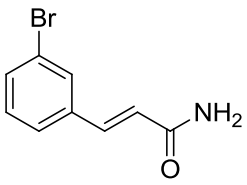
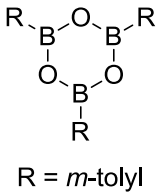
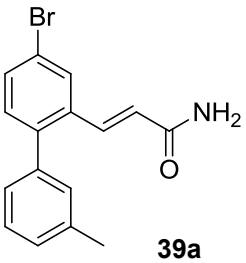
[a] Absolute, degassed solvents were used. [b] Calculated by relative intensities of the GC-MS spectra without internal standard. [c] *m*-cresol (14%) was also observed (only confirmed by GC-MS spectra). [d] 3-bromo-benzaldehyde (6%) was also observed as by-product (only confirmed by GC-MS spectra).

In accordance with literature known procedures of coupling diazonium tetrafluoroborate-salts lower temperatures (~0°C) gave less by-product formation than running the reaction at 35°C (Table 7.12). At 2°C and 2.5 mol% $Pd(OAc)_2$ in absolute, degassed MeOH the highest formation of desired product **39a** was observed (82%).

Table 7.12: Screening of temperatures for the diazonium-coupling of building block **38** and *m*-tolylboronic acid.



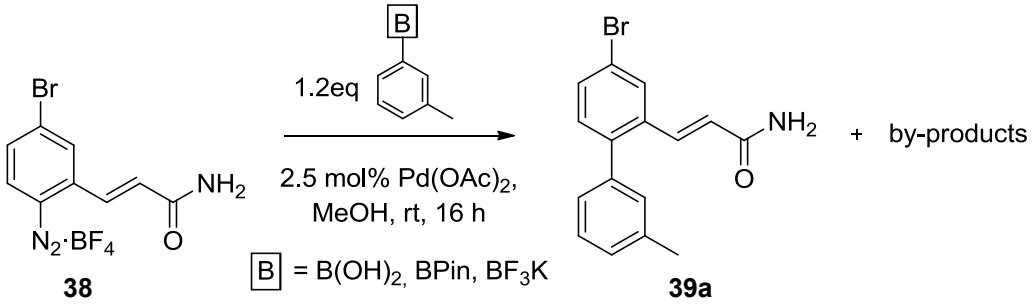
38 **39a**

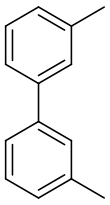
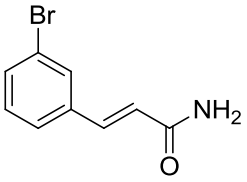
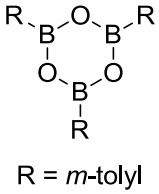
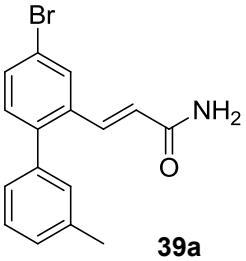
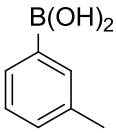
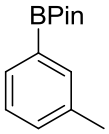
Entry	Temperature	By-Products[a]			Product[a]
		 **A**	 **B**	 R = *m*-tolyl **C**	 **39a**
1	2°C	8%	9%	1%	82%
2	rt (21°C)	6%	30%	/	64%
3	35°C	3%	40%	/	57%

[a] Calculated by relative intensities of the GC-MS spectra without internal standard.

Literature evidence suggests that the different boronic acid derivatives (such as boronic esters, MIDA-boronates, or BF_3K-salts) can also influence the reactivity of used building blocks (Table 7.13).[70] For that reason free *m*-tolylboronic boronic acid, pinacol ester derivative and the corresponding BF_3K-salts were tested for their suitability in the diazonium cross-coupling reaction.

Table 7.13: Screening of different boronic acid derivatives.



Entry	Boronic Acid Derivative	By-Products[a]			Product[a]
		 A	 B	 R = *m*-tolyl C	 39a
1		3%	29%	/	68%
2[b]		/	67%	/	18%
3		2%	45%	6%	47%

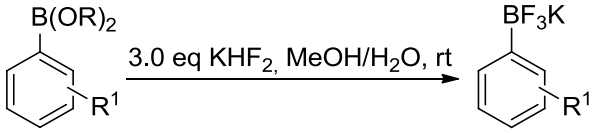
[a] Calculated by relative intensities of the GC-MS spectra without internal standard. [b] 85% conversion, based on *m*-tolylboronic acid pinacol ester.

While pinacol esters seem to be not suitable for the diazonium-coupling, free boronic acids and the BF_3K-salts are appropriate arylic derivatives for the diazonium cross-coupling.
Due to the fact that most of the synthesized building blocks A and C (see also chapter 7.1.2 and 7.1.4) are present in its pinacol ester form, they have to be converted to its free boronic acid form or to its BF_3K-salt.

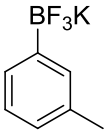
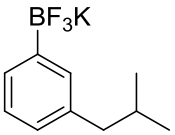
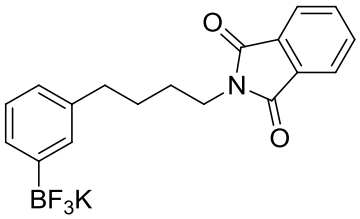
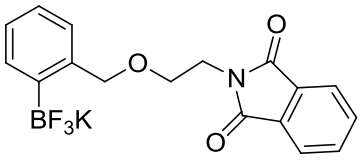
Literature reports suggest that the BF_3K-salts formed from pinacol esters are much easier to handle than from free boronic acids resulting by saponification.[71] For that reason the BF_3K-salts were further used within the Pd-catalyzed cross-coupling.

The trifluoroborate derivatives **40a-d** could be easily prepared from an aqueous MeOH solution (Table 7.14). After dissolving KHF_2 and the boronic acid derivatives in a MeOH/H_2O mixture, a colorless precipitate of the resulting trifluoroborate-salts **40a-d** was observed. After filtration and recrystallization the desired products were obtained as colorless solids.[72]

Table 7.14: Synthesis of trifluoroborate derivatives **40a-d**.



4f-g, **2a**, **2c** → **40a-d**

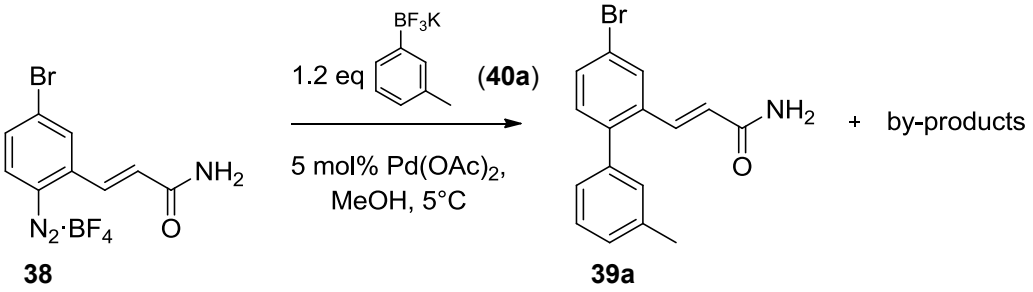
Entry	Compound	Purification[a]	Yield[b]
1	 **40a**	acetone/Et_2O = 12/25	94%
2	 **40b**	acetone	quant.
3	 **40c**	acetone	quant.
4	 **40d**	acetone/Et_2O = 12/22	90%

[a] Purification by recrystallization. [b] Isolated yields.

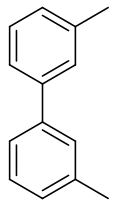
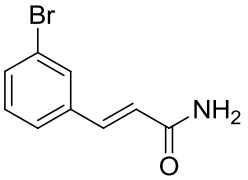
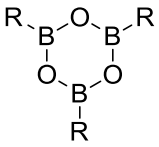
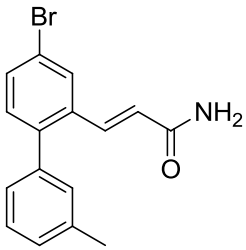
Starting from commercially available *m*-tolylboronic acid, potassium-salt **40a** was synthesized in one step (94%). Compound **40b** was prepared in five steps in an overall yield of 70%. Derivative **40c** was synthesized in six steps with an overall yield of 66% and BF_3K-salt **40d** was obtained in 44% yield (over three steps).

Changing all possible reaction parameters; i.e. catalysts, solvents and reaction temperature, best conditions were found to be 5 mol% $Pd(OAc)_2$, 1.2 eq BF_3K-salt in absolute, degassed MeOH at a temperature between -5°C and 5°C as it is shown in Table 7.15. Running the reaction to quantitative conversion, the desired building block AB (compound **39a**) was isolated after purification by flash column chromatography.

Table 7.15: Best reaction conditions of diazonium-coupling with potassium trifluoro(*m*-tolyl)borate (**40a**).



38 **39a**

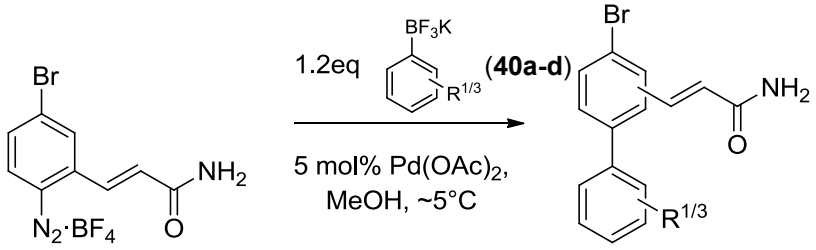
By-Products[a]			Product[a]
			
A	**B**	**C**	**39a**
4%	17%	/	79%

[a] Calculated by relative intensities of the GC-MS spectra without internal standard.

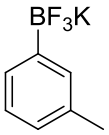
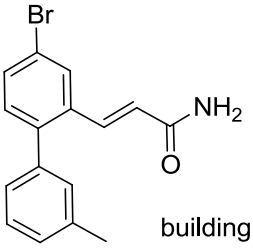
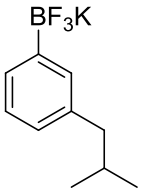
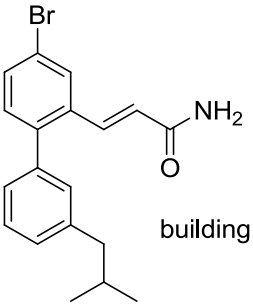
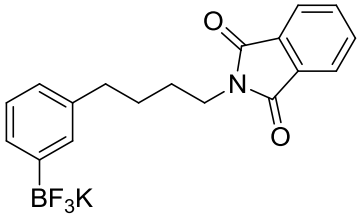
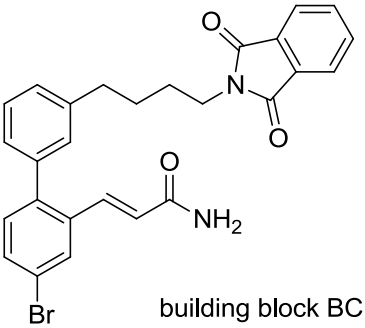
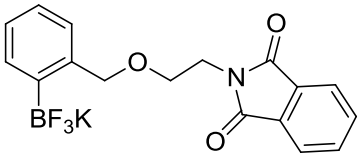
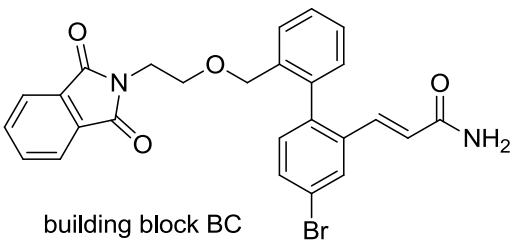
In a typical experiment, 1.0 eq diazonium tetrafluoroborate **38**, 1.2 eq potassium trifluoro-borate derivatives **40a-d** and 5 mol% $Pd(OAc)_2$ were dissolved in precooled absolute, degassed MeOH. After quantitative conversion the usually orange-brown suspension was concentrated to dryness and the crude product was purified by flash column chromatography.

Table 7.16 summarizes the diazonium cross-coupling of core unit **38** with different building blocks A and C in its BF_3K-salt form. The advantage of the convergent synthetic strategy of a core unit with two differentiated leaving groups is obvious: in only one step a diverse modification of building block AB or BC can be obtained. In addition the challenging synthesis of sterically demanding 2,2'-disubstituted biphenylic derivative **39d** was even accessible with this diazonium strategy (Table 7.16, entry 4).

Table 7.16: Synthesis of building blocks AB and BC using the diazonium strategy.



38 **39a-d**

Entry	BF_3K-Salt	Product	Yield[a]
1	 **40a**	 building block AB **39a**	55%
2	 **40b**	 building block AB **39b**	48%
3	 **40c**	 building block BC **39c**	49%
4	 **40d**	 building block BC **39d**	32%

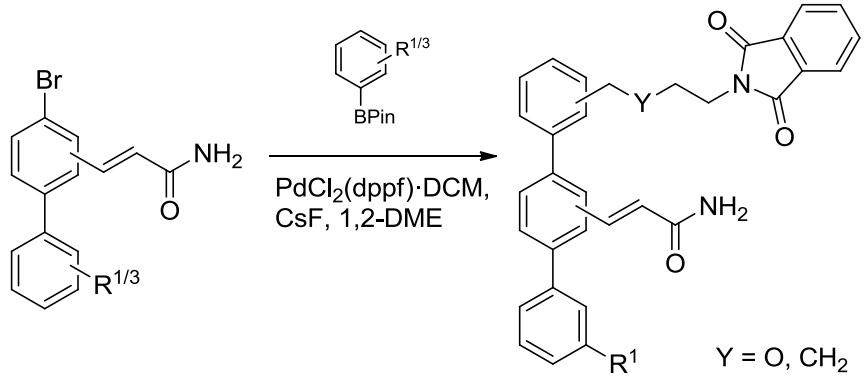
[a] Isolated yields.

While formation of by-product **B** was reduced using small amounts (~50 µmol) of diazonium tetrafluoroborate **38**, higher amounts (~2 mmol) promoted the formation of by-product **B**. However, the convergent diazonium approach provides a fast and convenient strategy for synthesizing compounds **39a-d** (compare Scheme 7.25, page 31). Substrate **39a** was isolated in seven steps with an overall yield of 33%. Derivative **39b** was obtained after 11 steps (22% overall) and compound **39c** (12 steps) in 21% overall yield. Also the sterically hindered biphenyl **39d** (9 steps) was isolated with an overall yield of 9%.

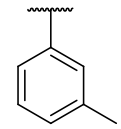
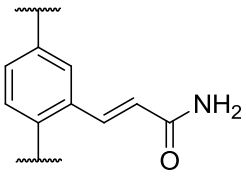
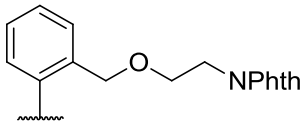
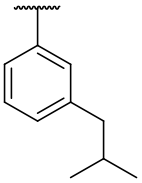
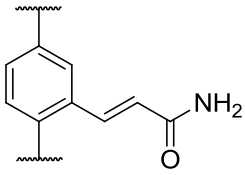
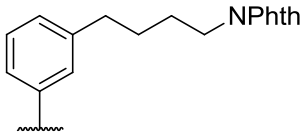
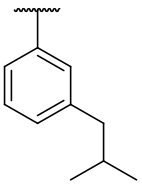
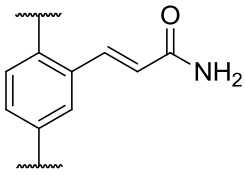
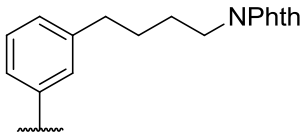
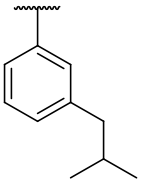
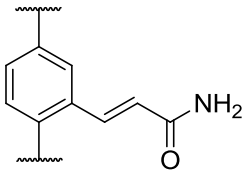
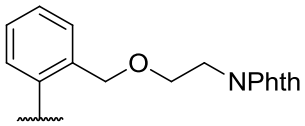
7.2.4 Synthesis of Terphenyls

Applying the convergent diazonium approach the resulting acrylic building blocks **39a-d** were coupled under established Suzuki-conditions using $PdCl_2(dppf)\cdot DCM$ as catalyst and CsF as base in absolute, degassed 1,2-DME (Table 7.17).

Table 7.17: Suzuki-coupling with acrylic building blocks **39a-d** and building block A or C.



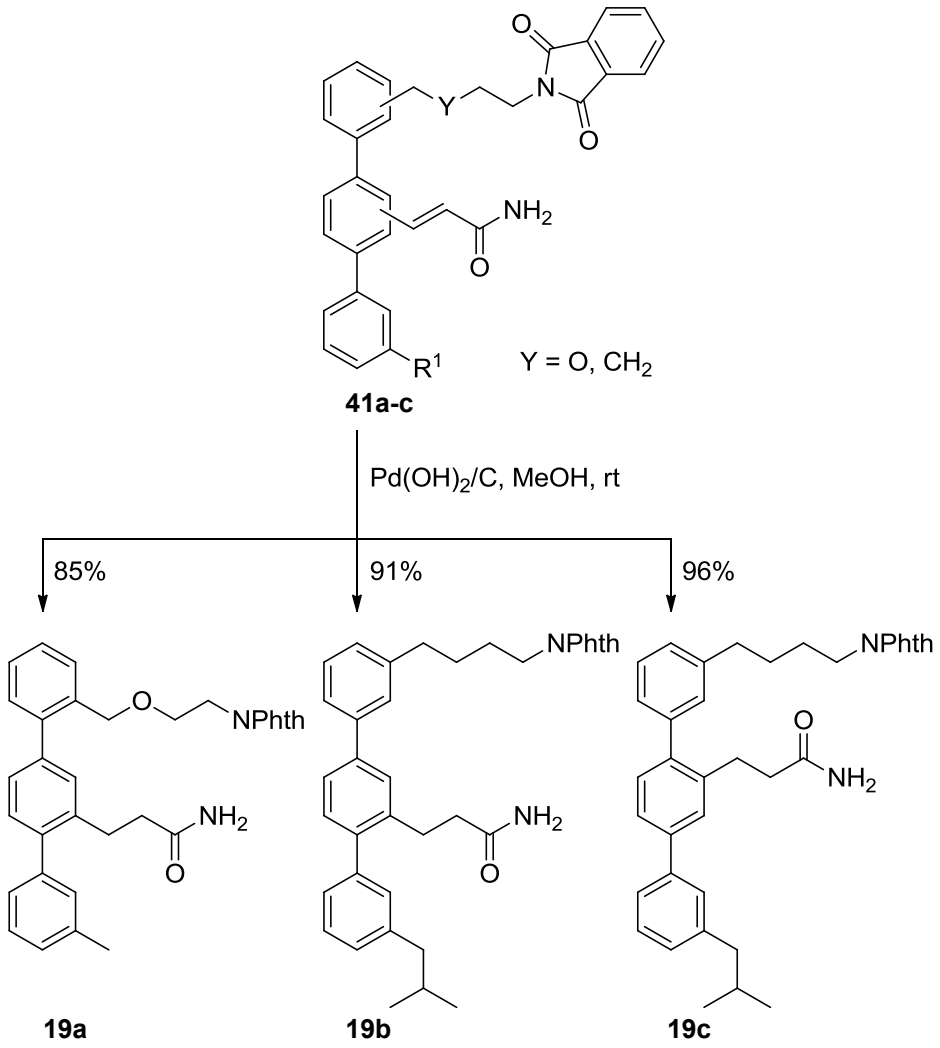
39a-d **41a-d**

Entry	Building Block A	Building Block B	Building Block C[a]	Compound[b]
1				**41a** (79%)
2				**41b** (85%)
3				**41c** (95%)
4				**41d** (85%)

[a] NPhth = isoindoline-1,3-dione. [b] Compound (isolated yields).

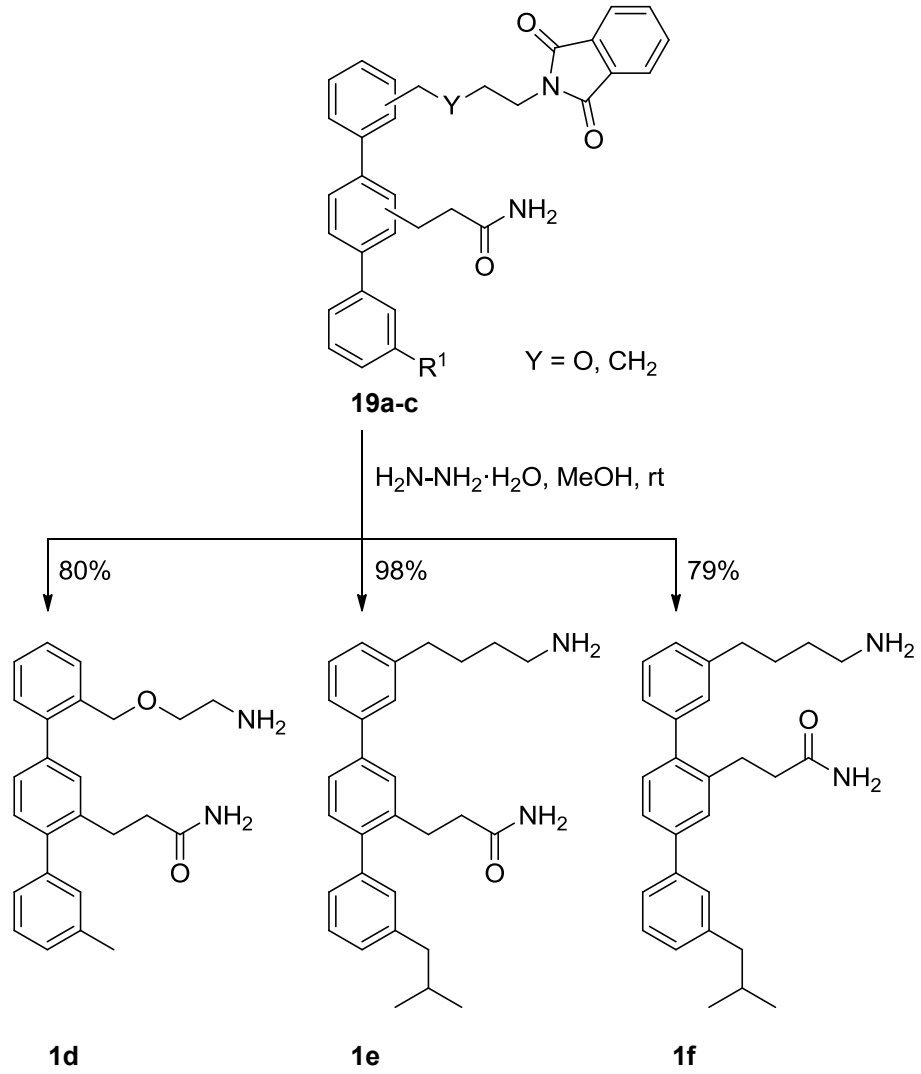
All of the acrylic phthalimide protected terphenylic precursors **41a-d** were isolated in good up to very good yields. Also derivative **41c** with the *ortho*-substituted acrylic side chain could be isolated in very good yields (Table 7.17, entry 3).

According to the previously described conditions the hydrogenation of the resulting phthalimide protected acrylic terphenyls **41a-c** was performed in MeOH at room temperature. After quantitative conversion the catalyst was filtered off and the obtained phthalimide protected terphenyls **19a-c** were used in the next step without further purification (Scheme 7.39).



Scheme 7.39: Reduction of phthalimide protected acrylic terphenyls **41a-c** to the corresponding terphenylic precursors **19a-c**.

In the final step the deprotection of the lysine side chain was performed according to the previously described procedure (see also chapter 7.1.6), using hydrazine monohydrate in MeOH at room temperature (Scheme 7.40).

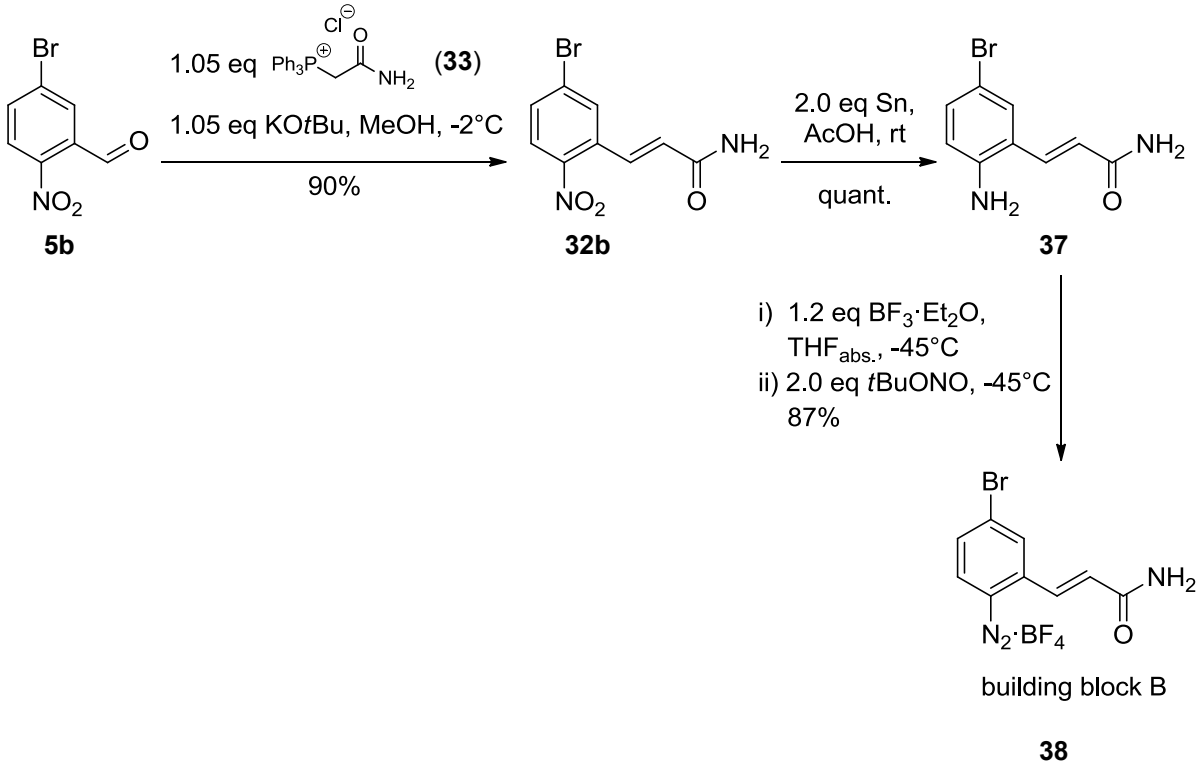


Scheme 7.40: The phthalimide protected teraryls **19a-c** were deprotected by hydrazine monohydrate.

As depicted in Scheme 7.40 lead-structure-based terphenyls **1d-f** were successfully synthesized applying the diazonium approach. Compound **1e** represents one of the computer modeled lead-structures which presumably inhibits the PPI between the surface of Rho GTPase and the α-helical protein ROCK (see also chapter 7.1, page 14).

7.2.5 Summary of the Diazonium Approach

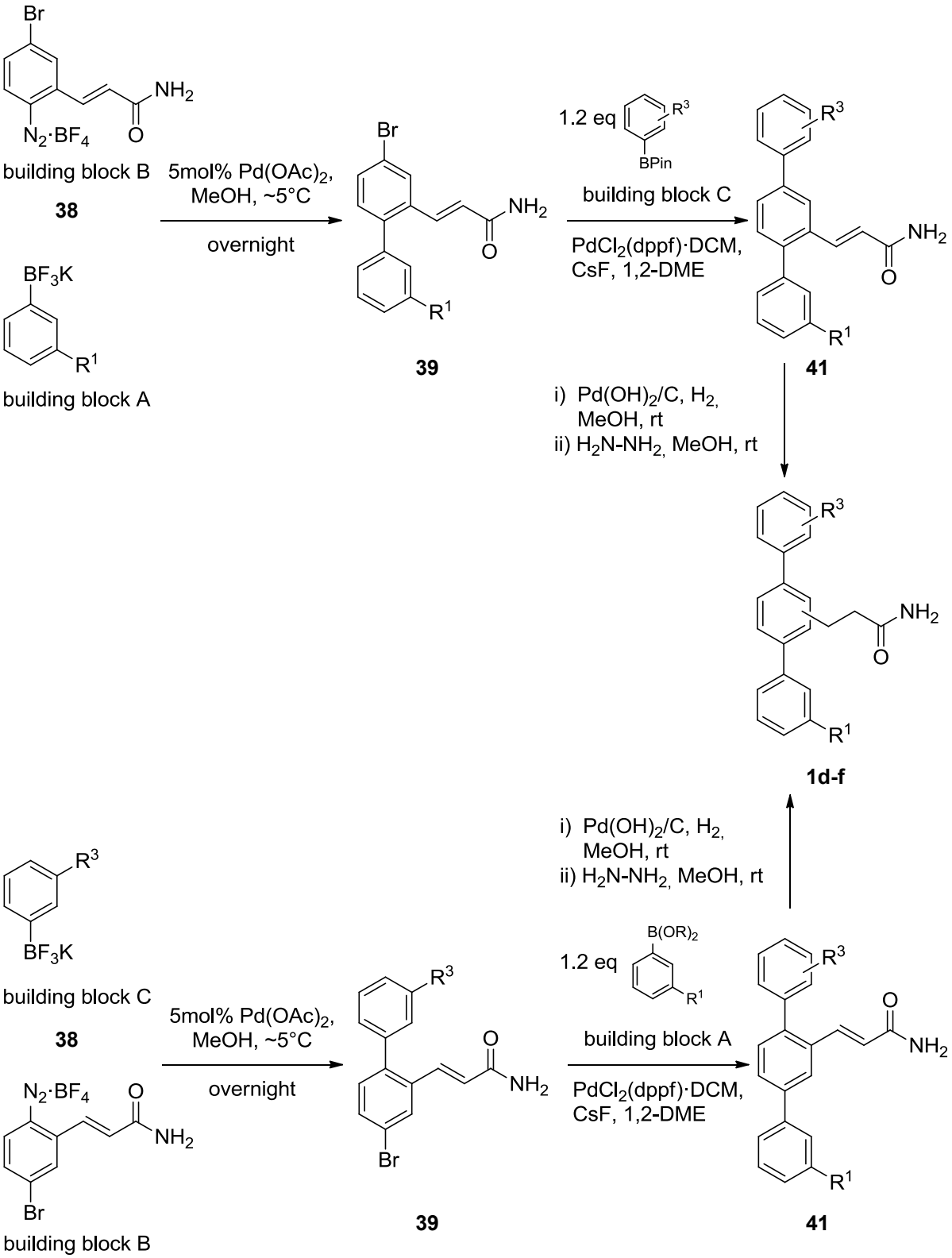
The basic concept of a convergent synthesis of terphenyls was the design of the central core unit **38** with two differentiated functional groups suitable for the Pd-catalyzed cross-coupling (Scheme 7.41).



Scheme 7.41: Synthesis of the diazonium core unit **38**.

After introducing the glutamine side chain under Wittig-conditions, the resulting nitrobenzene derivative **32b** was reduced utilizing Sn-powder under acidic conditions. The amine function was further converted to the corresponding diazonium-based building block B using $BF_3 \cdot Et_2O$ and *t*BuONO.

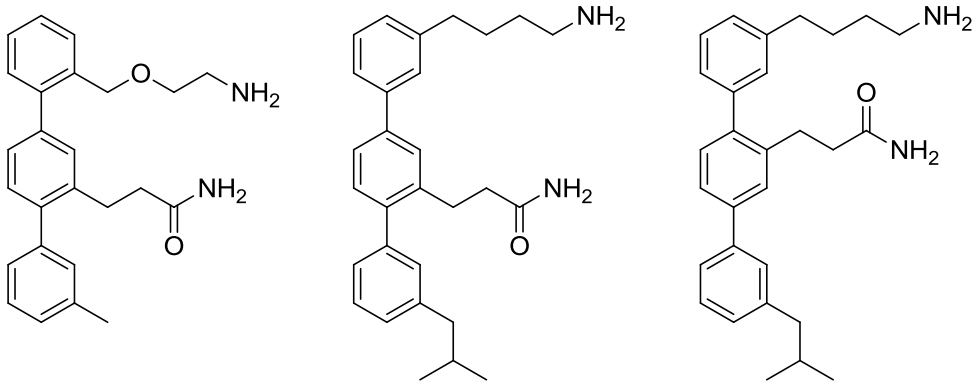
The convergent and regioselective synthetic strategy of the diazonium approach is summarized in Scheme 7.42. The diazonium coupling of building block B and building block A or C as BF_3K-salt was performed using $Pd(OAc)_2$ in absolute MeOH, directly followed by the second aryl-aryl coupling under established Suzuki-conditions.



Scheme 7.42: Synthetic strategy for the synthesis of terphenyls using the diazonium core unit **38**.

By changing the order of the two aryl-aryl coupling steps the substitution pattern of the final terphenyls can be varied for the middle core fragment (compare compound **1e** and **1f**).

Using this convergent approach three different lead-structure-based terphenyls could be synthesized. Compound **1d** is showing impressively the advantages of this convergent approach. The synthesis of lead-structure-based analoga can be fulfilled within one diversifying step, which is not possible using the linear approach. The computer modeled lead-structure **1e** was also synthesized employing the diazonium route with an overall yield of 11% within 19 steps. An alternative substitution pattern is achieved in compound **1f**.



3-Ala-2'-Gln-2''-*O*-Lys
9%, 12 steps
1d

3-Leu-2'-Gln-3''-Lys
11%, 19 steps
1e

3-Leu-3'-Gln-3''-Lys
10%, 19 steps
1f

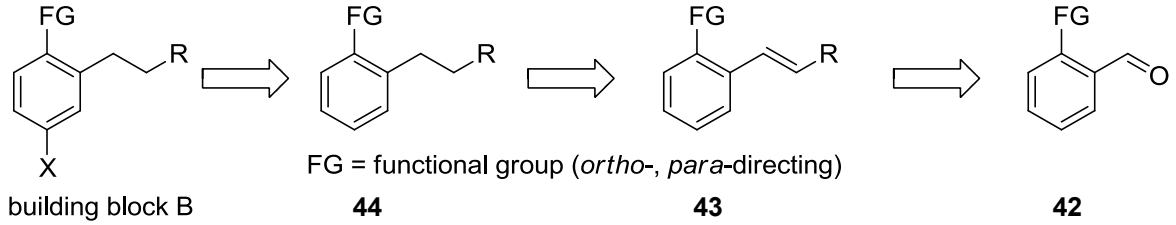
Scheme 7.43: Synthesized terphenyls based on the diazonium approach.

7.3 Synthesis of Teraryls using the Triflate Approach

It could be impressively demonstrated that the differentiated coupling of a diazonium core unit with a bromide in *para*-position (compound **38**) is suitable for a regioselective convergent synthesis of linear teraryls. The introduction of the side chain for the middle building block B under Wittig-conditions resulting in an α,β-unsaturated moiety seemed to be generally applicable. However, the reduction of the unsaturated side chain in the presence of a halide function in the aryl backbone leading to a unfavored protodehalogenation by-product (see also page 32). The acrylic side chain of the diazonium core unit is thereby the main drawback, because the acrylic moiety is in any case *ortho* to one of the leaving groups and this goes along with the possible formation of a π-complex during the Pd-catalyzed cross-coupling step (see also page 32). To circumvent this problem it would be of interest to introduce the halide function regioselectively in *para*-position to the second functional group after reduction of the unsaturated side chain. The directing effect of the substituents in the electrophilic substitution of the aromatic ring is thereby essential for the regioselective halogenation of arenes (Scheme 7.44).

A suitable synthetic access to a bifunctionalized core unit is reported by TROBE and some ideas and results of this master thesis have to be mentioned at this point.[73]

The retrosynthetic concept is depicted in Scheme 7.44. Starting from an *ortho*-substituted benzaldehyde derivative **42** the residue for the amino acid side chain can be introduced under well-established Wittig-conditions (see also pages 26, 34, 43 and 48).

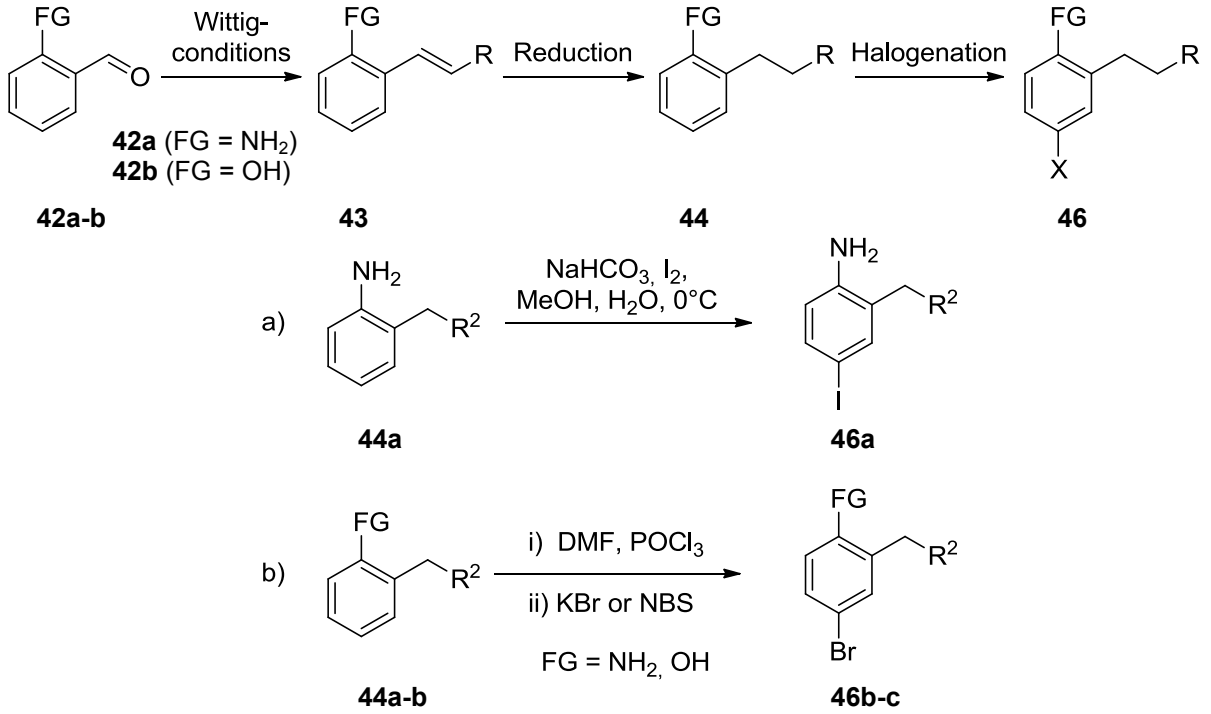


Scheme 7.44: Retrosynthetic approach of synthesizing building block B providing two functional groups, which are suitable for the Pd-catalyzed aryl-aryl cross-coupling.[73]

The resulting vinylbenzene derivative **43** can be easily reduced under hydrogenation conditions. The critical step thereby is the regioselective introduction of a halide in *para*-position to the functional group (FG) after reduction to the saturated 1,2-disubstituted phenyl derivative **44**.

Two possibilities were considered; variant a as a regioselective iodination of *ortho*-substituted amines, like KÖNIG and coworkers had used in the synthesis of triazol-based teraryls,[74] or

variant b as a modified Vilsmeier-Haack reaction followed by *in situ* bromination with KBr or *N*-bromosuccinimide (NBS) (Scheme 7.45).[75]

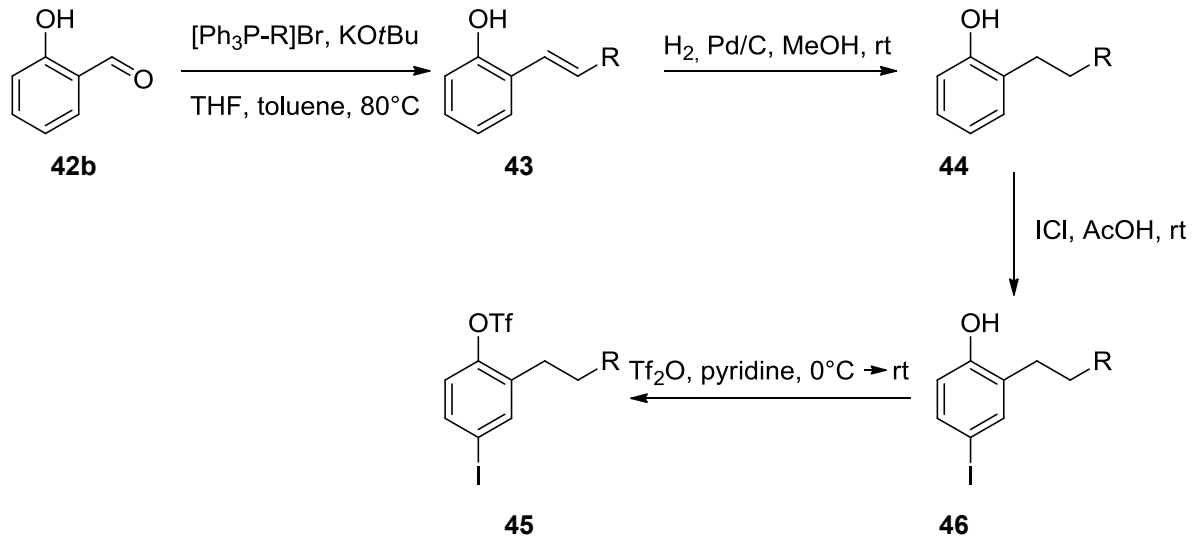


Scheme 7.45: Derivatization of the middle building block B.[73]

While KÖNIG could demonstrate the halogenation method for aniline derivatives like **44a** in high yields,[74,76] an alcohol function has the advantageous effect to be easily converted to its triflate form, which represents also an excellent leaving group in the Suzuki cross-coupling reaction (see also page 45).

Although the high regioselectivity could be demonstrated for a diazonium/halide system (see also chapter 7.2) a differentiation of a triflate/halide system should also lead to a regioselective and convergent approach using two Pd-catalyzed cross-coupling steps.

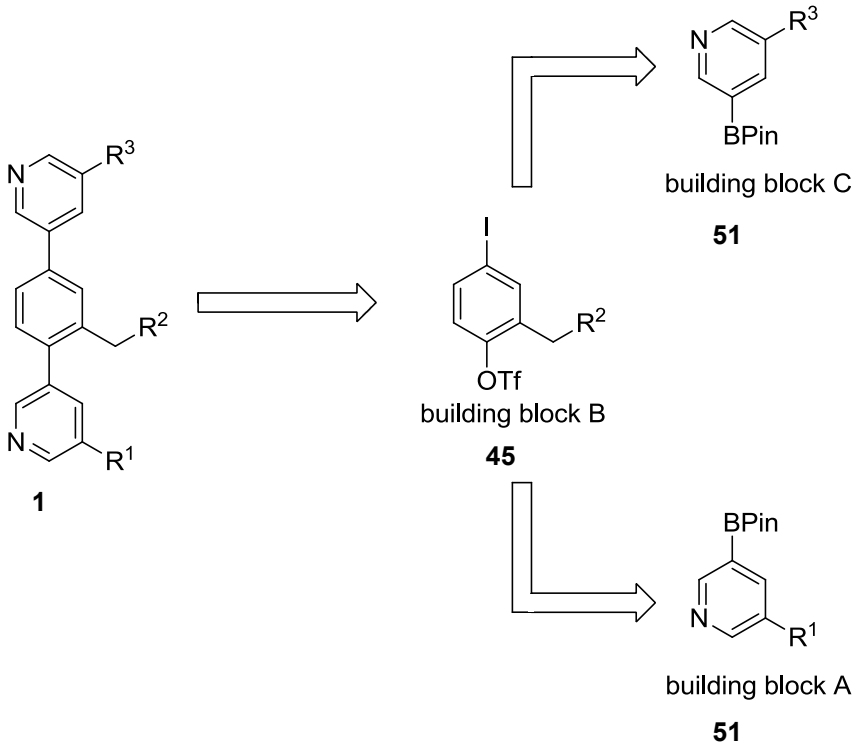
The basic concept for the synthesis of the triflate-based core unit **45** is summarized in Scheme 7.46.[73] 2-Hydroxybenzaldehyde (**42b**) was used as starting material to introduce the amino acid side chain under the already elaborated Wittig-conditions. After reducing the resulting unsaturated vinylic product **43**, the regioselective iodination was performed utilizing iodine monochloride (ICl) under acidic conditions. In the final step the alcohol function of compound **46** was converted to its triflate form, generating a suitable leaving group for the Pd-catalyzed Suzuki-coupling.[73]



Scheme 7.46: Synthetic route towards the triflate core unit.[73]

7.3.1 Retrosynthesis

The retrosynthetic approach was rather similar to the established diazonium approach. The successive Suzuki-couplings would lead to the desired terarylic scaffold by two consecutive and regioselective aryl-aryl coupling steps (Scheme 7.47). The first Suzuki-coupling should occur at the iodine position, due to the higher reactivity of the iodine function and the less steric hindrance. The resulting biarylic triflate should further be directly converted to the desired terarylic scaffold under a second Suzuki cross-coupling step.



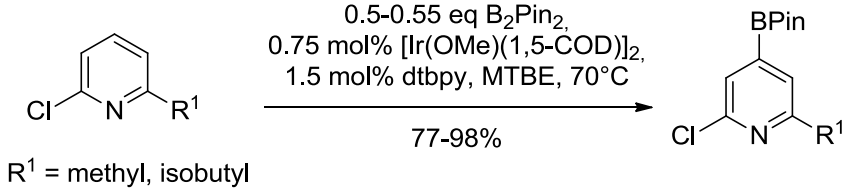
Scheme 7.47: Retrosynthesis for the twofold Suzuki-coupling using the triflate approach.[73]

Due to solubility problems under physiological conditions of the resulting teraryls, pyridine-based building blocks A and C were investigated to increase the polarity of the arylic backbone. In the next chapters (7.3.2-7.3.4) the syntheses of the corresponding pyridine-based building blocks **51** are presented.

7.3.2 Synthesis of Pyridine-Based Building Blocks A and C

While the benzene-based design is generally useful for α-helical mimetics bearing polar side chains, the intrinsically poor solubility of the terphenyl-based structure implies solubility problems for hydrophobic side chains under physiological conditions. To circumvent this problem, the design of more soluble teraryls based on pyridine-moieties was compiled.

The synthesis of pyridine derivatives **4a** and **4e** was already established by C-H activated borylation under Ir-catalyzed conditions (Scheme 7.48, see also chapter 7.1.2).

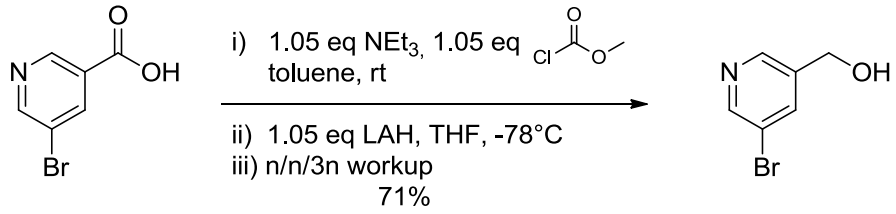


22a-b **4a**, **4e**

Scheme 7.48: Established Ir-catalyzed borylation of pyridines (see also pages 21-22).

Whereby the nitrogen atom of compounds **4a** and **4e** is *ortho* to the amino acid side chain (R^1), it could have an advantageous effect on the entropic cost of binding to have the polar nitrogen atom *meta* to the amino acid side chain. Because this would represent the more water exposed side of the terarylic backbone after binding on the surface of the protein.[15]

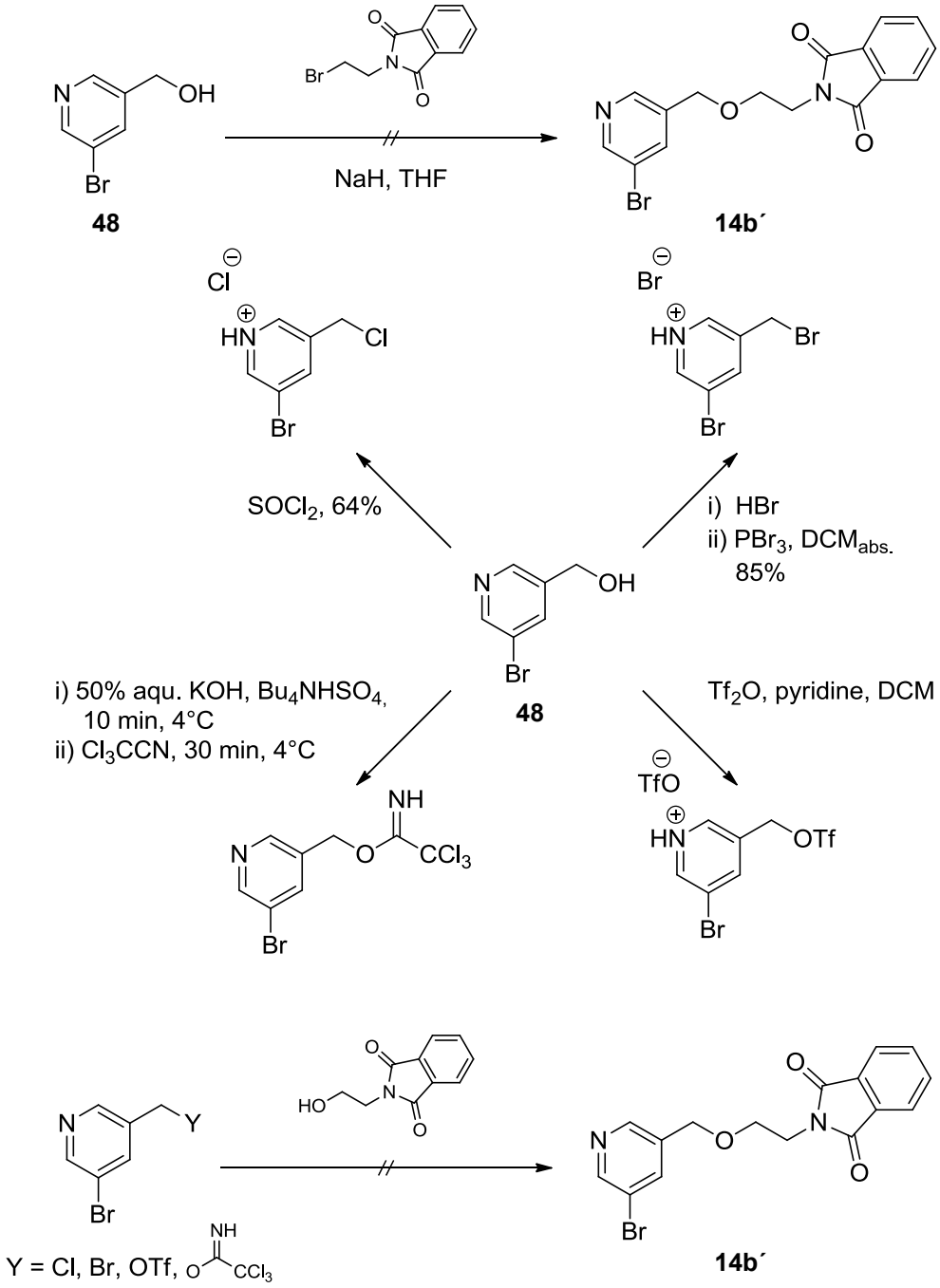
First of all a pyridine-based building block C was synthesized starting from nicotinic acid derivative **47** (Scheme 7.49). After reduction of the *in situ* generated active-ester, the corresponding benzyl alcohol **48** was isolated in good yields.



47 **48**

Scheme 7.49: Reduction of nicotinic acid derivative **47** by a LAH mediated reduction of the *in situ* generated active-ester.

In the next step the phthalimide protected lysine side chain should be introduced under previously established ether formation conditions (see also page 29). However, all attempts did not lead to the desired phthalimide protected pyridine-based building block C (Scheme 7.50).



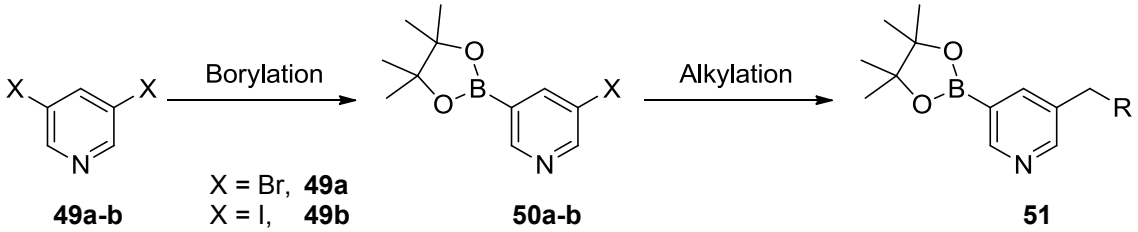
Scheme 7.50: Unsuccessful attempts for synthesizing pyridine-based building block C.

Beside different leaving groups like Cl, Br or OTf, also a trichloroacetimidate method, or modified Mitsunobu-conditions (not depicted) were examined for the ether formation. Nevertheless, no tested coupling reaction led to the desired pyridine-based building block C.

For that reason a totally new approach for synthesizing 3,5-disubstituted pyridine-based building blocks **51** had to be developed.

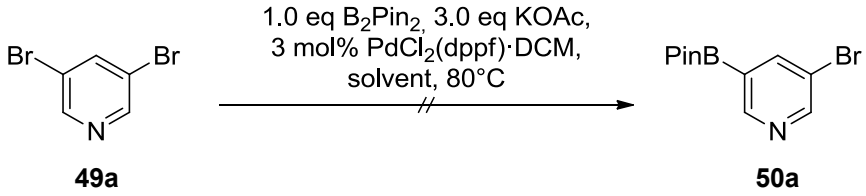
7.3.3 Modern Grignard Chemistry

The basic synthetic concept is shown in Scheme 7.51. Starting from 3,5-dihalopyridines like **49a** or **49b** the 3-halo-5-BPin-pyridine derivatives **50a-b** should be alkylated to the desired 3,5-disubstituted pyridine-base building block **51**.



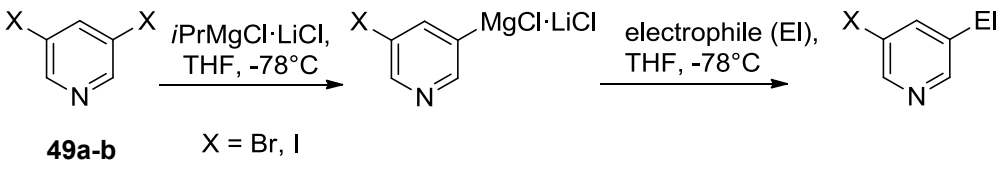
Scheme 7.51: Basic concept of synthesizing 5-pyridine boronic acid pinacol esters with amino acid side chains in 3-position.

The most obvious approach was to perform the borylation under previously described conditions using $PdCl_2(dppf)\cdot DCM$ and B_2Pin_2 as borylation agent (see also page 26). However, using 3,5-dibromopyridine (**49a**) as starting material only showed the formation of the desired product in very low yields. Screening of solvents (e.g., DMF or 1,4-dioxane) did not improve the formation of product **50a** (Scheme 7.52).



Scheme 7.52: Borylation of 3,5-dibromopyridine (**49a**) using B_2Pin_2 as borylation agent and $PdCl_2(dppf)\cdot DCM$ as catalyst.

Therefore another general approach had to be developed to obtain 3,5-disubstituted pyridine boronic ester **51** featuring the amino acid side chain as substituent in the 3-position. The literature known "Turbo-Grignard" chemistry introduced by KNOCHEL[77] and other research groups[78] seems to be a promising strategy for solving this problem (Scheme 7.53).

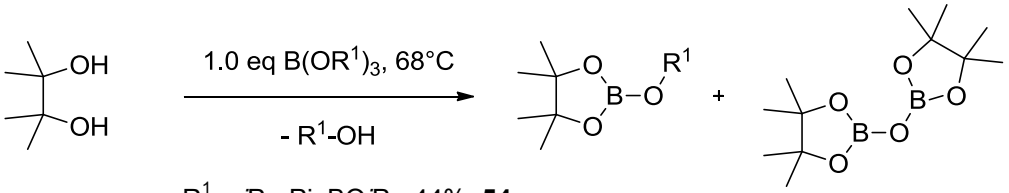


Scheme 7.53: "Turbo-Grignard" approach for synthesizing 3,5-disubstituted pyridines.[79]

This "Knochel approach" has the advantage that the halides can successively be substituted under electrophilic conditions.[79] The formation of the active pyridine-Grignard can be performed by stirring the corresponding halopyridine derivatives **49a-b** in the presence of a previously prepared *i*PrMgCl·LiCl solution (**52**) at -78°C.[79] After quantitative metal-halide exchange the *in situ* formed pyridine-Grignard can theoretically be quenched with any kind of electrophiles **53** like aldehydes or ketones.[79] Furthermore, the orthogonality of this "Turbo-Grignard" chemistry is impressive,[80] literature evidence suggested that not only nitriles, OMe or CF_3 groups are tolerated, also esters or amides can be tolerated by this design.[81]

Another advantageous effect of this approach is the borylation source. For the synthesis of pinacol ester derivatives the expensive B_2Pin_2 is often used as borylation agent (see also pages 21 or 26). Employing the Knochel-chemistry, cheap and readily available electrophiles like 2-alkoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane derivatives (PinBOAlk, **54a-b**) can be used as borylation agents (Scheme 7.54).[79]

The preparation of the 2-isopropoxy- (PinBO*i*Pr, **54a**) or 2-methoxy derivative (PinBOMe, **54b**) was performed in only moderate yields, due to the formation of the corresponding oxy bridged by-product (condensation of two molecules PinBOAlk) (Scheme 7.54). Nevertheless, this method was used to obtain the corresponding PinBO*i*Pr **54a** as a colorless liquid after distillation.[79]



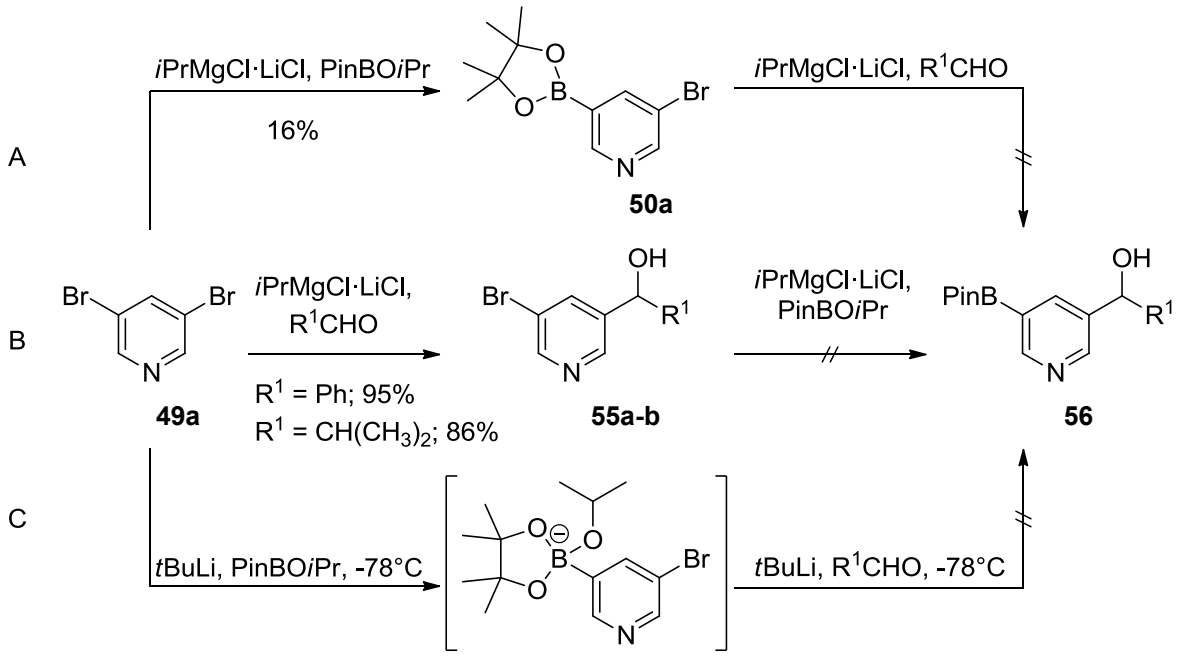
R^1 = *i*Pr: PinBO*i*Pr, 44%; **54a**
R^1 = Me: PinBOMe, 30%; **54b**

Scheme 7.54: Synthesis of 2-alkoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane derivatives **54a-b**.[79]

Initial attempts followed a modified protocol by KNOCHEL and coworkers using 3,5-dibromopyridine (**49a**) as starting material (Scheme 7.55, route A).[79] After formation of the pyridine-Grignard employing *i*PrMgCl·LiCl solution (**52**) followed by electrophilic quench utilizing PinBO*i*Pr (**54a**), the 3-bromo-5-BPin-pyridine derivative **50a** could be isolated in only poor yield (16%). This contrasts the good to excellent yields of 5-bromo benzylic alcohol derivatives **55a-b** which were obtained performing the electrophilic quench with benzaldehyde (**53a**) or isobutyraldehyde (**53b**) (Scheme 7.55, route B).

Also a twofold *t*BuLi mediated method according to a protocol of ZHICHKIN and coworkers was investigated (Scheme 7.55, route C).[82] After the first lithium-halide exchange and quenching the lithium-pyridine derivative with PinBO*i*Pr (**54a**), the formed isopropoxide protected pyridine-boronate was used for a second *in situ* quench with electrophiles like isobutyraldehyde (**53b**).

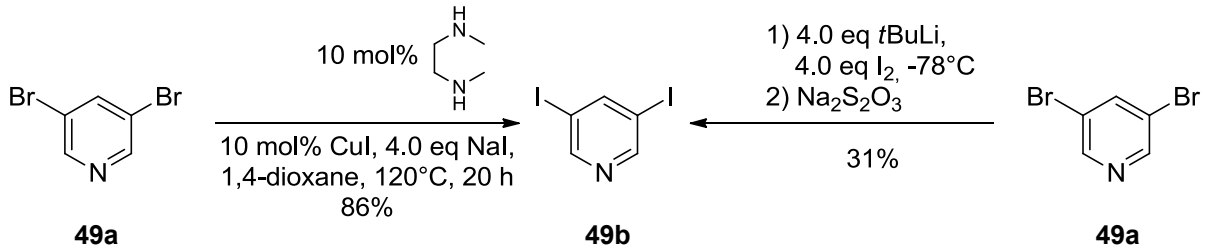
However, every chosen strategy turned out to be problematic for the second metal-halide exchange under the same reaction conditions due to increasing by-product formation and/or dramatically prolonged reaction times.



Scheme 7.55: Synthetic overview about synthesizing 5-BPin-3-benzylic alcohol pyridine derivatives **56** starting from 3,5-dibromopyridine (**49a**).

An opportunity to overcome this problem is to start from the more reactive 3,5-diiodopyridine (**49b**). Two different strategies were investigated to iodinate pyridine derivative **49a** (Scheme 7.56).

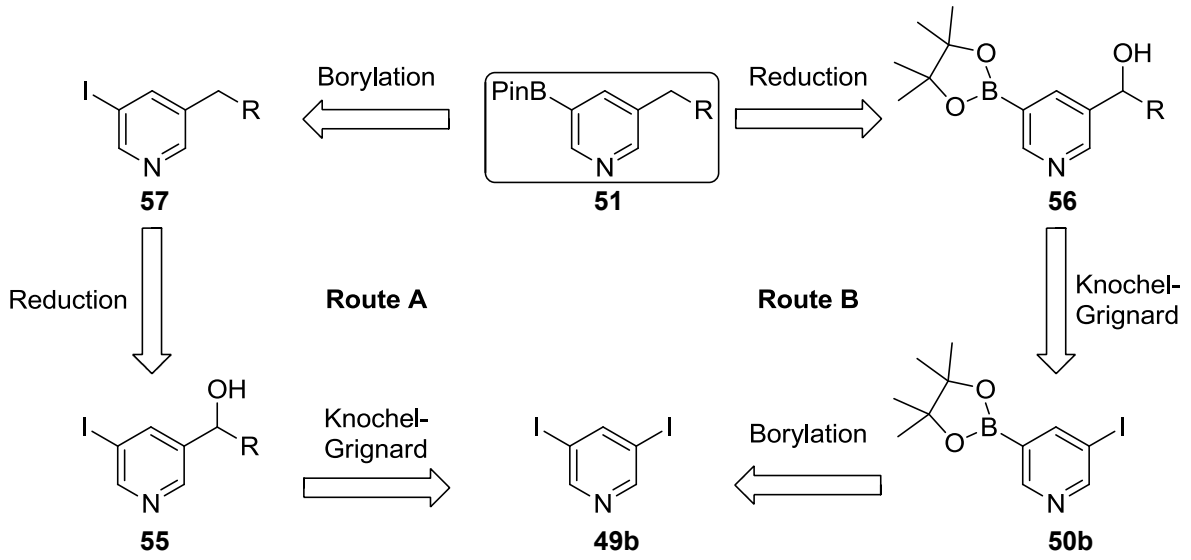
On the one hand a *t*BuLi mediated strategy was established, but due to the moderate isolated yield and the high by-product formation an alternative strategy was conceived.[83] The Buchwald´s variant of a Finkelstein-like iodination of haloarenes was the key step for a high yielding and easy access to the desired 3,5-diiodopyridine (**49b**) in a multi gram scale.[84]



Scheme 7.56: Synthesis of 3,5-diiodopyridine (**49b**) starting from 3,5-dibromopyridine (**49a**).[84]

7.3.4 Retrosynthesis

Having a cheap and high yielding access to the diiodo derivative **49b** in hands, a twofold Grignard formation to synthesize 3,5-disubstituted pyridine derivatives **51** seems to be accessible. The retrosynthetic analysis is depicted in Scheme 7.57. Starting from diiodo derivative **49b** the first metal-halide exchange should be used for introducing the pinacol ester function (Scheme 7.57, route B).

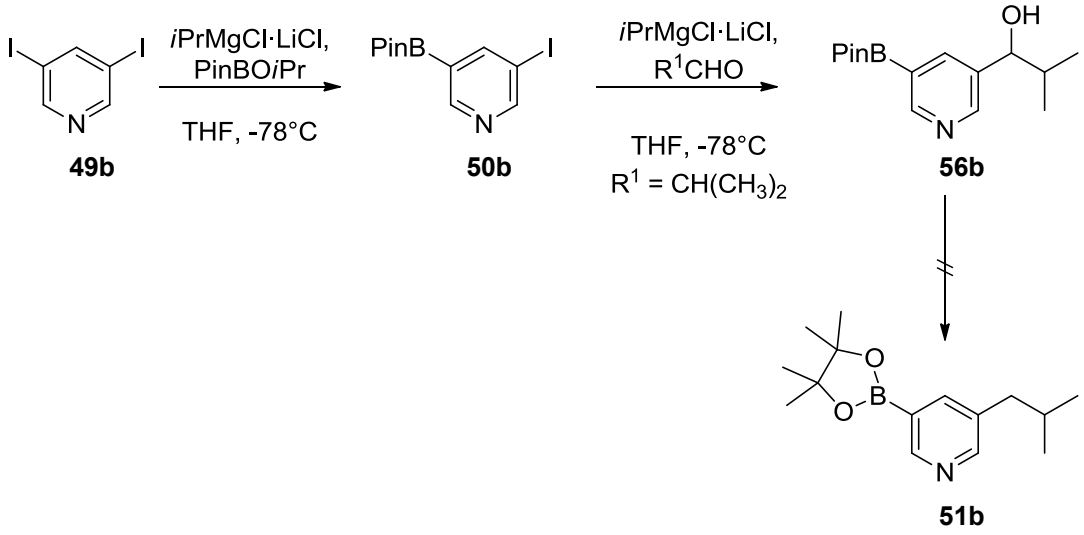


Scheme 7.57: Retrosynthesis of pyridine-based building blocks A and C.

During the second metal-halide exchange, the amino acid side chain ought to be introduced by the corresponding electrophiles like aldehydes or ketones. The reduction of the superfluent hydroxyl group to achieve the native alkyl form of the amino acid side chain (except Thr and Ser) should be feasible in the last step of the synthesis.

Furthermore, also a reverse order of the electrophiles might be suitable for this flexible twofold Grignard strategy (Scheme 7.57, route A). After formation of the secondary alcohol in the first Grignard reaction step, the reduction of the superfluent hydroxyl group should be also feasible at this stage of the synthesis. The resulting 3-iodo-5-alkyl pyridine derivative **57** might be borylated under mentioned conditions (see also page 26) in the last step of the synthesis.

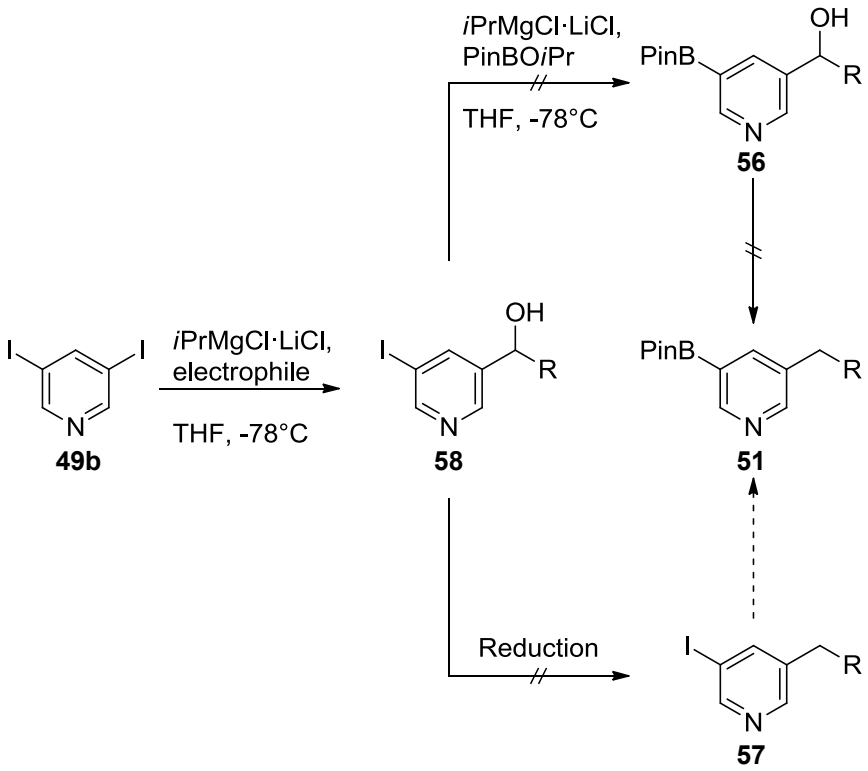
To validate the retrosynthetic concept, 3,5-diiodopyridine (**49b**) was tested to be suitable for a twofold Grignard formation (Scheme 7.58). The first Grignard formation was used to introduce the pinacol ester function utilizing *i*PrMgCl·LiCl solution (**52**) for quantitative metal-halide exchange at -78°C followed by electrophilic quench with PinBO*i*Pr (**54a**).



Scheme 7.58: Synthesis of pyridine-based 5-BPin-3-benzylic alcohol derivative **56a** starting from 3,5-diiodopyridine (**49b**) with 14% yield over two steps.

The resulting 3-iodo-5-BPin-pyridine derivative **50b** was subsequently treated with a second equivalent of *i*PrMgCl·LiCl solution (**52**) and after additional electrophilic quench using isobutyraldehyde (**53b**), the desired 5-BPin-3-benzylic alcohol derivative **56b** could be isolated as a colorless solid. However, the reduction of the superfluent alcohol function on this stage of the synthesis was not possible, due to the unexpected instability of product **56b**.

To overcome this problem an alternative modular strategy was used to introduce the amino acid side chain first and the resulting pyridine-based 5-iodo-3-benzylic alcohol derivative **58** was tried to be converted to the desired final building block **51** (Scheme 7.59).



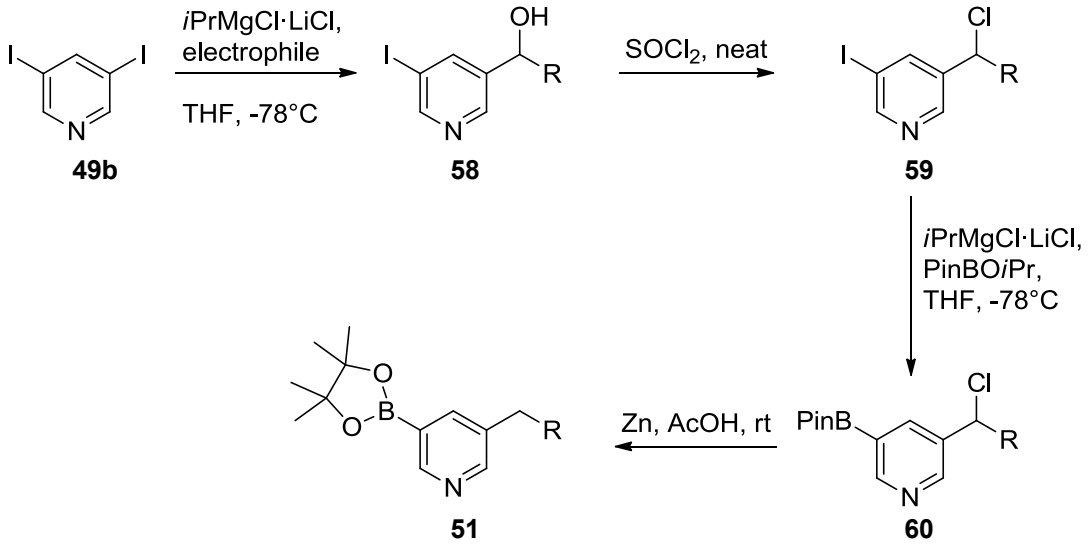
Scheme 7.59: Also the introduction of the amino acid side chain at the beginning of the synthesis did not lead to the desired product.

A possible strategy to remove the benzylic alcohol function of compound **58** is the acid-catalyzed elimination of H_2O leading to the unsaturated form, which easily occurs for tertiary alcohols. An alternative and more general route is the hydrogenation of the benzylic derivative **58** into its corresponding reduced form **57**. However, none of the common reduction methods (H_2, PtO_2, MeOH; H_2, Pd/C, MeOH; H_2, $Pd(OH)_2$/C, MeOH; Zn, AcOH) led to the desired reduced form, as any successful deoxygenation was plagued with a concomitant deiodination process as the main side reaction.

To overcome this problem the hydroxyl group was first converted into the corresponding chloride **59**, which should be amenable to dehalogenation by a less aggressive reducing agent (Scheme 7.60). The benzylic alcohol function was smoothly transformed into the corresponding 3-(chloromethyl)-5-iodopyridine derivative **59** using thionyl chloride ($SOCl_2$) under neat conditions.

The second metal-halide exchange on substrate **59** proceeds without any side reaction from the potential internal electrophile represented by the α-aryl chloride. Therefore, the electrophilic quench with PinBO*i*Pr (**54a**) formed the borylated 3-(chloromethyl)-5-BPin-pyridine derivatives **60**. As these compounds proved to be sensitive to heat and also not stable on silica gel, the intermediates were used without any further purification in the next

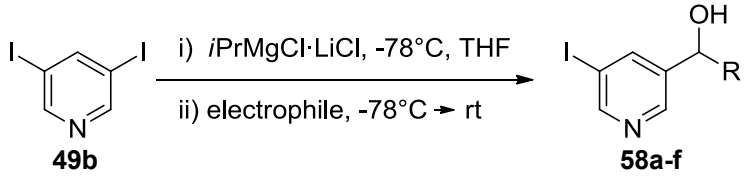
step in which they were smoothly dehalogenated using Zn-powder under acidic conditions. Importantly, this rather mild reduction method did not cause any deborylation of the desired 3,5-disubstituted pyridine-based building blocks **51**.



Scheme 7.60: Successful synthetic strategy for the synthesis of 3,5-disubstituted pyridine-based boronic acid pinacol esters **51a-f**.

In order to establish the scope and limitations of this synthetic approach, selected amino acid side chains, which should be representative not only for the reactivity of electrophiles (aldehydes or ketones), but also the different types of amino acid side chains (neutral, basic, acidic) were synthesized (Table 7.18).

Table 7.18: Synthesis of benzylic alcohols **58a-f** using modern Knochel-Grignard chemistry.



49b **58a-f**

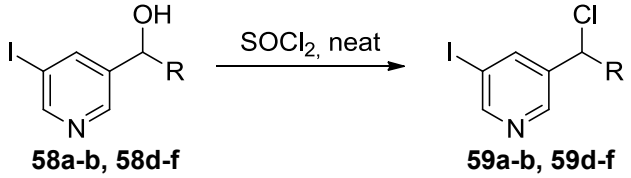
Entry	Carbonyl-Compound	Grignard Product	Yield[a]
1	**53a**	**58a**	99%
2	**53b**	**58b**	95%
3[b]	**53c**	**58c**	99%
4	**53d**	**58d**	68%
5[c]	**53e**	**58e**	83%
6	**53f**	**58f**	84%

[a] Isolated yields. [b] Crude product used in the next step without further purification. [c] The electrophile 4-oxobutanenitrile (**53e**) was synthesized from 4,4-diethoxybutanenitrile in acidic aqueous acetone.

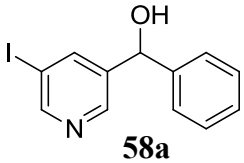
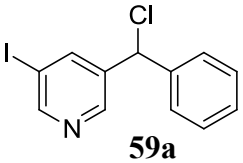
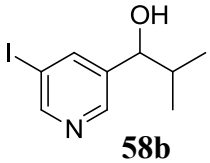
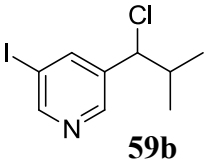
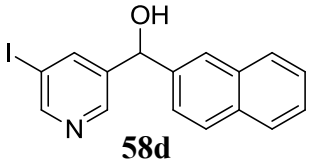
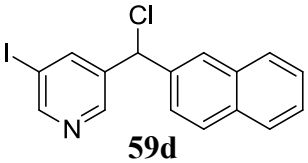
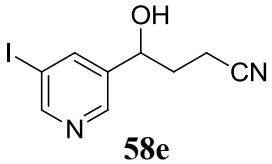
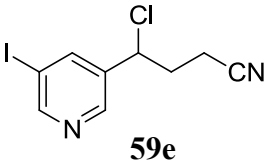
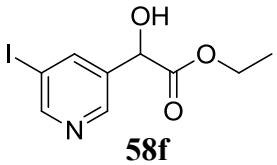
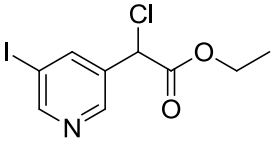
All of the employed electrophiles led to the corresponding benzylic alcohols **58a-f** in good to excellent yields. Not only electrophiles like benzaldehyde (**53a**) (Table 7.18, entry 1) could be used, also less reactive ketones like **53c** (entry 3) are excellent electrophiles by using this twofold Knochel-Grignard strategy.

To remove the superfluent hydroxyl group, the formed 3-(hydroxymethyl)-5-iodopyridine derivatives **58a-f** were further converted to its benzyl chloride form (Table 7.19).

Table 7.19: Chlorination of 3-(hydroxymethyl)-5-iodopyridine derivatives **58a-b** and **58d-f**.



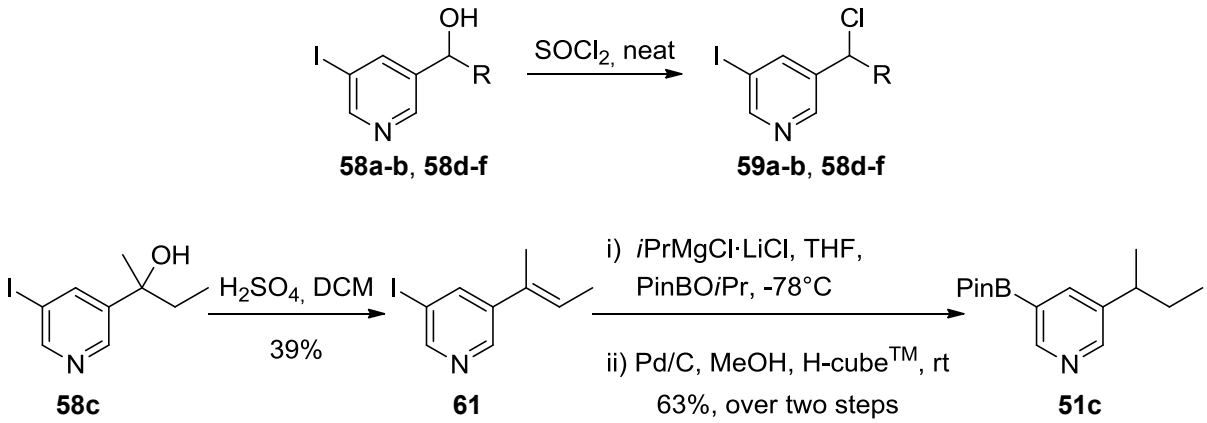
58a-b, 58d-f **59a-b, 59d-f**

Entry	Benzyl Alcohol	Benzyl Chloride	Yield[a]
1	 **58a**	 **59a**	91%
2	 **58b**	 **59b**	85%
3	 **58d**	 **59d**	74%
4	 **58e**	 **59e**	97%[b]
5	 **58f**	 **59f**	92%

[a] Isolated yields. [b] To achieve a clear solution a mixture of $SOCl_2$/DCM = 2/1 was used.

In a typical experiment, the corresponding pyridine-3-yl-methanol derivatives **58a-b** and **58d-f** were dissolved in freshly distilled $SOCl_2$ and after quantitative conversion the excess $SOCl_2$ was distilled off. The crude product was quenched with saturated Na_2CO_3 solution and purified by flash column chromatography.

The preparation of **59c** (starting from compound **58c**) was not accessible by this chlorination method due to the fast elimination of water in the presence of catalytic amounts of acid (Scheme 7.61).

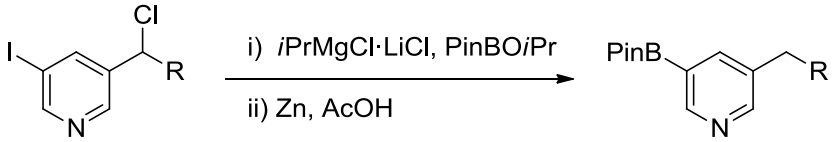


Scheme 7.61: Removing the benzylic alcohol function by converting the hydroxyl group into the corresponding chloride **59a-b** and **59d-f**, or by acidic elimination of water for tertiary alcohol **58c**.

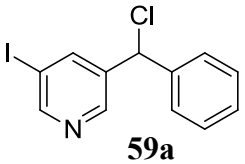
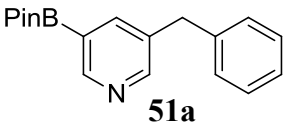
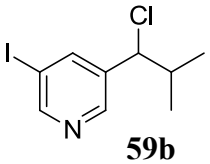
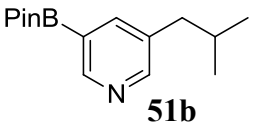
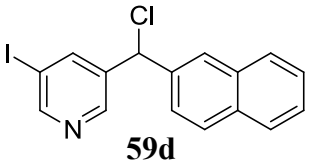
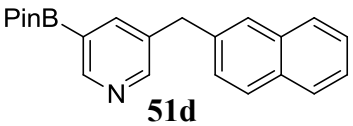
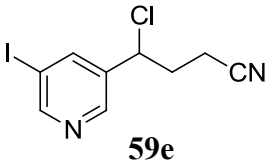
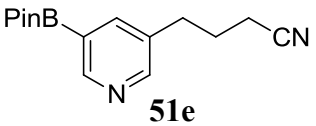
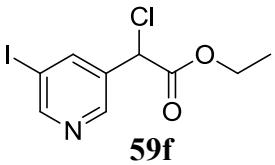
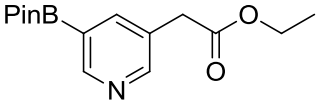
For that reason the elimination was achieved by treatment with catalytic amounts of H_2SO_4 in DCM solution. The resulting vinylic pyridine derivative **61** was borylated according to the mentioned protocol utilizing *i*PrMgCl·LiCl solution (**52**) and PinBO*i*Pr (**54**) as electrophile and the resulting unsaturated building block was hydrogenated under reductive conditions.

Keeping in mind the fact that the resulting 3-(chloromethyl)-5-BPin-pyridine derivatives **60a-b** and **60d-f** proved to be sensitive, the intermediates were used without any further purification (Table 7.20). The dechlorination was performed in a ~1.0M DCM/glacial acetic acid solution utilizing zinc dust (1.5 eq-5.0 eq). This rather mild reduction conditions did not cause any side reactions and the desired 3,5-disubstituted pyridine-based building blocks **51a-b** and **51d-f** were isolated by Kugelrohr-distillation.

Table 7.20: Due to the instability of the resulting products after the second Grignard formation, the formed 3-(chloromethyl)-5-BPin-pyridine derivatives **60a-b** and **60d-f** were reduced without further purification.



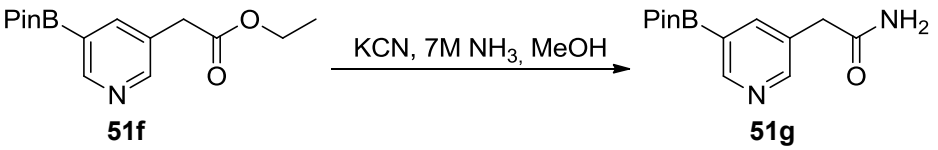
59a-b, **59d-f** → **51a-b**, **51d-f**

Entry	Benzyl Chloride	Building Block A or C	Yield[a]
1	 **59a**	 **51a**	84%
2	 **59b**	 **51b**	56%
3	 **59d**	 **51d**	63%
4	 **59e**	 **51e**	64%
5	 **59f**	 **51f**	71%

[a] Isolated yield over two steps.

For synthetic reasons the formation of building blocks **51e** (Table 7.20, entry 4) and **51f** (entry 5) were performed in its masked form, as these compounds are more stable in storage and more advantageous in the subsequent Suzuki-coupling assembly and purification step. The masked Lys-surrogate **51e** can easily be hydrogenated to the corresponding native primary amine at the teraryl stage, using Raney-Nickel in an ammonia/MeOH mixture (see also Scheme 7.64, page 84).

The ethylester group of building block **51f** can also be converted to its amide form (representing asparagine) under catalytic amounts of KCN in 7M ammonia/MeOH mixture without interfering the pinacol ester function (Scheme 7.62).

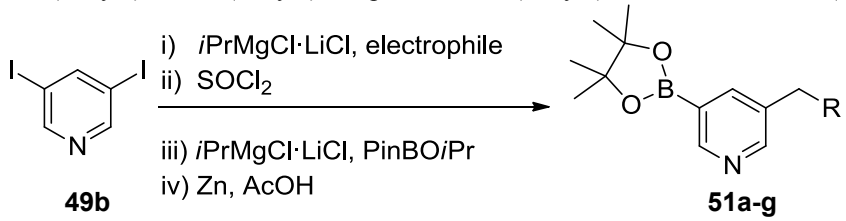


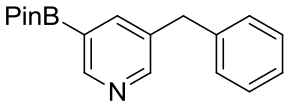
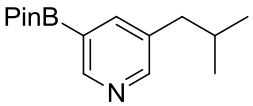
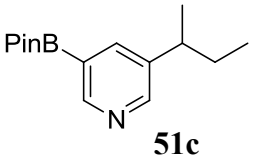
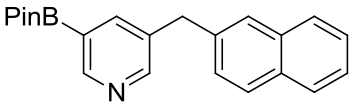
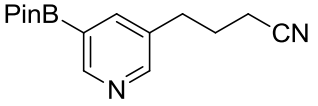
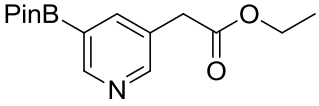
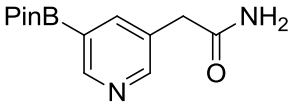
51f **51g**

Scheme 7.62: The ethylester function of building block **51f** can be easily converted in its amide form by using catalytic amounts of KCN (mimicking asparagine).

Table 7.21 summarizes the synthesized pyridine-based building blocks **51a-g** and its overall yields. It could be confirmed that not only nonpolar/hydrophobic (**51a-c**, entry 1-3), basic (**51e**, entry 5), acidic (**51f**, entry 6) or polar/neutral, (**51g**, entry 7) also non-natural (**51d**, entry 4) side chains are accessible by this approach with 24-73% overall yields for the four step reaction sequence, starting from 3,5-diiodopyridine (**49b**).

Table 7.21: Overall yields for the synthesis of building blocks A and C with representative residues (or a latent-form; entries 5 and 6) for all groups of amino acids (nonpolar/hydrophobic (entries 1-3), basic (entry 5), acidic (entry 6) and polar/neutral (entry 7) or even non-natural (entry 4).

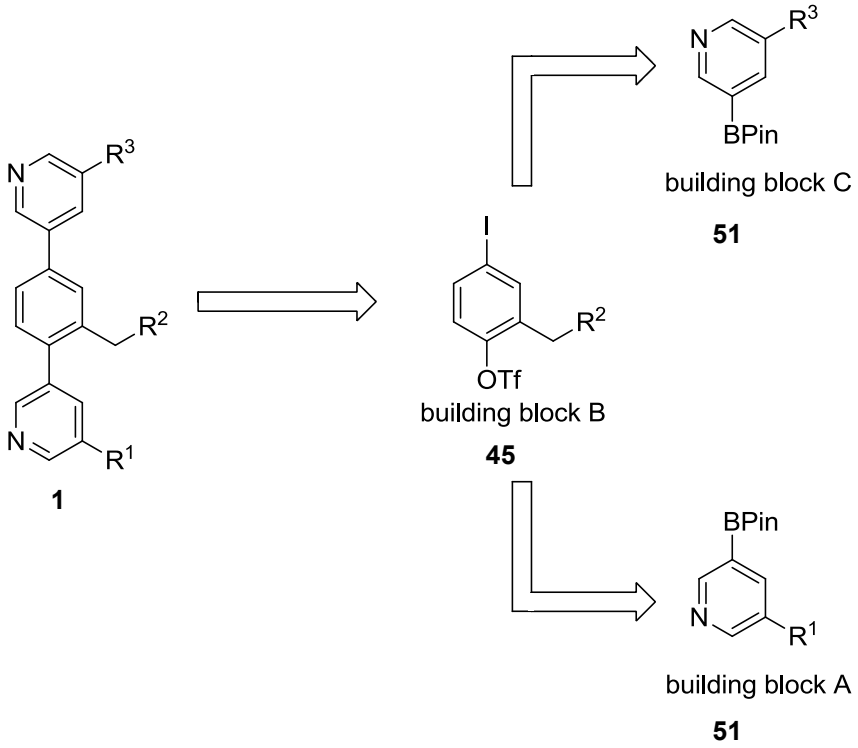


Entry	Product	Amino Acid Side Chain	Overall Yield[a]
1	 **51a**	"Phe", nonpolar/hydrophobic	76%
2	 **51b**	"Leu", nonpolar/hydrophobic	45%
3	 **51c**	"Ile", nonpolar/hydrophobic	24%[b]
4	 **51d**	non-natural/nonpolar/hydrophobic	27%
5	 **51e**	"Lys", basic	52%[c]
6	 **51f**	"Asp", acidic	55%
7	 **51g**	"Asn", polar/neutral	37%

[a] Isolated yields over four step synthesis starting from 3,5-diiodopyridine (**49b**). [b] The elimination product of compound **58c** (Table 7.18, entry 3) was reduced with 10% Pd/C, after borylation. [c] Compound **51g** was prepared from compound **51f** using catalytic amounts of KCN in 7M ammonia/MeOH mixture.

7.3.5 Synthesis of Teraryls

After developing a flexible strategy to obtain pyridine-based building blocks **51**, the twofold Suzuki-coupling for synthesizing linear teraryls starting from triflate derivative **45** was investigated in cooperation with M. TROBE.[73] Scheme 7.63 depicts the synthetic benefit of this triflate approach. The first Suzuki-coupling can be performed regioselectively at the iodine position, whereby the triflate function is not substituted at all. The resulting biarylic triflate derivative can be directly transformed to the desired terarylic scaffold under the second Suzuki cross-coupling without any purification step.

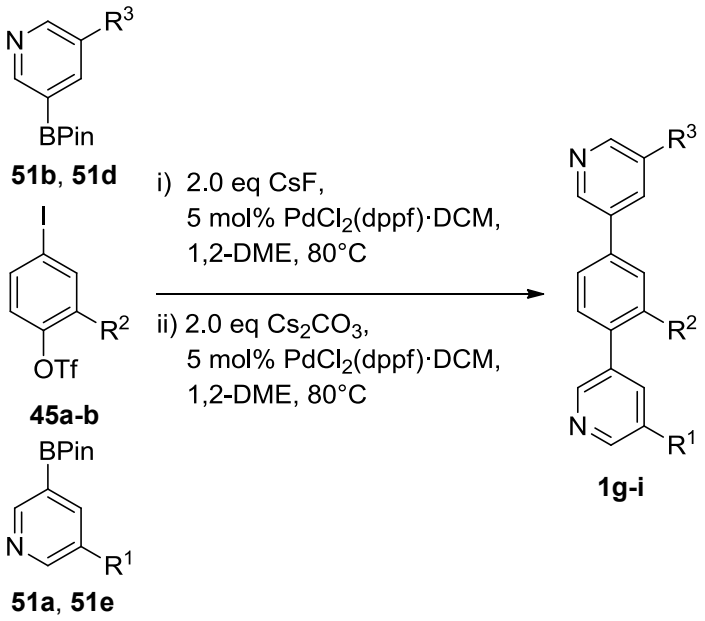


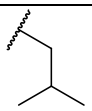
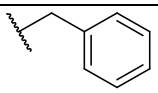
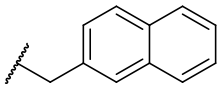
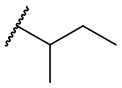
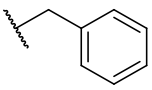
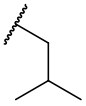
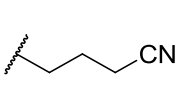
Scheme 7.63: Retrosynthesis for the twofold Suzuki-coupling steps using the triflate approach.[73]

According to Table 7.22, it is possible to obtain pyridine-based teraryls in a convergent, two-step-one-pot synthesis. The selective differentiation of the two leaving groups is based on their different reactivity, the steric accessibility and strength of the applied base during the Suzuki-coupling with $PdCl_2(dppf)\cdot DCM$ as catalyst.

The pyridine-based Leu-Val-Phe mimetic **1g** was prepared in 47% overall yield (Table 7.22, entry 1), the Naph-Ile-Phe **1h** in 66% yield (Table 7.22, entry 2). For the synthesis of the Leu-Val-Lys mimetic **1j** the second Suzuki-coupling was performed with building block **51e** to deliver compound **1i** in 46% yield (Table 7.22, entry 3).

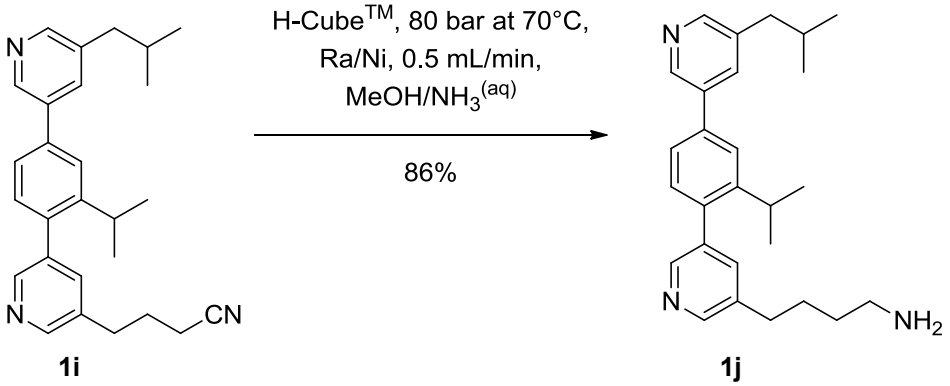
Table 7.22: Synthesis of pyridine-based teraryls **1g-i** using the convergent two-step-one-pot approach.



Entry	R^{1}[a]	R^{2}[a,b]	R^{3}[a]	Teraryl	Yield[c]
1	 "Leu"	 "Val"	 "Phe"	**1g**	47%
2	 "Naph"	 "Ile"	 "Phe"	**1h**	66%
3	 "Leu"	 "Val"	 "Lys"	**1i**	46%[d]

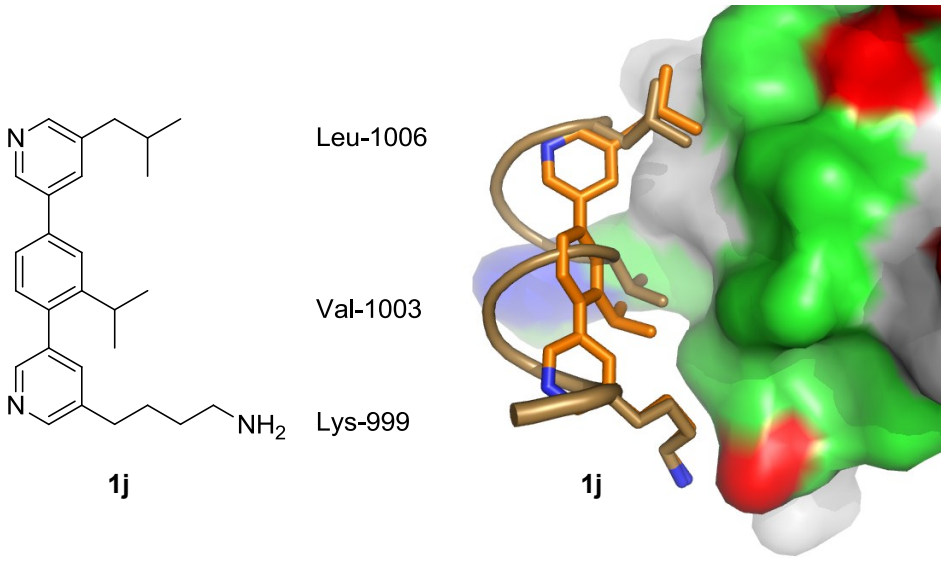
[a] Residues for the corresponding amino acids that are mimicked by these residues. [b] For the synthesis of the corresponding core units **45a-b** see literature.[73] [c] Isolated yields. [d] Lys side chain (R^{3}) in its latent form of a nitrile.

The lysine side chain in its latent form of a nitrile in **1i** can be easily reduced to the primary amine under reductive conditions using Raney-Nickel in an H-Cube™ flow reactor delivering the desired Leu-Val-Lys mimetic **1j** in 86% yield (Scheme 7.64).



Scheme 7.64: Reduction of the nitrile function furnished the final teraryl **1j**.

The pyridine-based teraryl **1j** represents a derivative of the second computer modeled lead-structure (Scheme 7.65). The three side chains (aminobutyl, isopropyl and isobutyl) of **1j** are mimicking the amino acid side chains of lysine-999, valine-1003 and leucine-1006, which represent the second binding motif of human RhoA and human ROCKI as it is depicted in Scheme 7.65 (compare also Scheme 7.1, page 14).[43c,47]



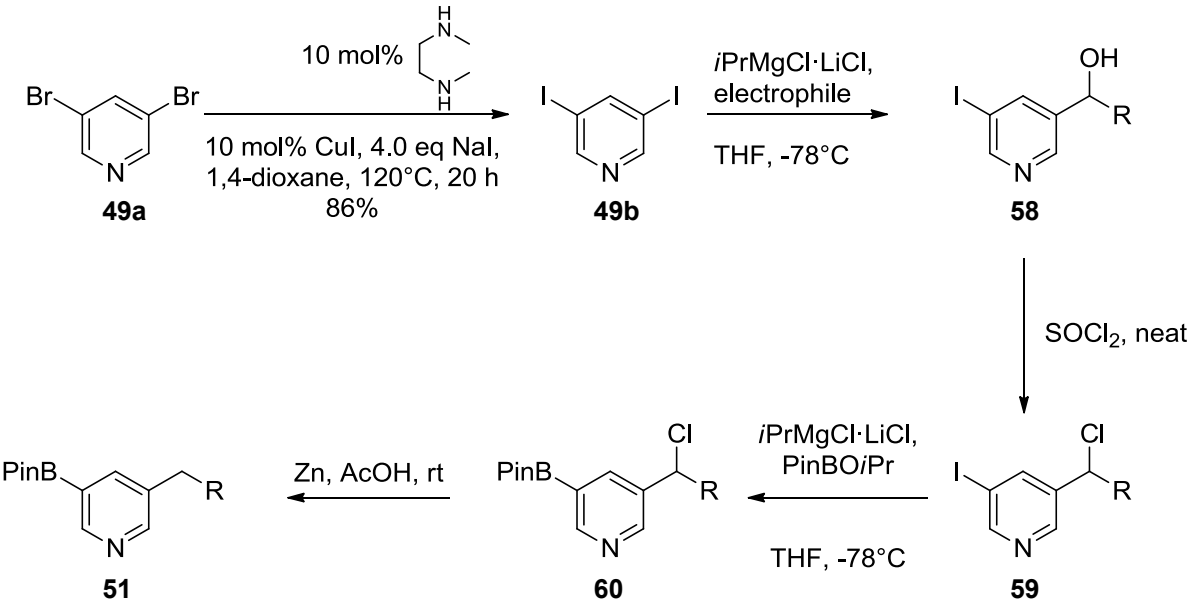
Scheme 7.65: Peptide mimetic **1j** (left) and the computer modeled docking experiment after binding at the surface of RhoA (right); calculations were performed by DVORSKY (PDB-file: 1S1C).[43c,47] The α-helix of human ROCKI is shown as cartoon loop (sand), peptide mimetic **1j** is illustrated as sticks (orange) and human RhoA is given as surface (green, red, blue and grey).*

7.3.6 Summary of the Triflate Approach

One of the main problems of terphenyl-based peptidomimetics is the poor solubility under physiological conditions. For that reason a general approach was investigated to synthesize 3,5-disubstituted pyridine-based boronic acid pinacol esters **51a-g** (Scheme 7.66). Starting from 3,5-diiodopyridine (**49b**) a twofold Knochel-Grignard formation was compiled to

* For the sake of clarity only the monomeric form is shown.

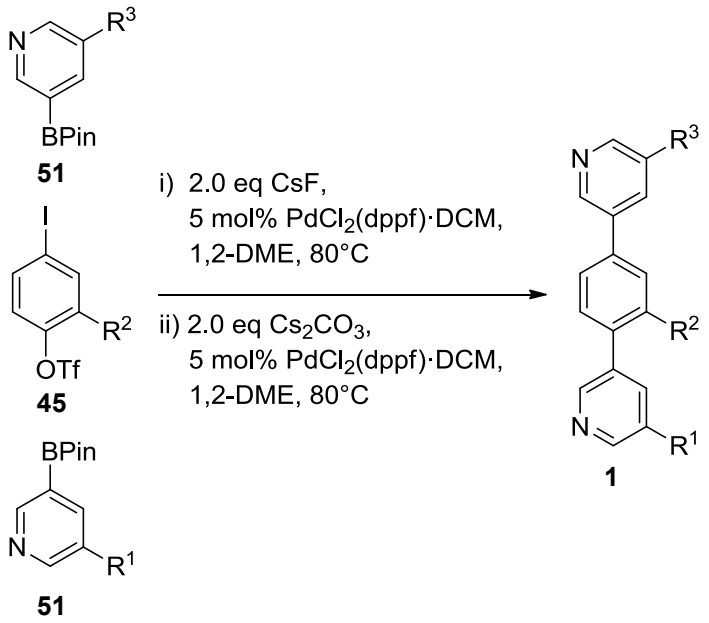
introduce the amino acid side chain and the pinacol ester function. With 3,5-dibromopyridine (**49a**) the twofold metal-halide exchange was not feasible, due to the poor reactivity of the bromine leaving group (see also page 71). Therefore the dibromo derivative **49a** was converted by a Finkelstein-like iodination reaction employing CuI and dimethylethane-1,2-diamine as ligand into its iodine form (Scheme 7.66).



Scheme 7.66: Synthetic strategy of the synthesis of 3,5-disubstituted pyridine-based boronic acid pinacol esters **51**.

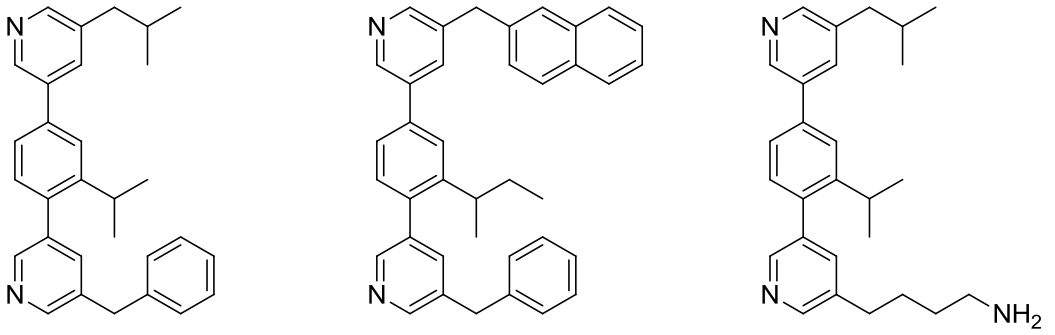
The direct reduction of the benzylic alcohol function of compound **58** was not feasible under chosen conditions, due to deiodinationen side reactions (see also Scheme 7.59, page 74). Therefore the alcohol function was transformed into its chloride form, which represents a less challenging reducible intermediate. After the second metal-halide exchange, the resulting products **60a-b** and **60d-f** were found to be not stable and were directly used within the reduction step employing Zn-powder under acidic conditions. Neither the potential internal electrophile represented by the α-aryl chloride of substrates **59a-b** and **59d-f**, nor the unsaturated side chain of compound **61** interfered with the second Grignard formation to introduce the pinacol ester function.

Using the triflate approach with only a set of 18 triflate core building blocks **45** and 18 3,5-disubstituted pyridine boronic acid pinacol esters **51**, any permutations of α-helix mimetics featuring all relevant proteinogenic amino acids (excluding Pro and Gly) can be prepared (Scheme 7.67).



Scheme 7.67: Two-step-one-pot approach of the triflate-based core unit **45**.[73]

In order to highlight the convergent teraryl synthetic strategy three representatives of pyridine-based teraryls **1g-h** and **1j** with a phenylic core unit were prepared (Scheme 7.68). According to the established procedure, it is possible to obtain linear teraryls in a convergent, two-step-one-pot synthesis.



5^{Py}-3-Phe-2-Val-5^{Py}-3-Leu	5^{Py}-3-Phe-2-Ile-5^{Py}-3-Naph	5^{Py}-3-Lys-2-Val-5^{Py}-3-Leu
9%, 11 steps	8%, 11 steps	5%, 12 steps
1g	**1h**	**1j**

Scheme 7.68: Synthesized pyridine-based teraryls using the triflate approach.

8 Summary and Outlook

8.1 Summary

Established targets in drug discovery are defined by addressing the active site of enzymes, which can be characterized as a pocket with typically solvent-shielded and hydrophobic and/or hydrophilic binding regions.[8d]

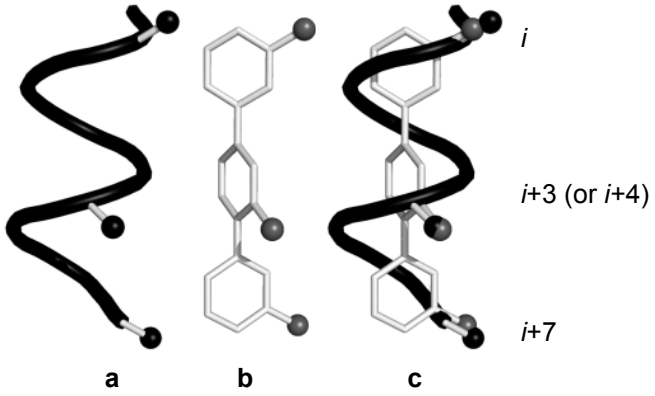
A different concept of addressing new targets in drug discovery is to interfere the formation of protein-complexes. Today it is commonly assumed that proteins fulfill their biological functions as participants of protein-complexes instead of acting in isolation.[20]

Typically, protein-protein-interaction domains comprise ~35-150 amino acids[2] and dozens of binding domains are known. Beside PTB- (Phospho-Tyr binding),[3] PDZ- (one of the most frequently encountered domains),[4] SH3- (proline rich binding)[5] or WW-domains (proline rich binding),[6] the motif of an α-helical interaction of one protein with the surface of the second one is the most common one.[7]

The contact areas could thereby be higher than 1000 $Å^2$, essentially defined by less rugged surfaces, which makes the design of small molecules for disrupting therapeutically relevant interactions very complicated.[21] Nevertheless, the intervention of such PPIs by small molecules would offer new opportunities for the treatment of human diseases.[22]

The specific exchange of amino acids at the contact area, e.g., by Ala-scan, has shown that only a few amino acids have an outstanding impact on the binding affinity of the protein-complex.[8d] Such “hotspots” of binding free energy seem to be rather prevalent in PPIs.[22-23]

Terphenylic or terhetarylic scaffolds are bioinspired motifs for the inhibition of protein-protein-interactions. HAMILTON and coworkers have presented a general approach to emulate α-helices by suitable positioning of amino acid side chains at the terphenylic scaffold (Scheme 8.1).[8b,8e,9a,46] In addition, the intrinsically helical structure of terphenyls has advantageous effects in mimicking peptidic α-helical subunits.[8c,8d,9b]

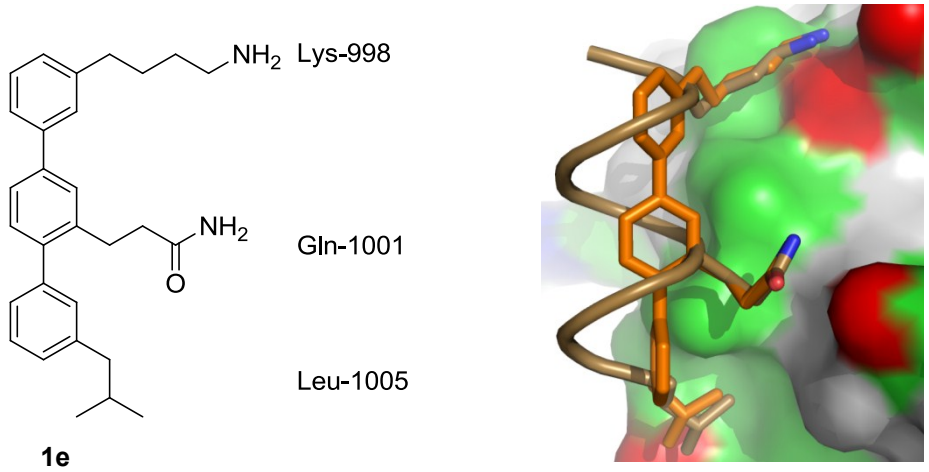


Scheme 8.1: Schematic representation of an α-helical subunit with its *i*, *i*+3 (or *i*+4) and *i*+7 amino acid residues (**a**). Terphenylic scaffolds with 2',3,3"-substitution pattern (**b**). Terphenyls can mimic the three-dimensional shape of an α-helix (**c**).

Within this work three novel synthetic strategies have been successfully developed that enable a convenient and flexible approach to linear benzene or hetaryl-based terarylic scaffolds.

8.1.1 Linear Approach

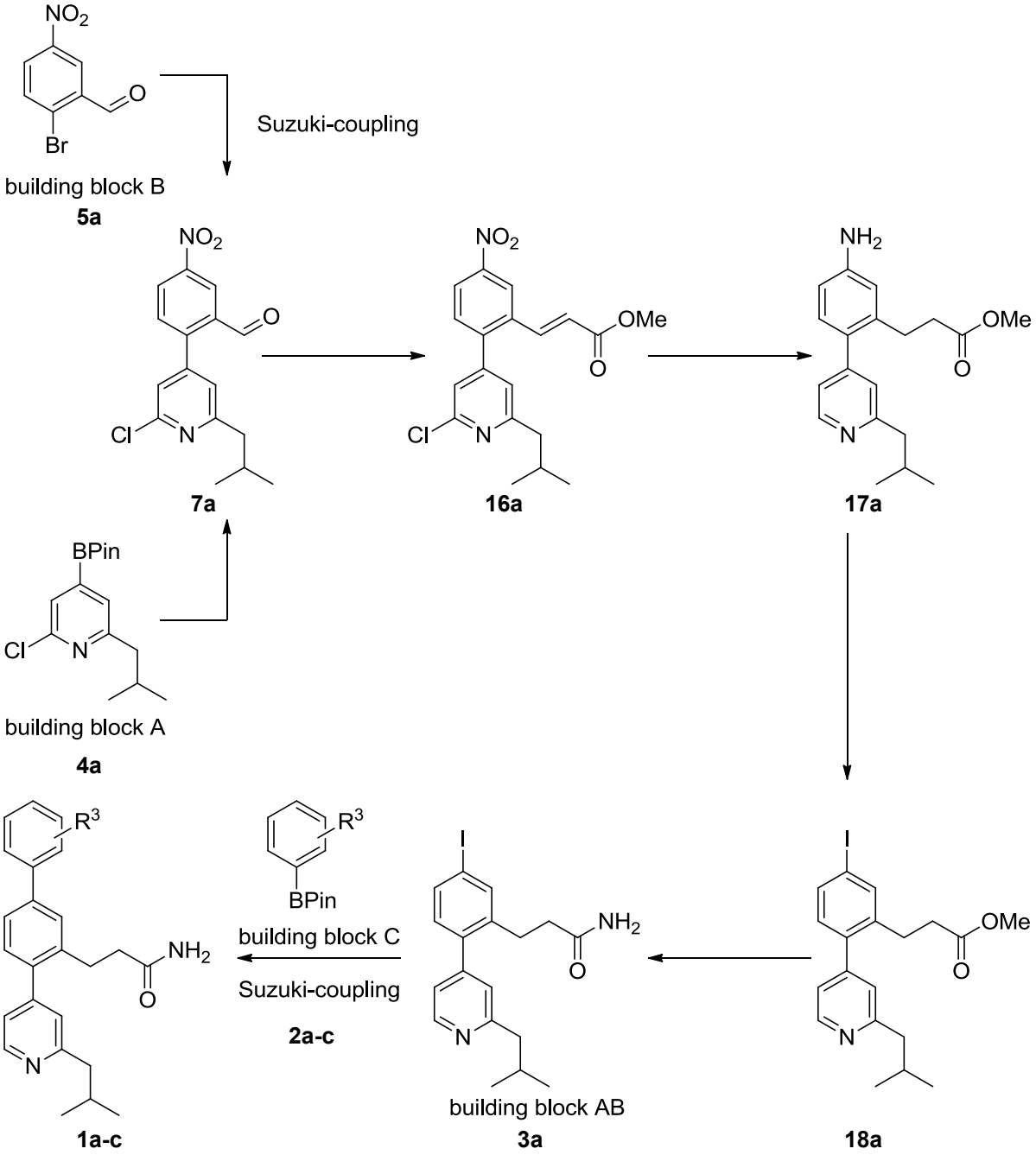
The terphenyl-based lead-structure **1e** is the first computer modeled compound for inhibition of the PPI between the surface of Rho GTPase and the α-helical protein ROCK (Scheme 8.2, see also page 9). The three side chains (aminobutyl, amidoethyl and isobutyl) of lead-structure **1e** are mimicking the amino acid side chains of lysine-998, glutamine-1001 and leucine-1005, which represent the main binding motif of human RhoA and human ROCKI as it is depicted in Scheme 8.2.[43c,47]



Scheme 8.2: Lead-structure **1e** (left) and the computer modeled docking experiment after binding at the surface of RhoA (right); calculations were performed by DVORSKY (PDB-file: 1S1C).[43c,47] The α-helix of human ROCKI is shown as cartoon loop (sand), lead-structure **1e** is illustrated as sticks (orange) and human RhoA is given as surface (green, red, blue and grey).*

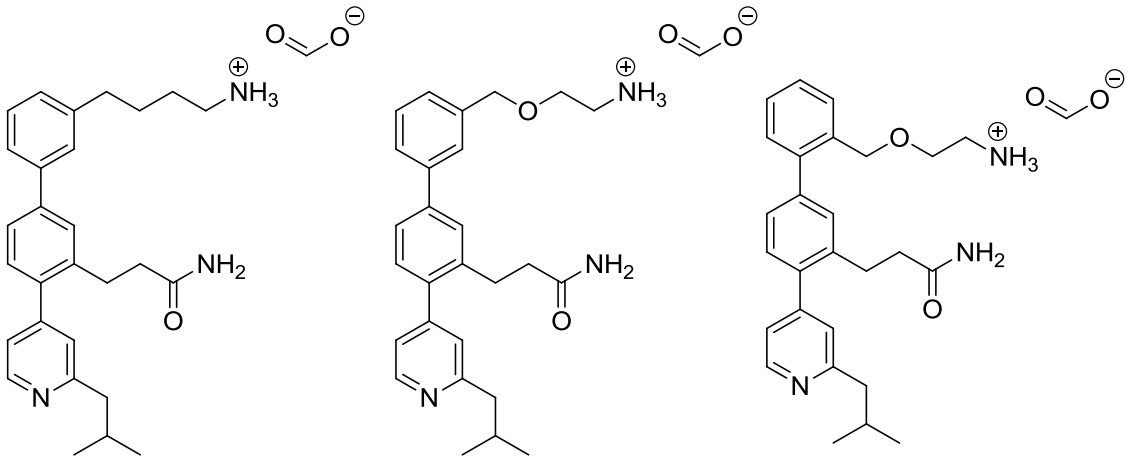
* For the sake of clarity only the monomeric form is shown.

An overview of the entire synthetic route of teraryls **1a-c** is given in Scheme 8.3. Starting from building blocks **5a** and **4a** the biarylic aldehyde **7a** was prepared. Introducing the glutamine side chain was realized over four steps. After a Wittig reaction the resulting methyl acrylate **16a** was reduced to its saturated form followed by iodination under modified Sandmeyer-conditions. The amide function was further introduced by a KCN-catalyzed amidation and a second Suzuki-coupling finally led to the terarylic scaffold. The desired teraryls **1a-c** were obtained after deprotection of the amine function of the lysine side chain.



Scheme 8.3: Synthesis of teraryls **1a-c** using the linear approach. Essential within this synthesis were the two Suzuki-coupling steps for assembling the terarylic scaffold.

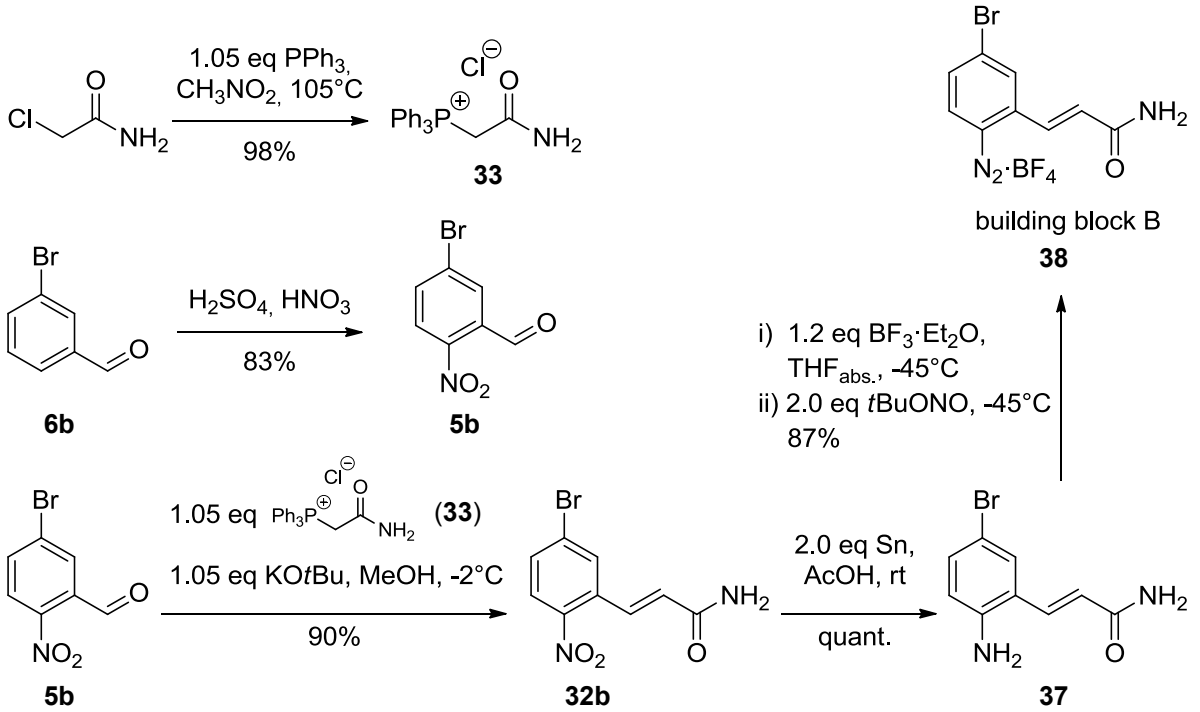
Three different teraryls have been successfully prepared using the linear approach (Scheme 8.4). Based on lead-structure **1e** the teraryl **1a** was synthesized in 17 steps with an overall yield of 14%. Teraryl **1b** and **1c** were obtained in 13 steps with an overall yield of 7% and 12%, respectively.



Scheme 8.4: Overview of the synthesized teraryls **1a-c** with their overall yields using the linear approach.

8.1.2 Diazonium Approach

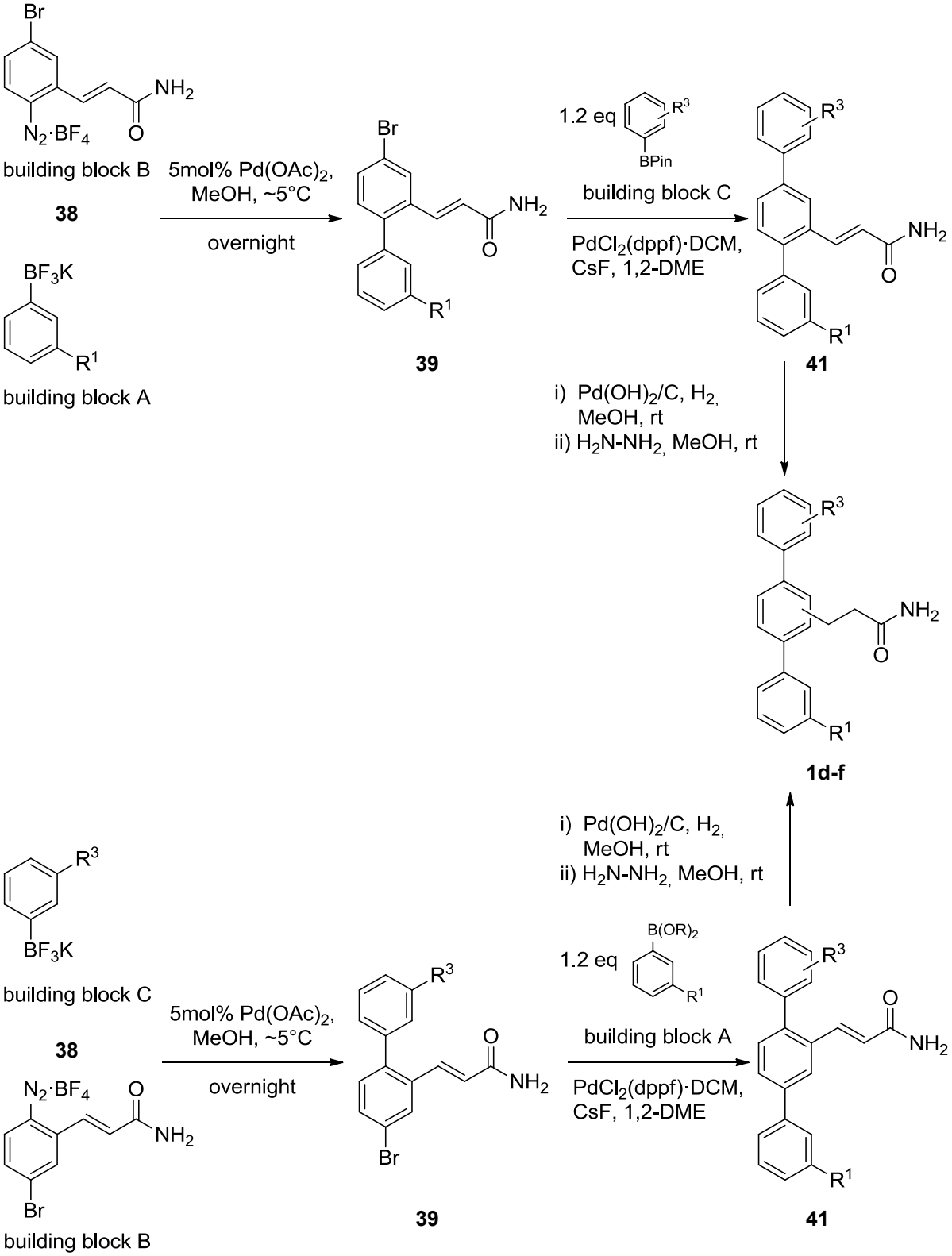
The fundamental idea of a convergent synthesis of terphenyls was the design of the central core unit **38** with two differentiated functional groups suitable for selective Pd-catalyzed cross-coupling reactions (Scheme 8.5).



Scheme 8.5: Synthesis of the diazonium core unit 38 with an overall yield of 64% over 5 steps.

After introducing the glutamine side chain under Wittig-conditions, the resulting nitrobenzene derivative **32b** was reduced employing Sn-powder under acidic conditions. The amine function was further converted to the corresponding diazonium-based building block B (compound **38**) using $BF_3 \cdot Et_2O$ and *t*BuONO at -45°C.

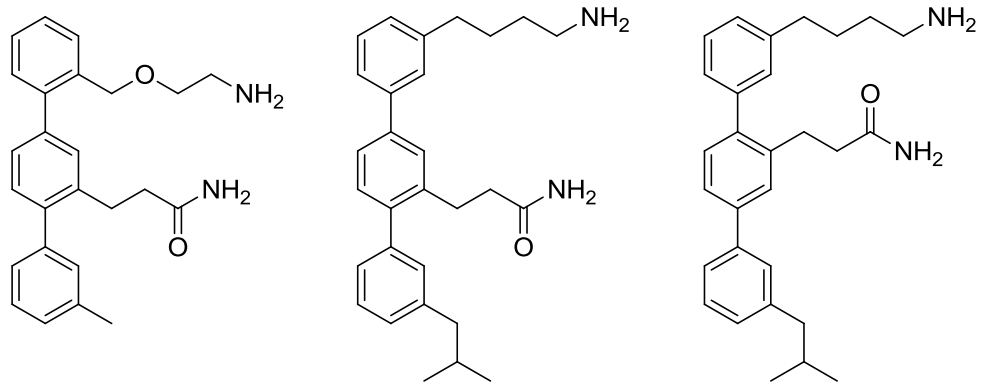
The convergent and regioselective synthetic strategy of the diazonium approach is summarized in Scheme 8.6. The diazonium coupling of building block B and building block A or C as corresponding BF_3K-salts was performed using $Pd(OAc)_2$ in absolute MeOH, which was subsequently followed by the second aryl-aryl coupling under established Suzuki-conditions.



Scheme 8.6: Synthetic strategy for the synthesis of terphenyls using the diazonium core unit **38**.

This diazonium approach is a convenient route to vary the substitution pattern of the final terphenylic scaffolds by changing the order of the two aryl-aryl coupling steps within the synthesis (e.g., compare **1e** and **1f**).

Three different lead-structure-based terphenyls (Scheme 8.7) have been designed and successfully prepared using this convergent approach. The opportunity to achieve such a synthetically sophisticated terphenyl has been impressively shown in the preparation of compound **1d**. Within only 12 steps the synthesis of this alternative terphenyl could be fulfilled. On the other hand, the synthesis of the computer modeled lead-structure **1e** was feasible within 19 steps and an overall yield of 11%. In addition, a terphenyl bearing an alternative substitution pattern (compound **1f**) was also prepared.



3-Ala-2'-Gln-2''-*O*-Lys
9%, 12 steps
1d

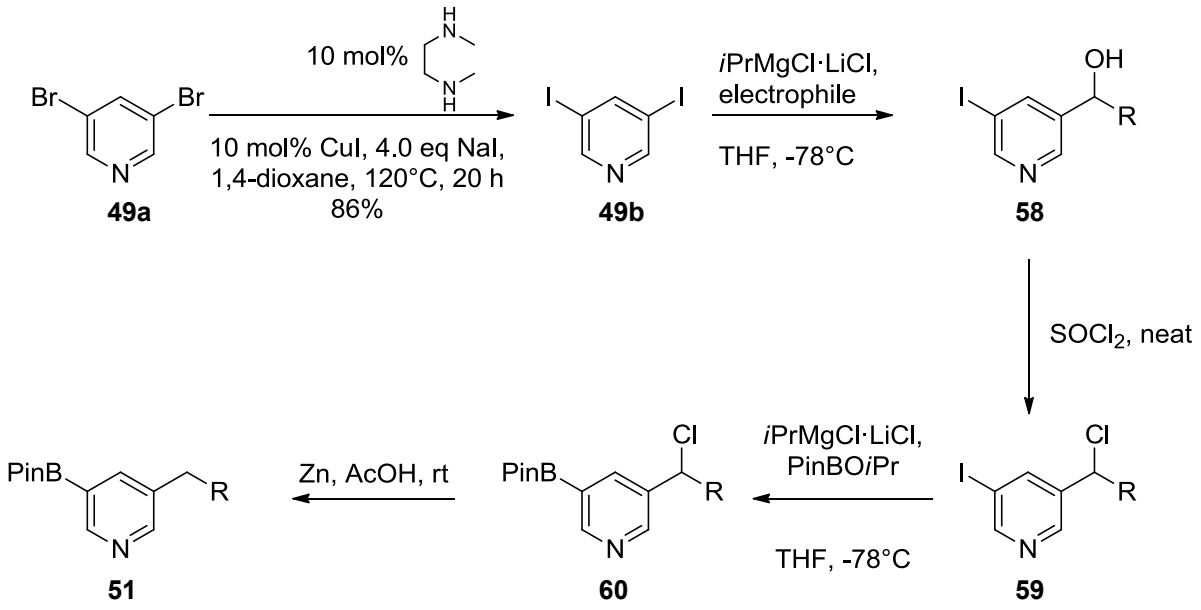
3-Leu-2'-Gln-3''-Lys
11%, 19 steps
1e

3-Leu-3'-Gln-3''-Lys
10%, 19 steps
1f

Scheme 8.7: Synthesized terphenyls based on the diazonium approach.

8.1.3 Triflate Approach

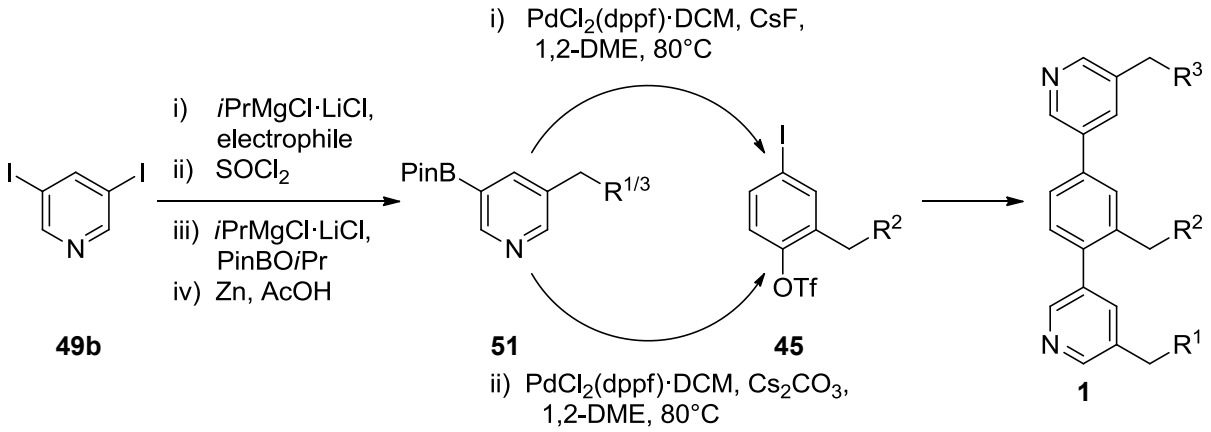
One major drawback of terphenyl-based peptidomimetics is the poor solubility under physiological conditions. In order to increase these solubility characteristics of the peptidomimetics, pyridine-based building blocks have been introduced into the backbone of the scaffold. In particular, a general approach has been developed to prepare 3,5-disubstituted pyridine-based boronic acid pinacol esters **51a-g** (Scheme 8.8). Starting from 3,5-diiodopyridine (**49b**) a twofold Knochel-Grignard formation was performed to introduce the amino acid side chain and the pinacol ester function. In contrast to this, starting from 3,5-dibromopyridine (**49a**) did not result in the desired product, due to the poor reactivity of the bromine leaving group (see also page 71). Therefore the dibromo derivative **49a** was converted by a Finkelstein-like iodination reaction employing CuI and dimethylethane-1,2-diamine as ligand into its iodine form (Scheme 8.8).[84]



Scheme 8.8: Synthetic strategy of the synthesis of 3,5-disubstituted pyridine-based boronic acid pinacol esters **51a-f**.

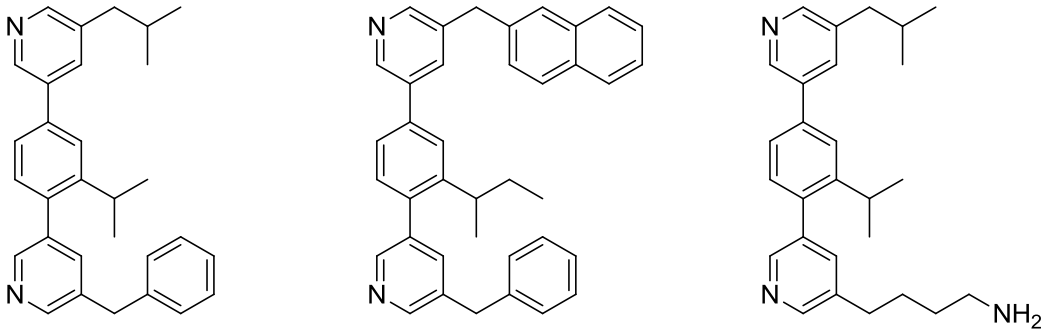
The reduction of the benzylic alcohol function of compound **58** in the next step turned out to be problematic due to deiodination side reactions (see also Scheme 7.59, page 74). Therefore the alcohol function was transformed into its chloride form first, which represents a less challenging reducible intermediate. After the second metal-halide exchange, the resulting intermediate **60** was not stable, so that the reduction employing Zn-powder under acidic conditions was performed without purification of compound-class **60**. Neither the potential internal electrophile represented by the α-aryl chloride of substrates **59a-b** and **59d-f**, nor the unsaturated side chain of compound **61** hampered the second Grignard formation to introduce the pinacol ester function.

By means of this triflate approach any permutations of α-helix mimetics bearing all relevant proteinogenic amino acids (excluding Pro and Gly) can be synthetically achieved with only a set of 18 triflate core building blocks **45** and 18 3,5-disubstituted pyridine boronic acid pinacol esters **51** (Scheme 8.9).



Scheme 8.9: Overview of the triflate approach including the four-step synthesis of pyridine-based building blocks **51**.

In order to highlight this unique and convergent synthetic pathway three selected and synthetically challenging representatives of pyridine-based teraryls **1g-h** and **1j** have been prepared (Scheme 8.10). According to the established procedure, it is now possible to obtain linear teraryls in a convenient and unique two-step-one-pot synthesis.



5^{Py}-3-Phe-2-Val-5^{Py}-3-Leu
9%, 11 steps
1g

5^{Py}-3-Phe-2-Ile-5^{Py}-3-Naph
8%, 11 steps
1h

5^{Py}-3-Lys-2-Val-5^{Py}-3-Leu
5%, 12 steps
1j

Scheme 8.10: Synthesized pyridine-based teraryls using the triflate approach.

Teraryl **1g** and **1h** were prepared in 11 steps with an overall yield of 9% and 8%, respectively. The lysine derivative **1j** was synthesized in 12 steps and 5% yield.

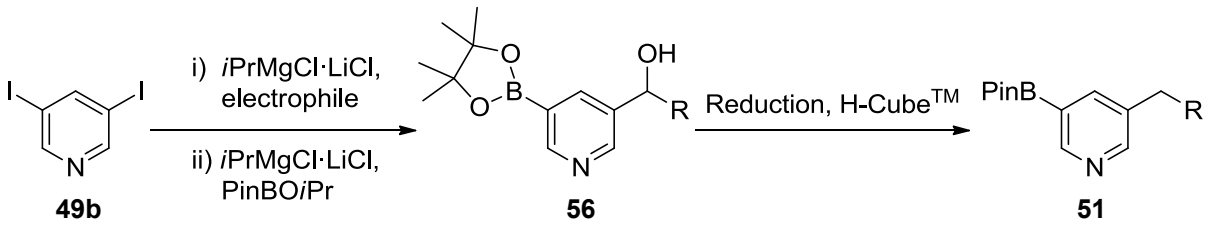
8.2 Outlook

The interaction of small molecules with biologically active targets is the central focus of drug discovery and the field of the inhibition of protein-protein-interactions has become one of its big challenges, whereby the area of research is still at its beginning. A major target of intervening PPIs, is the examination of their local action and the exact functional role of these small molecules, which are binding on the surface of the protein.

In addition, the design of a flexible and generally applicable approach of synthesizing a large library of hetaryl-based teraryls which comprises any possible permutation of α-helix mimetics featuring all relevant proteinogenic amino acids is not solved so far.[85] In the next chapters some ideas for further investigations in the field of PPI inhibition based on terarylic scaffold are suggested.

8.2.1 Pyridine-Based Building Blocks

The results of this thesis show the necessity of hetaryl-based building blocks for better solubility under physiological conditions and the synthesis of pyridine-based building blocks **51a-g** could be impressively demonstrated for different types of amino acid side chains (see also chapter 7.3.4, page 72). It could also be proven that a twofold Grignard formation starting from diiodo derivative **49b** is feasible by a two-step-one-pot approach (Scheme 8.11 or Scheme 7.58, page 73).



Scheme 8.11: Potential formation of pyridine-based building block **51** by reducing benzylic alcohol **56**.

Although the resulting 5-BPin-3-benzylic alcohol pyridine derivatives **56** were found to be sensitive to heat and also not stable on silica gel, the dehydroxylation might be performed utilizing different reducing catalysts like Pd-black or Pd/Al_2O_3.[86] Using the technique of a H-Cube™ allows the screening of different catalysts and additionally the optimization of temperature, pressure, pH or flow rate within a very short time.[87] Looking at the reduction conditions in more detail, the dehydroxylation of benzylic intermediates **56** might be performed by decreasing the overall number of steps for synthesizing different pyridine-based building blocks.

8.2.2 Coiled-Coil Peptidomimetics

In addition to non-hetaryl-based terphenyls two hetaryl-based helical peptidomimetics (compounds **1a** and **1j**) were synthesized, which might be suitable for the inhibition of the PPI of human ROCKI and human RhoA.

Figure 8.1 illustrates a schematic depiction of the proposed binding motifs of these two teraryls. Each teraryl is mimicking one helix of the dimeric human ROCKI, while this α-helical ROCKI dimer is connected over a coiled-coil interaction.

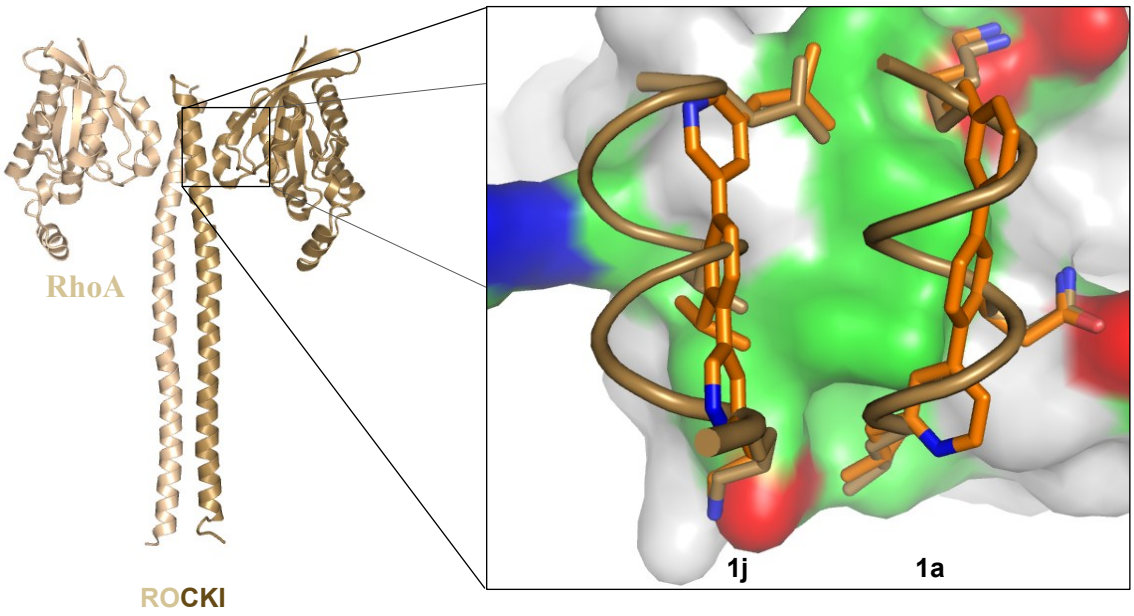
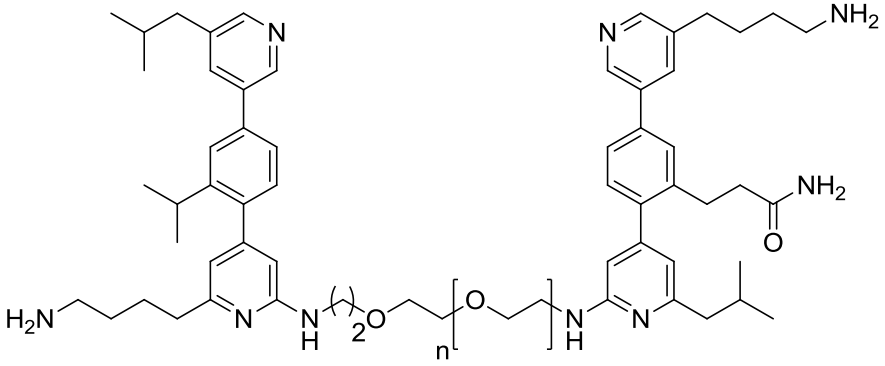


Figure 8.1: Dimeric protein-complex of human ROCKI and human RhoA depicted as cartoon (left). The "hotspot" of interaction surface and the teraryls **1a** and **1j** are mimicking the α-helix of ROCKI; PDB file 1S1C (right).[43c,47]

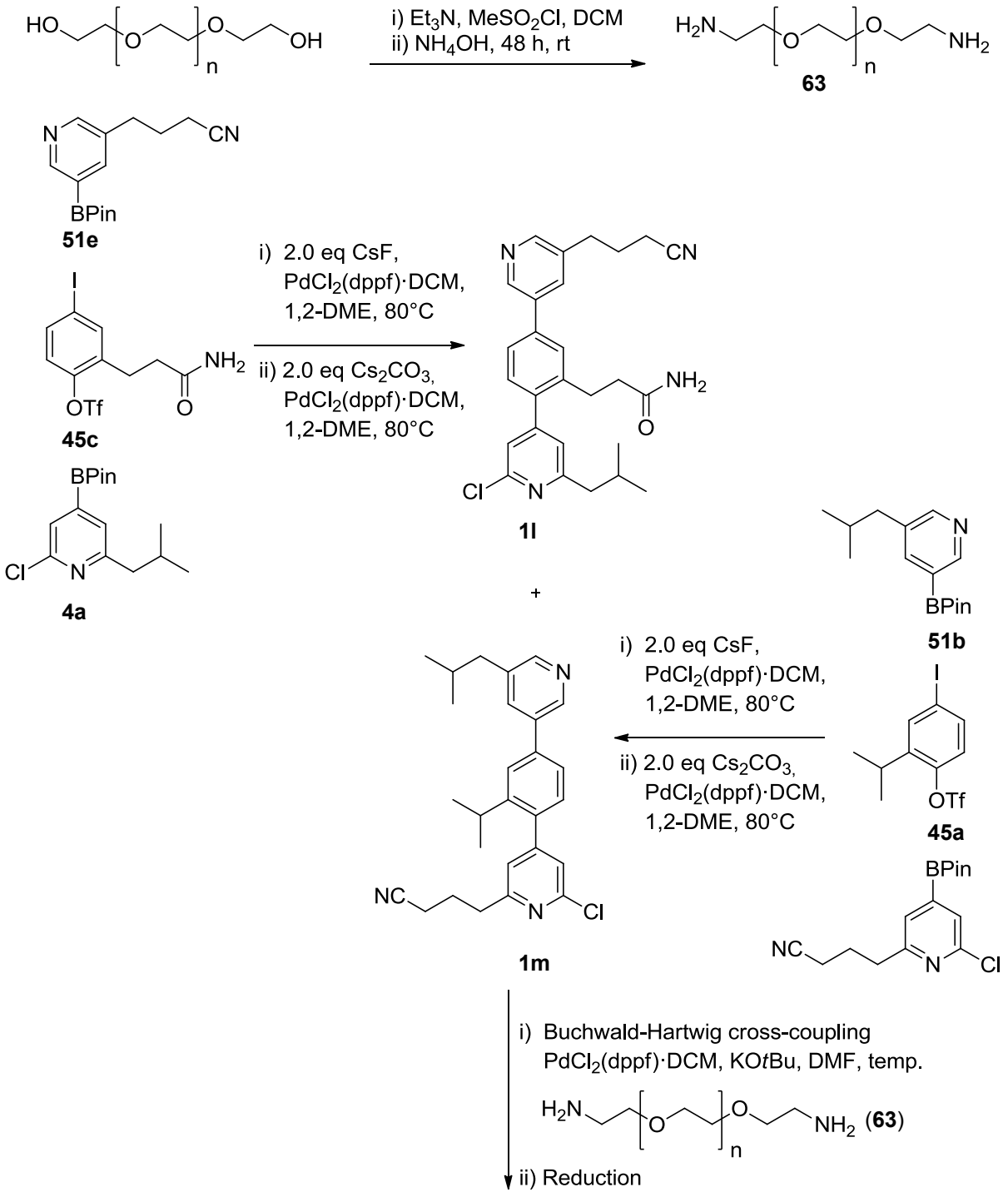
Each terarylic peptidomimetic should be able to specifically bind on the surface of RhoA for each of the helical subunit of the two ROCKIs. Linking these two potential inhibitors together as it is depicted in Scheme 8.12 generates a non-peptidic coiled-coil mimetic **62** with potentially higher binding affinity as it is expected for each single teraryl.



62

Scheme 8.12: Potential coiled-coil peptidomimetic for inhibition of PPI of RhoA/ROCKI protein-complex.

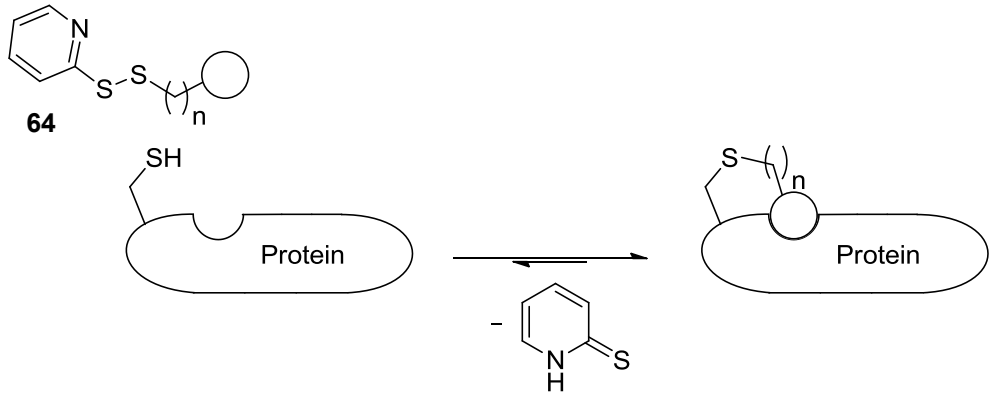
The retrosynthetic analysis is suggested in Scheme 8.13. After formation of an oligo ethylene glycol-based diamine **63**[88] the teraryls **1l-m** might be suitable for the coupling under Buchwald-Hartwig-conditions.[19a,89] The additional chloride function within the teraryls **1l-m** should enable the cross-linking of these two teraryls.



Scheme 8.13: Coupling two teraryls under Buchwald-Hartwig cross-coupling conditions presumably results in an oligo ethylene glycol bridged coiled-coil peptidomimetic **62**.

8.2.3 Tethering Experiments

As it has already been mentioned above, one of the major challenges in pharmaceutical research is to identify where exactly a drug is binding at a target protein. Due to the fact that the affinity and binding strength of a teraryl at the surface of a protein is rather weak compared to binding motifs of small molecules in a protein pocket, techniques like MS-MS are not suitable for these investigations. In order to solve this problem WELLS and coworkers and also other research groups have presented a general approach of tethering small molecules covalently at the target protein (Scheme 8.14).[90]

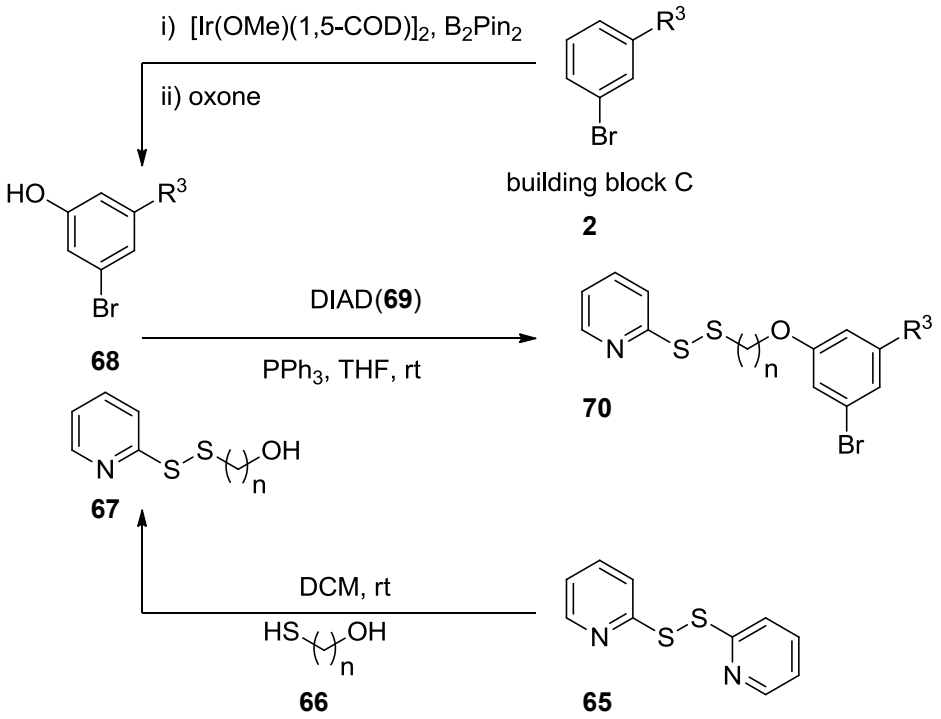


Scheme 8.14: Schematic depiction of tethering small molecules at a target protein. According to WELLS and coworkers a set of different teraryls containing a flexible disulfide linker can be covalently bound at the surface of a protein.

The basic concept of a tethering experiment is the covalent binding of small molecules (drugs) at the surface of a protein. Each drug contains a flexible organic linker with an terminal disulfide residue. The protein and the disulfide containing drug is mixed under reducing conditions to ensure a thiol-disulfide exchange at an accessible cysteine of the protein. If the drug binds at the protein, the thiol-disulfide exchange will be entropically favored and the equilibrium will be shifted toward the tethered form. The local region where the drug binds at the protein can further be identified by MS-MS methods.[90g]

Using this tethering technique a flexible organic linker with a disulfide residue has to be developed. Scheme 8.15 represents a proposed synthetic access to a modified building block containing an organic linker.

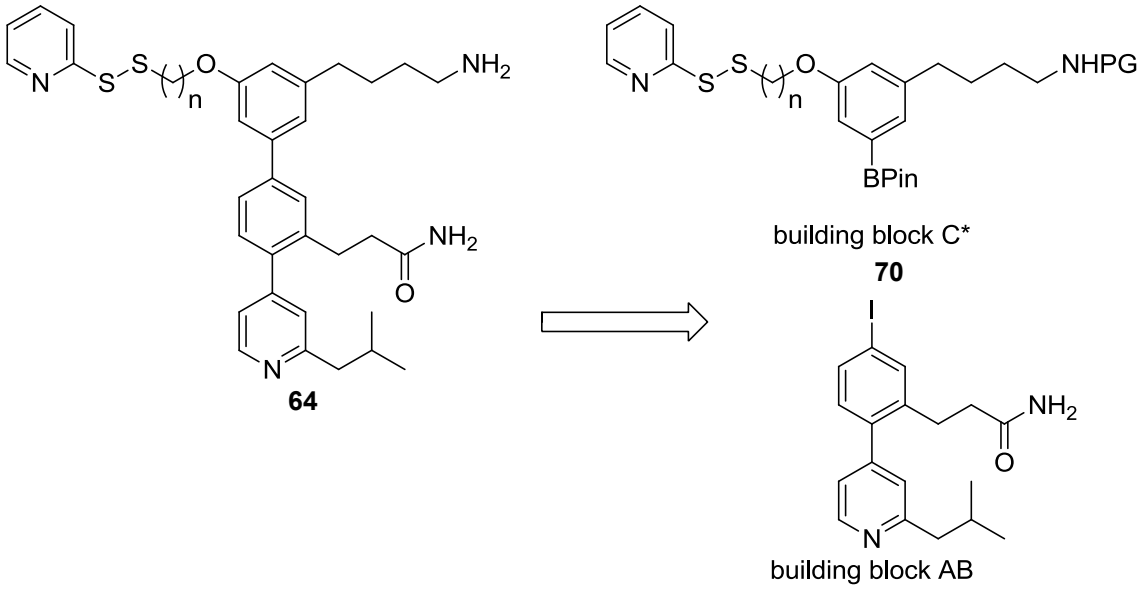
Building block C can easily be hydroxylated by regioselective borylation followed by oxidation with oxone resulting in phenol derivative **68**.[52,91] The flexible organic linker can further be introduced starting from 1,2-di(pyridin-2-yl)disulfane (**65**) and a *n*-alkyl mercaptoalcohol **66** (Scheme 8.15).



Scheme 8.15: Formation of a building block **70** containing a flexible organic linker.

The resulting pyridine-based disulfide **67** and compound **68** can then be coupled in the next step utilizing diisopropyl diazene-1,2-dicarboxylate (DIAD) (**69**) and PPh_3 in THF under Mitsunobu-conditions.[92] Beside a *n*-alkyl bridged linker also an ethylene glycol bridged linker might be suitable.

The obtained linker-containing compound **70** (building block C*) can further be used for the synthesis of a linker-containing teraryl like **64** according to previously described conditions (Scheme 8.16).



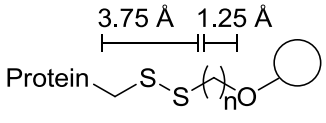
Scheme 8.16: Retrosynthesis of functionalized teraryl **64** for tethering experiments according to WELLS and coworkers.[90]

To investigate the impact of the length of the *n*-alkyl or ethylene glycol-based linker different computational examinations were performed by our cooperation partner R. DVORSKY. Thereby a variation of mutations of RhoA residues to cysteines and their linking to the terphenyl ligands were explored.

Table 8.1 shows the residues of RhoA that are adjacent to the upper building block of the bound terphenyl **64** and which are not interacting with the drug. Basically they could be mutated to cysteine and, as they are solvent exposed, subsequently linked to the terphenyl by tethering experiments.

The minimal and the half-circle distance are calculated for two different linkers; a *n*-alkyl and an oligo ethylene glycol linker. The length of one methylene or one ethylene glycol group in straight conformation corresponds to 1.25 Å or 3.50 Å, respectively. The overall length of a fully extended *n*-alkyl chain can be approximately calculated as the multiplication of the number of methylene groups, their respective lengths and addition of 3.75 Å that corresponds to the length of the -CH_2-S-S- group (Equation 8.1):

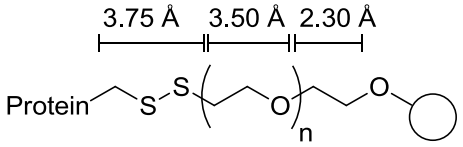
$$d_{alkyl} \approx 3.75 + n * 1.25$$



Equation 8.1: Formula for calculating the length of the *n*-alkyl linker.

In addition another simple formula could be derived for oligo ethylene glycol chains with the correction of 2.30 Å for the first monomeric group (Equation 8.2):

$$d_{ethylene\ glycol} \approx 3.75 + 2.30 + (n-1) * 3.50$$

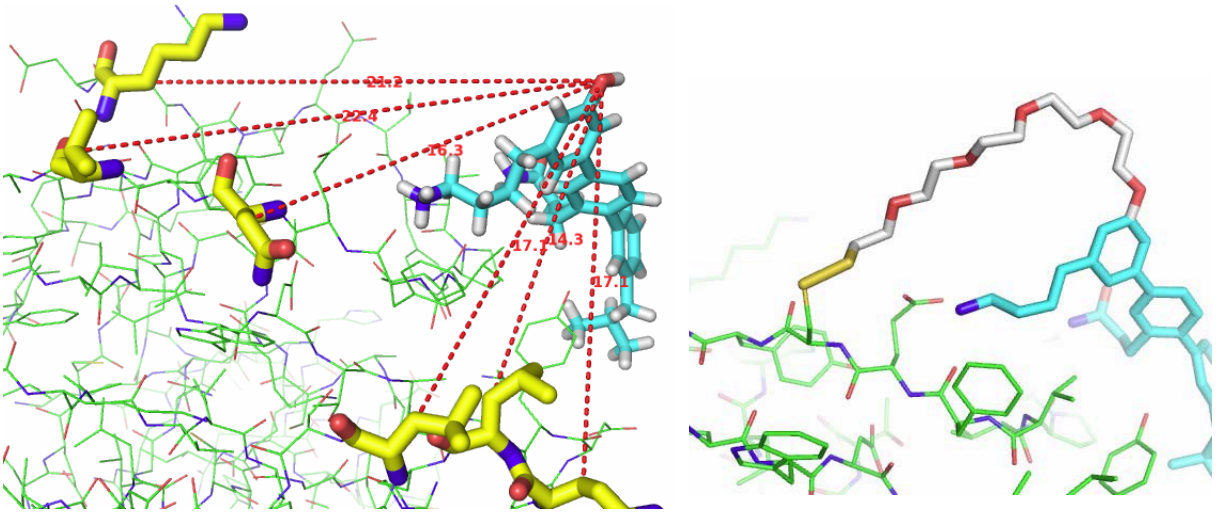


Equation 8.2: Formula for calculating the length of the oligo ethylene glycol linker.

Figure 8.2a is showing the positions of selected amino acids together with the mentioned distances. The number of monomers can then be calculated reversibly for the given length of the linkers (Equation 8.3, see also Table 8.1).

$$n_{alkyl} \approx \frac{d - 3.75}{1.25} \qquad n_{ethylene\ glycol} \approx \left(\frac{d - 6.05}{3.50}\right) + 1$$

Equation 8.3: Number of monomers for *n*-alkyl and ethylene glycol linkers.



a b

Figure 8.2: Selected amino acids together with determined distances (**a**). Schematic depiction of tethering one terphenyl substituted with an oligo ethylene glycol side chain which binds to an solvent exposed cysteine (performed by DVORSKY) (**b**).

Table 8.1: Potential RhoA mutations for linking teraryls with straight distances and calculated number of necessary monomers.

Residue		**Distance**[a]	**(-CH_2-)$_n$**		**(-CH_2-CH_2-O-)$_n$**	
Number	Type	[Å]	Minimal[b]	Half-Circle[b]	Minimal[b]	Half-Circle[b]
27	Lys	21.2	14	22	5	8
41	Asn	16.3	10	16	4	6
43	Val	22.4	15	23	6	9
68	Arg	17.1	11	17	4	7
69	Leu	14.3	8	13	3	5
72	Leu	17.1	11	17	4	7

[a] Straight distances of Cβ atoms of these residues to *meta*-oxygen on the upper building block (calculated by DVORSKY). [b] Calculated numbers of monomeric groups.

However, such minimal distances for the linkers would be the shortest possible length, but that would very likely be to short due to the binding angle and Van-der-Waals-interation of the linker.

For that reason the half-circle distance is often used. In this strategy the straight distance can be just scaled by factor π/2 and used for the calculation of necessary monomer numbers. The actual number of monomers should finally be selected between the numbers for straight and the numbers calculated for the half-circle. For example a RhoA mutation Asn-41 → Cys-41 (Table 8.1, entry 2) would need four ethylene glycol monomers for the straight distance and six monomers for the half-circle distance, so the final length should be containing five ethylene glycol groups at it is also depicted in Figure 8.2b.

9 Experimental Section

9.1 General Experimental Aspects, Materials and Methods

NMR spectra were recorded on a Bruker Avance III 300 MHz FT NMR spectrometer (300.36 MHz (^{1}H), 75.53 MHz (^{13}C)), or on a Varian Unity Inova 500 MHz NB high resolution FT NMR spectrometer (499.76 MHz (^{1}H), 125.67 MHz (^{13}C)) at 27°C. Chemical shifts δ [ppm] are referenced to residual protonated solvent signals as internal standard [D_6]DMSO: δ = 2.50 ppm (^{1}H); 39.52 ppm (^{13}C), [D_4]CD_3OD: δ = 3.31 ppm (^{1}H); 49.00 ppm (^{13}C) and $CDCl_3$: δ = 7.26 ppm (^{1}H); 77.16 ppm (^{13}C).[93] 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: H^{Py} (pyridyl), H^{Ar} (phenyl), H^{Naph} (naphthyl), H^{BPin} (boronic acid pinacol ester) and H^{Phth} (phthalimide); abbreviation C_q is used for quaternary carbon atoms. ^{13}C NMR resonances were assigned by APT or DEPT or ^{2}D-HSQC and ^{2}D-HMBC experiments. NMR signals for the residues of the terarylic systems mimicking amino acid side chains are superscripted with the common 3-letter-code (see also chapter 11, page 236).

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 (He 5.0; Air Liquide; "Alphagaz"; 1.085 mL/min; average velocity 41.6 cm/sec) in split mode 1/175 (inlet temperature: 250°C; injection volume: 2.0 µL; sample concentration: ~0.5 mg/mL in ethyl acetate (EtOAc), methanol (MeOH), dichloromethane (DCM), or diethyl ether (Et_2O)). 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), with a solvent delay of 2.60 min. Two general gradients MP_50_S (initial temperature: 50°C, 1.0 min; linear ramp: 40°C/min; final temperature: 300°C; final time: 5.0 min; post run 1.0 min; detecting range: 50.0 to 550.0 amu), or MP_100_L (initial temperature: 100°C, 1.0 min; linear ramp: 50°C/min; final temperature: 300°C; final time: 12.0 min; post run 1.0 min; detecting range: 100.0 to 600.0 amu) were applied.

When reactions were monitored by GC-MS, the samples were prepared using a microscale workup. This means, an aliquot was taken from the reaction mixture, quenched with ~1 mL aqueous solution and ~1 mL DCM, EtOAc, or Et_2O. After proper mixing and phase

separation, the organic layer was collected, dried over $MgSO_4$ and filtered through cotton in a Pasteur-pipette. Reaction mixtures containing transition metals were additionally filtered through a short pad of silica gel (~1 cm) over cotton in a Pasteur-pipette (eluted with EtOAc or MeOH).

Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60-F_{254} and spots were visualized by UV-light ($\lambda = 254$ and/or 366 nm), or by treatment with $KMnO_4$ solution (3.0 g $KMnO_4$, 20 g K_2CO_3 and 5% NaOH in 300 mL H_2O), or cerium ammonium molybdate solution (CAM) (CAM: 2.0 g Ce(IV)SO_4, 50 g $(NH_4)_2MoO_4$, 50 mL concentrated H_2SO_4 in 400 mL water) followed by warming with a heat gun.

Flash column chromatography was performed using silica gel 60 Å (35-70 µm particle size) from Acros Organics at an air pressure of ~1.5 bar. A 20 to 100-fold excess of silica gel was used with respect to the amount of dry raw material. The stationary phase was filled in an appropriate sized column resulting in a pad of 15-25 cm silica gel. For purification with a short column a pad of 3-5 cm silica gel was used. If the crude product was not soluble in the eluent, the sample was dissolved in a proper solvent (MeOH or EtOAc) and the double amount of silica gel (or Celite®545, particle size 0.02-0.1 mm) was added, followed by removing the solvent using a rotary evaporator and drying in vacuo.

For semi-preparative HPLC a Knauer Smartline Instrument with Autosampler 3800, Manager 5000, Pump 1000, UV Diode Array Detector 2600 and Fraction Collector Teledyne Isco Foxy Jr. FC100 modules were used. Semi-preparative HPLC was carried out utilizing a Macherey-Nagel VP 125/21 Nucleodur 100-5 C18 ec column (internal diameter: 21.0 mm) with a VP 20/16 Nucleodur C18 ec pre-column at a flow rate of 13.5-17 mL/min.

Analytical HPLC analysis was performed applying an Agilent Technologies 1200 Series (G1379B Degasser, G1312B Binary Pump SL, G1367C High Performance Autosampler SL, G1330 FC/ALS Thermostat, G1316B Thermostatted Column Compartment SL, G1365C Multiple Wavelength Detector SL) with an Agilent Technologies 6120 quadrupole LC/MS Detector with a G1918B Electrospray Ionization Source. Analytical HPLC was carried out utilizing a Macherey-Nagel EC 150/4 Nucleodur 100-5 C18 ec with a CC 8/4 Nucleodur 100-5 C18 ec pre-column, in ESI-positive mode. For analytical HPLC a general method was applied (otherwise denoted): 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: 37% MeOH lin. gradient, 4.0-10.0 min.: 37% MeOH const., 10.0-10.5 min: 70% MeOH lin. gradient, 10.5-15.0 min: 70% MeOH const., 15.0-15.5 min: 30% MeOH lin. gradient, 15.5-25.0 min: 30% MeOH const.).

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

High Resolution Mass Spectrometry (HRMS) was performed on an Agilent Technologies 7890A (G3440A) GC system equipped with an Agilent Technologies J&W GC-column DB-5MS (length: 30 m; inner-diameter: 0.250 mm; film: 0.25 µm) at a constant helium flow. The GC was coupled to a Waters GCT Premier Micromass. For Direct Inlet (DI-EI) only the Waters GCT Premier Micromass unit was used. A JEOL SX102A mass spectrometer was applied for FAB-HRMS and spectra were determined in a 3-nitrobenzyl alcohol (3-NOBA) matrix.

Melting points were determined on a "Mel-Temp" melting-point apparatus (Electrothermal) and are given uncorrected.

Boiling points ($b.p.^{exp.}$, $b.p.^{lit.}$) are listed in torr (if not otherwise mentioned).

Chemicals were purchased from Sigma-Aldrich, Fisher Scientific, Merck, or Alfa Aesar. All compounds were used without further purification unless otherwise noted.

Electrophiles used in Grignard reactions (benzaldehyde (**53a**), isobutyraldehyde (**53b**) and 2-butanone (**53c**)) were distilled under inert conditions and stored under an atmosphere of argon, over 3 Å molecular sieves at -28°C. 2-Naphthaldehyde (**53d**) was purified by sublimation ($sublim.^{exp.}$ = 60°C, $1 \cdot 10^{-3}$ mbar) and stored under an argon atmosphere in a freezer.[94]

Thionyl chloride ($SOCl_2$) and acetone were distilled prior to use, also tetrahydrofuran (THF) and Et_2O were distilled, to get rid of the stabilizer 2,6-di-*tert*-butyl-4-methylphenol (BHT).

Palladium(II) acetate ($Pd(OAc)_2$) was recrystallized under reflux from absolute, degassed glacial acetic acid (~25 mL/g) and was filtered under inert conditions. After drying in vacuo, the catalyst was stored under an atmosphere of argon at -28°C.[95]

For determination of concentration of the *n*-butyl lithium solution in *n*-hexane (*n*-BuLi) a procedure according to KOFRON and BACLAWSKI was used.[96] To 250 mg 2,2-diphenylacetic acid, dissolved in 10 mL absolute THF, *n*-BuLi was added dropwise, until a color change from colorless to yellow was detected. The added amount of *n*-BuLi corresponds to the amount of 2,2-diphenylacetic acid. The titer determination was accomplished before every use of the *n*-BuLi solution.

Ethanol (EtOH) was dried over sodium (Na) and diethyl phthalate. After inert distillation EtOH was stored over 3 Å molecular sieves in an amber glass Schlenk-flask under an atmosphere of argon. Triethylamine (NEt_3), DCM and MeOH were dried over CaH_2 and distilled under an argon atmosphere before use. Acetonitrile (ACN) was dried over NaH and

after inert distillation stored over 3 Å molecular sieves in an amber glass Schlenk-flask under an argon atmosphere. Et_2O, 1,2-dimethoxyethane (1,2-DME), 1,4-dioxane and THF were dried by heating at reflux under an atmosphere of argon over Na, until benzophenone indicated dryness by a deep blue color. Absolute Et_2O, 1,2-DME, 1,4-dioxane and THF were stored over 4 Å molecular sieves in an amber glass Schlenk-flask under an argon atmosphere. Methyl *tert*-butyl ether (MTBE) was purchased from Sigma-Aldrich (306975, anhydrous, 99.8%) and was used after degassing without further purification or drying methods. Molecular sieves were activated by filling a 500 mL round-bottomed flask to one third of its volume with molecular sieves (Sigma-Aldrich, beads, 8-12 mesh) and heating the flask in a heating mantle (~150°C) under oil pump vacuum for ~3 days, followed by cooling to room temperature under an atmosphere of argon. When referring to "oil pump vacuum" the applied pressure is usually in the region of 10^{-2}-10^{-3} mbar by using a rotary vane pump.

Degassing of reaction mixtures or solvents was performed by subjecting the accordant vessel to vacuum and refilling with an inert gas. This procedure was repeated at least three times (vacuum/gas cycles). Alternatively, degassing was carried out by passing a stream of argon through the reaction mixture/solvent. This means, a balloon filled with argon was placed on a syringe with needle and the needle was punched through a septum and dipped into the reaction mixture. Additionally the vessel was immersed in an ultrasonic bath.

When working at a temperature of 0°C, an ice-water bath served as the cooling agent. Temperatures of -4°C to -18°C were adjusted with ice/MeOH mixtures and -78°C was achieved by a dry ice/acetone mixture. For reactions requiring cryogenic temperatures over several hours, a cryostat was used. Kugelrohr-distillation (KRD) was performed applying a Büchi GKR-51. The boiling points during the Kugelrohr-distillation (b.p.^{KRD}) are given in mbar.

High pressure hydrogenation experiments were performed, utilizing a H-Cube^{TM} 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^{TM}), or a Raney-Nickel cartridge (Thales Nanotechnology Inc., THS 01112, Raney-Nickel CatCart^{TM}) was applied.

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

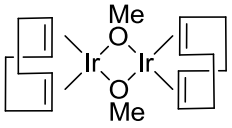
9.2 Synthesis of Teraryls using the Linear Approach

9.2.1 Synthesis of Building Blocks A

9.2.1.1 Representative procedure for the formation of boronic acid pinacol ester derivatives from the corresponding phenyl bromide derivatives

A flame dried and argon-flushed 100 mL Schlenk-flask was charged with 1.0 eq phenyl bromide derivative, 1.1 eq bis(pinacolato)diboron (B_2Pin_2), 2.0-3.0 eq potassium acetate (KOAc) and 3-5 mol% [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with DCM ($PdCl_2$(dppf)·DCM). After drying of the starting materials in vacuo and back-flushing with argon, the starting materials were suspended in absolute, degassed DMF and the orange mixture was stirred at 80°C. The reaction was monitored by GC-MS, after filtering a small aliquot of the reaction mixture through a small pad of SiO_2 and eluting with EtOAc. After quantitative conversion the reddish-brown suspension was filtered through a small pad of silica gel (~2x3 cm) and eluted with MeOH. After evaporation to dryness under reduced pressure, the crude product was purified by flash column chromatography (eluents are indicated).

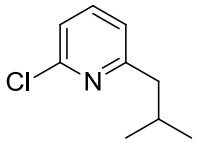
9.2.1.2 Bis(η^4-1,5-cyclooctadiene)-di-μ-methoxo-diiridium(I)



In a flame dried 25 mL Schlenk-flask, 155 mg di-μ-chlorobis(η^4-1,5-cyclooctadiene)-diiridium(I) ([IrCl(1,5-COD)]$_2$) (0.23 mmol, 1.0 eq) were suspended in 10 mL absolute, degassed MeOH. In a second 150 mL flame dried Schlenk-flask, a solution of 26 mg ground and vacuum dried potassium hydroxide (KOH) (0.46 mmol, 2.0 eq) in 5 mL absolute, degassed MeOH was prepared. At room temperature the orange [IrCl(1,5-COD)]$_2$ suspension was cannulated to the colorless KOH solution and the reaction mixture immediately turned into a pale yellow suspension. The mixture was stirred for 1.5 h until the orange precipitate was dissolved and 40 mL degassed water were added. The yellow precipitate was collected by inert filtration, followed by washing with degassed water (3x5 mL) and drying in vacuo.[97]

Yield: 124 mg (81%), crystalline yellow powder, $C_{18}H_{30}Ir_2O_2$ [662.86 g/mol].

9.2.1.3 2-Chloro-6-isobutylpyridine (22b)



22b

In a 100 mL two-neck round-bottom flask with argon-inlet, a solution of 4.24 mL diisopropylamine ((*i*Pr)$_2$NH) (3.06 g, 30.24 mmol, 1.0 eq) in 40 mL absolute, degassed THF was prepared. 17.58 mL *n*-BuLi (1.72M, 30.24 mol, 1.0 eq) were added dropwise at -58°C, raising the temperature to -30°C for 10 min. After cooling again to -58°C, 3.30 mL 2-chloro-6-methylpyridine (**22a**) (3.85 g, 30.18 mol, 1.0 eq) were added dropwise. During the addition the color changed from pale yellow over orange to deep red. After complete addition (~15 min) the reaction mixture was stirred for 30 min at -20°C. 5.07 mL 2-bromopropane (6.64 g, 53.99 mmol, 1.8 eq) were added dropwise at -20°C and the reaction mixture was stirred overnight, allowing to warm to room temperature. The reaction was quenched with 25 mL water and the aqueous phase was extracted with Et_2O (3x20 mL). The combined yellow organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The orange, oily crude product was purified by flash column chromatography (210 g SiO_2, 18x6 cm, cyclohexane/EtOAc = 10/0.25, R_f = 0.24) to afford a pale yellow oil.[19a]

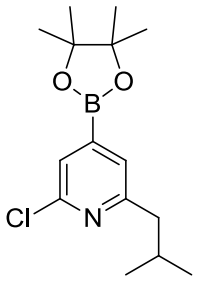
Yield: 3.79 g (74%), pale yellow oil, $C_9H_{12}ClN$ [169.65 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53 (t, ^3J (H,H) = 7.7 Hz, 1 H; H^{Py}), 7.13 (d, ^3J (H,H) = 7.9 Hz, 1 H; H^{Py}), 7.01 (d, ^3J (H,H) = 7.5 Hz, 1 H; H^{Py}), 2.61 (d, ^3J (H,H) = 7.3 Hz, 2 H; CH_2), 2.16-2.02 (m, 1 H; CH), 0.91 (d, ^3J (H,H) = 6.6 Hz, 6 H; CH_3) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 162.9 (C_q; C^{Py}), 150.8 (C_q; C^{Py}), 138.7 (C^{Py}), 122.1 (C^{Py}), 121.5 (C^{Py}), 47.2 (CH_2), 29.2 (CH), 22.4 (CH_3) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 4.45 min, *m/z* (%): 168 (5) [M^+−H], 154 (18) [M^+−CH_3], 140 (1) [M^+−C_2H_7], 127 (100) [M^+−C_3H_6], 91 (23) [$C_6H_5N^+$].

9.2.1.4 2-Chloro-6-isobutyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (4a)



4a

A 50 mL two-neck round-bottom flask with argon-inlet was charged with 1.75 g B_2Pin_2 (6.89 mmol, 0.5 eq), 69 mg $[Ir(OMe)(1,5\text{-}COD)]_2$ (0.10 mmol, 0.75 mol%) and 55 mg 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy) (0.20 mmol, 1.5 mol%). To the vacuum dried starting materials, dissolved in 20 mL absolute, degassed MTBE, a solution of 2.34 g 2-chloro-6-isobutylpyridine (**22b**) (13.79 mmol, 1.0 eq) in 10 mL absolute, degassed MTBE were added *via* cannula. The deep red solution was stirred at 70°C overnight. Without further workup the solvent was removed under reduced pressure and the product was purified by flash column chromatography (220 g SiO_2, 19x6 cm, cyclohexane/EtOAc = 9/1, R_f = 0.20, tailing), to obtain a colorless solid.[19a]

Yield: 3.98 g (98%), colorless solid, $C_{15}H_{23}BClNO_2$ [295.61 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (s, 1 H; H^{Py}), 7.35 (s, 1 H; H^{Py}), 2.62 (d, ^3J(H,H) = 7.3 Hz, 2 H; CH_2), 2.18-2.04 (m, 1 H; CH), 1.34 (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, $CDCl_3$): δ = 162.4 (C_q; C^{Py}), 150.8 (C_q; C^{Py}), 127.0 (C^{Py}), 126.6 (C^{Py}), 84.9 (C_q; C^{BPin}), 47.1 (CH_2), 29.3 (CH), 25.0 (CH_3^{BPin}), 22.5 (CH_3) ppm.*

GC-MS (EI, 70 eV; MP_50_S): t_R = 6.50 min, *m/z* (%): 294 (2) [M^+−H], 280 (10) [M^+−CH_3], 260 (1) [M^+−Cl], 253 (100) [M^+−C_3H_6].

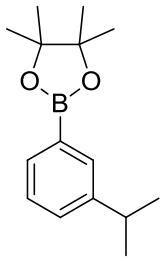
m.p.$^{exp.}$ = 54-56°C.

HRMS (EI): calcd (*m*/*z*) for [M^+−H]: 293.1469; found: 293.1444.†

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

† Monoisotopic peak [M^+−H] is given.

9.2.1.5 2-(3-Isopropylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4b)



4b

In a flame dried 100 mL Schlenk-flask 1.57 mL 1-bromo-3-isopropylbenzene (**10b**) (2.02 g, 10.15 mmol, 1.0 eq), 2.21 mL 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (HBPin) (1.95 g, 15.24 mmol, 1.5 eq) and 4.24 mL absolute triethylamine (3.08 g, 30.44 mmol, 3.0 eq) were dissolved in 25 mL absolute ACN. After degassing the deep red suspension, 249 mg $PdCl_2(dppf)\cdot DCM$ (0.30 mmol, 3 mol%) were added and the reaction mixture was stirred at 80°C until full conversion was detected by GC-MS (~19 h; mini workup: SiO_2, EtOAc). The reaction was quenched with 20 mL H_2O and the aqueous phase was extracted with EtOAc (3x50 mL). The combined yellow organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The deep brown crude product was purified by flash column chromatography (100 g SiO_2, 18x2.5 cm, cyclohexane/EtOAc = 98/2, R_f = 0.33, CAM).

Yield: 1.57 g (63%), colorless oil, which become a semi-solid upon standing, $C_{15}H_{23}BO_2$ [246.15 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69-7.64 (m, 2 H; H^{Ar}), 7.37-7.29 (m, 2 H; H^{Ar}), 2.94 (sept, ^3J (H,H) = 6.9 Hz, 1 H; CH), 1.36 (s, 12 H; CH_3^{BPin}), 1.27 (d, ^3J (H,H) = 6.9 Hz, 6 H; CH_3) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 148.2 (C_q; C^{Ar}), 133.0 (C^{Ar}), 132.5 (C^{Ar}), 129.5 (C^{Ar}), 127.9 (C^{Ar}), 83.8 (C_q; C^{BPin}), 34.3 (CH), 25.0 (CH_3^{BPin}), 24.2 (CH_3) ppm.*

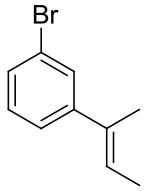
GC-MS (EI, 70 eV; MP_50_S): t_R = 5.94 min; *m/z* (%): 246 (51) [M^+], 231 (100) [M^+-CH_3], 203 (14) [$M^+-C_3H_7$], 173 (2) [$M^+-C_5H_{13}$], 147 (71) [$C_8H_8BO_2^+$].

m.p.$^{exp.}$ = <30°C.

Analytical data are in accordance with those reported.[98]

* Signal for the quaternary *ipso*-aromatic carbon (C_q; C^{Ar}) at the boronic acid pinacol ester function was not observed.

9.2.1.6 (*E*/*Z*)-1-Bromo-3-(but-2-en-2-yl)benzene (26)



26

In a flame dried 250 mL three-neck round-bottom flask with reflux condenser, dropping funnel and argon-inlet, 1.84 g magnesium turnings (75.69 mmol, 1.0 eq) were suspended in 20 mL absolute Et_2O. A solution of 9.19 g bromoethane (84.34 mmol, 1.1 eq) in 50 mL absolute Et_2O were added dropwise to the magnesium turnings and the mixture was stirred under reflux for 30 min. A solution of 15.05 g 1-(3-bromophenyl)ethanone (**24**) (75.61 mmol, 1.0 eq) in 50 mL absolute Et_2O were added and the yellow suspension was stirred under reflux until full conversion was detected by GC-MS. The mixture was quenched with 50 mL 5% aqueous HCl solution and after separation, the organic layer was washed with saturated $NaHCO_3$ solution. The organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Pure intermediate 2-(3-bromophenyl)butan-2-ol (**25**) was isolated after flash column chromatography (cyclohexane/EtOAc = 9/2, $R_f = 0.30$).[99] The pale yellow crude product was placed in a micro-distillation apparatus together with 100 µL of concentrated sulfuric acid. The formed water was distilled off, before the product was isolated at 31-32°C (0.1 torr). Compound **26** was isolated as a mixture of the corresponding *E*- and Z-isomer (*E*/*Z* = 6/4).[54]

Yield: 8.31 g (52%), colorless liquid, $C_{10}H_{11}Br$ [211.10 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51-7.27 (m, 2.3 H; H^{Ar}), 7.23-7.10 (m, 1.7 H; H^{Ar}), 5.87 (dq, ^3J (H,H) = 6.9 Hz, ^4J (H,H) = 1.3 Hz, 0.6 H; CH(*E*)), 5.58 (dq, ^3J (H,H) = 6.9 Hz, ^4J (H,H) = 1.4 Hz, 0.4 H; CH(*Z*)), 2.00 (bs, 3 H; CH_3), 1.80 (dd, ^3J (H,H) = 6.9 Hz, ^4J (H,H) = 0.8 Hz, 1.8 H; CH_3(*E*)), 1.59 (dd, ^3J (H,H) = 6.9 Hz, ^4J (H,H) = 1.5 Hz, 1.2 H; CH_3(*Z*)) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 146.3 (C_q; C^{Ar}), 144.3 (C_q; C^{Ar}), 135.6 (C_q; C=CH), 134.5 (C_q; C=CH), 131.2 (C^{Ar}), 129.8 (C^{Ar}), 129.6 (C^{Ar}), 129.4 (C^{Ar}), 128.8 (C^{Ar}), 126.9 (C^{Ar}), 124.3 (C^{Ar}), 124.0 (C^{Ar}), 122.8 (C^{Ar}), 122.6 (C_q; C^{Ar}), 122.3 (C_q; C^{Ar}), 25.3 (CH_3), 15.5 (CH_3), 15.0 (CH_3), 14.5 (CH_3) ppm.*

* NMR spectra showed both isomers (*E*/*Z*); unambiguously assignment of the signals was not possible.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.60 (s, 1 H; H^{Ar}), 7.37-7.33 (m, 2 H; H^{Ar}), 7.20 (t, ^3J (H,H) = 7.8 Hz, 1 H; H^{Ar}), 1.87-1.75 (m, 2 H; CH_2), 1.71 (bs, 1 H; OH), 1.53 (s, 3 H; CH_3), 0.79 (t, ^3J(H,H) = 7.4 Hz, 3 H; CH_3) ppm.*

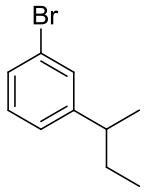
^{13}C NMR (126 MHz, $CDCl_3$): δ = 150.3 (C_q; C^{Ar}), 129.8 (C^{Ar}), 129.7 (C^{Ar}), 128.4 (C^{Ar}), 123.8 (C^{Ar}), 122.6 (C_q; C^{Ar}), 74.8 (C_q; C-OH), 36.7 (CH_2), 29.9 (CH_3), 8.3 (CH_3) ppm.*

GC-MS (EI, 70 eV; MP_50_S): $t_R^{Pro(E)}$ = 5.37 min; *m/z* (%): 212 (36) [M^+], 210 (35) [M^+], 197 (3) [M^+-CH_3], 195 (3) [M^+-CH_3], 157 (1) [$C_6H_4Br^+$], 155 (1) [$C_6H_4Br^+$], 131 (100) [M^+-Br], 116 (83) [M^+-CH_3Br]; $t_R^{Pro(Z)}$ = 4.99 min; *m/z* (%): 212 (38) [M^+], 210 (37) [M^+], 197 (3) [M^+-CH_3], 195 (3) [M^+-CH_3], 157 (1) [$C_6H_4Br^+$], 155 (1) [$C_6H_4Br^+$], 131 (100) [M^+-Br], 116 (81) [M^+-CH_3Br].

GC-MS (EI, 70 eV; MP_50_S): t_R^{ol} = 5.60 min; *m/z* (%): 230 (1) [M^+], 228 (1) [M^+], 212 (40) [M^+-H_2O], 210 (40) [M^+-H_2O], 201 (36) [$M^+-C_2H_5$], 199 (37) [$M^+-C_2H_5$], 131 (100) [M^+-H_2OBr], 116 (80) [$C_9H_8^+$].†

b.p.$^{exp.}$ = 31-32°C, 0.1 torr (b.p.$^{lit.}$ = 110-112°C, 17 torr).[54]

9.2.1.7 1-Bromo-3-(*sec*-butyl)benzene (10c)



10c

A 100 mL three-neck round-bottom flask equipped with two argon-inlets was charged with 8.31 g (*E*/*Z*)-1-bromo-3-(but-2-en-2-yl)benzene (**26**) (39.37 mmol, 1.0 eq) and 20 mL absolute EtOH were added. To this colorless solution 41 mg PtO_2 (0.18 mmol, 0.5 mol%) were added and the reaction mixture was stirred for 7 h at room temperature under hydrogen atmosphere (after evacuating and back-flushing with hydrogen gas (3x)). The catalyst was removed by filtration (small pad SiO_2, eluent: MeOH) and the solvent was removed under

* NMR data of the intermediate 2-(3-bromophenyl)butan-2-ol (**25**).
† GC-MS data of the intermediate 2-(3-bromophenyl)butan-2-ol (**25**).

reduced pressure using a rotary evaporator.* After flash column chromatography (80 g SiO_2, 26x3 cm, cyclohexane, $R_f = 0.74$), compound **10c** was isolated as a colorless liquid.[54]
Yield: 6.38 g (76%), colorless liquid, $C_{10}H_{13}Br$ [213.11 g/mol].

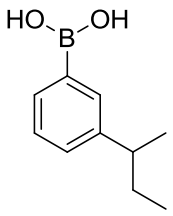
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33-7.30 (m, 2 H; H^{Ar}), 7.16 (t, ^3J (H,H) = 7.6 Hz, 1 H; H^{Ar}), 7.11 (d, ^3J (H,H) = 7.7 Hz, 1 H; H^{Ar}), 2.61-2.53 (m, 1 H; CH), 1.62-1.56 (m, 2 H; CH_2), 1.23 (d, ^3J (H,H) = 6.9 Hz, 3 H; CH_3), 0.83 (t, ^3J (H,H) = 7.4 Hz, 3 H; CH_3) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 150.2 (C_q; C^{Ar}), 130.3 (C^{Ar}), 130.0 (C^{Ar}), 129.0 (C^{Ar}), 125.9 (C^{Ar}), 122.5 (C_q; C^{Ar}), 41.7 (CH), 31.2 (CH_2), 21.8 (CH_3), 12.3 (CH_3) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 4.94 min; *m/z* (%): 214 (21) [M^+], 212 (21) [M^+], 199 (1) [M^+-CH_3], 197 (1) [M^+-CH_3], 185 (85) [$M^+-C_2H_5$], 183 (88) [$M^+-C_2H_5$], 171 (10) [$M^+-C_3H_8$], 169 (10) [$M^+-C_3H_8$], 133 (6) [M^+−Br], 104 (100) [$M^+-C_2H_5Br$].

Analytical data are in accordance with those reported.[100]

9.2.1.8 (3-(*sec*-Butyl)phenyl)boronic acid (4c)



4c

In a 250 mL Schlenk-flask 3.20 g 1-bromo-3-(*sec*-butyl)benzene (**10c**) (15.02 mmol, 1.0 eq) were dissolved in 100 mL absolute THF. The colorless solution was cooled to -78°C and 10.07 mL *n*-BuLi (1.64M, 16.51 mmol, 1.1 eq) were added. In a second 250 mL Schlenk-flask a solution of 10.39 mL ($B(OiPr)_3$) (8.47 g, 45.04 mmol, 3.0 eq) in 20 mL absolute THF was prepared, subsequently the colorless lithium mixture was added dropwise and stirring was continued for 1.5 h at -78°C. The colorless solution was allowed to warm to room temperature and the reaction was quenched with 30 mL 5% aqueous HCl solution. The aqueous phase was extracted with Et_2O (3x30 mL) and the colorless combined organic layers were dried over Na_2SO_4. After filtration and removing the solvent under reduced pressure, compound **4c** was isolated after flash column chromatography (65 g SiO_2, 24x3 cm, cyclohexane/EtOAc = 8/2, $R_f = 0.25$).

* The catalyst was filtered off using a pad of Celite® or SiO_2 under inert conditions and eluted with MeOH. The hydrogenation catalyst was washed with H_2O and stored in a glass bottle covered with water.

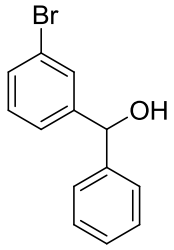
Yield: 1.93 g (72%), colorless solid, $C_{10}H_{15}BO_2$ [178.04 g/mol].

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.11 (d, ^3J (H,H) = 6.9 Hz, 1 H; H^{Ar}), 8.07 (s, 1 H; H^{Ar}), 7.49-7.41 (m, 2 H; H^{Ar}), 2.80-2.72 (m, 1 H; CH), 1.75-1.69 (m, 2 H; CH_2), 1.35 (d, ^3J (H,H) = 7.0 Hz, 3 H; CH_3), 0.91 (t, ^3J (H,H) = 7.4 Hz, 3 H; CH_3) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 147.2 (C_q; C^{Ar}), 134.5 (C^{Ar}), 133.4 (C^{Ar}), 131.5 (C^{Ar}), 128.1 (C^{Ar}), 41.8 (CH), 31.4 (CH_2), 22.1 (CH_3), 12.5 (CH_3) ppm.*

m.p.$^{exp.}$ = 50-53°C.

9.2.1.9 (3-Bromophenyl)(phenyl)methanol (27)



27

In a flame dried 100 mL three-neck round-bottom flask with reflux condenser, dropping funnel and argon-inlet, 433 mg magnesium turnings (17.81 mmol, 1.1 eq) were suspended in 15 mL absolute Et_2O. A solution of 2.80 g bromobenzene (17.83 mmol, 1.1 eq) in 10 mL absolute Et_2O were added dropwise to the magnesium turnings and stirred under reflux for 30 min. The brown Grignard suspension was added to a 100 mL two-neck round-bottom flask containing a solution of 3.00 g 3-bromobenzaldehyde (**6b**) (16.21 mmol, 1.0 eq) in 10 mL absolute Et_2O. The resulting yellow suspension was stirred under reflux for further 30 min. Under ice cooling the yellow mixture was quenched with 20 mL saturated NH_4Cl solution and the aqueous phase was extracted with Et_2O (3x35 mL). The combined organic phases were dried over Na_2SO_4, filtered and after evaporating the solvent under reduced pressure, compound **27** was isolated after flash column chromatography (157 g SiO_2, 27x4 cm, cyclohexane/EtOAc = 9/1, R_f = 0.30).[57]

Yield: 2.79 g (65%), colorless oil, which become a solid upon standing, $C_{13}H_{11}BrO$ [263.13 g/mol].

* Signal for the quaternary *ipso*-aromatic carbon (C_q; C^{Ar}) at the boronic acid function was not observed.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.57 (s, 1 H; H^{Ar}), 7.39 (d, ^{3}J (H,H) = 7.9 Hz, 1 H; H^{Ar}), 7.36-7.34 (m, 4 H; H^{Ar}), 7.32-7.27 (m, 2 H; H^{Ar}), 7.20 (t, ^{3}J (H,H) = 7.8 Hz, 1 H; H^{Ar}), 5.80 (s, 1 H; CH), 1.90 (bs, 1 H; OH) ppm.*,[57,101]

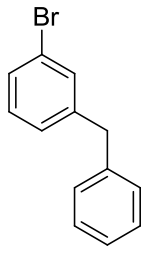
^{13}C NMR (126 MHz, $CDCl_3$): δ = 146.1 (C_q; C^{Ar}), 143.3 (C_q; C^{Ar}), 130.7 (C^{Ar}), 130.2 (C^{Ar}), 129.6 (C^{Ar}), 128.8 (C^{Ar}), 128.1 (C^{Ar}), 126.7 (C^{Ar}), 125.2 (C^{Ar}), 122.8 (C_q; C^{Ar}), 75.8 (CH) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 7.00 min; *m/z* (%): 264 (13) [M^+], 262 (14) [M^+], 183 (27) [M^+−Br], 165 (15) [M^+−H_2BrO], 105 (100) [$C_7H_5O^+$], 77 (67) [$C_6H_5^+$].

m.p.$^{exp.}$ = 36-38°C (m.p.$^{lit.}$ = 44.5-45°C).[102]

Analytical data are in accordance with those reported.[57]

9.2.1.10 1-Benzyl-3-bromobenzene (10d)



10d

In a 100 mL two-neck round-bottom flask with reflux condenser and argon-inlet, 277 mg lithium aluminum hydride (LAH) (7.30 mmol, 1.9 eq) and 1.02 g aluminum trichloride ($AlCl_3$) (7.65 mmol, 2.0 eq) were suspended in 15 mL absolute Et_2O. At -20°C a solution of 1.01 g (3-bromophenyl)(phenyl)methanol (**27**) (3.84 mmol, 1.0 eq) in 10 mL absolute Et_2O were added dropwise. After complete addition the pale blue suspension was stirred under reflux and allowed to warm to room temperature after 1 h. The reaction was quenched with 9 mL EtOAc, followed by carefully diluting with 14 mL of 20% aqueous H_2SO_4 solution. The grey suspension was extracted with Et_2O (3x35 mL) and the combined organic layers were washed with water (1x50 mL). After drying over Na_2SO_4, filtration and evaporation of the solvent under reduced pressure, the crude product was purified by flash column chromatography (64 g SiO_2, 21x3 cm, cyclohexane, R_f = 0.46).[57]
Yield: 920 mg (97%), colorless oil, $C_{13}H_{11}Br$ [247.13 g/mol].

* Several publication report the signal for the alcohol function as a doublet at ~2.50 ppm.

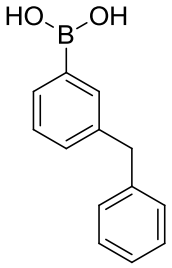
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36-7.31 (m, 4 H; H^{Ar}), 7.27-7.23 (m, 1 H; H^{Ar}, overlapping), 7.21-7.19 (m, 2 H; H^{Ar}), 7.17-7.13 (m, 2 H; H^{Ar}), 3.97 (s, 2 H; CH_2) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 143.6 (C_q; C^{Ar}), 140.3 (C_q; C^{Ar}), 132.0 (C^{Ar}), 130.1 (C^{Ar}), 129.4 (C^{Ar}), 129.0 (C^{Ar}), 128.7 (C^{Ar}), 127.7 (C^{Ar}), 126.5 (C^{Ar}), 122.7 (C_q; C^{Ar}), 41.7 (CH_2) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 6.42 min; *m/z* (%): 248 (37) [M^+], 246 (38) [M^+], 167 (100) [M^+−Br], 91 (7) [$C_7H_7^+$].

Analytical data are in accordance with those reported.[57]

9.2.1.11 (3-Benzylphenyl)boronic acid (4d)



4d

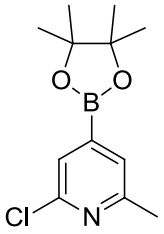
In a 250 mL Schlenk-flask 3.69 g 1-benzyl-3-bromobenzene (**10d**) (14.93 mmol, 1.0 eq) were dissolved in 80 mL absolute THF. The colorless solution was cooled to -78°C and 10.00 mL *n*-BuLi (1.64M, 16.40 mmol, 1.1 eq) were added. Immediately a color change to pale red was observed and after 1 h the color changes to pale yellow. In a second 250 mL Schlenk-flask a solution of 10.00 mL triisopropyl borate ($B(OiPr)_3$) (8.10 g, 43.07 mmol, 2.9 eq) in 20 mL absolute THF was prepared and the lithium mixture was added after 3 h. After stirring for 1.5 h at -78°C, the colorless solution was allowed to warm room temperature and the reaction was quenched with 25 mL 5% aqueous HCl solution. The aqueous phase was extracted with Et_2O (3x25 mL) and the colorless combined organic layers were dried over Na_2SO_4. After filtration and removing the solvent under reduced pressure, compound **4d** was isolated after flash column chromatography (80 g SiO_2, 25x3 cm, cyclohexane/EtOAc = 65/35, R_f = 0.27).
Yield: 1.61 g (51%), colorless solid, $C_{13}H_{13}BO_2$ [212.05 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92-7.88 (m, 2 H; H^{Ar}), 7.31-7.23 (m, 2 H; H^{Ar}, overlapping), 7.19-7.04 (m, 5 H; H^{Ar}), 3.96 (s, 2 H; CH_2) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 141.2 (C_q; C^{Ar}), 140.7 (C_q; C^{Ar}), 136.2 (C^{Ar}), 133.7 (C^{Ar}), 133.5 (C^{Ar}), 129.1 (C^{Ar}), 128.7 (C^{Ar}), 128.3 (C^{Ar}), 126.3 (C^{Ar}), 42.0 (CH_2) ppm.*

m.p.$^{exp.}$ = 104-108°C.

9.2.1.12 2-Chloro-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (4e)



4e

A 50 mL two-neck round-bottom flask with argon-inlet was consecutively charged with 652 mg B_2Pin_2 (2.57 mmol, 0.55 eq), 23 mg $[Ir(OMe)(1,5\text{-}COD)]_2$ (35 µmol, 0.75 mol%), 19 mg dtbpy (71 µmol, 1.5 mol%) and 514 µL 2-chloro-6-methylpyridine (**22a**) (596 mg, 4.67 mmol, 1.0 eq). After drying in vacuo and back-flushing with argon, 10 mL absolute, degassed MTBE were added to the mixture. The resulting deep red suspension was stirred overnight at 70°C and after quantitative conversion the reaction mixture was filtered through a pad of SiO_2 (2x2 cm, EtOAc). The solvent was removed under reduced pressure and the pale brown crude product was purified by flash column chromatography (120 g SiO_2, 24x4 cm, cyclohexane/EtOAc = 8/2, R_f = 0.20, strong tailing), to obtain a pale yellow, highly viscous oil.

Yield: 915 mg (77%), pale yellow, highly viscous oil, $C_{12}H_{17}BClNO_2$ [253.53 g/mol].

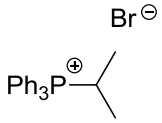
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (s, 1 H; H^{Py}), 7.40 (s, 1 H; H^{Py}), 2.52 (s, 3 H; CH_3), 1.34 (s, 12 H; CH_3^{BPin}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 159.0 (C_q; C^{Py}), 150.6 (C_q; C^{Py}), 126.9 (C^{Py}), 126.3 (C^{Py}), 84.9 (C_q; C^{BPin}), 25.0 (CH_3^{BPin}), 24.1 (CH_3) ppm.†

GC-MS (EI, 70 eV; MP_50_S): t_R = 5.99 min; *m/z* (%): 253 (58) [M^+], 238 (75) [M^+-CH_3], 167 (100) [$C_6H_3BClNO_2^+$], 153 (65) [$M^+-C_6H_{12}O$].

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

9.2.1.13 Isopropyltriphenylphosphonium bromide (28)



28

A Teflon®-coated autoclave-flask was charged with 15.00 g PPh_3 (57.19 mmol, 1.0 eq) and 19.00 mL isopropyl bromide (24.89 g, 0.20 mol, 3.5 eq). The autoclave was sealed and heated to 150°C (~12 bar). After 23 h the reaction mixture was allowed to cool to room temperature and the resulting pale orange solid was subsequently thoroughly washed with THF (4x25 mL) and Et_2O (2x25 mL). After filtration and drying of the filter cake, compound **28** was isolated as a colorless powder.[58]

Yield: 20.51 g (93%), colorless solid, $C_{21}H_{22}BrP$ [385.28 g/mol].

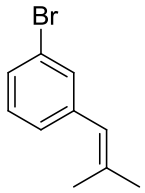
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01-7.95 (m, 6 H; H^{Ar}), 7.78-7.65 (m, 9 H; H^{Ar}), 5.62-5.47 (m, 1 H; CH), 1.33 (dd, ^3J (H,P) = 19.0 Hz, ^3J (H,H) = 6.8 Hz, 6 H; CH_3) ppm.

^{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_q; 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.$^{lit.}$ = 237.5-238.5°C).[58]

Analytical data are in accordance with those reported.[103]

9.2.1.14 1-Bromo-3-(2-methylprop-1-en-1-yl)benzene (10f)



10f

A flame dried 250 mL Schlenk-flask was charged with 10.93 g isopropyltriphenyl-phosphonium bromide (**28**) (28.37 mmol, 1.2 eq) and 100 mL absolute, degassed THF were added. After cooling to -35°C, a suspension of 3.45 g KO*t*Bu (30.74 mmol, 1.3 eq) in 20 mL absolute, degassed THF were added dropwise. Immediately a color change from white to dark-red was observed and the reaction mixture was allowed to warm to room temperature.

After stirring for 10 min at room temperature, followed by heating to 50°C for 1 h, the mixture was cooled to -55°C and 2.77 mL 3-bromobenzaldehyde (**6b**) (4.38 g, 23.67 mmol, 1.0 eq) in 20 mL absolute THF were added dropwise (2 drops/min). The suspension was stirred for 2.5 h at -55°C, followed by warming to room temperature overnight. The reaction was monitored by GC-MS, after filtering a small aliquot of the reaction mixture through a small pad of SiO_2 and eluting with cyclohexane. After quantitative conversion the mixture was quenched with 30 mL saturated NH_4Cl solution, subsequently followed by adding 50 mL H_2O. The aqueous phase was extracted with Et_2O (3x75 mL) and the combined yellow organic layers were dried over Na_2SO_4, filtered and concentrated to dryness. The yellow residue was suspended in cyclohexane and the insoluble triphenylphosphine oxide ($Ph_3P=O$) was filtered off and washed with cyclohexane (2x20 mL). Product **10f** was isolated as a colorless oil after flash column chromatography (252 g SiO_2, 19x6 cm, cyclohexane, $R_f = 0.65$).[48]

Yield: 4.34 g (87%), colorless oil, $C_{10}H_{11}Br$ [211.10 g/mol].

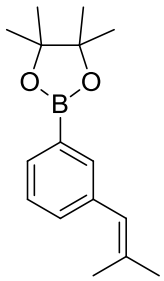
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37-7.30 (m, 2 H; H^{Ar}), 7.20-7.12 (m, 2 H; H^{Ar}), 6.20 (s, 1 H; CH), 1.90 (s, 3 H; CH_3), 1.85 (s, 3 H; CH_3) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 141.0 (C_q; C^{Ar}), 137.2 (C_q; CH=*C*$(CH_3)_2$), 131.7 (C^{Ar}), 129.7 (C^{Ar}), 128.9 (C^{Ar}), 127.5 (C^{Ar}), 124.0 (CH), 122.3 (C_q; C^{Ar}), 27.0 (CH_3), 19.5 (CH_3) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 4.93 min; *m/z* (%): 212 (5) [M^+], 210 (5) [M^+], 131 (75) [M^+−Br], 116 (87) [M^+−CH_3Br], 91 (100) [$C_7H_7^+$].

Analytical data are in accordance with those reported.[104]

9.2.1.15 4,4,5,5-Tetramethyl-2-(3-(2-methylprop-1-en-1-yl)phenyl)-1,3,2-dioxaborolane (29)



29

Compound **29** was prepared according to procedure 9.2.1.1 from 1.58 g 1-bromo-3-(2-methylprop-1-en-1-yl)benzene (**10f**) (7.48 mmol, 1.0 eq), 2.09 g B_2Pin_2 (8.23 mmol, 1.1 eq), 1.47 g KOAc (14.98 mmol, 2.0 eq) and 183 mg $PdCl_2(dppf)\cdot DCM$ (0.22 mmol, 3 mol%) in 15 mL absolute, degassed DMF. A complete Br/BPin exchange was detected after ~17 h and the black and oily crude product was purified by flash column chromatography (130 g SiO_2, 16x5 cm, cyclohexane/EtOAc = 100/3, R_f = 0.31).[48]

Yield: 1.76 g (91%), pale yellow-green liquid, which become a solid upon standing, $C_{16}H_{23}BO_2$ [258.16 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66-7.62 (m, 2 H; H^{Ar}), 7.34-7.32 (m, 2 H; H^{Ar}), 6.28 (bs, 1 H; CH), 1.90 (d, ^4J (H,H) = 0.8 Hz, 3 H; CH_3), 1.86 (d, ^4J (H,H) = 0.8 Hz, 3 H; CH_3), 1.35 (s, 12 H; CH_3^{BPin}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 138.2 (C_q; C^{Ar}), 135.6 (C_q; CH=*C*$(CH_3)_2$), 135.4 (C^{Ar}), 132.3 (C^{Ar}), 131.6 (C^{Ar}), 127.6 (C^{Ar}), 125.2 (CH), 83.9 (C_q; C^{BPin}), 26.9 (CH_3), 25.0 (CH_3^{BPin}), 19.5 (CH_3) ppm.*

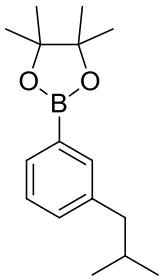
GC-MS (EI, 70 eV; MP_50_S): t_R = 6.17 min; *m/z* (%): 258 (100) [M^+], 243 (21) [M^+-CH_3], 158 (71) [$M^+-C_6H_{12}O$], 143 (39) [$M^+-C_7H_{15}O$].

m.p.$^{exp.}$ = 67-68°C.

HRMS (EI): calcd (*m/z*) for [M^+]: 258.1794; found: 258.1814.

* Signal for the quaternary *ipso*-aromatic carbon (C_q; C^{Ar}) at the boronic acid pinacol ester function was not observed.

9.2.1.16 2-(3-Isobutylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4f)



4f

In a 100 mL two-neck round-bottom flask with two argon-inlets 1.69 g 2-(3-isobutylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**29**) (6.55 mmol, 1.0 eq) were dissolved in 20 mL MeOH. To this pale yellow solution 74 mg PtO_2 (0.33 mmol, 5 mol%) were added. After ensuring hydrogen atmosphere, by evacuating and back-flushing with hydrogen gas (3x), the reaction mixture was stirred overnight (~10 h) at room temperature. The catalyst was removed by filtration (small pad SiO_2, eluent: MeOH) and the solvent was removed under reduced pressure using a rotary evaporator.* After flash column chromatography (66 g SiO_2, 22x3 cm, cyclohexane/EtOAc = 50/1, R_f = 0.36), product **4f** was isolated as a colorless liquid.[48]
Yield: 1.62 g (95%), colorless liquid, $C_{16}H_{25}BO_2$ [260.18 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65-7.60 (m, 2 H; H^{Ar}), 7.29-7.23 (m, 2 H; H^{Ar}), 2.48 (d, ^3J (H,H) = 7.2 Hz, 2 H; CH_2), 1.98-1.80 (m, 1 H; CH), 1.35 (s, 12 H; CH_3^{BPin}), 0.90 (d, ^3J (H,H) = 6.6 Hz, 6 H; CH_3) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 141.1 (C_q; C^{Ar}), 135.5 (C^{Ar}), 132.3 (C^{Ar}), 132.3 (C^{Ar}), 127.6 (C^{Ar}), 83.8 (C_q; C^{BPin}), 45.5 (CH_2), 30.4 (CH), 25.0 (CH_3^{BPin}), 22.6 (CH_3) ppm.†

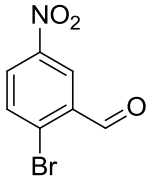
GC-MS (EI, 70 eV; MP_50_S): t_R = 5.93 min; *m/z* (%): 260 (22) [M^+], 245 (26) [M^+-CH_3], 217 (80) [$M^+-C_3H_7$], 203 (14) [$M^+-C_4H_9$], 161 (81) [$C_9H_{10}BO_2^+$].

HRMS (EI): calcd (*m*/*z*) for [M^+]: 260.1951; found: 260.1955.

* The catalyst was filtered off using a pad of Celite® or SiO_2 under inert conditions and eluted with MeOH. The hydrogenation catalyst was washed with H_2O and stored in a glass bottle covered with water.
† Signal for the quaternary *ipso*-aromatic carbon (C_q; C^{Ar}) at the boronic acid pinacol ester function was not observed.

9.2.2 Synthesis of Building Block B

9.2.2.1 2-Bromo-5-nitrobenzaldehyde (5a)



5a

A 100 mL two-neck round-bottom flask was charged with 13 mL concentrated sulfuric acid. At -15°C 2.46 mL 68% nitric acid (3.44 g, 37.12 mmol, 1.4 eq) were added dropwise to ensure a temperature below -7°C. 4.95 g 2-Bromobenzaldehyde (**6a**) (26.75 mmol, 1.0 eq) were added slowly keeping the temperature between -15°C and -10°C. After complete addition (~25 min) the mixture was allowed to warm to room temperature and was stirred for 5.5 h. The reaction mixture was poured onto 200 mL ice-water, whereby a pale yellow precipitate was formed. After filtration, the solid material was dissolved in EtOAc and the aqueous phase was extracted with EtOAc (3x50 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution until the pH of the aqueous phase was between 8 and 9. The pale yellow organic layer was dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The crude yellow product mixture of 2-bromo-5-nitrobenzaldehyde (**5a**) and 2-bromo-3-nitrobenzaldehyde (**5a´**) was purified by recrystallization from 15 mL MeOH under reflux.[60]

Yield: 5.38 g (87%), colorless powder, $C_7H_4BrNO_3$ [230.02 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.39 (s, 1 H; CHO), 8.72 (d, ^4J (H,H) = 2.8 Hz, 1 H; H^{Ar}), 8.29 (dd, ^3J (H,H) = 8.7 Hz, ^4J (H,H) = 2.8 Hz, 1 H; H^{Ar}), 7.89 (d, ^3J (H,H) = 8.7 Hz, 1 H; H^{Ar}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 189.5 (CHO), 147.8 (C_q; C^{Ar}), 135.4 (C^{Ar}), 134.5 (C_q; C^{Ar}), 133.1 (C_q; C^{Ar}), 128.9 (C^{Ar}), 124.9 (C^{Ar}) ppm.

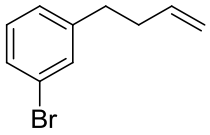
GC-MS (EI, 70 eV; MP_50_S): t_R = 5.76 min, *m/z* (%): 231 (91) [M^+], 229 (100) [M^+], 156 (9) [C_6H_3Br], 154 (9) [C_6H_3Br].

m.p.$^{exp.}$ = 96-98°C (m.p.$^{lit.}$ = 98°C).[60]

Analytical data are in accordance with those reported.[105]

9.2.3 Synthesis of Building Blocks C

9.2.3.1 1-Bromo-3-(but-3-en-1-yl)benzene (11)



11

In a flame dried 100 mL three-neck round-bottom flask with argon-inlet, reflux condenser and dropping funnel 1.07 g magnesium turnings (44.01 mmol, 1.1 eq) were suspended in 30 mL absolute Et_2O. A solution of 3.98 mL allyl bromide (**9**) (5.56 g, 45.96 mmol, 1.15 eq) in 10 mL absolute Et_2O was slowly added in a dropwise manner. After complete addition (~15 min) the reaction mixture was heated under reflux for 3 h. In a second flame dried 250 mL three-neck round-bottom flask with reflux condenser and argon-inlet a colorless solution of 10.00 g 3-bromobenzyl bromide (**8a**) (40.01 mmol, 1.0 eq) in 50 mL absolute THF was prepared. The pale brown Grignard suspension was allowed to cool to room temperature and was transferred *via* cannula to the colorless, ice cooled benzyl bromide solution **8a**, whereby a colorless precipitate was formed. After complete addition the reaction mixture was heated under reflux overnight. After cooling down to room temperature, the colorless suspension was quenched with 45 mL 2M H_2SO_4 solution at ~0°C and extracted with Et_2O (2x50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The pale yellow crude product was used in the next step without further purification. A pure sample was obtained after flash column chromatography (cyclohexane, $R_f = 0.56$) as a pale yellow liquid.

Yield: 8.34 g (99%), pale yellow liquid, $C_{10}H_{11}Br$ [211.10 g/mol].

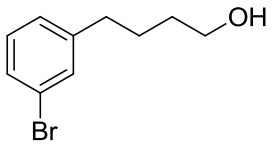
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35-7.32 (m, 2 H; H^{Ar}), 7.17-7.11 (m, 2 H; H^{Ar}), 5.87-5.79 (m, 1 H; CH), 5.05 (dd, ^3J (H,H) = 17.1 Hz, ^4J (H,H) = 1.4 Hz, 1 H; CH=CH_2), 5.00 (dd, ^3J (H,H) = 10.2 Hz, ^4J (H,H) =0.4 Hz, 1 H; CH=CH_2), 2.69 (t, ^3J (H,H) = 7.8 Hz, 2 H; CH_2), 2.36 (dd, ^3J (H,H) = 15.0 Hz, ^3J (H,H) = 7.2 Hz, 2 H; CH_2) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 144.3 (C_q; C^{Ar}), 137.6 (CH), 131.6 (C^{Ar}), 130.0 (C^{Ar}), 129.1 (C^{Ar}), 127.3 (C^{Ar}), 122.5 (C_q; C^{Ar}), 115.5 (CH=*C*H_2), 35.3 (CH_2), 35.1 (CH_2) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 5.06 min; *m/z* (%): 212 (6) [M^+], 210 (6) [M^+], 171 (97) [$M^+-C_3H_5$], 169 (100) [$M^+-C_3H_5$], 131 (52) [M^+−Br], 90 (28) [$C_7H_6^+$].

Analytical data are in accordance with those reported.[106]

9.2.3.2 4-(3-Bromophenyl)butan-1-ol (12)



12

In a flame dried 250 mL Schlenk-flask 4.17 g 9-borabicyclo[3.3.1]nonane dimer (9-BBN) (17.09 mmol, 0.75 eq) were suspended in 80 mL *n*-hexane. A solution of 4.81 g 1-bromo-3-(but-3-en-1-yl)benzene (**11**) (22.78 mmol, 1.0 eq) dissolved in 50 mL *n*-hexane was slowly added. The mixture was stirred at room temperature overnight, followed by addition of 6M NaOH (3.80 mL, 22.80 mmol, 1.0 eq) and 7.48 mL H_2O_2 (35 wt%) (2.97 g, 87.33 mmol, 3.8 eq). The mixture was stirred at 50°C overnight and after cooling to room temperature the organic layer was separated and washed subsequently with saturated $Na_2S_2O_3$ solution (1x30 mL), water (1x30 mL) and brine (1x30 mL). The aqueous extracts were combined, saturated with Na_2CO_3, filtered and reextracted with Et_2O (3x50 mL). All organic fractions were combined, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (250 g SiO_2, 20x6 cm, cyclohexane/EtOAc = 75/25, R_f = 0.24), to achieve product **12** as a pale yellow oil.
Yield: 4.46 g (85%), pale yellow oil, $C_{10}H_{13}BrO$ [229.11 g/mol].

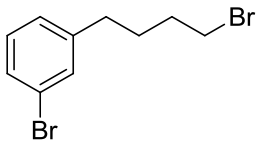
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34-7.30 (m, 2 H; H^{Ar}), 7.16-7.09 (m, 2 H; H^{Ar}), 3.66 (t, ^3J (H,H) = 6.4 Hz, 2 H; CH_2), 2.62 (t, ^3J (H,H) = 7.6 Hz, 2 H; CH_2), 1.72-1.65 (m, 2 H; CH_2), 1.62-1.56 (m, 2 H; CH_2), 1.43 (bs, 1 H; OH) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 144.8 (C_q; C^{Ar}), 131.6 (C^{Ar}), 130.0 (C^{Ar}), 129.0 (C^{Ar}), 127.2 (C^{Ar}), 122.5 (C_q; C^{Ar}), 62.8 (CH_2), 35.4 (CH_2), 32.3 (CH_2), 27.5 (CH_2) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 6.16 min, *m/z* (%): 230 (12) [M^+], 228 (15) [M^+], 184 (98) [$M^+-C_2H_6O$], 182 (100) [$M^+-C_2H_6O$], 171 (36) [$M^+-C_3H_7O$], 169 (36) [$M^+-C_3H_7O$], 131 (86) [M^+-H_2BrO].

Analytical data are in accordance with those reported; in literature [D_6]DMSO was used.[107]

9.2.3.3 1-Bromo-3-(4-bromobutyl)benzene (13)



13

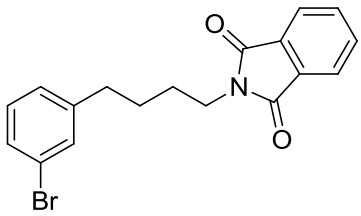
A 100 mL flame dried Schlenk-flask was charged with 4.46 g 4-(3-bromophenyl)-butan-1-ol (**12**) (19.47 mmol, 1.0 eq). Under external ice cooling, 4.53 mL tribromophosphine (PBr_3) (13.05 g, 48.21 mmol, 2.5 eq) were carefully added. After stirring at room temperature for 50 min, the reaction mixture was poured onto crushed ice. The aqueous solution was adjusted to pH ~8 (saturated $NaHCO_3$ solution) and extracted with DCM (3x60 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 flash column chromatography (80 g SiO_2, 28x3 cm, cyclohexane, $R_f = 0.43$), to achieve product **13** as a pale yellow oil.
Yield: 5.20 g (91%), pale yellow oil, $C_{10}H_{12}Br_2$ [292.01 g/mol].

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (s, 1 H; H^{Ar}), 7.32 (d, ^3J (H,H) = 6.8 Hz, 1 H; H^{Ar}, overlapping), 7.15 (t, ^3J (H,H) = 8.0 Hz, 1 H; H^{Ar}), 7.10 (d, ^3J (H,H) = 7.6 Hz, 1 H; H^{Ar}), 3.42 (t, ^3J (H,H) = 6.6 Hz, 2 H; CH_2), 2.62 (t, ^3J (H,H) = 7.6 Hz, 2 H; CH_2), 1.91-1.86 (m, 2 H; CH_2), 1.80-1.74 (m, 2 H; CH_2) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 144.3 (C_q; C^{Ar}), 131.6 (C^{Ar}), 130.1 (C^{Ar}), 129.2 (C^{Ar}), 127.2 (C^{Ar}), 122.6 (C_q; C^{Ar}), 34.8 (CH_2), 33.6 (CH_2), 32.2 (CH_2), 29.7 (CH_2) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 6.41 min; *m/z* (%): 294 (7) [M^+], 292 (14) [M^+], 290 (7) [M^+], 171 (97) [M^+−C_3H_6Br], 169 (100) [M^+−C_3H_6Br], 131 (12) [M^+−HBr_2].

9.2.3.4 2-(4-(3-Bromophenyl)butyl)isoindoline-1,3-dione (14a)



14a

In a flame dried 25 mL Schlenk-flask 1.44 g 1-bromo-3-(4-bromobutyl)benzene (**13**) (4.93 mmol, 1.0 eq) were suspended in 10 mL absolute DMF and after degassing 1.18 g potassium phthalimide (KNPhth) (6.37 mmol, 1.3 eq) were added in one portion. The pale

yellow reaction mixture was stirred overnight at 80°C and subsequently quenched with 5 mL 5% aqueous $NaHCO_3$ solution. The pH of the aqueous phase was adjusted with saturated $NaHCO_3$ solution to ~8-9 and extracted with EtOAc (3x25 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure on a rotary evaporator. The crude yellow oily product was purified by flash column chromatography (210 g SiO_2, 28x5 cm, cyclohexane/EtOAc = 8/2, R_f = 0.39).
Yield: 1.62 g (92%), colorless solid, $C_{18}H_{16}BrNO_2$ [358.23 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87-7.81 (m, 2 H; H^{Phth}), 7.73-7.68 (m, 2 H; H^{Phth}), 7.31 (d, ^4J (H,H) = 1.4 Hz, 1 H; H^{Ar}), 7.30 (dd, ^3J (H,H) = 6.9 Hz, ^4J (H,H) = 1.4 Hz, 1 H; H^{Ar}, overlapping), 7.15-7.07 (m, 2 H; H^{Ar}), 3.71 (t, ^3J (H,H) = 6.8 Hz, 2 H; CH_2), 2.62 (t, ^3J (H,H) = 7.3 Hz, 2 H; CH_2), 1.77-1.58 (m, 4 H; CH_2) ppm.

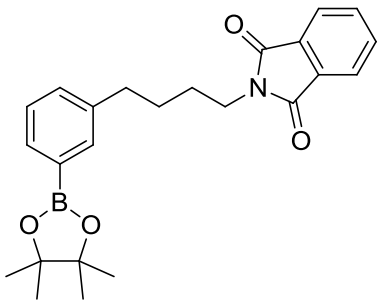
^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.6 (C_q; C=O^{Phth}), 144.4 (C_q; C^{Ar}), 134.0 (C^{Phth}), 132.2 (C_q; C^{Phth}), 131.6 (C^{Ar}), 130.0 (C^{Ar}), 129.1 (C^{Ar}), 127.2 (C^{Ar}), 123.3 (C^{Phth}), 122.5 (C_q; C^{Ar}), 37.8 (CH_2), 35.2 (CH_2), 28.5 (CH_2), 28.2 (CH_2) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 8.65 min; *m/z* (%): 359 (10) [M^+], 357 (10) [M^+], 278 (1) [M^+−Br], 188 (20) [$C_{11}H_{10}NO_2^+$], 171 (13) [$C_7H_6Br^+$], 169 (14) [$C_7H_6Br^+$], 160 (100) [$C_9H_6NO_2^+$].

m.p.$^{exp.}$ = 89-91°C.

HRMS (EI): calcd (*m*/*z*) for [M^+]: 357.0364; found: 357.0387.

9.2.3.5 2-(4-(3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)butyl)isoindoline-1,3-dione (2a)



2a

Compound **2a** was prepared according to procedure 9.2.1.1 from 2.55 g 2-(4-(3-bromo-phenyl)butyl)isoindoline-1,3-dione (**14a**) (7.12 mmol, 1.0 eq), 1.99 g B_2Pin_2 (7.84 mmol,

1.1 eq), 1.40 g KOAc (14.27 mmol, 2.0 eq) and 174 mg $PdCl_2(dppf)\cdot DCM$ (0.21 mmol, 3 mol%) in 30 mL absolute, degassed DMF. The Br/BPin exchange was completed after ~17 h. The black crude product was purified by flash column chromatography (206 g SiO_2, 27x5 cm, cyclohexane/EtOAc = 85/15, R_f = 0.32), to achieve product **2a** as a colorless solid. Alternatively the crude product can be purified by recrystallization from cyclohexane (~6 mL/g, reflux).

Yield: 2.72 g (94%), colorless solid, $C_{24}H_{28}BNO_4$ [405.29 g/mol].

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.83-7.80 (m, 2 H; H^{Phth}), 7.70-7.67 (m, 2 H; H^{Phth}), 7.63-7.61 (m, 2 H; H^{Ar}), 7.30-7.26 (m, 2 H; H^{Ar}), 3.70 (t, ^3J (H,H) = 6.9 Hz, 2 H; CH_2), 2.65 (t, ^3J (H,H) = 7.4 Hz, 2 H; CH_2), 1.74-1.64 (m, 4 H; CH_2), 1.34 (s, 12 H; CH_3^{BPin}) ppm.

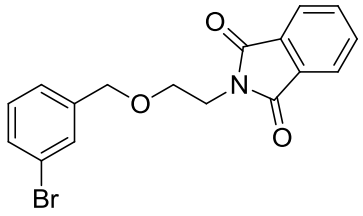
^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.5 (C_q; $C{=}O^{Phth}$), 141.3 (C_q; C^{Ar}), 134.8 (C^{Ar}), 133.9 (C^{Phth}), 132.4 (C^{Ar}), 132.2 (C_q; C^{Phth}), 131.5 (C^{Ar}), 127.8 (C^{Ar}), 123.2 (C^{Phth}) 83.8 (C_q; C^{BPin}), 37.9 (CH_2), 35.5 (CH_2), 28.9 (CH_2), 28.4 (CH_2), 25.0 (CH_3^{BPin}) ppm.*

GC-MS (EI, 70 eV; MP_50_S): t_R = 10.26 min; *m/z* (%): 405 (5) [M^+], 305 (77) [$M^+-C_6H_{12}O$], 202 (100) [$M^+-C_{12}H_{12}NO_2$], 160 (66) [$C_9H_6NO_2^+$].

m.p.$^{exp.}$ = 96-99°C.

HRMS (EI): calcd (*m*/*z*) for [M^+]: 405.2116; found: 405.2135.

9.2.3.6 2-(2-((3-Bromobenzyl)oxy)ethyl)isoindoline-1,3-dione (14b)



14b

In a flame dried and argon-flushed 100 mL Schlenk-flask 231 mg NaH (60% dispersion in mineral oil) (5.78 mmol, 1.0 eq) were suspended in 2.5 mL absolute DMF at 0°C. A solution of 1.10 g 2-(2-hydroxyethyl)isoindoline-1,3-dione (**15**) (5.75 mmol, 1.0 eq) in 4 mL DMF was added dropwise and after stirring for 10 min at 40°C, a solution of 1.44 g 3-bromobenzyl

* Signal for the quaternary *ipso*-aromatic carbon (C_q; C^{Ar}) at the boronic acid pinacol ester function was not observed.

bromide (**8a**) (5.76 mmol, 1.0 eq) in 6 mL absolute DMF was added to the pale yellow reaction mixture. After 40 min at 70°C and stirring at room temperature overnight, the reaction mixture was quenched with 6 mL H_2O and extracted with EtOAc (3x60 mL). The pale yellow crude product was purified by flash column chromatography (132 g SiO_2, 30x4 cm, cyclohexane/EtOAc = 8/2, R_f = 0.22), to obtain a colorless oil.[19a]

Yield: 1.12 g (54%), colorless oil, which become a solid upon standing, $C_{17}H_{14}BrNO_3$ [360.20 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87-7.82 (m, 2 H; H^{Phth}), 7.73-7.68 (m, 2 H; H^{Phth}), 7.45 (dd, ^3J (H,H) = 7.9 Hz, ^4J (H,H) = 0.9 Hz, 1 H; H^{Ar}), 7.39 (d, ^3J (H,H) = 7.5 Hz, 1 H; H^{Ar}), 7.26-7.21 (m, 1 H; H^{Ar}, overlapping), 7.08 (dt, ^3J (H,H) = 7.8 Hz, ^3J (H,H) = 1.6 Hz, 1 H; H^{Ar}), 4.58 (s, 2 H; CH_2), 3.98 (t, ^3J (H,H) = 5.6 Hz, 2 H; CH_2), 3.81 (t, ^3J (H,H) = 5.6 Hz, 2 H; CH_2) ppm.

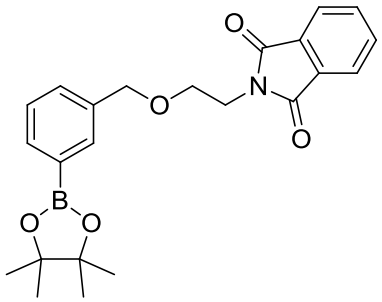
^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 168.4 (C_q; $C{=}O^{Phth}$), 137.4 (C_q; C^{Ar}), 134.0 (C^{Phth}), 132.5 (C^{Ar}), 132.3 (C_q; C^{Phth}), 129.0 (C^{Ar}), 129.0 (C^{Ar}), 127.5 (C^{Ar}), 123.4 (C^{Phth}), 122.6 (C_q; C^{Ar}), 72.1 (CH_2), 67.6 (CH_2), 37.7 (CH_2) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 9.22 min; *m/z* (%): 361 (2) [M^+], 359 (2) [M^+], 280 (3) [M^+−Br], 190 (13) [$C_{10}H_8NO_3^+$], 175 (60) [$C_{10}H_9NO_2^+$], 171 (14) [$C_7H_6Br^+$], 169 (14) [$C_7H_6Br^+$], 160 (100) [$C_9H_6NO_2^+$], 90 (10) [$C_7H_6^+$].

m.p.$^{exp.}$ = 86-88°C (m.p.$^{lit.}$ = 90-91°C).[19a]

HRMS (FAB): calcd (*m*/*z*) for [M^++H] 360.0235; found 360.0208.

9.2.3.7 2-(2-((3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)oxy)ethyl)isoindoline-1,3-dione (2b)



2b

Compound **2b** was prepared according to procedure 9.2.1.1 from 2.50 g 2-2-(3-bromobenzyl)-oxy)ethyl)isoindoline-1,3-dione (**14b**) (6.94 mmol, 1.0 eq), 1.94 g B_2Pin_2 (7.64 mmol, 1.1 eq), 1.36 g KOAc (13.86 mmol, 2.0 eq) and 284 mg $PdCl_2$(dppf)·DCM (0.35 mmol, 5 mol%). The conversion was quantitative after 27 h of stirring at 80°C. Purification by flash column chromatography (170 g SiO_2, 21x5 cm, cyclohexane/ EtOAc = 8/2, R_f = 0.33) to achieve compound **2b** as a colorless solid.[19a]

Yield: 1.77 g (60%), colorless solid, $C_{23}H_{26}BNO_5$ [407.27 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86-7.81 (m, 2 H; H^{Phth}), 7.73-7.68 (m, 3 H; H^{Ar}, H^{Phth}), 7.41-7.31 (m, 2 H; H^{Ar}), 7.21 (dt, ^3J (H,H) = 7.3 Hz, ^4J (H,H) = 1.2 Hz, 1 H; H^{Ar}), 4.80 (s, 2 H; CH_2), 3.95 (t, ^3J (H,H) = 5.9 Hz, 2 H; CH_2), 3.76 (t, ^3J (H,H) = 5.9 Hz, 2 H; CH_2), 1.33 (s, 12 H; CH_3^{BPin}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 168.4 (C_q; $C{=}O^{Phth}$), 144.4 (C_q; C^{Ar}), 135.8 (C^{Ar}), 134.0 (C^{Phth}), 132.3 (C_q; C^{Phth}), 131.1 (C^{Ar}), 127.7 (C^{Ar}), 126.8 (C^{Ar}), 123.3 (C^{Phth}), 83.7 (C_q; C^{BPin}), 72.0 (CH_2), 67.1 (CH_2), 37.7 (CH_2), 25.0 (CH_3^{BPin}) ppm.*

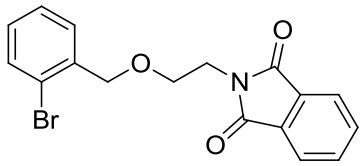
GC-MS (EI, 70 eV; MP_50_S): t_R = 10.72 min; *m/z* (%): 407 (<1) [M^+], 392 (1) [M^+−CH_3], 217 (9) [$C_{13}H_{18}BO_2^+$], 190 (8) [$C_{10}H_8NO_3^+$], 174 (100) [$C_{10}H_8NO_2^+$], 160 (49) [$C_9H_6NO_2^+$].

m.p.$^{exp.}$ = 68-71°C.

HRMS (FAB): calcd (*m/z*) for [M^++H] 408.1982; found 408.1996.

* Signal for the quaternary *ipso*-aromatic carbon (C_q; C^{Ar}) at the boronic acid pinacol ester function was not observed.

9.2.3.8 2-(2-((2-Bromobenzyl)oxy)ethyl)isoindoline-1,3-dione (14c)



14c

In a flame dried and argon-flushed 100 mL Schlenk-flask 1.41 g NaH (35.25 mmol, 1.3 eq) were suspended in 26 mL absolute DMF at 0°C. A solution of 5.35 g 2-(2-hydroxyethyl)isoindoline-1,3-dione (**15**) (27.98 mmol, 1.0 eq) in 18 mL DMF was slowly added and after stirring for 30 min at 40°C a solution of 7.00 g 2-bromobenzyl bromide (**8b**) (28.00 mmol, 1.0 eq) in 15 mL absolute DMF were added to the colorless reaction mixture and warmed to 70°C for 1.5 h. After cooling down to room temperature, the suspension was quenched with 250 mL H_2O and extracted with EtOAc (3x100 mL). The pale yellow crude product was purified by flash column chromatography (240 g SiO_2, 20x6 cm, cyclohexane/EtOAc = 8/2, R_f = 0.31). Alternatively the crude can be purified by recrystallization from cyclohexane/THF (15/3).

Yield: 6.04 g (60%), colorless solid, $C_{17}H_{14}BrNO_3$ [360.20 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88-7.82 (m, 2 H; H^{Phth}), 7.74-7.70 (m, 2 H; H^{Phth}), 7.46 (dd, ^3J (H,H) = 7.9 Hz, ^4J (H,H) = 0.9 Hz, 1 H; H^{Ar}), 7.40 (bd, ^3J (H,H) = 6.9 Hz, 1 H; H^{Ar}), 7.23 (dt, ^3J (H,H) = 7.6 Hz, ^4J (H,H) = 0.8 Hz, 1 H; H^{Ar}, overlapping), 7.09 (dt, ^3J (H,H) = 7.8 Hz, ^4J (H,H) = 1.6 Hz, 1 H; H^{Ar}), 4.58 (s, 2 H; CH_2), 3.98 (t, ^3J (H,H) = 5.6 Hz, 2 H; CH_2), 3.81 (t, ^3J (H,H) = 5.6 Hz, 2 H; CH_2) ppm.

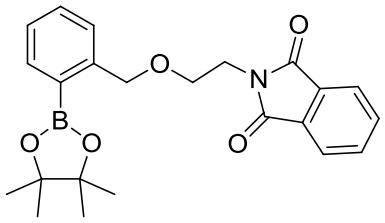
^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 168.4 (C_q; $C{=}O^{Phth}$), 137.4 (C_q; C^{Ar}), 134.1 (C^{Phth}), 132.5 (C^{Ar}), 132.3 (C_q; C^{Phth}), 129.1 (C^{Ar}), 129.0 (C^{Ar}), 127.5 (C^{Ar}), 123.4 (C^{Phth}), 122.6 (C_q; C^{Ar}), 72.2 (CH_2), 67.6 (CH_2), 37.7 (CH_2) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 9.18 min; *m/z* (%): 361 (1) [M^+], 359 (1) [M^+], 280 (2) [M^+−Br], 190 (10) [$C_{10}H_8NO_3^+$], 171 (19) [$C_7H_6Br^+$], 169 (20) [$C_7H_6Br^+$], 160 (100) [$C_9H_6NO_2^+$].

m.p.$^{exp.}$ = 86-88°C.

HRMS (EI): calcd (*m*/*z*) for [M^+]: 359.0157; found: 359.0173.

9.2.3.9 2-(2-((2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)oxy)ethyl)isoindoline-1,3-dione (2c)



2c

Compound **2c** was prepared according to procedure 9.2.1.1 from 1.51 g 2-(2-((2-bromobenzyl)oxy)ethyl)isoindoline-1,3-dione (**14c**) (4.19 mmol, 1.0 eq), 1.17 g B_2Pin_2 (4.61 mmol, 1.1 eq), 1.24 g KOAc (12.63 mmol, 3.0 eq) and 103 mg $PdCl_2(dppf)\cdot DCM$ (0.13 mmol, 3 mol%) in 20 mL absolute, degassed DMF. The Br/BPin exchange was completed overnight. The black, oily crude product was purified by flash column chromatography (90 g SiO_2, 30x3 cm, cyclohexane/EtOAc = 8/2, R_f = 0.40).

Yield: 1.38 g (81%), colorless solid, $C_{23}H_{26}BNO_5$ [407.27 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86-7.81 (m, 2 H; H^{Phth}), 7.74 (bd, ^3J (H,H) = 7.7 Hz, 1 H; H^{Ar}), 7.71-7.67 (m, 2 H; H^{Phth}), 7.41-7.32 (m, 2 H; H^{Ar}), 7.21 (dt, ^3J (H,H) = 7.3 Hz, ^4J (H,H) = 1.2 Hz, 1 H; H^{Ar}), 4.80 (s, 2 H; CH_2), 3.95 (t, ^3J (H,H) = 5.9 Hz, 2 H; CH_2), 3.76 (t, ^3J (H,H) = 5.9 Hz, 2 H; CH_2), 1.33 (s, 12 H; CH_3^{BPin}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 168.4 (C_q; $C{=}O^{Phth}$), 144.5 (C_q; C^{Ar}), 135.8 (C^{Ar}), 134.0 (C^{Phth}), 132.3 (C_q; C^{Phth}), 131.1 (C^{Ar}), 127.7 (C^{Ar}), 126.8 (C^{Ar}), 123.3 (C^{Phth}), 83.8 (C_q; C^{BPin}), 72.1 (CH_2), 67.1 (CH_2), 37.8 (CH_2), 25.0 (CH_3^{BPin}) ppm.*

GC-MS (EI, 70 eV; MP_50_S): t_R = 10.62 min; *m/z* (%): 407 (<1) [M^+], 217 (8) [$C_{13}H_{18}BO_2^+$], 190 (8) [$C_{10}H_8NO_3^+$], 174 (78) [$C_{10}H_8NO_2^+$], 160 (100) [$C_9H_6NO_2^+$].

m.p.$^{exp.}$ = 73-75°C.

HRMS (EI): calcd (*m*/*z*) for [M^+]: 407.1908; found: 407.1933.

* Signal for the quaternary *ipso*-aromatic carbon (C_q; C^{Ar}) at the boronic acid pinacol ester function was not observed.

9.2.4 Synthesis of Building Blocks AB

9.2.4.1 Representative procedure for Suzuki-coupling with aryl halides and aryl boronic acid or boronic acid pinacol ester derivatives

A flame dried and argon-flushed 50 mL Schlenk-flask was charged with 1.0 eq aryl halide derivative, 1.0-1.2 eq aryl boronic acid (or pinacol ester), 2.0 eq cesium fluoride (CsF) and 3-5 mol% $PdCl_2(dppf)\cdot DCM$. After drying of the starting materials in vacuo and back-flushing with argon, absolute, degassed 1,2-DME was added and the orange suspension was heated to 80°C. The reaction was monitored by GC-MS, after filtering a small aliquot of the reaction mixture through a small pad of SiO_2 and eluting with MeOH. After quantitative conversion the beige suspension was filtered through a small pad of silica gel (2x3 cm) and eluted with MeOH. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (eluents are indicated for each experiment).

9.2.4.2 Representative procedure for the Wittig reaction in the synthesis of the corresponding methyl 3-(phenyl)acrylates

In a flame dried 100 mL Schlenk-flask, 1.0-1.5 eq methyl 2-(triphenylphosphoranylidene)-acetate (**30**) (preparation see page 133) and 1.0 eq of the corresponding biaryl-carbaldehyde derivative were dissolved in absolute, degassed THF. After indicated time (0.5-2.5 h) of stirring at room temperature, the almost colorless suspension was concentrated in vacuo and purified by flash column chromatography (eluents are listed for every experiment).

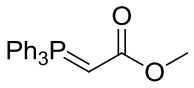
9.2.4.3 Representative procedure for the reduction of methyl 3-(phenyl)acrylates to the corresponding methyl 3-phenylpropanoate derivatives

In a 100 mL two-neck round-bottom flask with two argon-inlets, 1.0 eq methyl 3-(phenyl)acrylate was dissolved in absolute MeOH. To this typically pale yellow solution 10 wt% $Pd(OH)_2/C$ were added.[*] After ensuring hydrogen atmosphere, by evacuating and back-flushing with hydrogen gas (3x), the reaction mixture was stirred at indicated time (~2-7.5 h) at room temperature. The catalyst was filtered off (5x3 cm SiO_2, eluent: MeOH) and the solvent was removed under reduced pressure.[†] The methyl 3-phenylpropanoate derivatives were isolated after flash column chromatography (eluents are denoted).

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

[†] The catalyst was filtered off using a pad of Celite® or SiO_2 under inert conditions and eluted with MeOH. The hydrogenation catalyst was washed with H_2O and stored in a glass bottle covered with water.

9.2.4.4 Methyl 2-(triphenylphosphoranylidene)acetate (30)



30

In a flame dried two-neck round-bottom flask, 17.97 g PPh_3 (68.51 mmol, 1.0 eq) were dissolved in 90 mL degassed EtOAc. To this colorless solution 7.16 mL methyl 2-bromo-acetate (11.57 g, 75.64 mmol, 1.1 eq) were added dropwise, whereby a colorless precipitate was formed. After stirring for 1.5 h at room temperature, the colorless precipitate was collected by filtration, washed with Et_2O (3x50 mL) and dried in vacuo. The obtained Wittig-salt was dissolved in 50 mL DCM and a solution of 3.02 g NaOH (75.50 mmol, 1.1 eq) in 100 mL water was added. The mixture was vigorously stirred for ~5 min and the two layers were separated. The colorless aqueous phase was extracted with DCM (3x20 mL) and the combined organic layers were dried over Na_2SO_4. After filtration and removing the solvent under reduced pressure, compound **30** was isolated as a colorless solid.[19a,61]

Yield: 20.55 g (90%), colorless solid, $C_{21}H_{19}O_2P$ [334.35 g/mol].

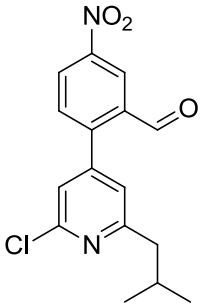
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68-7.43 (m, 15 H; H^{Ar}), 3.54 (bs, 3 H; CH_3), 2.90 (bs, 1 H; CH) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 171.7 (C_q; $COOCH_3$), 133.1 (d, ^3J (C,P) = 10 Hz, C^{Ar}), 132.1 (d, ^4J (C,P) = 2 Hz, C^{Ar}), 128.9 (d, ^2J (C,P) = 12 Hz, C^{Ar}), 128.0 (d, ^1J (C,P) = 89 Hz, C_q; C^{Ar}), 50.0 (CH_3), 29.9 (d, ^1J (C,P) = 128 Hz, CH) ppm.

m.p.$^{exp.}$ = 164-166°C (m.p.$^{lit.}$ = 167-168°C).[61]

Analytical data are in accordance with those reported.[61]

9.2.4.5 2-(2-Chloro-6-isobutylpyridin-4-yl)-5-nitrobenzaldehyde (7a)



7a

In a flame dried 100 mL two-neck round-bottom flask with argon-inlet, consecutively 1.10 g 2-bromo-5-nitrobenzaldehyde (**5a**) (4.78 mmol, 1.0 eq), 1.81 g CsF (11.92 mmol, 2.5 eq) and 146 mg $PdCl_2$(dppf)·DCM (0.18 mmol, 4 mol%) were added and after drying and back-flushing with argon, 30 mL absolute, degassed 1,2-DME were added to form a suspension. To this reddish mixture a solution of 1.76 g 2-chloro-6-isobutyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-pyridine (**4a**) (5.95 mmol, 1.2 eq) in 20 mL absolute, degassed 1,2-DME were added dropwise. After degassing, the mixture was stirred at 80°C for 3 h, filtered through a 2 cm pad of silica gel and eluted with MeOH. The filtrate was evaporated to dryness and purified by flash column chromatography (210 g SiO_2, 26x5 cm, cyclohexane/EtOAc = 85/15, R_f = 0.30) to afford a pale yellow oil.[19a]

Yield: 1.40 g (92%), pale yellow oil, $C_{16}H_{15}ClN_2O_3$ [318.75 g/mol].

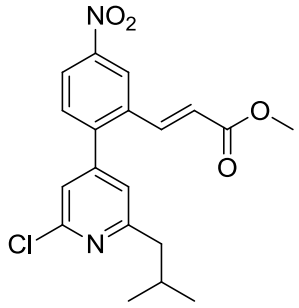
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.99 (s, 1 H; CHO), 8.86 (d, ^4J (H,H) = 2.4 Hz, 1 H; H^{Ar}), 8.51 (dd, ^3J (H,H) = 8.4 Hz, ^4J (H,H) = 2.4 Hz, 1 H; H^{Ar}), 7.63 (d, ^3J (H,H) = 8.4 Hz, 1 H; H^{Ar}), 7.22 (d, ^4J (H,H) = 0.9 Hz, 1 H; H^{Py}), 7.04 (d, ^4J (H,H) = 1.0 Hz, 1 H; H^{Py}), 2.71 (d, ^3J (H,H) = 7.2 Hz, 2 H; CH_2), 2.23-2.09 (m, 1 H; CH), 0.96 (d, ^3J (H,H) = 6.6 Hz, 6 H; CH_3) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 188.4 (CHO), 163.7 (C_q; C^{Py}), 151.7 (C_q; C^{Py}), 148.6 (C_q; C^{Ar}), 146.8 (C_q; C^{Py}), 146.7 (C_q; C^{Ar}), 134.6 (C_q; C^{Ar}), 132.0 (C^{Ar}), 127.9 (C^{Ar}), 123.9 (C^{Ar}), 122.8 (C^{Py}), 121.7 (C^{Py}), 47.2 (CH_2), 29.3 (CH), 22.5 (CH_3) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 8.19 min, *m/z* (%): 318 (3) [M^+], 303 (13) [M^+−CH_3], 276 (100) [M^+−C_3H_6], 257 (5) [M^+−CH_3NO_2].

HRMS (FAB): calcd (*m/z*) for [M^++H] 319.0849; found 319.0860.

9.2.4.6 (*E*/*Z*)-Methyl 3-(2-(2-chloro-6-isobutylpyridine-4-yl)-5-nitrophenyl)-acrylate (16a)



16a

Compound **16a** was prepared according to procedure 9.2.4.2 from 1.24 g 2-(2-chloro-6-isobutylpyridin-4-yl)-5-nitrobenzaldehyde (**7a**) (3.89 mmol, 1.0 eq) and 1.43 g ylide **30** (4.28 mmol, 1.1 eq) in 60 mL absolute, degassed THF. After 1 h of stirring at room temperature, full conversion was detected by GC-MS. The colorless suspension was concentrated to dryness and purified by flash column chromatography (100 g SiO_2, 26x3.5 cm, cyclohexane/EtOAc = 8/2, R_f = 0.21) to afford compound **16a** as a pale yellow oil.[*,19a]

Yield: 1.43 g (98%), pale yellow, highly viscous oil, which become a solid upon standing, $C_{19}H_{19}ClN_2O_4$ [374.82 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.54 (d, ^4J (H,H) = 2.0 Hz, 1 H; H^{Ar}), 8.29 (dd, ^3J (H,H) = 8.5 Hz, ^4J (H,H) = 2.1 Hz, 1 H; H^{Ar}), 7.54 (d, ^3J (H,H) = 15.9 Hz, 1 H; CH), 7.52 (d, ^3J (H,H) = 8.4 Hz, 1 H; H^{Ar}), 7.14 (s, 1 H; H^{Py}), 6.96 (s, 1 H; H^{Py}), 6.56 (d, ^3J (H,H) = 15.9 Hz, 1 H; CH), 3.78 (s, 3 H; OCH_3), 2.69 (d, ^3J (H,H) = 7.3 Hz, 2 H; CH_2^{Leu}), 2.22-2.08 (m, 1 H; CH^{Leu}), 0.96 (d, $^3J_{H,H}$ = 6.6 Hz, 6 H; CH_3^{Leu}) ppm.[†]

^{13}C NMR (76 MHz, $CDCl_3$): δ = 166.0 (C_q; $COOCH_3$), 163.4 (C_q; C^{Py}), 151.6 (C_q; C^{Py}), 148.7 (C_q; C^{Py}), 148.4 (C_q; C^{Ar}), 144.4 (C_q; C^{Ar}), 139.9 (CH), 134.5 (C_q; C^{Ar}), 131.3 (C^{Ar}), 124.4 (C^{Ar}), 123.3 (CH), 122.8 (C^{Py}), 122.3 (C^{Ar}), 121.5 (C^{Py}), 52.2 (OCH_3), 47.3 (CH_2^{Leu}), 29.3 (CH^{Leu}), 22.5 (CH_3^{Leu}) ppm.[‡]

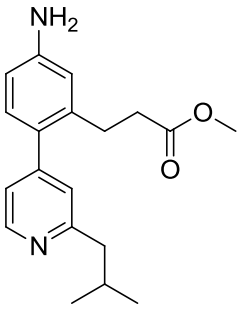
GC-MS (EI, 70 eV; MP_50_S): t_R = 9.91 min, *m/z* (%): 374 (3) [M^+], 359 (25) [M^+-CH_3], 332 (100) [$M^+-C_3H_8$], 315 (10) [$M^+-C_2H_3O_2$], 302 (5) [$M^+-C_3H_4O_2$], 273 (73) [$M^+-C_4H_5O_3$].[*]

[*] The *Z*-isomer could not be detected by GC-MS.
[†] Only in ^{1}H NMR spectrum the *Z*-isomer could be detected [6.82 (d, ^3J (H,H) = 12.1 Hz, <0.1 H; CH(*Z*)), 6.11 (d, ^3J (H,H) = 12.1 Hz, <0.1 H; CH(*Z*))].
[‡] In ^{13}C NMR no signals for the minor *Z*-isomer were observed.

m.p.$^{exp.}$ = 83-85°C.

HRMS (EI): calcd (*m*/*z*) for [M^+−H]: 373.0955; found: 373.0933.

9.2.4.7 Methyl 3-(5-amino-2-(2-isobutylpyridine-4-yl)phenyl)propanoate (17a)



17a

In a flame dried 100 mL two-neck round-bottom flask with argon-inlet, 1.46 g acrylate **16a** (3.90 mmol, 1.0 eq) and 146 mg ($Pd(OH)_2$/C (10 wt%) were suspended in 50 mL absolute MeOH.* The black suspension was stirred at room temperature for ~45 h under hydrogen atmosphere (after evacuating and back-flushing with hydrogen gas (3x)). The solution was filtered through a 3 cm pad of Celite® and eluted with MeOH.† After complete conversion the solvent was evaporated in vacuo and the reddish oil was purified by flash column chromatography (110 g SiO_2, 28x3.5 cm, cyclohexane/EtOAc/NEt_3 = 10/10/0.05, R_f = 0.20).[19a]

Yield: 1.07 g (88%), reddish, highly viscous oil, which become a solid upon standing, $C_{19}H_{24}N_2O_2$ [312.41 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.52 (d, ^3J (H,H) = 5.8 Hz, 1 H; H^{Py}), 7.05-6.97 (m, 3 H; H^{Py}, H^{Py}, H^{Ar}), 6.61-6.58 (m, 2 H; H^{Ar}), 3.74 (bs, 2 H; NH_2), 3.60 (s, 3 H; OCH_3), 2.87 (t, ^3J (H,H) = 8.0 Hz, 2 H; CH_2), 2.68 (d, ^3J (H,H) = 7.2 Hz, 2 H; CH_2^{Leu}), 2.41 (t, ^3J (H,H) = 8.0 Hz, 2 H; CH_2), 2.18-2.04 (m, 1 H; CH^{Leu}), 0.94 (d, ^3J (H,H) = 6.6 Hz, 6 H; CH_3^{Leu}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 173.1 (C_q; $COOCH_3$), 161.4 (C_q; C^{Py}), 149.9 (C_q; C^{Py}), 149.0 (C^{Py}), 146.8 (C_q; C^{Ar}), 138.9 (C_q; C^{Ar}), 131.1 (C^{Ar}), 129.8 (C_q; C^{Ar}), 124.4 (C^{Py}), 122.0 (C^{Py}), 115.7 (C^{Ar}), 113.4 (C^{Ar}), 51.7 (OCH_3), 47.7 (CH_2^{Leu}), 35.3 (CH_2), 29.5 (CH^{Leu}), 28.4 (CH_2), 22.6 (CH_3^{Leu}) ppm.

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

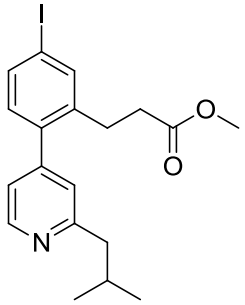
† The catalyst was filtered off using a pad of Celite® or SiO_2 under inert conditions and eluted with MeOH. The hydrogenation catalyst was washed with H_2O and stored in a glass bottle covered with water.

GC-MS (EI, 70 eV; MP_50_S): t_R = 8.68 min, *m/z* (%): 312 (21) [M^+], 297 (26) [M^+-CH_3], 282 (3) [$M^+-C_2H_6$], 270 (85) [$M^+-C_3H_6$], 269 (29) [$M^+-C_3H_7$], 255 (14) [$M^+-C_4H_9$], 237 (8) [$M^+-C_2H_5NO_2$], 211 (100) [$M^+-C_5H_9O_2$].

m.p.$^{exp.}$ = 46-49°C.

HRMS (EI): calcd (*m/z*) for [M^+]: 312.1838; found: 312.1841.

9.2.4.8 Methyl 3-(5-iodo-2-(2-isobutylpyridine-4-yl)phenyl)propanoate (18a)



18a

In a 100 mL two-neck round-bottom flask with argon-inlet 986 mg amine **17a** (3.16 mmol, 1.0 eq) were dissolved in 2 mL glacial acetic acid (>99.7%). Under external ice cooling (~0°C) 825 µL fuming HCl (>37%) were added dropwise. To this ice cold mixture a solution of $NaNO_2$ (261 mg, 3.78 mmol, 1.2 eq) in 1.5 mL ice-water were added dropwise, rapidly followed by addition of KI/I_2 (KI: 942 mg, 5.67 mmol, 1.8 eq; I_2: 801 mg, 3.16 mmol, 1.0 eq) in 990 µL ice-water. The resulting reddish brown reaction mixture was sonicated until a homogeneous solution was formed. The mixture was stirred at room temperature overnight. 10 mL saturated $Na_2S_2O_3$ solution were added and the aqueous phase was extracted with EtOAc (3x30 mL). The combined organic layers were washed with saturated Na_2CO_3 solution (2x20 mL) until the aqueous phase indicated a pH of ~9. After drying over Na_2SO_4 and filtration, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (112 g SiO_2, 28x3.5 cm, cyclohexane/EtOAc = 75/25, R_f = 0.24), to obtain a reddish orange oil.[19a]

Yield: 1.15 g (86%), reddish orange oil, $C_{19}H_{22}INO_2$ [423.29 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.56 (d, ^3J (H,H) = 5.7 Hz, 1 H; H^{Py}), 7.64 (d, ^4J (H,H) = 1.5 Hz, 1 H; H^{Ar}), 7.59 (dd, ^3J (H,H) = 8.0 Hz, ^4J (H,H) = 1.7 Hz, 1 H; H^{Ar}), 7.02-7.00 (m, 2 H; H^{Py}), 6.88 (d, ^3J (H,H) = 8.0 Hz, 1 H; H^{Ar}), 3.58 (s, 3 H; OCH_3), 2.84 (t,

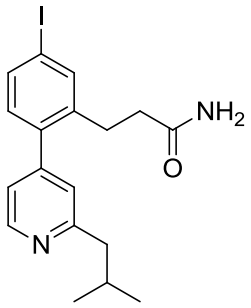
^{3}J (H,H) = 8.0 Hz, 2 H; CH_2), 2.67 (d, ^{3}J (H,H) = 7.2 Hz, 2 H; CH_2^{Leu}), 2.39 (t, ^{3}J (H,H) = 8.1 Hz, 2 H; CH_2), 2.17-2.03 (m, 1 H; CH^{Leu}), 0.93 (d, ^{3}J (H,H) = 6.6 Hz, 6 H; CH_3^{Leu}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 172.5 (C_q; $COOCH_3$), 161.9 (C_q; C^{Py}), 149.4 (C^{Py}), 148.4 (C_q; C^{Py}), 139.9 (C_q; C^{Ar}), 139.2 (C_q; C^{Ar}), 138.2 (C^{Py}), 135.8 (C^{Py}), 131.4 (C^{Ar}), 123.7 (C^{Ar}), 121.3 (C^{Ar}), 94.4 (C_q; C^{Ar}), 51.8 (OCH_3), 47.7 (CH_2^{Leu}), 34.9 (CH_2), 29.4 (CH^{Leu}), 27.9 (CH_2), 22.5 (CH_3^{Leu}) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 8.84 min, *m/z* (%): 423 (7) [M^+], 408 (20) [M^+-CH_3], 381 (100) [$M^+-C_3H_6$], 366 (17) [$M^+-C_4H_9$], 322 (70) [$C_{14}H_{13}IN^+$], 308 (28) [$C_{13}H_{11}IN^+$].

HRMS (EI): calcd (*m*/*z*) for [M^+-H]: 422.0617; found: 422.0613.

9.2.4.9 3-(5-Iodo-2-(2-isobutylpyridine-4-yl)phenyl)propanamide (3a)



3a

In a 15 mL "Ace pressure tube®, front seal" (Aldrich Z181099) with a "Duro-Silicone O-ring" 1.16 g methylester **18a** (2.74 mmol, 1.0 eq) and 27 mg KCN (0.41 mmol, 15 mol%) were suspended in 10 mL of ammonia (7M solution in MeOH). The flask was sealed and the mixture was stirred at 50°C for 3 days. The solvent was evaporated in vacuo and the crude product was purified by flash column chromatography (100 g SiO_2, 26x3.5 cm, EtOAc/MeOH = 10/0.5, R_f = 0.20) to afford a colorless solid.[19a]

Yield: 939 mg (84%), colorless solid, $C_{18}H_{21}IN_2O$ [408.28 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.56 (d, ^{3}J (H,H) = 5.7 Hz, 1 H; H^{Py}), 7.68 (d, ^{4}J (H,H) = 1.6 Hz, 1 H; H^{Ar}), 7.61 (dd, ^{3}J (H,H) = 8.0 Hz, ^{3}J (H,H) = 1.7 Hz, 1 H; H^{Ar}), 7.04-704 (m, 2 H; H^{Py}), 6.90 (d, ^{3}J (H,H) = 8.0 Hz, 1 H; H^{Ar}), 5.52 (bs, 1 H; $CONH_2$), 5.31 (bs, 1 H; $CONH_2$), 2.88 (t, ^{3}J (H,H) = 8.0 Hz, 2 H; CH_2^{Gln}), 2.69 (d, ^{3}J (H,H) = 7.2 Hz, 2 H; CH_2^{Leu}), 2.31 (t, ^{3}J (H,H) = 7.9 Hz, 2 H; CH_2^{Gln}), 2.18-2.04 (m, 1 H; CH^{Leu}), 0.94 (d, ^{3}J (H,H) = 6.6 Hz, 3 H; CH_3^{Leu}) ppm.

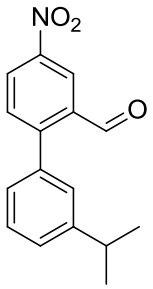
^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 173.5 (C_q; $CONH_2$), 161.9 (C_q; C^{Py}), 149.3 (C^{Py}), 148.7 (C_q; C^{Py}), 140.3 (C_q; C^{Ar}), 139.1 (C_q; C^{Ar}), 138.3 (C^{Py}), 135.8 (C^{Py}), 131.4 (C^{Ar}), 123.8 (C^{Ar}), 121.4 (C^{Ar}), 94.5 (C_q; C^{Ar}), 47.7 (CH_2^{Leu}), 36.4 (CH_2^{Gln}), 29.4 (CH^{Leu}), 28.1 (CH_2^{Gln}), 22.6 (CH_3^{Leu}) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 10.34 min, *m/z* (%): 408 (3) [M^+], 393 (9) [M^+−CH_3], 366 (100) [M^+−C_3H_6], 336 (6) [M^+−C_3H_6NO], 322 (10) [$C_{14}H_{13}IN^+$], 307 (7) [$C_{13}H_{10}IN^+$].

m.p.$^{exp.}$ = 141-144°C (m.p.$^{lit.}$ = 142-143°C).[19a]

HRMS (FAB): calcd (*m*/*z*) for [M^++H] 409.0777; found 409.0760.

9.2.4.10 3'-Isopropyl-4-nitro-[1,1'-biphenyl]-2-carbaldehyde (7b)



7b

Compound **7b** was prepared according to procedure 9.2.4.1 from 427 mg 2-bromo-5-nitro-benzaldehyde (**5a**) (1.86 mmol, 1.0 eq), 503 mg 2-(3-isopropylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**4b**) (2.04 mmol, 1.1 eq), 565 mg CsF (3.72 mmol, 2.0 eq) and 76 mg $PdCl_2$(dppf)·DCM (93 µmol, 5 mol%) in 10 mL absolute, degassed 1,2-DME. The reaction was completed after ~24 h and product **7b** was isolated after flash column chromatography (65 g SiO_2, 22x3 cm, cyclohexane/EtOAc = 9/1, R_f = 0.41).
Yield: 498 mg (99%), pale yellow oil, $C_{16}H_{15}NO_3$ [269.30 g/mol].

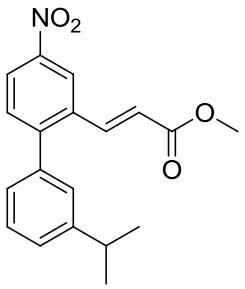
^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.00 (s, 1 H; CHO), 8.85 (d, ^4J (H,H) = 2.5 Hz, 1 H; H^{Ar}), 8.46 (dd, ^3J (H,H) = 8.5 Hz, ^4J (H,H) = 2.5 Hz, 1 H; H^{Ar}), 7.68 (d, ^3J (H,H) = 8.5 Hz, 1 H; H^{Ar}), 7.49-7.39 (m, 2 H; H^{Ar}), 7.26-7.21 (m, 2 H; H^{Ar}, overlapping), 3.05-2.96 (m, 1 H; CH), 1.31 (d, ^3J (H,H) = 6.9 Hz, 6 H; CH_3) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 190.4 (CHO), 151.7 (C_q; C^{Ar}), 150.0 (C_q; C^{Ar}), 147.5 (C_q; C^{Ar}), 135.7 (C_q; C^{Ar}), 134.6, (C_q; C^{Ar}) 132.3 (C^{Ar}), 129.1 (C^{Ar}), 128.2 (C^{Ar}), 127.8 (C^{Ar}), 127.5 (C^{Ar}), 127.4 (C^{Ar}), 123.1 (C^{Ar}), 34.3 (CH), 24.1 (CH_3) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 7.85 min; *m/z* (%): 269 (32) [M^+], 254 (28) [M^+−CH_3], 226 (100) [M^+−C_3H_7], 180 (22) [$C_{13}H_8O^+$].

HRMS (EI): calcd (*m/z*) for [M^+]: 269.1052; found: 269.1060.

9.2.4.11 (*E*/*Z*)-Methyl 3-(3'-isopropyl-4-nitro-[1,1'-biphenyl]-2-yl)acrylate (16b)



16b

Compound **16b** was prepared according to procedure 9.2.4.2 from 566 mg 3'-isopropyl-4-nitro-[1,1'-biphenyl]-2-carbaldehyde (**7b**) (2.10 mmol, 1.0 eq) and 718 mg ylide **30** (2.15 mmol, 1.0 eq) in 10 mL absolute, degassed THF. Quantitative conversion was detected after 2 h by GC-MS and after flash column chromatography a colorless mixture of the corresponding *E*/*Z*-isomers (*E*/*Z* = 8/2) was obtained (65 g SiO_2, 22x3 cm, cyclohexane/EtOAc = 9/1, R_f = 0.33).
Yield: 679 mg (99%), colorless solid, $C_{19}H_{19}NO_4$ [325.36 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.54 (d, ^4J (H,H) = 2.3 Hz, 1 H; H^{Ar}), 8.26 (dd, ^3J (H,H) = 8.5 Hz, ^4J (H,H) = 2.3 Hz, 1 H; H^{Ar}), 7.71 (d, ^3J (H,H) = 16.0 Hz, 1 H; CH(*E*)), 7.57 (d, ^3J (H,H) = 8.5 Hz, 1 H; H^{Ar}), 7.41-7.14 (m, 4 H; H^{Ar}, overlapping), 6.83 (d, ^3J (H,H) = 12.2 Hz, 0.2 H; CH(*Z*)), 6.54 (d, ^3J (H,H) = 16.0 Hz, 1 H; CH(*E*)), 6.04 (d, ^3J (H,H) = 12.2 Hz, 0.2 H; CH(*Z*)), 3.77 (s, 3 H; OCH_3), 3.04-2.91 (m, 1 H; CH), 1.29 (d, ^3J (H,H) = 6.9 Hz, 6 H; CH_3) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 166.7 (C_q; $COOCH_3$), 149.5 (C_q; C^{Ar}), 149.1 (C_q; C^{Ar}), 147.3 (C_q; C^{Ar}), 142.0 (CH(*E*)), 137.8 (C_q; C^{Ar}), 134.2 (C_q; C^{Ar}), 131.7 (C^{Ar}), 128.9 (C^{Ar}), 128.0 (C^{Ar}), 127.3 (C^{Ar}), 127.1 (C^{Ar}), 124.1 (C^{Ar}), 122.1 (C^{Ar}), 121.5 (CH(*E*)), 52.0 (OCH_3), 34.2 (CH), 24.1 (CH_3) ppm.*

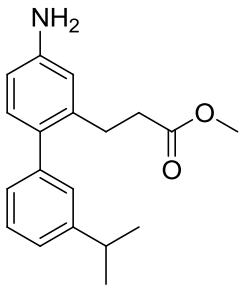
* For the sake of clarity only chemical shifts for the major *E*-isomer are listed.

GC-MS (EI, 70 eV; MP_50_S): $t_R(E)$ = 8.74 min; *m/z* (%): 325 (24) [M^+], 310 (4) [M^+-CH_3], 294 (6) [M^+-CH_3O], 250 (51) [$M^+-C_2H_3O_3$], 224 (100) [$M^+-C_4H_5O_3$]; $t_R(Z)$ = 8.42 min; *m/z* (%):325 (23) [M^+], 310 (4) [M^+-CH_3], 294 (8) [M^+-CH_3O], 282 (11) [$M^+-C_3H_7$], 250 (67) [$M^+-C_2H_3O_3$], 235 (10) [$M^+-C_4H_{10}O_2$], 224 (100) [$M^+-C_4H_5O_3$].

m.p.$^{exp.}$ = 78-80°C.

HRMS (EI) *Z*-isomer: calcd (*m/z*) for [M^+]: 325.1314; found: 325.1319; *E*-isomer: calcd (*m/z*) for [M^+]: 325.1314; found: 325.1321.

9.2.4.12 Methyl 3-(4-amino-3'-isopropyl-[1,1'-biphenyl]-2-yl)propanoate (17b)



17b

Compound **17b** was prepared according to procedure 9.2.4.3 from 649 mg (*E*/*Z*)-methyl 3-(3'-isopropyl-4-nitro-[1,1'-biphenyl]-2-yl)acrylate (**16b**) (1.99 mmol, 1.0 eq) and 65 mg $Pd(OH)_2/C$ (10 wt%) in 70 mL absolute MeOH.* The catalyst was filtered off after 3 h and purification by flash column chromatography (72 g SiO_2, 24x3 cm, cyclohexane/THF = 7/3, R_f = 0.29) afforded compound **17b** was as a pale yellow oil.†

Yield: 589 mg (99%), pale yellow oil, $C_{19}H_{23}NO_2$ [297.39 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (t, ^3J (H,H) = 7.6 Hz, 1 H; H^{Ar}), 7.19-7.14 (m, 2 H; H^{Ar}), 7.10-7.03 (m, 2 H; H^{Ar}), 6.65-6.62 (m, 2 H; H^{Ar}), 3.60 (s, 3 H; OCH_3), 3.49 (bs, 2 H; NH_2, overlapping), 2.95-2.84 (m, 3 H; CH, CH_2), 2.43 (t, ^3J (H,H) = 8.0 Hz, 2 H; CH_2), 1.27 (d, ^3J (H,H) = 6.9 Hz, 6 H; CH_3) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 173.5 (C_q; $COOCH_3$), 148.8 (C_q; C^{Ar}), 145.1 (C_q; C^{Ar}), 141.5 (C_q; C^{Ar}), 139.1 (C_q; C^{Ar}), 133.4 (C_q; C^{Ar}), 131.4 (C^{Ar}), 128.2 (C^{Ar}), 127.7 (C^{Ar}),

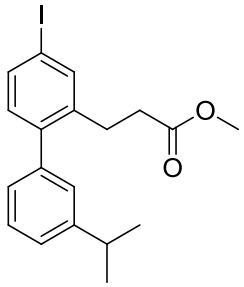
* Palladium hydroxide on activated charcoal, moistened with water, 15-20% Pd basis (based on dry substance), Fluka 76063.
† The catalyst was filtered off using a pad of Celite® or SiO_2 under inert conditions and eluted with MeOH. The hydrogenation catalyst was washed with H_2O and stored in a glass bottle covered with water.

127.0 (C^{Ar}), 124.8 (C^{Ar}), 116.0 (C^{Ar}), 113.6 (C^{Ar}), 51.7 (OCH_3), 35.4 (CH_2), 34.2 (CH), 28.6 (CH_2), 24.2 (CH_3) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 8.11 min; *m/z* (%): 297 (100) [M^+], 281 (<1) [M^+-NH_2], 266 (6) [M^+-CH_5N], 250 (4) [M^+-CH_5NO], 238 (5) [$M^+-C_3H_9N$], 222 (8) [$M^+-C_2H_5NO_2$], 194 (22) [$C_{15}H_{14}^+$].

HRMS (EI): calcd (*m/z*) for [M^+]: 297.1729; found: 297.1731.

9.2.4.13 Methyl 3-(4-iodo-3'-isopropyl-[1,1'-biphenyl]-2-yl)propanoate (18b)



18b

In a 100 mL two-neck round-bottom flask with argon-inlet 495 mg amine **17b** (1.66 mmol, 1.0 eq) were dissolved in 1.05 mL glacial acetic acid (>99.7%). Under ice cooling (~0°C) 438 µL fuming HCl (>37%) were added dropwise. To this ice cold mixture a solution of $NaNO_2$ (115 mg, 1.67 mmol, 1.0 eq) in 788 µL ice-water was added, rapidly followed by KI/I_2 (KI: 497 mg, 2.99 mmol, 1.8 eq; I_2: 422 mg, 1.66 mmol, 1.0 eq) in 525 µL ice-water. The resulting reddish brown reaction mixture was sonicated until a homogeneous solution was formed. The mixture was stirred at room temperature overnight. 20 mL saturated $Na_2S_2O_3$ solution were added and the aqueous phase was extracted with EtOAc (3x30 mL). The combined organic layers were washed with saturated Na_2CO_3 solution (2x25 mL) until the aqueous phase indicated a pH of ~9. After drying over Na_2SO_4 and filtration, the solvent was evaporated in vacuo and the crude product was purified by flash column chromatography (30 g SiO_2, 23x2 cm, cyclohexane/EtOAc = 100/2.5, R_f = 0.23).
Yield: 437 mg (64%), colorless oil, $C_{19}H_{21}IO_2$ [408.27 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63 (d, ^4J (H,H) = 1.6 Hz, 1 H; H^{Ar}), 7.58 (dd, ^3J (H,H) = 8.0 Hz, ^4J (H,H) = 1.7 Hz, 1 H; H^{Ar}), 7.33 (t, ^3J (H,H) = 7.6 Hz, 1 H; H^{Ar}), 7.26-7.21 (m, 1 H; H^{Ar}, overlapping), 7.11 (s, 1 H; H^{Ar}), 7.07 (dd, ^3J (H,H) = 7.4 Hz, ^4J (H,H) = 1.3 Hz, 1 H;

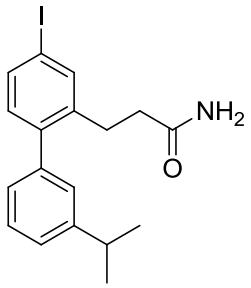
H^{Ar}), 6.95 (d, ^3J (H,H) = 8.0 Hz, 1 H; H^{Ar}), 3.61 (s, 3 H; OCH_3), 2.99-2.84 (m, 3 H; CH, CH_2), 2.41 (t, ^3J (H,H) = 8.0 Hz, 2 H; CH_2), 1.27 (d, ^3J (H,H) = 6.9 Hz, 6 H; CH_3) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 173.0 (C_q; $COOCH_3$), 149.1 (C_q; C^{Ar}), 142.1 (C_q; C^{Ar}), 140.5 (C_q; C^{Ar}), 140.4 (C_q; C^{Ar}), 138.0 (C^{Ar}), 135.5 (C^{Ar}), 132.2 (C^{Ar}), 128.5 (C^{Ar}), 127.1 (C^{Ar}), 126.4 (C^{Ar}), 125.6 (C^{Ar}), 93.1 (C_q; C^{Ar}), 51.7 (OCH_3), 35.1 (CH_2), 34.2 (CH), 28.2 (CH_2), 24.1 (CH_3) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 8.39 min; *m/z* (%): 408 (100) [M^+], 393 (1) [M^+−CH_3], 377 (9) [M^+−CH_3O], 361 (84) [M^+−C_2H_7O], 333 (25) [$C_{16}H_{14}I^+$], 266 (1) [M^+−CH_3I], 250 (3) [M^+−CH_3IO], 207 (30) [$C_{15}H_{11}O^+$], 191 (34) [$C_{14}H_{11}^+$], 165 (51) [$C_{13}H_9^+$].

HRMS (EI): calcd (*m/z*) for [M^+]: 408.0586; found: 408.0598.

9.2.4.14 3-(4-Iodo-3'-isopropyl-[1,1'-biphenyl]-2-yl)propanamide (3b)



3b

In a 15 mL "Ace pressure tube®, front seal" (Aldrich Z181099) with a "Duro-Silicone O-ring" 427 mg methylester **18b** (1.05 mmol, 1.0 eq) and 11 mg KCN (0.17 mmol, 16 mol%) were suspended in 5 mL of ammonia (7M solution in MeOH). The flask was sealed and the mixture was stirred at 50°C for 7 days. The solvent was evaporated in vacuo and the crude product was purified by flash column chromatography (34 g SiO_2, 24x2 cm, cyclohexane/EtOAc = 1/1, R_f = 0.27) to afford a pale yellow oil.[19a]

Yield: 375 mg (91%), pale yellow, highly viscous oil, $C_{18}H_{20}INO$ [393.26 g/mol].

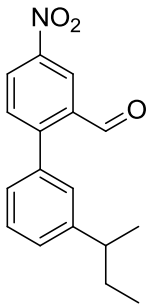
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (d, ^4J (H,H) = 1.4 Hz, 1 H; H^{Ar}), 7.59 (dd, ^3J (H,H) = 8.0 Hz, ^4J (H,H) = 1.6 Hz, 1 H; H^{Ar}), 7.33 (t, ^3J (H,H) = 7.5 Hz, 1 H; H^{Ar}), 7.26-7.21 (m, 1 H; H^{Ar}, overlapping), 7.12 (s, 1 H; H^{Ar}), 7.08 (d, ^3J (H,H) = 7.4 Hz, 1 H; H^{Ar}), 6.96 (d, ^3J (H,H) = 8.0 Hz, 1 H; H^{Ar}), 5.47 (bs, 1 H; $CONH_2$), 5.16 (bs, 1 H; $CONH_2$), 2.98-2.87 (m, 3 H; CH, CH_2), 2.28 (t, ^3J (H,H) = 8.0 Hz, 2 H; CH_2), 1.27 (d, ^3J (H,H) = 6.9 Hz, 6 H; CH_3) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 174.2 (C_q; $CONH_2$), 149.3 (C_q; C^{Ar}), 141.9 (C_q; C^{Ar}), 140.6 (C_q; C^{Ar}), 140.4 (C_q; C^{Ar}), 138.1 (C^{Ar}), 135.5 (C^{Ar}), 132.1 (C^{Ar}), 128.5 (C^{Ar}), 127.1 (C^{Ar}), 126.4 (C^{Ar}), 125.7 (C^{Ar}), 93.2 (C_q; C^{Ar}), 36.7 (CH_2), 34.2 (CH), 28.7 (CH_2), 24.2 (CH_3) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 9.62 min; *m/z* (%): 393 (48) [M^+], 361 (100) [M^+−H_2NO], 350 (4) [M^+−C_3H_7], 319 (6) [M^+−C_3H_8NO], 207 (28) [$C_{16}H_{15}^+$], 178 (43) [$C_{14}H_{10}^+$].

HRMS (EI): calcd (*m/z*) for [M^+]: 393.0590; found: 393.0626.

9.2.4.15 3'-(*sec*-Butyl)-4-nitro-[1,1'-biphenyl]-2-carbaldehyde (7c)



7c

Compound **7c** was prepared according to procedure 9.2.4.1 from 308 mg 2-bromo-5-nitro-benzaldehyde (**5a**) (1.34 mmol, 1.0 eq), 263 mg (3-(*sec*-butyl)phenyl)boronic acid (**4c**) (1.48 mmol, 1.1 eq), 407 mg CsF (2.68 mmol, 2.0 eq) and 55 mg $PdCl_2$(dppf)·DCM (67 µmol, 5 mol%) in 6 mL absolute, degassed 1,2-DME. The reaction was completed after ~2.5 h and product **7c** was isolated after flash column chromatography (27 g SiO_2, 20x2 cm, cyclohexane/EtOAc = 95/5, R_f = 0.27).

Yield: 369 mg (97%), colorless solid, $C_{17}H_{17}NO_3$ [283.32 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.99 (s, 1 H; CHO), 8.85 (d, ^4J (H,H) = 2.4 Hz, 1 H; H^{Ar}), 8.46 (dd, ^3J (H,H) = 8.5 Hz, ^4J (H,H) = 2.5 Hz, 1 H; H^{Ar}), 7.68 (d, ^3J (H,H) = 8.5 Hz, 1 H; H^{Ar}), 7.46 (t, ^3J (H,H) = 7.6 Hz, 1 H; H^{Ar}), 7.35 (d, ^3J (H,H) = 7.8 Hz, 1 H; H^{Ar}), 7.26-7.19 (m, 2 H; H^{Ar}, overlapping), 2.75-2.63 (m, 1 H; CH), 1.69-1.58 (m, 2 H; CH_2), 1.29 (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.

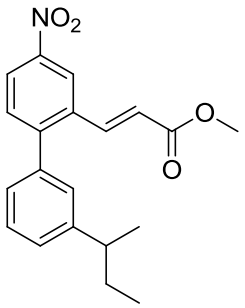
^{13}C NMR (76 MHz, $CDCl_3$): δ = 190.3 (CHO), 151.8 (C_q; C^{Ar}), 148.8 (C_q; C^{Ar}), 147.5 (C_q; C^{Ar}), 135.7 (C_q; C^{Ar}), 134.6 (C_q; C^{Ar}), 132.3 (C^{Ar}), 129.1 (C^{Ar}), 128.9 (C^{Ar}), 128.4 (C^{Ar}), 127.5 (C^{Ar}), 127.4 (C^{Ar}), 123.1 (C^{Ar}), 41.8 (CH), 31.3 (CH_2), 21.9 (CH_3), 12.4 (CH_3) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 8.08 min; *m/z* (%): 283 (26) [M^+], 254 (100) [M^+−CHO], 226 (40) [M^+−C_4H_9], 180 (21) [$C_{13}H_8O^+$].

m.p.$^{exp.}$ = 40-41°C.

HRMS (EI): calcd (*m*/*z*) for [M^+]: 283.1208; found: 283.1223.

9.2.4.16 (*E*/*Z*)-Methyl 3-(3'-(*sec*-butyl)-4-nitro-[1,1'-biphenyl]-2-yl)acrylate (16c)



16c

Compound **16c** was prepared according to procedure 9.2.4.2 from 318 mg 3'-(*sec*-butyl)-4-nitro-[1,1'-biphenyl]-2-carbaldehyde (**7c**) (1.12 mmol, 1.0 eq) and 564 mg ylide **30** (1.69 mmol, 1.5 eq) in 10 mL absolute, degassed THF. After stirring for 2.5 h at room temperature the crude product was purified by flash column chromatography (62 g SiO_2, 21x3 cm, cyclohexane/EtOAc = 100/5, R_f = 0.21) and compound **16c** was isolated as a mixture of *E*/*Z*-isomers (*E*/*Z* = 8/2).

Yield: 379 mg (quant.), colorless solid, $C_{20}H_{21}NO_4$ [339.39 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.53 (d, ^4J (H,H) = 2.3 Hz, 1 H; H^{Ar}), 8.26 (dd, ^3J (H,H) = 8.5 Hz, ^4J (H,H) = 2.3 Hz, 1 H; H^{Ar}), 7.70 (d, ^3J (H,H) = 16.0 Hz, 0.8 H; CH(*E*)), 7.57 (d, ^3J (H,H) = 8.5 Hz, 1 H; H^{Ar}), 7.41 (t, ^3J (H,H) = 7.6 Hz, 1 H; H^{Ar}), 7.30-7.26 (m, 1 H; H^{Ar}, overlapping), 7.19-7.11 (m, 2 H; H^{Ar}), 6.82 (d, ^3J (H,H) = 12.2 Hz, 0.2 H; CH(*Z*)), 6.53 (d, ^3J (H,H) = 16.0 Hz, 0.8 H; CH(*E*)), 6.04 (d, ^3J (H,H) = 12.2 Hz, 0.2 H; CH(*Z*)), 3.76 (s, 3 H; OCH_3), 2.72-2.61 (m, 1 H; CH), 1.68-1.58 (m, 2 H; CH_2), 1.27 (d, ^3J (H,H) = 7.0 Hz, 3 H; CH_3), 0.86 (t, ^3J (H,H) = 7.3 Hz, 3 H; CH_3) ppm.

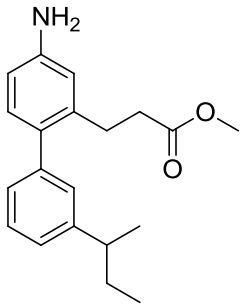
^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 166.6 (C_q; $COOCH_3$), 149.1 (C_q; C^{Ar}), 148.3 (C_q; C^{Ar}), 147.3 (C_q; C^{Ar}), 142.0 (CH(*E*)), 137.8 (C_q; C^{Ar}), 134.2 (C_q; C^{Ar}), 131.7 (C^{Ar}), 128.9 (C^{Ar}), 128.6 (C^{Ar}), 127.9 (C^{Ar}), 127.1 (C^{Ar}), 124.1 (C^{Ar}), 122.2 (C^{Ar}), 121.5 (CH(*E*)), 52.0 (OCH_3), 41.8 (CH), 31.2 (CH_2), 22.0 (CH_3), 12.4 (CH_3) ppm.*

GC-MS (EI, 70 eV; MP_50_S): t_R(*E*) = 9.08 min; *m/z* (%): 339 (25) [M^+], 310 (51) [$M^+-C_2H_5$], 308 (4) [M^+-CH_3O], 280 (20) [$M^+-C_2H_3O_2$], 266 (3) [$M^+-C_4H_9O$], 250 (65) [$M^+-C_4H_9O_2$], 236 (23) [$C_{16}H_{12}O_2^+$], 224 (100) [$C_{15}H_{12}O_2^+$]; t_R(*Z*) = 8.70 min; *m/z* (%): 339 (20) [M^+], 310 (37) [$M^+-C_2H_5$], 308 (5) [M^+-CH_3O], 282 (10) [$M^+-C_4H_9$], 280 (24) [$M^+-C_2H_3O_2$], 265 (13) [$M^+-C_3H_6O_2$], 250 (70) [$M^+-C_4H_9O_2$], 236 (27) [$C_{16}H_{12}O_2^+$], 224 (100) [$C_{15}H_{12}O_2^+$].

m.p.$^{exp.}$ = 84-88°C.

HRMS (EI) *Z*-isomer: calcd (*m/z*) for [M^+]: 339.1471; found: 339.1477; *E*-isomer: calcd (*m/z*) for [M^+]: 339.1471; found: 339.1480.

9.2.4.17 Methyl 3-(4-amino-3'-(*sec*-butyl)-[1,1'-biphenyl]-2-yl)propanoate (17c)



17c

Compound **17c** was prepared according to procedure 9.2.4.3 from 359 mg (*E*/*Z*)-methyl 3-(3'-(*sec*-butyl)-4-nitro-[1,1'-biphenyl]-2-yl)acrylate (**16c**) (1.06 mmol, 1.0 eq) and 36 mg $Pd(OH)_2$/C (10 wt%) in 40 mL absolute MeOH.† After 3.5 h the catalyst was filtered off and the product **17c** was used in the next step without further purification (cyclohexane/THF = 7/3, R_f = 0.25).‡

Yield: 329 mg (quant.), colorless, highly viscous oil, which become a solid upon standing, $C_{20}H_{25}NO_2$ [311.42 g/mol].

* For the sake of clarity only chemical shifts for the major *E*-isomer are listed.
† Palladium hydroxide on activated charcoal, moistened with water, 15-20% Pd basis (based on dry substance), Fluka 76063.
‡ The catalyst was filtered off using a pad of Celite® or SiO_2 under inert conditions and eluted with MeOH. The hydrogenation catalyst was washed with H_2O and stored in a glass bottle covered with water.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33-7.26 (m, 1 H; H^{Ar}, overlapping), 7.14-7.03 (m, 4 H; H^{Ar}), 6.66-6.62 (m, 2 H; H^{Ar}), 3.59 (s, 3 H; OCH_3), 3.22 (bs, 2 H; NH_2), 2.87 (t, ^{3}J (H,H) = 8.0 Hz, 2 H; CH_2), 2.67-2.56 (m, 1 H; CH), 2.41 (t, ^{3}J (H,H) = 8.0 Hz, 2 H; CH_2), 1.66-1.56 (m, 2 H; CH_2^{Ile}), 1.25 (d, ^{3}J (H,H) = 6.9 Hz, 3 H; CH_3), 0.83 (t, ^{3}J (H,H) = 7.4 Hz, 3 H; CH_3) ppm.

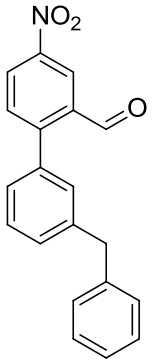
^{13}C NMR (76 MHz, $CDCl_3$): δ = 173.5 (C_q; $COOCH_3$), 147.5 (C_q; C^{Ar}), 145.0 (C_q; C^{Ar}), 141.4 (C_q; C^{Ar}), 139.2 (C_q; C^{Ar}), 133.6 (C_q; C^{Ar}), 131.4 (C^{Ar}), 128.3 (C^{Ar}), 128.2 (C^{Ar}), 127.0 (C^{Ar}), 125.5 (C^{Ar}), 116.1 (C^{Ar}), 113.7 (C^{Ar}), 51.6 (OCH_3), 41.8 (CH), 35.3 (CH_2), 31.4 (CH_2^{Ile}), 28.7 (CH_2), 22.0 (CH_3), 12.4 (CH_3) ppm.

GC-MS (EI, 70 eV; MP_100_L): t_R = 6.36 min; *m/z* (%): 311 (100) [M^+], 295 (<1) [M^+−NH_2], 280 (5) [M^+−CH_5N], 264 (1) [M^+−CH_5NO], 194 (9) [$C_{14}H_{12}N^+$], 180 (12) [$C_{13}H_{10}N^+$].

m.p.$^{exp.}$ = 44-46°C.

HRMS (EI): calcd (*m*/*z*) for [M^+]: 311.1885; found: 311.1892.

9.2.4.18 3'-Benzyl-4-nitro-[1,1'-biphenyl]-2-carbaldehyde (7d)



7d

Compound **7d** was prepared according to procedure 9.2.4.1 from 326 mg 2-bromo-5-nitro-benzaldehyde (**5a**) (1.42 mmol, 1.0 eq), 330 mg (3-benzylphenyl)boronic acid (**4d**) (1.56 mmol, 1.1 eq), 430 mg CsF (2.83 mmol, 2.0 eq) and 58 mg $PdCl_2$(dppf)·DCM (71 mmol, 5 mol%) in 6 mL absolute, degassed 1,2-DME. The reaction was completed after ~2.5 h and product **7d** was isolated after flash column chromatography (44 g SiO_2, 16x3 cm, cyclohexane/EtOAc = 93/7, R_f = 0.21).

Yield: 414 mg (92%), colorless solid, $C_{20}H_{15}NO_3$ [317.34 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.00 (s, 1 H; CHO), 8.87 (d, ^4J (H,H) = 2.4 Hz, 1 H; H^{Ar}), 8.48 (dd, ^3J (H,H) = 8.5 Hz, ^4J (H,H) = 2.4 Hz, 1 H; H^{Ar}), 7.67 (d, ^3J (H,H) = 8.5 Hz, 1 H; H^{Ar}), 7.50 (t, ^3J (H,H) = 7.5 Hz, 1 H; H^{Ar}), 7.42-7.24 (m, 8 H; H^{Ar}, H^{Phe}), 4.11 (s, 2 H; CH_2) ppm.

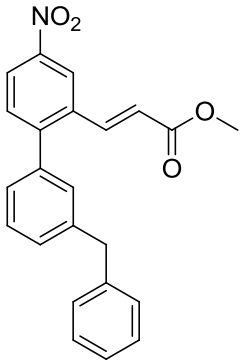
^{13}C NMR (76 MHz, $CDCl_3$): δ = 190.2 (CHO), 151.3 (C_q; C^{Ar}), 147.6 (C_q; C^{Ar}), 142.4 (C_q; C^{Ar}), 140.3 (C_q; C^{Phe}), 135.9 (C_q; C^{Ar}), 134.6 (C_q; C^{Ar}), 132.3 (C^{Ar}), 130.4 (C^{Ar}), 130.2 (C^{Ar}), 129.2 (C^{Ar}), 129.0 (C^{Phe}), 128.9 (C^{Phe}), 127.9 (C^{Ar}), 127.4 (C^{Ar}), 126.6 (C^{Phe}), 123.1 (C^{Ar}), 41.9 (CH_2) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 9.95 min; *m/z* (%): 317 (45) [M^+], 240 (11) [M^+−C_6H_5], 226 (100) [M^+−C_7H_7], 180 (18) [$C_{13}H_8O^+$], 91 (24) [$C_7H_7^+$].

m.p.$^{exp.}$ = 44-47°C.

HRMS (EI): calcd (*m/z*) for [M^+]: 317.1052; found: 317.1062.

9.2.4.19 (*E*/*Z*)-Methyl 3-(3'-benzyl-4-nitro-[1,1'-biphenyl]-2-yl)acrylate (16d)



16d

Compound **16d** was prepared according to procedure 9.2.4.2 from 360 mg 3'-benzyl-4-nitro-[1,1'-biphenyl]-2-carbaldehyde (**7d**) (1.13 mmol, 1.0 eq) and 569 mg ylide **30** (1.70 mmol, 1.5 eq) in 10 mL absolute, degassed THF. Quantitative conversion was detected after 2.5 h stirring at room temperature. Compound **16d** was isolated as a mixture of *E*/*Z*-isomers (*E*/*Z* = 9/1) after flash column chromatography (70 g SiO_2, 23x3 cm, cyclohexane/EtOAc = 9/1, R_f = 0.32).

Yield: 420 mg (quant.), pale yellow, highly viscous oil, $C_{23}H_{19}NO_4$ [373.40 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51 (d, ^4J (H,H) = 2.3 Hz, 1 H; H^{Ar}), 8.24 (dd, ^3J (H,H) = 8.5 Hz, ^4J (H,H) = 2.3 Hz, 1 H; H^{Ar}), 7.67 (d, ^3J (H,H) = 16.0 Hz, 1 H; CH(*E*)), 7.52 (d,

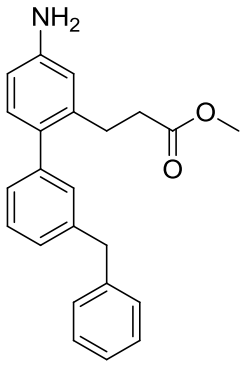
^3J (H,H) = 8.5 Hz, 1 H; H^{Ar}), 7.41 (t, ^3J (H,H) = 7.6 Hz, 1 H; H^{Ar}), 7.33-7.12 (m, 8 H; H^{Ar}, H^{Phe}, overlapping), 6.74 (d, ^3J (H,H) = 12.2 Hz, <0.1 H; CH(*Z*)), 6.52 (d, ^3J (H,H) = 16.0 Hz, 1 H; CH(*E*)), 5.94 (d, ^3J (H,H) = 12.2 Hz, <0.1 H; CH(*Z*)), 4.05 (s, 2 H; CH_2), 3.79 (s, 3 H; OCH_3) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 166.6 (C_q; $COOCH_3$), 148.8 (C_q; C^{Ar}), 147.4 (C_q; C^{Ar}), 141.9 (C_q; C^{Ar}), 141.8 (CH(*E*)), 140.5 (C_q; C^{Phe}), 138.1 (C_q; C^{Ar}), 134.3 (C_q; C^{Ar}), 131.7 (C^{Ar}), 130.1 (C^{Ar}), 129.6 (C^{Ar}), 129.1 (C^{Phe}), 129.0 (C^{Ar}), 128.8 (C^{Phe}), 127.4 (C^{Ar}), 126.5 (C^{Phe}), 124.1 (C^{Ar}), 122.2 (C^{Ar}), 121.6 (CH(*E*)), 52.0 (OCH_3), 41.9 (CH_2) ppm.*

GC-MS (EI, 70 eV; MP_50_S): t_R(*E*) = 11.89 min; *m/z* (%): 373 (25) [M^+], 342 (3) [M^+-CH_3O], 314 (18) [$M^+-C_2H_3O_2$], 282 (3) [$C_{16}H_{12}NO_4^+$], 236 (17) [$C_{16}H_{12}O_2^+$], 91 (100) [$C_7H_7^+$]; t_R(*Z*) = 11.14 min; *m/z* (%): 373 (15) [M^+], 342 (3) [M^+-CH_3O], 326 (2) [$M^+-CH_3O_2$], 314 (16) [$M^+-C_2H_3O_2$], 282 (5) [$C_{16}H_{12}NO_4^+$], 236 (11) [$C_{16}H_{12}O_2^+$], 91 (100) [$C_7H_7^+$].

HRMS (EI) *Z*-isomer: calcd (*m/z*) for [M^+]: 373.1314; found: 373.1317; *E*-isomer: calcd (*m/z*) for [M^+]: 373.1314; found: 373.1322.

9.2.4.20 Methyl 3-(4-amino-3'-benzyl-[1,1'-biphenyl]-2-yl)propanoate (17d)



17d

Compound **17d** was prepared according to procedure 9.2.4.3 from 378 mg (*E*/*Z*)-methyl 3-(3'-benzyl-4-nitro-[1,1'-biphenyl]-2-yl)acrylate (**16d**) (1.01 mmol, 1.0 eq) and 38 mg $Pd(OH)_2$/C (10 wt%) in 40 ml absolute MeOH.† The catalyst was filtered off after 3.5 h and after flash

* In ^{13}C NMR no signals for the minor *Z*-isomer were observed.
† Palladium hydroxide on activated charcoal, moistened with water, 15-20% Pd basis (based on dry substance), Fluka 76063.

column chromatography (43 g SiO_2, 17x3 cm, cyclohexane/THF = 7/3, R_f = 0.31), compound **17d** was isolated as a colorless oil.*

Yield: 349 mg (quant.), colorless oil, $C_{23}H_{23}NO_2$ [345.43 g/mol].

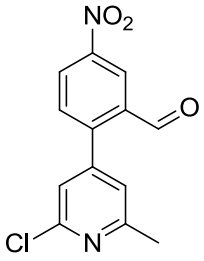
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37-7.14 (m, 9 H; H^{Ar}, H^{Phe}, overlapping), 7.04 (d, ^3J (H,H) = 7.8 Hz, 1 H; H^{Ar}), 6.64-6.60 (m, 2 H; H^{Ar}), 4.06 (s, 2 H; CH_2^{Phe}), 3.65 (s, 3 H; OCH_3), 3.54 (bs, 2 H; NH_2, overlapping), 2.88 (t, ^3J (H,H) = 8.0 Hz, 2 H; CH_2), 2.42 (t, ^3J (H,H) = 8.0 Hz, 2 H; CH_2) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 173.5 (C_q; $COOCH_3$), 145.7 (C_q; C^{Ar}), 141.8 (C_q; C^{Ar}), 141.2 (C_q; C^{Ar}), 141.0 (C_q; C^{Phe}), 139.1 (C_q; C^{Ar}), 132.7 (C_q; C^{Ar}), 131.4 (C^{Ar}), 130.2 (C^{Ar}), 129.1 (C^{Phe}), 128.6 (C^{Phe}), 128.4 (C^{Ar}), 127.3 (C^{Ar}), 127.2 (C^{Ar}), 126.2 (C^{Phe}), 115.7 (C^{Ar}), 113.3 (C^{Ar}), 51.6 (OCH_3), 42.0 (CH_2^{Phe}), 35.3 (CH_2), 28.6 (CH_2) ppm.

GC-MS (EI, 70 eV; MP_100_L): t_R = 8.50 min; *m/z* (%): 345 (100) [M^+], 330 (<1) [M^+−CH_3], 314 (6) [M^+−CH_3O], 254 (2) [M^+−C_7H_7], 252 (2) [$C_{17}H_{16}O_2^+$], 193 (16) [$C_{15}H_{13}^+$], 91 (10) [$C_7H_7^+$].

HRMS (EI): calcd (*m*/*z*) for [M^+]: 345.1729; found: 345.1744.

9.2.4.21 2-(2-Chloro-6-methylpyridin-4-yl)-5-nitrobenzaldehyde (7e)



7e

Compound **7e** was prepared according to procedure 9.2.4.1 from 793 mg 2-bromo-5-nitro-benzaldehyde (**5a**) (3.45 mmol, 1.0 eq), 874 mg 2-chloro-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**4e**) (3.45 mmol, 1.0 eq), 1.05 g CsF (6.91 mmol, 2.0 eq) and 141 mg $PdCl_2$(dppf)·DCM (0.17 mmol, 5 mol%) in 30 mL absolute, degassed 1,2-DME. The reaction was stirring overnight and product **7e** was isolated after flash column chromatography (143 g SiO_2, 28x4 cm, cyclohexane/EtOAc = 75/25, R_f = 0.30).

Yield: 683 mg (72%), pale yellow solid, $C_{13}H_9ClN_2O_3$ [276.68 g/mol].

* The catalyst was filtered off using a pad of Celite® or SiO_2 under inert conditions and eluted with MeOH. The hydrogenation catalyst was washed with H_2O and stored in a glass bottle covered with water.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.99 (s, 1 H; CHO), 8.86 (d, ^4J (H,H) = 2.0 Hz, 1 H; H^{Ar}), 8.51 (dd, ^3J (H,H) = 8.4 Hz, ^4J (H,H) = 2.2 Hz, 1 H; H^{Ar}), 7.62 (d, ^3J (H,H) = 8.4 Hz, 1 H; H^{Ar}), 7.21 (s, 1 H; H^{Py}), 7.10 (s, 1 H; H^{Py}), 2.64 (s, 3 H; CH_3) ppm.

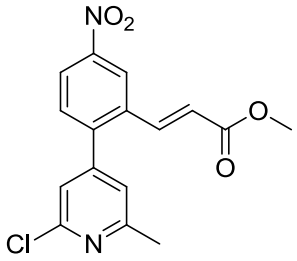
^{13}C NMR (76 MHz, $CDCl_3$): δ = 188.5 (CHO), 160.4 (C_q; C^{Py}), 151.6 (C_q; C^{Py}), 148.6 (C_q; C^{Ar}), 147.0 (C_q; C^{Py}), 146.7 (C_q; C^{Ar}), 134.6 (C_q; C^{Ar}), 131.9 (C^{Ar}), 128.0 (C^{Ar}), 123.8 (C^{Ar}), 122.6 (C^{Py}), 121.6 (C^{Py}), 24.5 (CH_3) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 7.71 min; *m/z* (%): 276 (100) [M^+], 260 (37) [M^+−O], 247 (17) [M^+−CHO], 241 (60) [M^+−Cl], 150 (7) [$C_7H_4NO_3^+$], 126 (23) [$C_6H_5ClN^+$].

m.p.$^{exp.}$ = 116-119°C.

HRMS (EI): calcd (*m*/*z*) for [M^+]: 276.0302; found: 276.0296.

9.2.4.22 (*E/Z*)-Methyl 3-(2-(2-chloro-6-methylpyridin-4-yl)-5-nitrophenyl)acrylate (16e)



16e

Compound **16e** was prepared according to procedure 9.2.4.2 from 602 mg 2-(2-chloro-6-methylpyridin-4-yl)-5-nitrobenzaldehyde (**7e**) (2.18 mmol, 1.0 eq) and 728 mg ylide **30** (2.18 mmol, 1.0 eq) in 30 mL absolute, degassed THF. Quantitative conversion was detected after less than 30 min and product **16e** was obtained as a mixture of *E*/*Z*-isomers (*E*/*Z* = 9/1) after flash column chromatography (43 g SiO_2, 29x2 cm, cyclohexane/EtOAc = 75/25, R_f = 0.35).*

Yield: 717 mg (99%), colorless solid, $C_{16}H_{13}ClN_2O_4$ [332.74 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.55 (d, ^4J (H,H) = 2.1 Hz, 1 H; H^{Ar}), 8.29 (dd, ^3J (H,H) = 8.5 Hz, ^4J (H,H) = 2.2 Hz, 1 H; H^{Ar}), 7.54 (d, ^3J (H,H) = 15.7 Hz, 1 H; CH), 7.50 (d,

* Only one isomer was detected by HRMS (EI). No molecular peak was observed for [M^+], but a fragment characteristic for isotopic distribution of [M^+−$C_2H_3O_2$] was found.

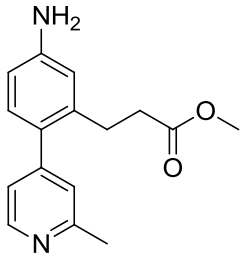
^{3}J (H,H) = 8.3 Hz, 1 H; H^{Ar}, overlapping), 7.12 (s, 1 H; H^{Py}), 7.02 (s, 1 H; H^{Py}), 6.57 (d, ^{3}J (H,H) = 15.9 Hz, 1 H; CH), 3.80 (s, 3 H; OCH_3), 2.62 (s, 3 H; CH_3) ppm.*

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 166.2 (C_q; $COOCH_3$), 160.2 (C_q; C^{Py}), 151.4 (C_q; C^{Py}), 149.0 (C_q; C^{Py}), 148.4 (C_q; C^{Ar}), 144.4 (C_q; C^{Ar}), 139.8 (CH), 134.4 (C_q; C^{Ar}), 131.3 (C^{Ar}), 124.4 (C^{Ar}), 123.2 (CH), 122.4 (C^{Ar}), 122.2 (C^{Py}), 121.5 (C^{Py}), 52.3 (OCH_3), 24.5 (CH_3) ppm.†

GC-MS (EI, 70 eV; MP_50_S): t_R(*E*) = 8.52 min; *m/z* (%): 332 (<1) [M^+], 301 (8) [M^+-CH_3O], 273 (100) [$M^+-C_2H_3O_2$], 227 (77) [$M^+-C_2H_3NO_4$], 177 (12) [$C_{13}H_7N^+$]; t_R(*Z*) = 8.24 min; *m/z* (%): 332 (10) [M^+], 317 (27) [M^+-CH_3], 301 (22) [M^+-CH_3O], 273 (100) [$M^+-C_2H_3O_2$], 227 (94) [$M^+-C_2H_3NO_4$], 177 (17) [$C_{13}H_7N^+$].

m.p.$^{exp.}$ = 176-179°C.

9.2.4.23 Methyl 3-(5-amino-2-(2-methylpyridin-4-yl)phenyl)propanoate (17e)



17e

Compound **17e** was prepared according to procedure 9.2.4.3 from 717 mg (*E*/*Z*)-methyl 3-(2-(2-chloro-6-methylpyridin-4-yl)-5-nitrophenyl)acrylate (**16e**) (2.15 mmol, 1.0 eq) and 72 mg $Pd(OH)_2$/C (10 wt%) in 60 mL absolute MeOH.‡ After 7.5 h the catalyst was filtered off and purification by flash column chromatography (42 g SiO_2, 23x2.5 cm, cyclohexane/EtOAc/NEt_3 = 2/8/0.1, R_f = 0.25), yielded compound **17e** as a pale yellow oil.§

Yield: 530 mg (91%), pale yellow oil, which become a solid upon standing, $C_{16}H_{18}N_2O_2$ [270.33 g/mol].

* In ^{1}H NMR no signals for the minor *Z*-isomer were observed.
† In ^{13}C NMR no signals for the minor *Z*-isomer were observed.
‡ Palladium hydroxide on activated charcoal, moistened with water, 15-20% Pd basis (based on dry substance), Fluka 76063.
§ The catalyst was filtered off using a pad of Celite® or SiO_2 under inert conditions and eluted with MeOH. The hydrogenation catalyst was washed with H_2O and stored in a glass bottle covered with water.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.48 (d, ^3J (H,H) = 5.1 Hz, 1 H; H^{Py}), 7.08 (s, 1 H; H^{Py}), 7.04 (dd, ^3J (H,H) = 5.1 Hz, ^4J (H,H) = 1.1 Hz, 1 H; H^{Py}), 6.97 (dd, ^3J (H,H) = 7.2 Hz, ^4J (H,H) = 1.5 Hz, 1 H; H^{Ar}), 6.60-6.57 (m, 2 H; H^{Ar}), 3.80 (bs, 2 H; NH_2), 3.61 (s, 3 H; OCH_3, overlapping), 2.87 (t, ^3J (H,H) = 8.0 Hz, 2 H; CH_2), 2.59 (s, 3 H; CH_3), 2.42 (t, ^3J (H,H) = 8.0 Hz, 2 H; CH_2) ppm.

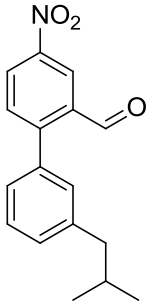
^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 173.2 (C_q; $COOCH_3$), 158.2 (C_q; C^{Py}), 150.3 (C_q; C^{Py}), 148.8 (C^{Py}), 146.9 (C_q; C^{Ar}), 138.8 (C_q; C^{Ar}), 131.1 (C^{Ar}), 129.7 (C_q; C^{Ar}), 124.3 (C^{Py}), 121.9 (C^{Py}), 115.6 (C^{Ar}), 113.4 (C^{Ar}), 51.7 (OCH_3), 35.3 (CH_2), 28.2 (CH_2), 24.5 (CH_3) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 8.01 min; *m/z* (%): 270 (100) [M^+], 255 (7) [M^+−CH_3], 239 (13) [M^+−CH_3O], 211 (67) [M^+−$C_2H_3O_2$], 196 (48) [M^+−$C_3H_6O_2$], 181 (15) [$C_{13}H_{11}N^+$].

m.p.$^{exp.}$ = 96-98°C.

HRMS (EI): calcd (*m/z*) for [M^+]: 270.1368; found: 270.1379.

9.2.4.24 3'-Isobutyl-4-nitro-[1,1'-biphenyl]-2-carbaldehyde (7f)



7f

Compound **7f** was prepared according to procedure 9.2.4.1 from 467 mg 2-bromo-5-nitro-benzaldehyde (**5a**) (2.03 mmol, 1.0 eq), 528 mg 2-(3-isobutylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**4f**) (2.03 mmol, 1.0 eq), 617 mg CsF (4.06 mmol, 2.0 eq) and 83 mg $PdCl_2$(dppf)·DCM (0.10 mmol, 5 mol%) in 10 mL absolute, degassed 1,2-DME. The reaction was stirred overnight (~13 h) and product **7f** was isolated after flash column chromatography (72 g SiO_2, 23x3 cm, cyclohexane/EtOAc = 92/8, R_f = 0.44).
Yield: 523 mg (91%), pale yellow, highly viscous oil, $C_{17}H_{17}NO_3$ [283.32 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.00 (s, 1 H; CHO), 8.84 (d, ^4J (H,H) = 2.4 Hz, 1 H; H^{Ar}), 8.46 (dd, ^3J (H,H) = 8.5 Hz, ^4J (H,H) = 2.5 Hz, 1 H; H^{Ar}), 7.67 (d, ^3J (H,H) = 8.5 Hz, 1 H; H^{Ar}), 7.45 (t, ^3J (H,H) = 7.6 Hz, 1 H; H^{Ar}), 7.31 (d, ^3J (H,H) = 7.8 Hz, 1 H; H^{Ar}),

7.25-7.21 (m, 1 H; H^{Ar}), 7.17 (s, 1 H; H^{Ar}), 2.57 (d, ^3J (H,H) = 7.2 Hz, 2 H; CH_2), 1.91 (m, 1 H; CH), 0.94 (d, ^3J (H,H) = 6.6 Hz, 6 H; CH_3) ppm.

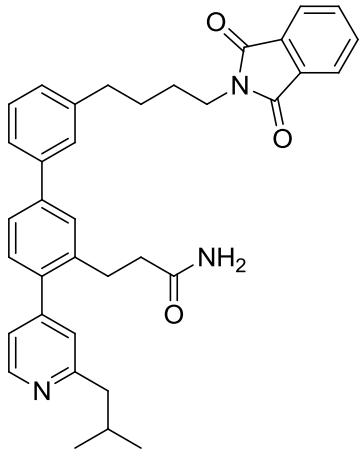
^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 190.3 (CHO), 151.6 (C_q; C^{Ar}), 147.5 (C_q; C^{Ar}), 142.8 (C_q; C_{Ar}), 135.5 (C_q; C^{Ar}), 134.6 (C_q; C^{Ar}), 132.3 (C^{Ar}), 130.8 (C^{Ar}), 130.4 (C^{Ar}), 128.9 (C^{Ar}), 127.4 (C^{Ar}), 127.4 (C^{Ar}), 123.1 (C^{Ar}), 45.4 (CH), 30.4 (CH_2), 22.5 (CH_3) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 7.58 min; *m/z* (%): 283 (19) [M^+], 268 (2) [M^+−CH_3], 240 (15) [M^+−C_3H_7], 226 (91) [M^+−C_4H_9], 180 (7) [$C_{13}H_8^+$], 165 (100) [$C_{12}H_7N^+$].

HRMS (EI): calcd (*m*/*z*) for [M^+]: 283.1208; found: 283.1228.

9.2.5 Synthesis of Teraryls

9.2.5.1 3-(3'-(4-(1,3-Dioxoisoindolin-2-yl)butyl)-4-(2-isobutylpyridine-4-yl)-[1,1'-biphenyl]-3-yl)propanamide (19a)



19a

A flame dried 50 mL Schlenk-flask was consecutively charged with 128 mg 3-(5-iodo-2-(2-isobutylpyridine-4-yl)phenyl)propanamide (**3a**) (0.31 mmol, 1.0 eq), 121 mg BF_3K-salt **40c** (0.31 mmol, 1.0 eq), 130 mg K_2CO_3 (0.94 mmol, 3.0 eq) and 2 mg $Pd(OAc)_2$ (9 µmol, 3 mol%). After drying and back-flushing with argon 15 mL absolute, degassed MeOH were added to form a pale yellow suspension. The reaction mixture was stirred for 4 h at 60°C and after quantitative conversion the reddish-brown suspension was filtered through a pad of Celite® and eluted with MeOH. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (30 g SiO_2, 24x2 cm, EtOAc/MeOH/ NEt_3 = 100/7/0.02, R_f = 0.23).

Yield: 155 mg (89%), colorless solid, $C_{36}H_{37}N_3O_3$ [559.70 g/mol].

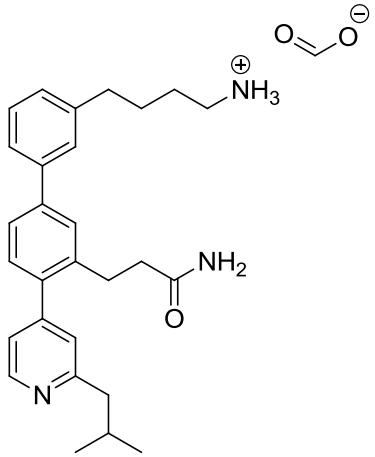
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.59 (d, ^3J (H,H) = 5.7 Hz, 1 H; H^{Py}), 7.84-7.81 (m, 2 H; H^{Phth}), 7.71-7.68 (m, 2 H; H^{Phth}), 7.56 (d, ^4J (H,H) = 1.4 Hz, 1 H; H^{Ar}), 7.50 (dd, ^3J (H,H) = 7.9 Hz, ^4J (H,H) = 1.7 Hz, 1 H; H^{Ar}), 7.43-7.41 (m, 2 H; H^{Ar}), 7.35 (t, ^3J (H,H) = 7.8 Hz, 1 H; H^{Ar}), 7.25 (d, ^3J (H,H) = 8.5 Hz, 1 H; H^{Ar}, overlapping), 7.18 (bd, ^3J (H,H) = 7.4 Hz, 1 H; H^{Ar}), 7.14 (bs, 1 H; H^{Py}), 7.14 (bd, ^3J (H,H) = 3.9 Hz, 1 H; H^{Py}, overlapping), 5.57 (bs, 1 H; $CONH_2$), 5.45 (bs, 1 H; $CONH_2$), 3.73 (t, ^3J (H,H) = 6.5 Hz, 2 H; CH_2^{Lys}), 3.03 (t, ^3J (H,H) = 8.0 Hz, 2 H; CH_2^{Gln}), 2.76-2.71 (m, 4 H; CH_2^{Leu}, CH_2^{Lys}), 2.41 (t, ^3J (H,H) = 8.0 Hz, 2 H; CH_2^{Gln}), 2.18-2.09 (m, 1 H; CH^{Leu}), 1.76-1.73 (m, 4 H; CH_2^{Lys}), 0.96 (d, ^3J (H,H) = 6.6 Hz, 6 H; CH_3^{Leu}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 174.1 (C_q; $CONH_2$), 168.6 (C_q; $C{=}O^{Phth}$), 161.6 (C_q; C^{Py}), 149.7 (C_q; C^{Py}), 149.1 (C^{Py}), 142.7 (C_q; C^{Ar}), 141.8 (C_q; C^{Ar}), 140.5 (C_q, C^{Ar}), 138.3 (C_q; C^{Ar}), 138.3 (C_q, C^{Ar}), 134.1 (C^{Phth}), 132.2 (C_q; C^{Phth}), 130.3 (C^{Ar}), 129.0 (C^{Ar}), 128.3 (C^{Ar}), 127.9 (C^{Ar}), 127.4 (C^{Ar}), 125.4 (C^{Ar}), 124.8 (C^{Ar}), 124.2 (C^{Py}), 123.3 (C^{Phth}), 121.7 (C^{Py}), 47.6 (CH_2^{Leu}), 37.9 (CH_2^{Lys}), 36.9 (CH_2^{Gln}), 35.5 (CH_2^{Lys}), 29.5 (CH^{Leu}), 28.7 (CH_2^{Lys}), 28.7 (CH_2^{Gln}), 28.3 (CH_2^{Lys}), 22.6 (CH_3^{Leu}) ppm.

m.p.$^{exp.}$ = 43-47°C.

HRMS (DI-EI): calcd (*m/z*) for [M^+]: 559.2835; found: 559.2861.

9.2.5.2 4-(3'-(3-Amino-3-oxopropyl)-4'-(2-isobutylpyridin-4-yl)-[1,1'-biphenyl]-3-yl)butan-1-ammonium formiate (1a)



1a

In an argon-flushed 100 mL Schlenk-flask 191 mg 3-(3'-(4-(1,3-dioxoisoindolin-2-yl)butyl)-4-(2-isobutylpyridine-4-yl)-[1,1'-biphenyl]-3-yl)propanamide (**19a**) (0.34 mmol, 1.0 eq) were

dissolved in 20 mL degassed MeOH. After addition of 166 µL $H_2NNH_2 \cdot H_2O$ (171 mg, 3.42 mmol, 10.0 eq), the pale yellow solution was stirred at room temperature until full conversion was monitored by TLC (~8 d). The colorless suspension was concentrated under reduced pressure and the crude product was purified by flash column chromatography (20 g SiO_2, 22x2 cm, MeOH/NEt_3 = 50/0.1, R_f = 0.08) to achieve compound **1a** as a pale yellow, highly viscous oil. After preparative HPLC* product **1a** was isolated as a colorless solid.
Yield: 119 mg (73%), colorless solid, $C_{29}H_{37}N_3O_3$ [475.62 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.52 (bs, 1 H; H^{Py}), 8.30 (bs, 1 H; $HCOO^-$), 7.56 (bs, 1 H; H^{Py}), 7.45-7.09 (m, 11 H; NH_3^+, H^{Ar}, H^{Py}), 6.67 (bs, 1 H; $CONH_2$), 6.50 (bs, 1 H; $CONH_2$), 2.90 (bs, 4 H; CH_2^{Lys}, CH_2^{Gln}), 2.68 (d, ^3J (H,H) = 6.9 Hz, 2 H; CH_2^{Leu}), 2.61 (bs, 2 H; CH_2^{Lys}), 2.35 (bs, 2 H; CH_2^{Gln}), 2.12-2.04 (m, 1 H; CH^{Leu}), 1.66 (bs, 4 H; CH_2^{Lys}), 0.93 (d, ^3J (H,H) = 6.5 Hz, 6 H; CH_3^{Leu}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 175.7 (C_q; $CONH_2$), 167.4 (C_q; $HCOO^-$), 161.3 (C_q; C^{Py}), 150.2 (C_q; C^{Py}),148.4 (C^{Py}), 142.2 (C_q; C^{Ar}), 141.5 (C_q; C^{Ar}), 140.5 (C_q; C^{Ar}), 138.4 (C_q; C^{Ar}), 138.1 (C_q; C^{Ar}), 130.2 (C^{Ar}), 129.1 (C^{Ar}), 128.3 (C^{Ar}), 128.0 (C^{Ar}), 127.3 (C^{Ar}), 125.2 (C^{Ar}), 124.9 (C^{Ar}), 124.5 (C^{Py}), 122.0 (C^{Py}), 47.1 (CH_2^{Leu}), 39.5 (CH_2^{Lys}), 36.7 (CH_2^{Gln}), 35.1 (CH_2^{Lys}), 29.5 (CH^{Leu}), 28.3 (CH_2^{Lys}), 28.0 (CH_2^{Gln}), 27.1 (CH_2^{Lys}), 22.6 (CH_3^{Leu}) ppm.

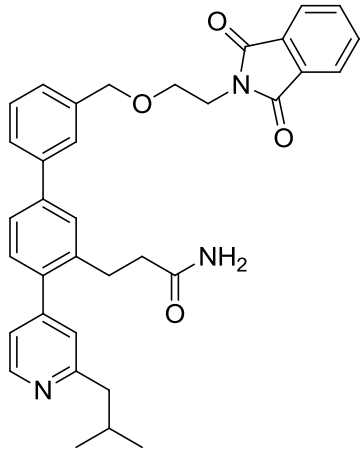
m.p.$^{exp.}$ = 35-38°C.

HPLC (Nucleodur, ESI^+): t_R = 10.81 min; *m/z*: 430 [M^++H], 452 [M^++Na]; λ_{max} = 250, 314 nm.

HRMS (DI-EI): calcd (*m/z*) for [M^+]: 429.2780; found: 429.2819.†

* MeOH/water gradient with 1.0% (v/v) HCOOH at a flow rate of 17.0 mL/min: 0.0 min: 30% MeOH const., 0.0-4.0 min: 37% MeOH lin. gradient, 4.0-8.0 min.: 37% MeOH const., 8.0-8.5 min: 70% MeOH lin. gradient, 8.5-11.0 min: 70% MeOH const., 11.0-11.5 min: 30% MeOH lin. gradient, 11.5-15.0 min: 30% MeOH const.
† HRMS (DI-EI) spectrum also showed degradation fragments because of decomposition during heating process.

9.2.5.3 3-(3'-((2-(1,3-Dioxoisoindolin-2-yl)ethoxy)methyl)-4-(2-isobutylpyridine-4-yl)-[1,1'-biphenyl]-3-yl)propanamide (19b)



19b

Compound **19b** was prepared according to procedure 9.2.4.1 from 216 mg 3-(5-iodo-2-(2-isobutylpyridine-4-yl)phenyl)propanamide (**3a**) (0.53 mmol, 1.0 eq), 237 mg pinacol ester **2b** (0.58 mmol, 1.1 eq), 161 mg CsF (1.06 mmol, 2.0 eq) and 13 mg $PdCl_2$(dppf)·DCM (16 µmol, 3 mol%) in 35 mL absolute, degassed 1,2-DME. The reaction was stirred for 1.5 h at 80°C and product **19b** was isolated after flash column chromatography (23 g SiO_2, 16x2 cm, EtOAc/MeOH/NEt_3 = 500/35/0.75, R_f = 0.17).[19a]

Yield: 262 mg (88%), colorless solid, $C_{35}H_{35}N_3O_4$ [561.67 g/mol].

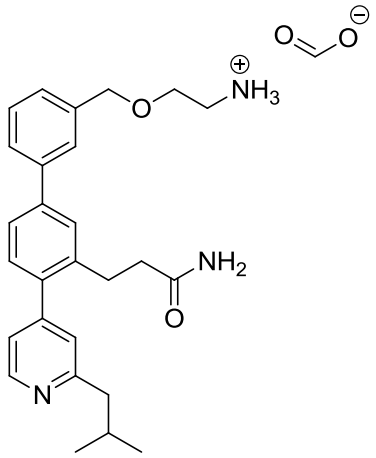
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.69 (d, ^3J (H,H) = 4.9 Hz, 1 H; H^{Py}), 7.94-7.88 (m, 2 H; H^{Phth}), 7.8-7.78 (m, 2 H; H^{Phth}), 7.56 (dd, ^3J (H,H) = 5.8 Hz, ^4J (H,H) = 3.1 Hz, 1 H; H^{Py}), 7.47 (bs, 1 H; H^{Py}), 7.43-7.24 (m, 7 H; H^{Ar}, overlapping), 5.95 (bs, 1 H, $CONH_2$), 5.62 (bs, 1 H, $CONH_2$), 4.55 (s, 2 H; CH_2^{Lys}), 3.99 (t, ^3J (H,H) = 5.8 Hz, 2 H; CH_2^{Lys}), 3.79 (t, ^3J (H,H) = 5.8 Hz, 2 H; CH_2^{Lys}), 3.10 (t, ^3J (H,H) = 7.8 Hz, 2 H; CH_2^{Gln}), 2.82 (d, ^3J (H,H) = 7.2 Hz, 2 H; CH_2^{Leu}), 2.55 (t, ^3J (H,H) = 7.8 Hz, 2 H; CH_2^{Gln}), 2.32-2.18 (m, 1 H; CH^{Leu}), 1.07 (d, ^3J (H,H) = 6.6 Hz, 6 H; CH_3^{Leu}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 174.2 (C_q; $CONH_2$), 168.5 (C_q; $C{=}O^{Phth}$), 161.6 (C_q; C^{Py}), 149.6 (C_q; C^{Py}), 149.1 (C^{Py}), 141.5 (C_q; C^{Ar}), 141.1 (C_q; C^{Ar}), 138.3 (C_q; C^{Ar}), 137.6 (C_q; C^{Ar}), 134.9 (C_q; C^{Ar}), 134.2 (C^{Phth}), 132.1 (C_q; C^{Phth}), 130.2 (C^{Ar}), 130.1 (C^{Ar}), 129.8 (C^{Ar}), 129.7 (C^{Ar}), 128.1 (C^{Ar}), 127.7 (C^{Ar}), 127.4 (C^{Ar}), 124.3 (C^{Py}), 123.4 (C^{Phth}), 121.8 (C^{Py}), 71.0 (CH_2^{Lys}), 66.9 (CH_2^{Lys}), 47.6 (CH_2^{Leu}), 37.8 (CH_2^{Lys}), 36.6 (CH_2^{Gln}), 29.5 (CH^{Leu}), 28.5 (CH_2^{Gln}), 22.6 (CH_3^{Leu}) ppm.

m.p.$^{exp.}$ = 157-158°C.

HRMS (DI-EI): calcd (*m*/*z*) for [M^+]: 561.2628; found: 561.2637.

9.2.5.4 2-((3'-(3-Amino-3-oxopropyl)-4'-(2-isobutylpyridin-4-yl)-[1,1'-biphenyl]-3-yl)methoxy)ethanammonium formiate (1b)



1b

In an argon-flushed 100 mL Schlenk-flask 268 mg 3-(3'-((2-(1,3-dioxoisoindolin-2-yl)-ethoxy)methyl)-4-(2-isobutylpyridine-4-yl)-[1,1'-biphenyl]-3-yl)propanamide (**19b**) (0.48 mmol, 1.0 eq) were dissolved in 70 mL degassed MeOH. After addition of 232 µL $H_2NNH_2 \cdot H_2O$ (239 mg, 4.77 mmol, 10.0 eq), the pale yellow solution was stirred at room temperature until full conversion was monitored by TLC (~6 d). The colorless suspension was concentrated under reduced pressure and the crude product was purified by flash column chromatography (35 g SiO_2, 26x2 cm, MeOH/NEt_3 = 50/0.1, R_f = 0.14) to achieve compound **1b** as a pale yellow, highly viscous oil. After preparative HPLC* product **1b** was isolated as a colorless solid.[19a]

Yield: 174 mg (76%), colorless solid, $C_{28}H_{35}N_3O_4$ [477.60 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.73 (bs, 3 H; NH_3^+), 8.64 (d, ^3J (H,H) = 5.1 Hz, 1 H; H^{Py}), 8.31 (bs, 1 H; $HCOO^-$), 7.47-7.22 (m, 9 H; H^{Ar}, H^{Py}, overlapping), 7.01 (bs, 1 H; $CONH_2$), 6.53 (bs, 1 H; $CONH_2$), 4.51 (s, 2 H; CH_2^{Lys}), 3.65 (bs, 2 H; CH_2^{Lys}), 3.07 (bs, 2 H; CH_2^{Lys}), 2.95 (bs, 2 H; CH_2^{Gln}), 2.77 (d, ^3J (H,H) = 7.1 Hz, 2 H; CH_2^{Leu}), 2.31 (bs, 2 H; CH_2^{Gln}), 2.24-2.10 (m, 1 H; CH^{Leu}), 1.00 (d, ^3J (H,H) = 6.6 Hz, 6 H; CH_3^{Leu}) ppm.

* MeOH/water gradient with 1.0% (v/v) HCOOH at a flow rate of 17.0 mL/min: 0.0 min: 29% MeOH const., 0.0-4.0 min: 36% MeOH lin. gradient, 4.0-8.0 min.: 36% MeOH const., 8.0-8.5 min: 70% MeOH lin. gradient, 8.5-11.0 min: 70% MeOH const., 11.0-11.5 min: 29% MeOH lin. gradient, 11.5-15.0 min: 29% MeOH const.

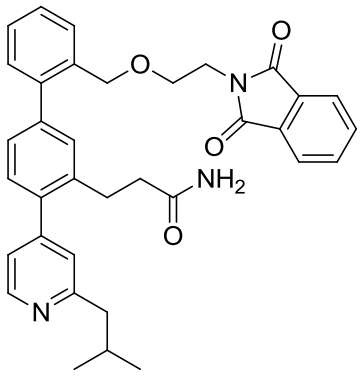
^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 175.8 (C_q; $CONH_2$), 167.5 (C_q; $HCOO^-$), 161.4 (C_q; C^{Py}), 150.2 (C_q; C^{Py}), 148.6 (C^{Py}), 141.6 (C_q; C^{Ar}), 141.0 (C_q; C^{Ar}), 138.2 (C_q; C^{Ar}), 137.6 (C_q; C^{Ar}), 134.4 (C_q; C^{Ar}), 130.8 (C^{Ar}), 130.3 (C^{Ar}), 130.1 (C^{Ar}), 129.9 (C^{Ar}), 128.4 (C^{Ar}), 127.8 (C^{Ar}), 127.4 (C^{Ar}), 124.5 (C^{Py}), 122.0 (C^{Py}), 71.3 (CH_2^{Lys}), 65.9 (CH_2^{Lys}), 47.1 (CH_2^{Leu}), 39.5 (CH_2^{Lys}), 36.5 (CH_2^{Gln}), 29.5 (CH^{Leu}), 28.3 (CH_2^{Gln}), 22.6 (CH_3^{Leu}) ppm.

m.p.$^{exp.}$ = 41-44°C.

HPLC (Nucleodur, ESI^+): t_R = 6.59 min; *m/z*: 432 [M^++H], 454 [M^++Na]; λ_{max} = 238, 274, 298 nm.

HRMS (DI-EI): calcd (*m/z*) for [M^+−H] 430.2495; found 430.2498.

9.2.5.5 3-(2'-((2-(1,3-Dioxoisoindolin-2-yl)ethoxy)methyl)-4-(2-isobutylpyridine-4-yl)-[1,1'-biphenyl]-3-yl)propanamide (19c)



19c

Compound **19c** was prepared according to procedure 9.2.4.1 from 145 mg 3-(5-iodo-2-(2-isobutylpyridine-4-yl)phenyl)propanamide (**3a**) (0.36 mmol, 1.0 eq), 173 mg pinacol ester **2c** (0.42 mmol, 1.2 eq), 108 mg CsF (0.71 mmol, 2.0 eq) and 9 mg $PdCl_2$(dppf)·DCM (11 µmol, 3 mol%) in 20 mL absolute, degassed 1,2-DME. The reaction was stirred for 3.5 h at 80°C and product **19c** was isolated after flash column chromatography (24 g SiO_2, 17x2 cm, EtOAc/MeOH/NEt_3 = 50/5/0.05, R_f = 0.29).

Yield: 197 mg (98%), colorless solid, $C_{35}H_{35}N_3O_4$ [561.67 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.69 (d, ^3J (H,H) = 5.4 Hz, 1 H; H^{Py}), 7.92-7.88 (m, 2 H; H^{Phth}), 7.82-7.78 (m, 2 H; H^{Phth}), 7.56 (dd, ^3J (H,H) = 5.7 Hz, ^4J (H,H) = 3.1 Hz, 1 H; H^{Py}), 7.47 (bs, 1 H; H^{Py}), 7.42-7.30 (m, 4 H; H^{Ar}), 7.26-7.24 (m, 3 H; H^{Ar}, overlapping), 5.94 (bs, 1 H; $CONH_2$), 5.57 (bs, 1 H; $CONH_2$), 4.55 (s, 2 H; CH_2^{Lys}), 3.98 (t, ^3J (H,H) = 5.8 Hz, 2 H;

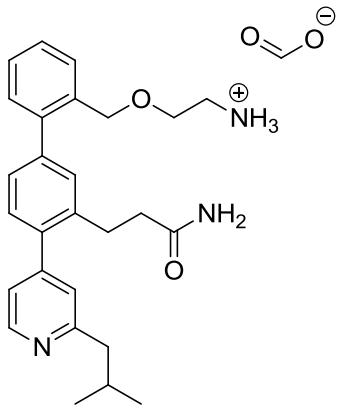
CH_2^{Lys}), 3.79 (t, ^3J (H,H) = 5.8 Hz, 2 H; CH_2^{Lys}), 3.10 (t, ^3J (H,H) = 7.8 Hz, 2 H; CH_2^{Gln}), 2.82 (d, ^3J (H,H) = 7.2 Hz, 2 H; CH_2^{Leu}), 2.55 (t, ^3J (H,H) = 7.8 Hz, 2 H; CH_2^{Gln}), 2.32-2.18 (m, 1 H; CH^{Leu}), 1.07 (d, ^3J (H,H) = 6.6 Hz, 6 H; CH_3^{Leu}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 174.2 (C_q; $CONH_2$), 168.5 (C_q; $C{=}O^{Phth}$), 161.6 (C_q; C^{Py}), 149.6 (C_q; C^{Py}), 149.1 (C^{Py}), 141.5 (C_q; C^{Ar}), 141.1 (C_q; C^{Ar}), 138.3 (C_q; C^{Ar}), 137.6 (C_q; C^{Ar}), 134.9 (C_q; C^{Ar}), 134.2 (C^{Phth}), 132.1 (C_q; C^{Phth}), 130.2 (C^{Ar}), 130.1 (C^{Ar}), 129.8 (C^{Ar}), 129.7 (C^{Ar}), 128.1 (C^{Ar}), 127.8 (C^{Ar}), 127.4 (C^{Ar}), 124.3 (C^{Py}), 123.4 (C^{Phth}), 121.8 (C^{Py}), 71.0 (CH_2^{Lys}), 66.9 (CH_2^{Lys}), 47.7 (CH_2^{Leu}), 37.8 (CH_2^{Lys}), 36.7 (CH_2^{Gln}), 29.5 (CH^{Leu}), 28.5 (CH_2^{Gln}), 22.6 (CH_3^{Leu}) ppm.

m.p.$^{exp.}$ = 151-152°C.

HRMS (DI-EI): calcd (*m*/*z*) for [M^+]: 561.2628; found: 561.2626.*

9.2.5.6 2-((3'-(3-Amino-3-oxopropyl)-4'-(2-isobutylpyridin-4-yl)-[1,1'-biphenyl]-2-yl)methoxy)ethanammonium formiate (1c)



1c

In an argon-flushed 100 mL Schlenk-flask 181 mg 3-(2'-((2-(1,3-dioxoisoindolin-2-yl)-ethoxy)methyl)-4-(2-isobutylpyridine-4-yl)-[1,1'-biphenyl]-3-yl)propanamide (**19c**) (0.32 mmol, 1.0 eq) were dissolved in 35 mL degassed MeOH. After addition of 157 µL $H_2NNH_2{\cdot}H_2O$ (162 mg, 3.24 mmol, 10.0 eq), the pale yellow solution was stirred until full conversion was monitored by TLC (~3 d). The colorless suspension was concentrated under reduced pressure and the crude product was purified by flash column chromatography (23 g SiO_2, 16x2 cm, MeOH/NEt_3 = 50/0.1, R_f = 0.14) to achieve compound **1c** as a pale

* The [M^+] signal was very weak, therefore the experimental isotope pattern does not match exactly to the theoretical one.

yellow, highly viscous oil. After preparative HPLC* product **1c** was isolated as a colorless solid.

Yield: 118 mg (77%), colorless solid, $C_{28}H_{35}N_3O_4$ [477.60 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.77 (bs, 3 H; NH_3^+), 8.66 (d, ^3J (H,H) = 3.9 Hz, 1 H; H^{Py}), 8.25 (bs, 1 H; $HCOO^-$), 7.47-7.26 (m, 9 H; H^{Ar}, H^{Py}, overlapping), 6.96 (bs, 1 H; $CONH_2$), 6.41 (bs, 1 H; $CONH_2$), 4.50 (s, 2 H; CH_2^{Lys}), 3.66 (bs, 2 H; CH_2^{Lys}), 3.09 (bs, 2 H; CH_2^{Lys}), 2.95 (bs, 2 H; CH_2^{Gln}), 2.78 (d, ^3J (H,H) = 7.1 Hz, 2 H; CH_2^{Leu}), 2.32 (bs, 2 H; CH_2^{Gln}), 2.21-2.08 (m, 1 H; CH^{Leu}), 0.99 (d, ^3J (H,H) = 6.6 Hz, 6 H; CH_3^{Leu}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 175.9 (C_q; $CONH_2$), 166.8 (C_q; $HCOO^-$), 161.0 (C_q; C^{Py}), 150.9 (C_q; C^{Py}), 147.9 (C^{Py}), 141.7 (C_q; C^{Ar}), 141.2 (C_q; C^{Ar}), 138.0 (C_q; C^{Ar}), 137.6 (C_q; C^{Ar}), 134.3 (C_q; C^{Ar}), 130.9 (C^{Ar}), 130.4 (C^{Ar}), 130.3 (C^{Ar}), 129.9 (C^{Ar}), 128.6 (C^{Ar}), 127.8 (C^{Ar}), 127.6 (C^{Ar}), 124.8 (C^{Py}), 122.3 (C^{Py}), 71.5 (CH_2^{Lys}), 65.7 (CH_2^{Lys}), 46.6 (CH_2^{Leu}), 39.6 (CH_2^{Lys}), 36.6 (CH_2^{Gln}), 29.6 (CH^{Leu}), 28.3 (CH_2^{Gln}), 22.5 (CH_3^{Leu}) ppm.

m.p.$^{exp.}$ = 77-79°C.

HPLC (Nucleodur, ESI^+): t_R = 6.63 min; *m/z*: 432 [M^++H], 454 [M^++Na]; λ_{max} = 234, 274, 298 nm.

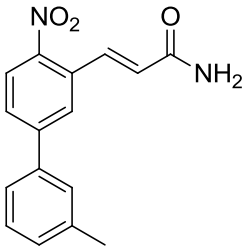
HRMS (DI-EI): calcd (*m/z*) for [M^+−H]: 430.2495; found: 430.2493.

* MeOH/water gradient with 1.0% (v/v) HCOOH at a flow rate of 17.0 mL/min: 0.0 min: 29% MeOH const., 0.0-4.0 min: 36% MeOH lin. gradient, 4.0-8.0 min.: 36% MeOH const., 8.0-8.5 min: 70% MeOH lin. gradient, 8.5-11.0 min: 70% MeOH const., 11.0-11.5 min: 29% MeOH lin. gradient, 11.5-15.0 min: 29% MeOH const.

9.3 Synthesis of Terphenyls using the Diazonium Approach

9.3.1 Synthesis of the Diazonium-Based Building Blocks

9.3.1.1 (*E*)-3-(3'-Methyl-4-nitro-[1,1'-biphenyl]-3-yl)acrylamide (34a)



34a

Compound **34a** was prepared according to procedure 9.2.4.1 from 333 mg (*E*)-3-(5-bromo-2-nitrophenyl)acrylamide (**32b**) (preparation see page 166) (1.23 mmol, 1.0 eq), 200 mg *m*-tolylboronic acid (1.47 mmol, 1.2 eq), 373 mg CsF (2.46 mmol, 2.0 eq) and 30 mg $PdCl_2$(dppf)·DCM (37 µmol, 3 mol%) in 13 mL absolute, degassed 1,2-DME. After full conversion (~1 h), product **34a** was purified by flash column chromatography (68 g SiO_2, 24x3 cm, cyclohexane/EtOAc = 3/7, R_f = 0.33).*

Yield: 343 mg (99%), pale yellow solid, $C_{16}H_{14}N_2O_3$ [282.29 g/mol].

^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.13 (d, ^3J (H,H) = 8.5 Hz, 1 H; H^{Ar}), 7.97 (s, 1 H; H^{Ar}), 7.88 (d, ^3J (H,H) = 8.4 Hz, 1 H; H^{Ar}), 7.77 (d, ^3J (H,H) = 15.6 Hz, 1 H; CH), 7.64-7.58 (m, 3 H; H^{Ar}, $CONH_2$), 7.42 (t, ^3J (H,H) = 7.5 Hz, 1 H; H^{Ar}), 7.32-7.28 (m, 2 H; H^{Ar}, $CONH_2$), 6.76 (d, ^3J (H,H) = 15.6 Hz, 1 H; CH), 2.40 (s, 3 H; CH_3) ppm.

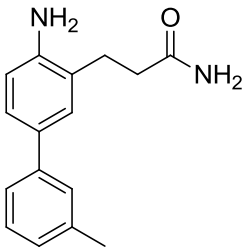
^{13}C NMR (76 MHz, [D$_6$]DMSO, APT): δ = 165.9 (C_q; $CONH_2$), 146.9 (C_q; C^{Ar}), 145.4 (C_q; C^{Ar}), 138.5 (C_q; C^{Ar}), 137.5 (C_q; C^{Ar}), 134.3 (CH), 131.1 (C_q; C^{Ar}), 129.7 (C^{Ar}), 129.1 (C^{Ar}), 128.0 (C^{Ar}), 127.8 (C^{Ar}), 127.6 (C^{Ar}), 126.7 (C^{Ar}), 125.5 (C^{Ar}), 124.4 (CH), 21.0 (CH_3) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 9.22 min; *m/z* (%): 282 (1) [M^+], 266 (<1) [M^+−H_2N], 250 (1) [M^+−H_2NO], 236 (100) [M^+−NO_2], 210 (21) [$C_{13}H_8NO_2^+$], 166 (20) [$C_{13}H_{10}^+$], 151 (7) [$C_{12}H_7^+$].

m.p.$^{exp.}$ = 158-162°C.

* No molecular peak was detected by HRMS (EI) for [M^+], but a fragment characteristic for isotopic distribution of [M^+−NO_2] was found.

9.3.1.2 3-(4-Amino-3'-methyl-[1,1'-biphenyl]-3-yl)propanamide (35a)



35a

Compound **35a** was prepared according to procedure 9.2.4.3 from 625 mg (*E*)-3-(3'-methyl-4-nitro-[1,1'-biphenyl]-3-yl)acrylamide (**34a**) (2.21 mmol, 1.0 eq) and 63 mg $Pd(OH)_2/C$ (10 wt%) in 40 mL absolute MeOH.* After stirring overnight at room temperature, the catalyst was filtered off and purification by flash column chromatography (58 mg SiO_2, 20x3 cm, EtOAc/MeOH = 9/1, R_f = 0.32) to achieve compound **35a** as a pale yellow oil.†,‡

Yield: 561 mg (quant.), pale yellow, highly viscous oil, $C_{16}H_{18}N_2O$ [254.33 g/mol].

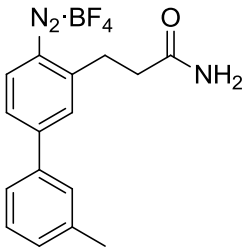
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34-7.26 (m, 5 H; H^{Ar}, overlapping), 7.09 (d, ^3J (H,H) = 7.0 Hz, 1 H; H^{Ar}), 6.73 (d, ^3J (H,H) = 8.1 Hz, 1 H; H^{Ar}), 5.47 (bs, 2 H; $CONH_2$), 3.99 (bs, 2 H; NH_2), 2.93 (t, ^3J (H,H) = 7.2 Hz, 2 H; CH_2), 2.60 (t, ^3J (H,H) = 7.1 Hz, 2 H; CH_2), 2.40 (s, 3 H; CH_3) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 175.1 (C_q; $CONH_2$), 144.1 (C_q; C^{Ar}), 141.2 (C_q; C^{Ar}), 138.3 (C_q; C^{Ar}), 132.0 (C_q; C^{Ar}), 128.7 (C^{Ar}), 128.6 (C^{Ar}), 127.3 (C^{Ar}), 127.2 (C^{Ar}), 126.3 (C^{Ar}), 125.6 (C_q; C^{Ar}), 123.6 (C^{Ar}), 116.5 (C^{Ar}), 35.6 (CH_2), 26.6 (CH_2), 21.7 (CH_3) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 8.77 min; *m/z* (%): 254 (75) [M^+], 238 (18) [M^+-H_2N], 237 (100) [M^+-H_3N], 223 (<1) [M^+-CH_5N], 210 (17) [M^+-CH_2NO], 196 (77) [$M^+-C_2H_4NO$], 182 (15) [$C_{13}H_{12}N^+$], 165 (30) [$C_{13}H_9^+$], 91 (15) [$C_7H_7^+$].

* Palladium hydroxide on activated charcoal, moistened with water, 15-20% Pd basis (based on dry substance), Fluka 76063.
† The catalyst was filtered off using a pad of Celite® or SiO_2 under inert conditions and eluted with MeOH. The hydrogenation catalyst was washed with H_2O and stored in a glass bottle covered with water.
‡ HRMS (DI-EI) gave no unambiguous results because of decomposition during heating process.

9.3.1.3 3-(3-Amino-3-oxopropyl)-3'-methyl-[1,1'-biphenyl]-4-diazonium tetrafluoroborate (36a)



36a

In a flame dried 100 mL two-neck round-bottom flask with argon-inlet 549 mg 3-(4-amino-3'-methyl-[1,1'-biphenyl]-3-yl)propanamide (**35a**) (2.16 mmol, 1.0 eq) were dissolved in 30 mL absolute, degassed THF. After cooling to -45°C, 325 µL boron trifluoride ethyl etherate ($BF_3 \cdot Et_2O$) (374 mg, 2.64 mmol, 1.2 eq) were added to the pale yellow solution followed by addition of 576 µL *tert*-butyl nitrite (*t*BuONO) (90%, pure) (446 mg, 4.32 mmol, 2.0 eq). The orange-red suspension was stirred at -25°C for 15 min and after warming to -5°C for additional 2 h. The reaction mixture was concentrated at -5°C to half of its volume (~15 mL) and the formed orange precipitate was collected by filtration and after drying, air stable compound **36a** was isolated.*

Yield: 535 mg (70%), orange solid, $C_{16}H_{16}BF_4N_3O$ [353.12 g/mol].

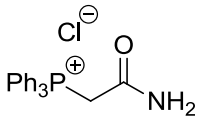
^{1}H NMR (300 MHz, $[D_4]CD_3OD$): δ = 7.68-7.20 (m, 7 H; H^{Ar}), 3.00 (t, ^3J (H,H) = 6.2 Hz, 2 H; CH_2), 2.80 (t, ^3J (H,H) = 6.1 Hz, 2 H; CH_2), 2.41 (s, 3 H; CH_3) ppm.

^{13}C NMR (76 MHz, $[D_4]CD_3OD$): δ = 178.1 (C_q; $CONH_2$), 144.1 (C_q; C^{Ar}), 140.7 (C_q; C^{Ar}), 139.9 (C_q; C^{Ar}), 137.4 (C_q; C^{Ar}), 130.9 (C^{Ar}), 130.0 (C^{Ar}), 129.8 (C^{Ar}), 129.5 (C_q; C^{Ar}), 128.7 (C^{Ar}), 127.7 (C^{Ar}), 125.2 (C^{Ar}), 124.8 (C^{Ar}), 37.1 (CH_2), 25.6 (CH_2), 21.5 (CH_3) ppm.

m.p.$^{exp.}$ = 144-148°C (spontaneous decomposition).

* HRMS (DI-EI) gave no unambiguous results because of decomposition during heating process.

9.3.1.4 (2-Amino-2-oxoethyl)triphenylphosphonium chloride (33)



33

In a flame dried 50 mL two-neck round-bottom flask with reflux condenser and argon-inlet 7.86 g PPh_3 (29.97 mmol, 1.05 eq) and 2.67 g 2-chloroacetamide (28.55 mmol, 1.0 eq) were dried in vacuo. The dried starting materials were suspended in 33 mL freshly distilled nitromethane and the mixture was stirred for 19 h at 105°C. The pale yellow solution was allowed to cool to room temperature and the formed colorless precipitate was isolated by filtration, washed with EtOAc (2x10 mL), Et_2O (1x15 mL) and dried in vacuo.[67]
Yield: 9.93 g (98%), colorless powder, $C_{20}H_{19}ClNOP$ [355.80 g/mol].

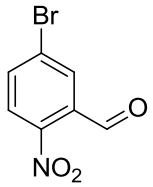
^{1}H NMR (300 MHz, [D_6]DMSO): δ = 8.43 (bs, 1 H; $CONH_2$), 7.90-7.71 (m, 15 H; H^{Ar}), 7.62 (bs, 1 H; $CONH_2$), 5.13 (d, ^2J (H,P) = 14.9 Hz, 2 H; CH_2) ppm.

^{13}C NMR (76 MHz, [D_6]DMSO): δ = 165.0 (d, ^2J (C,P) = 5 Hz, C_q; $CONH_2$), 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_q; C^{Ar}), 31.2 (d, ^1J (C,P) = 58 Hz, CH_2) ppm.

m.p.$^{exp.}$ = 215-218°C (m.p.$^{lit.}$ = 227-229°C).[108]

Analytical data are in accordance with those reported.[67]

9.3.1.5 5-Bromo-2-nitrobenzaldehyde (5b)



5b

At 0°C 5 mL HNO_3 (60-70% solution in H_2O) and 10 mL H_2SO_4 (96% solution in H_2O) were mixed in a 100 mL round-bottom flask and 4.12 g 3-bromobenzaldehyde (**6b**) (22.27 mmol, 1.0 eq) were added in small portions. During the addition a yellow/orange precipitate was formed and after 30 min at 0°C, the suspension was stirred for 45 min at room temperature. The mixture was poured into 60 mL ice cold saturated $NaHCO_3$ solution and extracted with

EtOAc (3x25 mL). The combined yellow organic layers were washed with saturated $NaHCO_3$ solution until the pH of the aqueous phase was ~8-9 and dried over Na_2SO_4. After filtration and evaporation of the solvent, the dark-orange crude product was purified by flash column chromatography (230 g SiO_2, 31x4.5 cm, cyclohexane/EtOAc = 9/1, R_f = 0.31).[64a]
Yield: 4.26 g (83%), pale yellow solid, $C_7H_4BrNO_3$ [230.02 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.41 (s, 1 H; CHO), 8.06 (d, ^4J (H,H) = 2.2 Hz, 1 H; H^{Ar}), 8.03 (d, ^3J (H,H) = 8.6 Hz, 1 H; H^{Ar}), 7.88 (dd, ^3J (H,H) = 8.6 Hz, ^4J (H,H) = 2.2 Hz, 1 H; H^{Ar}) ppm.

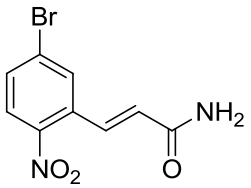
^{13}C NMR (76 MHz, $CDCl_3$): δ = 186.9 (CHO), 148.2 (C_q; C^{Ar}), 136.6 (C^{Ar}), 132.8 (C^{Ar}), 132.7 (C_q; C^{Ar}), 129.7 (C_q; C^{Ar}), 126.3 (C^{Ar}) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 5.41 min; *m/z* (%): 231 (1) [M^+], 229 (1) [M^+], 201 (67) [M^+-O_2], 199 (68) [M^+-O_2], 184 (23) [M^+-HNO_2], 182 (23) [M^+-HNO_2], 173 (96) [$C_5H_2BrNO^+$], 171 (100) [$C_5H_2BrNO^+$].

m.p.$^{exp.}$ = 62-66°C (m.p.$^{lit.}$ = 63-66°C).[64a]

Analytical data are in accordance with those reported.[64b]

9.3.1.6 (*E*)-3-(5-Bromo-2-nitrophenyl)acrylamide (32b)



32b

In a flame dried 100 mL two-neck round-bottom flask with argon-inlet 1.66 g (2-amino-2-oxoethyl)triphenylphosphonium chloride (**33**) (4.67 mmol, 1.05 eq) and 524 mg KO*t*Bu (4.67 mmol, 1.05 eq) were suspended under ice/NaCl cooling in 40 mL absolute, degassed MeOH. After 20 min 1.02 g 5-bromo-2-nitrobenzaldehyde (**5b**) (4.43 mmol, 1.0 eq) were added in one portion and after 45 min stirring at -2°C the mixture was concentrated to dryness without further workup. The salmon-colored crude product was recrystallized from 190 mL

MeOH/EtOAc (70/25) and after hot filtration the formed pale yellow crystals were isolated by filtration.*

Yield: 1.08 g (90%), pale yellow fine crystals/wool, $C_9H_7BrN_2O_3$ [271.07 g/mol].

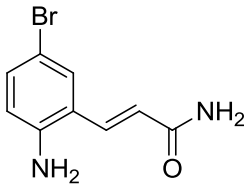
^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.00 (d, ^3J (H,H) = 8.7 Hz, 1 H; H^{Ar}), 7.97 (d, ^4J (H,H) = 2.0 Hz, 1 H; H^{Ar}), 7.84 (dd, ^3J (H,H) = 8.7 Hz, ^4J (H,H) = 2.1 Hz, 1 H; H^{Ar}), 7.63 (d, ^3J (H,H) = 15.6 Hz, 1 H; CH), 7.61 (bs, 1 H; $CONH_2$, overlapping), 7.35 (bs, 1 H; $CONH_2$), 6.66 (d, ^3J (H,H) = 15.6 Hz, 1 H; CH) ppm.

^{13}C NMR (76 MHz, [D$_6$]DMSO, APT): δ = 165.5 (C_q; $CONH_2$), 147.1 (C_q; C^{Ar}), 133.0 (CH), 132.8 (C^{Ar}), 132.4 (C_q; C^{Ar}), 131.3 (C^{Ar}), 128.5 (CH), 127.4 (C_q; C^{Ar}), 126.7 (C^{Ar}) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 7.35 min, *m/z* (%): 226 (100) [M^+−H_2NO_2], 224 (94) [M^+−H_2NO_2], 145 (19) [M^+−$BrNO_2$].

m.p.$^{exp.}$ = 242-248°C (decomposition).

9.3.1.7 (*E*)-3-(2-Amino-5-bromophenyl)acrylamide (37)



37

In a flame dried 250 mL two-neck round-bottom flask with argon-inlet 3.74 g (*E*)-3-(5-bromo-2-nitrophenyl)acrylamide (**32b**) (13.78 mmol, 1.0 eq) and 3.27 g tin powder (325 mesh) (27.55 mmol, 2.0 eq) were dried in vacuo. After back-flushing with argon, 100 mL degassed acetic acid (96% in water) were added and the deep-greyish suspension was stirred under exclusion of light at room temperature until full conversion (~2d) was detected by GC-MS (mini-workup: saturated NaOH/EtOAc/$MgSO_4$). During the reaction a color change from grey over green to yellow was observed. After quantitative conversion the reaction mixture was concentrated under reduced pressure to a half and the pale yellow suspension was quenched with saturated NaOH solution. After heating to 55°C the aqueous phase was filtered and the warm aqueous phase was extracted with EtOAc (4x50 mL). The

* Only the *E*-isomer crystallized under chosen conditions.

combined organic layers were dried over Na_2SO_4, filtered and after removing the solvent under reduced pressure, compound **37** was isolated as a yellow powder.
Yield: 3.32 g (quant.), bright-yellow solid, $C_9H_9BrN_2O$ [241.08 g/mol].

TLC: R_f = 0.20 (EtOAc, tailing).

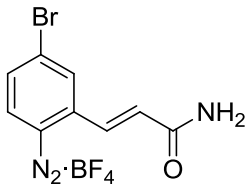
^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.51 (d, ^3J (H,H) = 15.7 Hz, 1 H; CH), 7.40 (bs, 1 H; $CONH_2$, overlapping), 7.39 (d, ^4J (H,H) = 2.3 Hz, 1 H; H^{Ar}), 7.15 (dd, ^3J (H,H) = 8.7 Hz, ^4J (H,H) = 2.3 Hz, 1 H; H^{Ar}), 7.05 (bs, 1 H; $CONH_2$), 6.64 (d, ^3J (H,H) = 8.7 Hz, 1 H; H^{Ar}), 6.42 (d, ^3J (H,H) = 15.6 Hz, 1 H; CH), 5.61 (bs, 2 H; Ar-NH_2) ppm.

^{13}C NMR (76 MHz, [D$_6$]DMSO): δ = 167.0 (C_q; $CONH_2$), 146.8 (C_q; C^{Ar}), 133.8 (CH), 132.4 (C^{Ar}), 128.4 (C^{Ar}), 121.9 (C^{Ar}), 120.7 (C_q; C^{Ar}), 118.1 (CH), 107.0 (C_q; C^{Ar}) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 7.60 min; *m/z* (%): 242 (35) [M^+], 240 (36) [M^+], 226 (54) [M^+−NH_2], 224 (62) [M^+−NH_2], 198 (13) [M^+−CH_2NO], 196 (15) [M^+−CH_2NO], 117 (61) [M^+−CH_2BrNO].

m.p.$^{exp.}$ = 195-197°C.

9.3.1.8 (*E*)-2-(3-Amino-3-oxoprop-1-en-1-yl)-4-bromobenzenediazonium tetrafluoroborate (38)



38

In a flame dried 500 mL two-neck round-bottom flask with argon-inlet 3.32 g (*E*)-3-(2-amino-5-bromophenyl)acrylamide (**37**) (13.77 mmol, 1.0 eq) were dissolved in 250 mL absolute, degassed THF. After cooling to -45°C, 2.08 mL $BF_3{\cdot}Et_2O$ (2.39 g, 16.84 mmol, 1.2 eq) were added to the orange-yellow solution followed by addition of 3.64 mL *t*BuONO (90%, pure) (2.82 g, 27.35 mmol, 2.0 eq). The reddish-brown suspension was stirred at -15°C for 3.5 h and after warming to -5°C for additional 11 h. The reaction mixture was concentrated at -5°C to half of its volume (~130 mL), before adding 130 mL

absolute, degassed *n*-hexane (-5°C). The formed skin-colored precipitate was collected by filtration and after drying, air stable compound **38** was isolated.*

Yield: 4.09 g (87%), pale yellow, skin-colored solid, $C_9H_7BBrF_4N_3O$ [339.88 g/mol].

^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.65 (d, ^3J (H,H) = 8.8 Hz, 1 H; H^{Ar}), 8.56 (s, 1 H; H^{Ar}), 8.21 (d, ^3J (H,H) = 8.7 Hz, 1 H; H^{Ar}), 7.81 (bs, 1 H; $CONH_2$), 7.61 (d, ^3J (H,H) = 15.4 Hz, 1 H; CH), 7.58 (bs, 1 H; $CONH_2$, overlapping), 7.13 (d, ^3J (H,H) = 15.6 Hz, 1 H; CH) ppm.

^{13}C NMR (76 MHz, [D$_6$]DMSO, APT): δ = 164.9 (C_q; $CONH_2$), 139.5 (C_q; C^{Ar}), 136.5 (C_q; C^{Ar}), 134.5 (CH), 134.3 (C^{Ar}), 133.1 (C^{Ar}), 131.6 (C^{Ar}), 128.7 (CH), 113.7 (C_q; C^{Ar}) ppm.

m.p.$^{exp.}$ = 141-143°C (spontaneous decomposition).

9.3.2 Synthesis of Building Blocks AB and BC

9.3.2.1 Representative procedure for formation of potassium trifluoroborate derivatives from corresponding phenyl boronic acids or -esters

A 100 mL round-bottom flask was charged with 1.0 eq boronic acid pinacol ester (or boronic acid) and 3.0 eq hydrogen potassium fluoride (KHF_2). A premixed MeOH/H_2O solution (volume ratios are given) was added and the colorless solution was stirred at room temperature for the indicated time. After quantitative conversion (disappearance of the starting material on TLC) the colorless suspension was evaporated under reduced pressure to dryness and the crude product was dissolved in acetone and precipitated by dropwise addition of Et_2O (typically twice of the volume of acetone). After filtration and washing of the precipitate with Et_2O, pure colorless potassium trifluoroborate-salt was isolated.

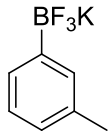
9.3.2.2 Representative procedure for diazonium-coupling with diazonium tetrafluoroborates and potassium trifluoroborate derivatives

A flame dried and argon-flushed 100 mL Schlenk-flask was charged with 1.0 eq diazonium tetrafluoroborate, 1.2 eq potassium trifluoroborate derivative and 5-6 mol% $Pd(OAc)_2$. After drying in vacuo and back-flushing with argon the Schlenk-flask was cooled (temperatures are given) and cold absolute, degassed MeOH was added *via* cannula to the reaction mixture. The orange-brown suspension was stirred for the indicated time and temperature. The reaction was monitored by GC-MS, after filtering a small aliquot of the reaction mixture through a small

* HRMS (DI-EI) gave no unambiguous results because of decomposition during heating process.

pad of SiO_2 and eluting with MeOH. After quantitative conversion the reaction mixture was concentrated to dryness without further workup and the crude product was purified by flash column chromatography (eluents are denoted).

9.3.2.3 Potassium trifluoro(*m*-tolyl)borate (40a)



40a

Compound **40a** was prepared according to procedure 9.3.2.1 from 728 mg *m*-tolylboronic acid (5.35 mmol, 1.0 eq) and 1.25 g KHF_2 (16.00 mmol, 3.0 eq) in 15 mL MeOH/H_2O (2/1). The BPin/BF_3K exchange was completed after 2 h. After removing the solvent under reduced pressure, the colorless solid was redissolved in 12 mL acetone and precipitated with 25 mL Et_2O.

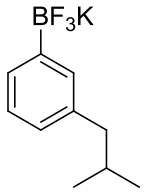
Yield: 1.00 g (94%), colorless solid, $C_7H_7BF_3K$ [198.03 g/mol].

^{1}H NMR (300 MHz, [D_6]DMSO): δ = 7.14-7.09 (m, 2 H; H^{Ar}), 6.97 (t, ^3J (H,H) = 7.3 Hz, 1 H; H^{Ar}), 6.83 (d, ^3J (H,H) = 7.3 Hz, 1 H; H^{Ar}), 2.22 (s, 3 H; CH_3) ppm.

^{13}C NMR (76 MHz, [D_6]DMSO, APT): δ = 134.3 (C_q; C^{Ar}), 132.3 (C^{Ar}), 128.4 (C^{Ar}), 126.1 (C^{Ar}), 125.5 (C^{Ar}), 21.4 (CH_3) ppm.*

m.p.$^{exp.}$ = 243-246°C (m.p.$^{lit.}$ = 243-248°C).[109]

9.3.2.4 Potassium trifluoro(3-isobutylphenyl)borate (40b)



40b

Compound **40b** was prepared according to procedure 9.3.2.1 from 716 mg 2-(3-isobutyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**4f**) (2.75 mmol, 1.0 eq) and 645 mg KHF_2 (8.26 mmol, 3.0 eq) in 60 mL MeOH/H_2O (3/1). The BPin/BF_3K exchange was completed overnight (~16 h). After removing the solvent under reduced pressure, the colorless solid was

* Signal for the quaternary *ipso*-aromatic carbon (C_q; C^{Ar}) at the trifluoroborate function was not observed.

redissolved in 15 mL acetone and after filtration and evaporation, the colorless residue was used in the next step without further purification.

Yield: 658 mg (quant.), colorless solid, $C_{10}H_{13}BF_3K$ [240.11 g/mol].

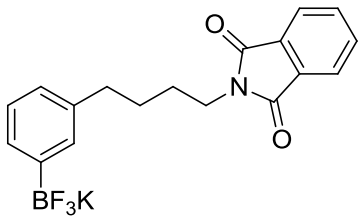
^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.14-7.12 (m, 2 H; H^{Ar}), 6.98 (t, ^3J (H,H) = 7.4 Hz, 1 H; H^{Ar}), 6.80 (d, ^3J (H,H) = 7.4 Hz, 1 H; H^{Ar}), 2.35 (d, ^3J (H,H) = 7.1 Hz, 2 H; CH_2), 1.87-1.69 (m, 1 H; CH), 0.86 (d, ^3J (H,H) = 6.6 Hz, 6 H; CH_3) ppm.*

^{13}C NMR (76 MHz, [D$_6$]DMSO, APT): δ = 138.2 (C$_q$; C^{Ar}), 132.2 (C^{Ar}), 128.8 (C^{Ar}), 125.9 (C^{Ar}), 125.5 (C^{Ar}), 45.3 (CH_2), 29.8 (CH), 22.3 (CH_3) ppm.*,†

m.p.$^{exp.}$ = 96-100°C.

HRMS (DI-EI): calcd (*m*/*z*) for [M^+−FK]: 182.1080; found: 182.1090.

9.3.2.5 Potassium (3-(4-(1,3-dioxoisoindolin-2-yl)butyl)phenyl)trifluoroborate (40c)



40c

Compound **40c** was prepared according to procedure 9.3.2.1 from 739 mg 2-(4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)butyl)isoindoline-1,3-dione (**2a**) (1.82 mmol, 1.0 eq) and 427 mg KHF_2 (5.47 mmol, 3.0 eq) in 30 mL MeOH/H_2O (1/1). The BPin/BF_3K exchange was completed after ~16 h. After evaporation to dryness the colorless solid was redissolved in 7 mL acetone and after filtration and evaporation, the colorless residue was used in the next step without further purification.

Yield: 700 mg (quant.), colorless solid, $C_{18}H_{16}BF_3KNO_2$ [385.23 g/mol].

^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.88-7.81 (m, 4 H; H^{Phth}), 7.11 (d, ^3J (H,H) = 8.6 Hz, 2 H; H^{Ar}), 6.96 (t, ^3J (H,H) = 7.3 Hz, 1 H; H^{Ar}), 6.82 (d, ^3J (H,H) = 7.4 Hz, 1 H; H^{Ar}), 3.60 (t, ^3J (H,H) = 6.7 Hz, 2 H; CH_2), 2.52-2.47 (m, 2 H; CH_2, overlapping), 1.64-1.49 (m, 4 H; CH_2) ppm.

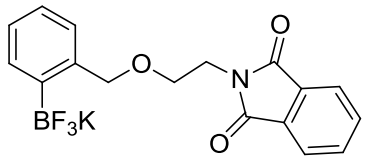
* Signals for the free pinacol were also observed.
† Signal for the quaternary *ipso*-aromatic carbon (C$_q$; C^{Ar}) at the trifluoroborate function was not observed.

^{13}C NMR (76 MHz, [D$_6$]DMSO, APT): δ = 167.9 (C$_q$; C=O^{Phth}), 139.0 (C$_q$; C^{Ar}), 134.3 (C^{Phth}), 131.6 (C$_q$; C^{Phth}), 131.5 (C^{Ar}), 128.8 (C^{Ar}), 126.1 (C^{Ar}), 124.8 (C^{Ar}), 123.0 (C^{Phth}), 37.3 (CH$_2$), 35.2 (CH$_2$), 28.7 (CH$_2$), 27.8 (CH$_2$) ppm.*

m.p.$^{exp.}$ = 56-59°C.

HRMS (DI-EI): calcd (*m*/*z*) for [M^+−FK]: 327.1245; found: 327.1263.

9.3.2.6 Potassium (2-((2-(1,3-dioxoisoindolin-2-yl)ethoxy)methyl)phenyl)trifluoroborate (40d)



40d

Compound **40d** was prepared according to procedure 9.3.2.1 from 386 mg 2-(2-((2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)oxy)ethyl)isoindoline-1,3-dione (**2c**) (0.95 mmol, 1.0 eq) and 222 mg KHF$_2$ (2.84 mmol, 3.0 eq) in 60 mL MeOH/H$_2$O (3/1). The BPin/BF$_3$K exchange was completed overnight (~13 h) and after removing the solvent, the colorless solid was recrystallized from 12 mL acetone and 22 mL Et$_2$O.
Yield: 332 mg (90%), colorless solid, C$_{17}$H$_{14}$BF$_3$KNO$_3$ [387.20 g/mol].

^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.90-7.83 (m, 4 H; H^{Phth}), 7.32 (dd, ^3J (H,H) = 7.1 Hz, ^4J (H,H) = 1.1 Hz, 1 H; H^{Ar}), 7.06 (d, ^3J (H,H) = 7.2 Hz, 1 H; H^{Ar}), 6.93-6.82 (m, 2 H; H^{Ar}), 4.62 (s, 2 H; CH$_2$), 3.81 (t, ^3J (H,H) = 5.7 Hz, 2 H; CH$_2$), 3.60 (t, ^3J (H,H) = 5.7 Hz, 2 H; CH$_2$) ppm.

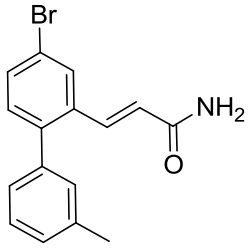
^{13}C NMR (76 MHz, [D$_6$]DMSO, APT): δ = 167.8 (C$_q$; C=O^{Phth}), 141.3 (C$_q$; C^{Ar}), 134.4 (C^{Phth}), 131.6 (C$_q$; C^{Phth}), 131.4 (C^{Ar}), 125.0 (C^{Ar}), 124.6 (C^{Ar}), 124.2 (C^{Ar}), 123.0 (C^{Phth}), 71.2 (CH$_2$), 66.1 (CH$_2$), 37.6 (CH$_2$) ppm.*

m.p.$^{exp.}$ = 185-188°C.

HRMS (DI-EI): calcd (*m*/*z*) for [M^+−FK]: 329.1038; found: 329.1074.

* Signal for the quaternary *ipso*-aromatic carbon (C$_q$; C^{Ar}) at the trifluoroborate function was not observed.

9.3.2.7 (*E*)-3-(4-Bromo-3'-methyl-[1,1'-biphenyl]-2-yl)acrylamide (39a)



39a

Compound **39a** was prepared according to procedure 9.3.2.2 from 200 mg (*E*)-2-(3-amino-3-oxoprop-1-en-1-yl)-4-bromobenzenediazonium tetrafluoroborate (**38**) (0.59 mmol, 1.0 eq), 140 mg potassium trifluoro(*m*-tolyl)borate (**40a**) (0.71 mmol, 1.2 eq) and 7 mg $Pd(OAc)_2$ (31 µmol, 5 mol%) in 20 mL absolute, degassed MeOH at -78°C. The mixture was allowed to warm to 9°C within 9.5 h and further stirring at room temperature (~9 h) completed the reaction. The crude product was purified by flash column chromatography (71 g SiO_2, 24x3 cm, cyclohexane/EtOAc = 1/1, R_f = 0.26) to achieve product **39a** as a colorless solid.*

Yield: 102 mg (55%), colorless solid, $C_{16}H_{14}BrNO$ [316.19 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, ^4J (H,H) = 1.9 Hz, 1 H; H^{Ar}), 7.53 (d, ^3J (H,H) = 15.9 Hz, 1 H; CH), 7.51 (dd, ^3J (H,H) = 8.1 Hz, ^4J (H,H) = 2.1 Hz, 1 H; H^{Ar}, overlapping), 7.32-7.26 (m, 1 H; H^{Ar}), 7.22-7.17 (m, 2 H; H^{Ar}), 7.07-7.03 (m, 2 H; H^{Ar}), 6.37 (d, ^3J (H,H) = 15.7 Hz, 1 H; CH), 5.92 (bs, 1 H; $CONH_2$), 5.77 (bs, 1 H; $CONH_2$), 2.38 (s, 3 H; CH_3) ppm.

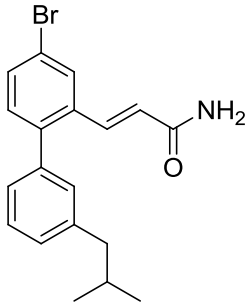
^{13}C NMR (300 MHz, $CDCl_3$, APT): δ = 167.6 (C_q; $CONH_2$), 141.9 (C_q; C^{Ar}), 140.1 (CH), 138.9 (C_q; C^{Ar}), 138.3 (C_q; C^{Ar}), 134.8 (C_q; C^{Ar}), 132.4 (C^{Ar}), 132.2 (C^{Ar}), 130.3 (C^{Ar}), 129.5 (C^{Ar}), 128.8 (C^{Ar}), 128.5 (C^{Ar}), 126.9 (C^{Ar}), 122.0 (CH), 121.6 (C_q; C^{Ar}), 21.6 (CH_3) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 8.49 min; *m/z* (%): 317 (1) [M^+], 315 (1) [M^+], 273 (11) [M^+−CH_2NO] , 271 (12) [M^+−CH_2NO], 192 (100) [M^+−CH_2BrNO].

m.p.$^{exp.}$ = 83-86°C.

* No molecular peak was found by HRMS (EI).

9.3.2.8 (*E*)-3-(4-Bromo-3'-isobutyl-[1,1'-biphenyl]-2-yl)acrylamide (39b)



39b

Compound **39b** was prepared according to procedure 9.3.2.2 from 680 mg (*E*)-2-(3-amino-3-oxoprop-1-en-1-yl)-4-bromobenzenediazonium tetrafluoroborate (**38**) (2.00 mmol, 1.0 eq), 576 mg potassium trifluoro(3-isobutylphenyl)borate (**40b**) (2.40 mmol, 1.2 eq) and 23 mg $Pd(OAc)_2$ (0.10 mmol, 5 mol%) in 50 mL absolute, degassed MeOH. After addition at -35°C the mixture was slowly allowed to warm to 5°C in the cooling bath (4 h) and stirred overnight at 5°C. The crude product was purified by flash column chromatography (80 g SiO_2, 36x3 cm, cyclohexane/EtOAc = 6/4, R_f = 0.29) to achieve compound **39b** as a pale yellow solid.

Yield: 346 mg (48%), pale yellow solid, $C_{19}H_{20}BrNO$ [358.27 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, ^4J (H,H) = 1.9 Hz, 1 H; H^{Ar}), 7.54 (d, ^3J (H,H) = 15.8 Hz, 1 H; CH), 7.52 (dd, ^3J (H,H) = 8.2 Hz, ^4J (H,H) = 2.0 Hz, 1 H; H^{Ar}, overlapping), 7.32 (t, ^3J (H,H) = 7.6 Hz, 1 H; H^{Ar}), 7.23 (d, ^3J (H,H) = 8.3 Hz, 1 H; H^{Ar}), 7.17 (d, ^3J (H,H) = 7.6 Hz, 1 H; H^{Ar}), 7.09-7.04 (m, 2 H; H^{Ar}), 6.37 (d, ^3J (H,H) = 15.7 Hz, 1 H; CH), 5.75 (bs, 2 H; $CONH_2$), 2.50 (d, ^3J (H,H) = 7.2 Hz, 2 H; CH_2), 1.97-1.79 (m, 1 H; CH), 0.92 (d, ^3J (H,H) = 6.6 Hz, 6 H; CH_3) ppm.

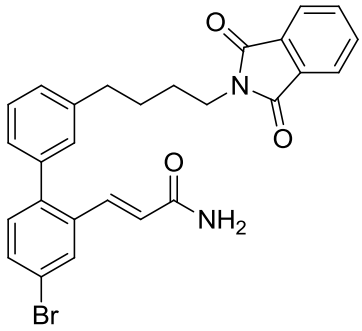
^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 167.4 (C_q; $CONH_2$), 142.1 (C_q; C^{Ar}), 142.0 (C_q; C^{Ar}), 140.3 (CH), 138.7 (C_q; C^{Ar}), 134.9 (C_q; C^{Ar}), 132.4 (C^{Ar}), 132.2 (C^{Ar}), 130.5 (C^{Ar}), 129.7 (C^{Ar}), 128.9 (C^{Ar}), 128.4 (C^{Ar}), 127.1 (C^{Ar}), 122.0 (CH), 121.6 (C_q; C^{Ar}), 45.5 (CH_2), 30.4 (CH), 22.5 (CH_3) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 9.25 min; *m/z* (%): 359 (4) [M^+], 357 (3) [M^+], 315 (17) [M^+−CH_2NO], 313 (17) [M^+−CH_2NO], 271 (31) [M^+−$C_4H_{10}NO$], 269 (30) [M^+−$C_4H_{10}NO$], 234 (63) [M^+−CH_2BrNO], 191 (99) [$C_6H_8BrNO^+$], 189 (100) [$C_6H_8BrNO^+$].

m.p.$^{exp.}$ = 155-157°C.

HRMS (EI): calcd (*m*/*z*) for [M^+]: 357.0728; found: 357.0742.

9.3.2.9 (*E*)-3-(4-Bromo-3'-(4-(1,3-dioxoisoindolin-2-yl)butyl)-[1,1'-biphenyl]-2-yl)acrylamide (39c)



39c

Compound **39c** was prepared according to procedure 9.3.2.2 from 340 mg (*E*)-2-(3-amino-3-oxoprop-1-en-1-yl)-4-bromobenzenediazonium tetrafluoroborate (**38**) (1.00 mmol, 1.0 eq), 462 mg potassium (3-(4-(1,3-dioxoisoindolin-2-yl)butyl)phenyl)trifluoroborate (**40c**) (1.20 mmol, 1.2 eq) and 11 mg $Pd(OAc)_2$ (49 µmol, 5 mol%) in 25 mL absolute, degassed MeOH. After addition at -20°C and warming to 0°C after 1 h, the reaction mixture was stirred overnight at 0°C. After complete conversion the crude product was purified by flash column chromatography (60 g SiO_2, 25x3 cm, cyclohexane/EtOAc = 3/7, R_f = 0.43) to achieve product **39c** as a colorless solid.

Yield: 247 mg (49%), colorless solid, $C_{27}H_{23}BrN_2O_3$ [503.39 g/mol].

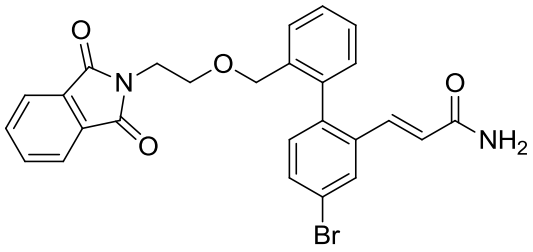
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85-7.79 (m, 2 H; H^{Phth}), 7.76 (d, ^4J (H,H) = 1.9 Hz, 1 H; H^{Ar}), 7.72-7.68 (m, 2 H; H^{Phth}), 7.54-7.49 (m, 2 H; H^{Ar}, CH), 7.33-7.16 (m, 3 H; H^{Ar}), 7.09-7.06 (m, 2 H; H^{Ar}), 6.37 (d, ^3J (H,H) = 15.7 Hz, 1 H; CH), 5.82 (bs, 2 H; $CONH_2$), 3.71 (t, ^3J (H,H) = 6.6 Hz, 2 H; CH_2), 2.68 (t, ^3J (H,H) = 6.8 Hz, 2 H; CH_2), 1.71 (bs, 4 H; CH_2) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 168.6 (C_q; $C{=}O^{Phth}$), 167.5 (C_q; $CONH_2$), 142.4 (C_q; C^{Ar}), 141.7 (C_q; C^{Ar}), 140.1 (CH), 139.0 (C_q; C^{Ar}), 134.9 (C_q; C^{Ar}), 134.0 (C^{Phth}), 132.4 (C^{Ar}), 132.3 (C_q; C^{Phth}), 132.2 (C^{Ar}), 129.9 (C^{Ar}), 129.7 (C^{Ar}), 128.6 (C^{Ar}), 128.2 (C^{Ar}), 127.3 (C^{Ar}), 123.3 (C^{Phth}), 122.3 (CH), 121.6 (C_q; C^{Ar}), 38.0 (CH_2), 35.4 (CH_2), 28.7 (CH_2), 28.1 (CH_2) ppm.

m.p.$^{exp.}$ = 164-166°C.

HRMS (DI-EI): calcd (*m*/*z*) for [M^+]: 502.0892; found: 502.0925.

9.3.2.10 (*E*)-3-(4-Bromo-2'-((2-(1,3-dioxoisoindolin-2-yl)ethoxy)methyl)-[1,1'-biphenyl]-2-yl)acrylamide (39d)



39d

Compound **39d** was prepared according to procedure 9.3.2.2 from 204 mg (*E*)-2-(3-amino-3-oxoprop-1-en-1-yl)-4-bromobenzenediazonium tetrafluoroborate (**38**) (0.60 mmol, 1.0 eq), 279 mg potassium (2-((2-(1,3-dioxoisoindolin-2-yl)ethoxy)methyl)-phenyl)trifluoroborate (**40d**) (0.72 mmol, 1.2 eq) and 8 mg $Pd(OAc)_2$ (36 µmol, 6 mol%) in 25 mL absolute, degassed MeOH. After addition at -20°C and warming to 0°C after 1 h, the reaction was stirring overnight at 0°C. After complete conversion the crude product was purified by flash column chromatography (60 g SiO_2, 26x3 cm, cyclohexane/THF = 4/6, R_f = 0.36) to achieve product **39d** as a pale yellow solid.*

Yield: 97 mg (32%), pale yellow solid, $C_{26}H_{21}BrN_2O_4$ [505.36 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84-7.80 (m, 2 H; H^{Phth}), 7.76-7.72 (m, 2 H; H^{Phth}), 7.64 (d, ^4J (H,H) = 1.9 Hz, 1 H; H^{Ar}), 7.42 (d, ^4J (H,H) = 1.7 Hz, 1 H; H^{Ar}), 7.39 (d, ^4J (H,H) = 2.2 Hz, 1 H; H^{Ar}), 7.28-7.25 (m, 2 H; H^{Ar}, overlapping), 7.11 (d, ^3J (H,H) = 15.9 Hz, 1 H; CH), 7.08-7.01 (m, 2 H; H^{Ar}), 6.23 (d, ^3J (H,H) = 15.9 Hz, 1 H; CH), 5.99 (bs, 1 H; $CONH_2$), 5.64 (bs, 1 H; $CONH_2$), 4.20 (q, ^2J (H,H) = 11.8 Hz, 2 H; CH_2), 3.79 (t, ^3J (H,H) = 5.6 Hz, 2 H; CH_2), 3.56-3.47 (m, 2 H; CH_2) ppm.

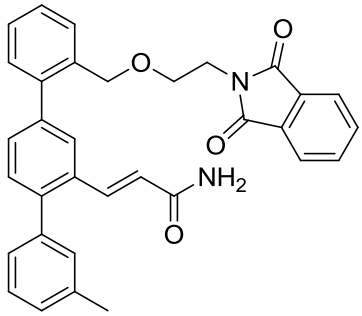
^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 168.4 (C_q; $CONH_2$), 167.7 (C_q; $C{=}O^{Phth}$), 139.9 (C_q; C^{Ar}), 138.6 (CH), 138.2 (C_q; C^{Ar}), 135.9 (C_q; C^{Ar}), 135.5 (C_q; C^{Ar}), 134.2 (C^{Phth}), 132.2 (C^{Ar}), 132.1 (C^{Ar}), 130.2 (C^{Ar}), 129.4 (C^{Ar}), 129.1 (C^{Ar}), 128.5 (C^{Ar}), 127.9 (C^{Ar}), 123.5 (C^{Phth}), 123.0 (CH), 121.9 (C_q; C^{Ar}), 70.7 (CH_2), 67.4 (CH_2), 37.7 (CH_2) ppm.†

m.p.$^{exp.}$ = 68-75°C.

* HRMS (DI-EI) gave no unambiguous results because of decomposition during heating process.
† No signal for the quaternary carbon atoms of the phthalimide-moiety (C_q; C^{Phth}) was observed; should be visible at ~132.1 ppm.

9.3.3 Synthesis of Terphenyls

9.3.3.1 (*E*)-3-(2''-((2-(1,3-Dioxoisoindolin-2-yl)ethoxy)methyl)-3-methyl-[1,1':4',1''-terphenyl]-2'-yl)acrylamide (41a)



41a

Compound **41a** was prepared according to procedure 9.2.4.1 from 182 mg (*E*)-3-(4-bromo-3'-methyl-[1,1'-biphenyl]-2-yl)acrylamide (**39a**) (0.58 mmol, 1.0 eq), 281 mg 2-(2-((2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)oxy)ethyl)isoindoline-1,3-dione (**2c**) (0.69 mmol, 1.2 eq), 175 mg CsF (1.15 mmol, 2.0 eq) and 24 mg $PdCl_2(dppf)\cdot DCM$ (29 µmol, 5 mol%) in 20 mL absolute, degassed 1,2-DME at 80°C. The aryl-aryl coupling was completed within 15 h. After flash column chromatography (70 g SiO_2, 24x3 cm, cyclohexane/EtOAc = 4/6, R_f = 0.30), product **41a** was isolated as a colorless solid.
Yield: 237 mg (79%), colorless solid, $C_{33}H_{28}N_2O_4$ [516.59 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (bs, 3 H; H^{Phth}, H^{Ar}), 7.71 (bs, 3 H; H^{Phth}, CH), 7.46 (d, ^3J (H,H) = 7.0 Hz, 1 H; H^{Ar}), 7.35 (bs, 7 H; H^{Ar}), 7.20-7.14 (m, 3 H; H^{Ar}, CH), 6.71 (bs, 1 H; $CONH_2$), 6.50 (bs, 1 H; $CONH_2$), 4.44 (s, 2 H; CH_2), 3.94-3.93 (m, 2 H; CH_2), 3.77-3.76 (m, 2 H; CH_2), 2.41 (s, 3 H; CH_3) ppm.

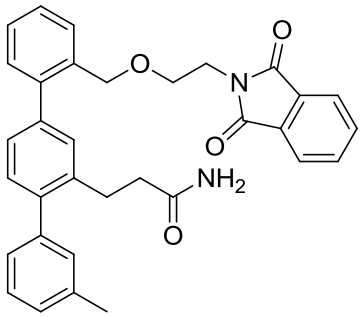
^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 168.6 (C_q; $C{=}O^{Phth}$), 142.0 (C_q; C^{Ar}), 141.7 (C_q; C^{Ar}), 141.4 (C^{Ar}), 139.9 (C_q; C^{Ar}), 139.8 (C_q; C^{Ar}), 138.1 (C_q; C^{Ar}), 134.7 (C_q; C^{Ar}), 134.2 (CH), 132.5 (C_q; C^{Ar}), 132.1 (C_q; C^{Phth}), 130.6 (C^{Ar}), 130.5 (C^{Ar}), 130.4 (C^{Ar}), 130.3 (C^{Ar}), 128.5 (C^{Ar}), 128.3 (C^{Ar}), 128.3 (C^{Ar}), 127.8 (C^{Ar}), 127.7 (C^{Ar}), 127.2 (C^{Ar}), 123.5 (CH), 71.5 (CH_2), 67.0 (CH_2), 38.1 (CH_2), 21.7 (CH_3) ppm.*

m.p.$^{exp.}$ = 69-74°C.

HRMS (DI-EI): calcd (*m*/*z*) for [M^+]: 516.2049; found: 516.2054.

* No signal for the quaternary carbon atom of the amide function (C_q; $CONH_2$) was observed, should be visible at ~168.1 ppm. It might be overlapping with the signal of the quaternary carbon atom of the phthalimide moiety (C_q; $C{=}O^{Phth}$).

9.3.3.2 3-(2''-((2-(1,3-Dioxoisoindolin-2-yl)ethoxy)methyl)-3-methyl-[1,1':4',1''-terphenyl]-2'-yl)propanamide (19a)



19a

In a 50 mL two-neck round-bottom flask with two argon-inlets 193 mg (*E*)-3-(2"-((2-(1,3-dioxoisoindolin-2-yl)ethoxy)methyl)-3-methyl-[1,1':4',1"-terphenyl]-2'-yl)acrylamide (**41a**) (0.37 mmol, 1.0 eq) were dissolved in 60 mL MeOH and 19 mg $Pd(OH)_2/C$ (10 wt%) were added to the pale yellow solution.* After ensuring hydrogen atmosphere, by evacuating and back-flushing with hydrogen gas (3x), the reaction mixture was stirred overnight (~17 h) at room temperature. After filtering off the catalyst (5x3 cm SiO_2, eluent: MeOH) and evaporating the solvent using a rotary evaporator, compound **19a** was isolated as a pale yellow solid.† The product was used in the next step without further purification.

Yield: 164 mg (85%), pale yellow solid, $C_{33}H_{30}N_2O_4$ [518.60 g/mol].

TLC: R_f = 0.23 (cyclohexane/EtOAc = 4/6).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82-7.81 (m, 2 H; H^{Phth}), 7.71-7.70 (m, 2 H; H^{Phth}), 7.48-7.45 (m, 1 H; H^{Ar}), 7.35-7.27 (m, 5 H; H^{Ar}), 7.18 (bs, 5 H; H^{Ar}), 5.68 (bs, 1 H; $CONH_2$), 5.45 (bs, 1 H; $CONH_2$), 4.48 (s, 2 H; CH_2^{Lys}), 3.90 (t, ^3J (H,H) = 5.2 Hz, 2 H; CH_2^{Lys}), 3.69 (t, ^3J (H,H) = 5.2 Hz, 2 H; CH_2^{Lys}), 3.02 (bs, 2 H; CH_2^{Gln}), 2.41 (bs, 5 H; CH_2^{Gln}, CH_3^{Ala}, overlapping) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 168.5 (C_q; $C{=}O^{Phth}$), 141.8 (C_q; C^{Ar}), 141.2 (C_q; C^{Ar}), 141.0 (C_q; C^{Ar}), 140.0 (C_q; C^{Ar}), 138.0 (C_q; C^{Ar}), 137.8 (C_q; C^{Ar}), 135.1 (C_q; C^{Ar}), 134.1 (C^{Phth}), 132.2 (C_q; C^{Phth}), 130.2 (C^{Ar}), 130.1 (C^{Ar}), 130.1 (C^{Ar}), 130.0 (C^{Ar}), 129.5 (C^{Ar}),

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

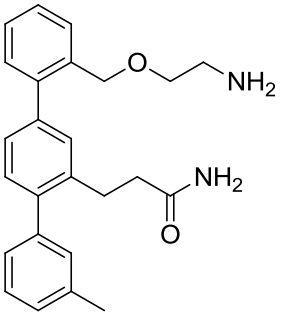
† The catalyst was filtered off using a pad of Celite® or SiO_2 under inert conditions and eluted with MeOH. The hydrogenation catalyst was washed with H_2O and stored in a glass bottle covered with water.

128.3 (C^{Ar}), 128.0 (C^{Ar}), 127.9 (C^{Ar}), 127.5 (C^{Ar}), 127.1 (C^{Ar}), 126.3 (C^{Ar}), 123.4 (C^{Phth}), 71.0 (CH_2^{Lys}), 67.0 (CH_2^{Lys}), 37.8 (CH_2^{Lys}), 37.2 (CH_2^{Gln}), 29.0 (CH_2^{Gln}), 21.7 (CH_3^{Ala}) ppm.*

m.p.$^{exp.}$ = 58-57°C.

HRMS (DI-EI): calcd (*m*/*z*) for [M^+]: 518.2206; found: 518.2217.

9.3.3.3 3-(2''-((2-Aminoethoxy)methyl)-3-methyl-[1,1':4',1''-terphenyl]-2'-yl)propanamide (1d)



1d

In a 25 mL round-bottom flask 46 mg 3-(2''-((2-(1,3-dioxoisoindolin-2-yl)ethoxy)methyl)-3-methyl-[1,1':4',1''-terphenyl]-2'-yl)propanamide (**19a**) (89 µmol, 1.0 eq) were dissolved in 2 mL MeOH. After addition of 43 µL $H_2NNH_2 \cdot H_2O$ (44 mg, 0.88 mmol, 10.0 eq) the pale yellow solution was stirred until full conversion was monitored by TLC. The colorless suspension was concentrated under reduced pressure to dryness and the crude product was purified by flash column chromatography (3.5 g SiO_2, 9x1 cm, MeOH, R_f = 0.10) to achieve compound **1d** as a colorless solid.

Yield: 28 mg (80%), colorless solid, $C_{25}H_{28}N_2O_2$ [388.50 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54-7.51 (m, 1 H; H^{Ar}), 7.40-7.30 (m, 5 H; H^{Ar}), 7.26 (bs, 2 H; H^{Ar}), 7.18-7.15 (m, 3 H; H^{Ar}), 6.08 (bs, 1 H; $CONH_2$), 5.54 (bs, 1 H; $CONH_2$), 4.47 (s, 2 H; CH_2^{Lys}), 3.51 (t, ^3J (H,H) = 5.1 Hz, 2 H; CH_2^{Lys}), 3.00 (t, ^3J (H,H) = 8.1 Hz, 2 H; CH_2^{Gln}), 2.88 (t, ^3J (H,H) = 5.0 Hz, 2 H; CH_2^{Lys}), 2.41 (s, 3 H; CH_3^{Ala}), 2.37 (t, ^3J (H,H) = 8.1 Hz, 2 H; CH_2^{Gln}, overlapping), 1.89 (bs, 2 H; NH_2) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 174.8 (C_q; $CONH_2$), 141.9 (C_q; C^{Ar}), 141.2 (C_q; C^{Ar}), 141.0 (C_q; C^{Ar}), 140.1 (C_q; C^{Ar}), 138.1 (C_q; C^{Ar}), 137.9 (C_q; C^{Ar}), 135.3 (C_q; C^{Ar}), 130.3 (C^{Ar}),

* No signal for the quaternary carbon atom of the amide function (C_q; $CONH_2$) was observed, should be visible at ~168.1 ppm. It might be overlapping with the signal of the quaternary carbon atom of the phthalimide moiety (C_q; $C{=}O^{Phth}$).

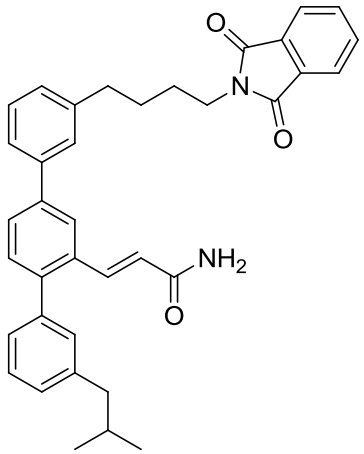
130.3 (C^{Ar}), 130.1 (C^{Ar}), 130.1 (C^{Ar}), 130.0 (C^{Ar}), 128.3 (C^{Ar}), 128.2 (C^{Ar}), 128.0 (C^{Ar}), 127.6 (C^{Ar}), 127.1 (C^{Ar}), 126.3 (C^{Ar}), 72.3 (CH_2^{Lys}), 71.4 (CH_2^{Lys}), 41.9 (CH_2^{Lys}), 37.2 (CH_2^{Gln}), 29.2 (CH_2^{Gln}), 21.6 (CH_3^{Ala}) ppm.

m.p.$^{exp.}$ = 107-109°C.

HPLC (Nucleodur, ESI^+): t_R = 12.58 min; *m/z*: 389 [M^++H], 411 [M^++Na]; λ_{max} = 210, 222, 294 nm.

HRMS (DI-EI): calcd (*m*/*z*) for [M^+]: 388.2151; found: 388.2190.

9.3.3.4 (*E*)-3-(3''-(4-(1,3-Dioxoisoindolin-2-yl)butyl)-3-isobutyl-[1,1':4',1''-terphenyl]-2'-yl)acrylamide (41b)



41b

Compound **41b** was prepared according to procedure 9.2.4.1 from 100 mg (*E*)-3-(4-bromo-3'-isobutyl-[1,1'-biphenyl]-2-yl)acrylamide (**39b**) (0.28 mmol, 1.0 eq), 124 mg 2-(4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)butyl)isoindoline-1,3-dione (**2a**) (0.31 mmol, 1.1 eq), 85 mg CsF (0.56 mmol, 2.0 eq) and 7 mg $PdCl_2$(dppf)·DCM (9 µmol, 3 mol%) in 12 mL absolute, degassed 1,2-DME at 80°C. The aryl-aryl coupling was completed within 10 h. The crude product was purified by flash column chromatography (9 g SiO_2, 18x1.5 cm, cyclohexane/EtOAc = 1/1, R_f =0.26) to achieve product **41b** as a colorless solid.

Yield: 132 mg (85%), colorless solid, $C_{37}H_{36}N_2O_3$ [556.69 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88-7.82 (m, 3 H; H^{Phth}, CH), 7.75-7.62 (m, 4 H; H^{Phth}, H^{Ar}), 7.46-7.42 (m, 3 H; H^{Ar}), 7.39-7.33 (m, 2 H; H^{Ar}), 7.20-7.14 (m, 4 H; H^{Ar}), 6.57 (d, ^3J (H,H) = 15.7 Hz, 1 H; CH), 5.86 (bs, 1 H; $CONH_2$), 5.79 (bs, 1 H; $CONH_2$), 3.75 (t,

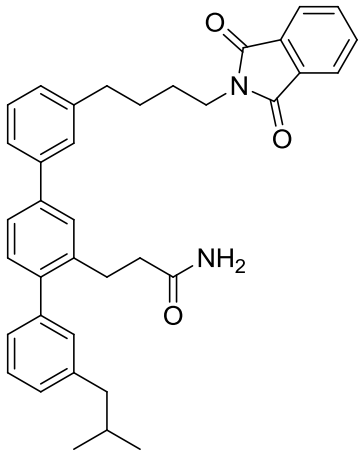
^{3}J (H,H) = 6.2 Hz, 2 H; CH_2^{Lys}), 2.76 (bs, 2 H; CH_2^{Lys}), 2.53 (d, ^{3}J (H,H) = 7.1 Hz, 2 H; CH_2^{Leu}), 1.98-1.85 (m, 1 H; CH^{Leu}), 1.78-1.76 (m, 4 H; CH_2^{Lys}), 0.95 (d, ^{3}J (H,H) = 6.6 Hz, 6 H; CH_3^{Leu}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 168.7 (C_q; $C{=}O^{Phth}$), 168.0 (C_q; $CONH_2$), 142.7 (C_q; C^{Ar}), 142.1 (C_q; C^{Ar}), 142.0 (C_q; C^{Ar}), 141.6 (CH), 140.6 (C_q; C^{Ar}), 140.5 (C_q; C^{Ar}), 139.5 (C_q; C^{Ar}), 134.1 (C^{Phth}), 133.2 (C_q; C^{Ar}), 132.2 (C_q; C^{Phth}), 131.2 (C^{Ar}), 130.8 (C^{Ar}), 129.1 (C^{Ar}), 128.6 (C^{Ar}), 128.4 (C^{Ar}), 128.3 (C^{Ar}), 128.0 (C^{Ar}), 127.3 (C^{Ar}), 127.2 (C^{Ar}), 125.7 (C^{Ar}), 124.8 (C^{Ar}), 123.4 (C^{Phth}), 121.1 (CH), 45.6 (CH_2^{Leu}), 38.0 (CH_2^{Lys}), 35.4 (CH_2^{Lys}), 30.4 (CH^{Leu}), 28.5 (CH_2^{Lys}), 28.3 (CH_2^{Lys}), 22.6 (CH_3^{Leu}) ppm.

m.p.$^{exp.}$ = 168-170°C.

HRMS (DI-EI): calcd (*m*/*z*) for [M^+]: 566.2726; found: 556.2737.

9.3.3.5 3-(3''-(4-(1,3-Dioxoisoindolin-2-yl)butyl)-3-isobutyl-[1,1':4',1''-terphenyl]-2'-yl)propanamide (19b)



19b

In a 50 mL two-neck round-bottom flask with two argon-inlets 87 mg (*E*)-3-(3''-(4-(1,3-dioxoisoindolin-2-yl)butyl)-3-isobutyl-[1,1':4',1''-terphenyl]-2'-yl)acrylamide (**41b**) (0.16 mmol, 1.0 eq) were dissolved in a mixture of 32 mL MeOH/EtOH (11/5) and 9 mg $Pd(OH)_2$/C (10 wt%) were added to this colorless solution.* After ensuring hydrogen atmosphere, by evacuating and back-flushing with hydrogen gas (3x), the reaction mixture was stirred for 23 h at room temperature. After the catalyst was filtered off (3x3 cm SiO_2, eluent: MeOH),

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

the solvent was removed under reduced pressure and product **19b** was isolated as a colorless solid.* The product was used in the next step without further purification.

Yield: 81 mg (91%), colorless solid, $C_{37}H_{38}N_2O_3$ [558.71 g/mol].

TLC: R_f = 0.43 (cyclohexane/EtOAc = 6/4).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85-7.81 (m, 2 H; H^{Phth}), 7.73-7.69 (m, 2 H; H^{Phth}), 7.54-7.42 (m, 4 H; H^{Ar}), 7.37-7.27 (m, 3 H; H^{Ar}), 7.18-7.14 (m, 4 H; H^{Ar}), 5.36 (bs, 1 H; $CONH_2$), 5.20 (bs, 1 H; $CONH_2$), 3.74 (t, ^3J (H,H) = 6.5 Hz, 2 H; CH_2^{Lys}), 3.05 (t, ^3J (H,H) = 6.5 Hz, 2 H; CH_2^{Gln}), 2.74 (t, ^3J (H,H) = 6.8 Hz, 2 H; CH_2^{Lys}), 2.53 (d, ^3J (H,H) = 7.1 Hz, 2 H; CH_2^{Leu}), 2.36 (t, ^3J (H,H) = 6.5 Hz, 2 H; CH_2^{Gln}), 1.97-1.84 (m, 1 H; CH^{Leu}), 1.76-1.74 (m, 4 H; CH_2^{Lys}), 0.93 (d, ^3J (H,H) = 6.6 Hz, 6 H; CH_3^{Leu}) ppm.

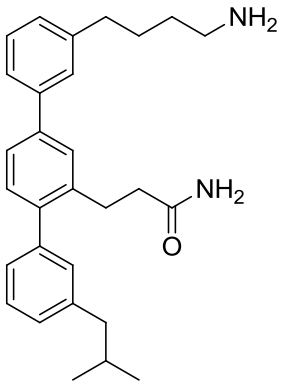
^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 174.6 (C_q; $CONH_2$), 168.6 (C_q; $C{=}O^{Phth}$), 142.7 (C_q; C^{Ar}), 141.9 (C_q; C^{Ar}), 141.1 (C_q; C^{Ar}), 141.1 (C_q; C^{Ar}), 140.9 (C_q; C^{Ar}), 140.7 (C_q; C^{Ar}), 138.5 (C_q; C^{Ar}), 134.0 (C^{Phth}), 132.3 (C_q; C^{Phth}), 130.8 (C^{Ar}), 130.1 (C^{Ar}), 128.9 (C^{Ar}), 128.2 (C^{Ar}), 128.1 (C^{Ar}), 128.1 (C^{Ar}), 127.7 (C^{Ar}), 127.4 (C^{Ar}), 126.6 (C^{Ar}), 125.2 (C^{Ar}), 124.8 (C^{Ar}), 123.3 (C^{Phth}), 45.6 (CH_2^{Leu}), 37.9 (CH_2^{Gln}), 37.1 (CH_2^{Lys}), 35.6 (CH_2^{Gln}), 30.5 (CH^{Leu}), 29.3 (CH_2^{Lys}), 28.8 (CH_2^{Lys}), 28.3 (CH_2^{Lys}), 22.5 (CH_3^{Leu}) ppm.

m.p.$^{exp.}$ = 118-120°C.

HRMS (DI-EI): calcd (*m*/*z*) for [M^+]: 558.2883; found: 558.2883.

* The catalyst was filtered off using a pad of Celite® or SiO_2 under inert conditions and eluted with MeOH. The hydrogenation catalyst was washed with H_2O and stored in a glass bottle covered with water.

9.3.3.6 3-(3''-(4-Aminobutyl)-3-isobutyl-[1,1':4',1''-terphenyl]-2'-yl)propanamide (1e)



1e

In a 25 mL round-bottom flask 53 mg 3-(3''-(4-(1,3-dioxoisoindolin-2-yl)butyl)-3-isobutyl-[1,1':4',1''-terphenyl]-2'-yl)propanamide (**19b**) (95 µmol, 1.0 eq) were dissolved in 5 mL MeOH. After addition of 46 µL $H_2NNH_2 \cdot H_2O$ (47 mg, 0.95 mmol, 10.0 eq) the colorless solution was stirred until full conversion was detected by TLC. The colorless solution was stirred for 13 h. Because of slow conversion, 46 µL $H_2NNH_2 \cdot H_2O$ (47 mg, 0.95 mmol, 10.0 eq) were additionally added and the solution was further stirred for 3 days. Afterwards, the colorless suspension was concentrated under reduced pressure to dryness. Purification by flash column chromatography (5.4 g SiO_2, 14x1 cm, MeOH, R_f = 0.09) afforded compound **1e** as a pale yellow oil.

Yield: 40 mg (98%), pale yellow oil, $C_{29}H_{36}N_2O$ [428.61 g/mol].

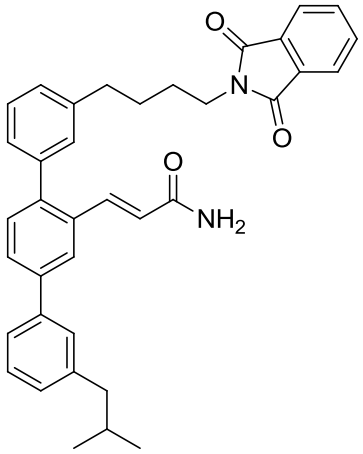
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49 (bs, 1 H; H^{Ar}), 7.46-7.39 (m, 3 H; H^{Ar}), 7.34-7.22 (m, 3 H; H^{Ar}), 7.14-7.10 (m, 4 H; H^{Ar}), 5.63 (bs, 1 H; $CONH_2$), 5.29 (bs, 1 H; $CONH_2$), 2.99 (t, ^3J (H,H) = 7.9 Hz, 2 H; CH_2^{Gln}), 2.72-2.63 (m, 4 H; CH_2^{Lys}), 2.49 (d, ^3J (H,H) = 7.1 Hz, 2 H; CH_2^{Leu}), 2.28 (t, ^3J (H,H) = 7.9 Hz, 2 H; CH_2^{Gln}), 2.20 (bs, 2 H; NH_2, overlapping), 1.93-1.80 (m, 1 H; CH^{Leu}), 1.72-1.62 (m, 2 H; CH_2^{Lys}), 1.54-1.45 (m, 2 H; CH_2^{Lys}), 0.89 (d, ^3J (H,H) = 6.6 Hz, 6 H; CH_3^{Leu}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 174.8 (C_q; $CONH_2$), 143.0 (C_q; C^{Ar}), 141.9 (C_q; C^{Ar}), 141.1 (C_q; C^{Ar}), 141.0 (C_q; C^{Ar}), 140.9 (C_q; C^{Ar}), 140.7 (C_q; C^{Ar}), 138.6 (C_q; C^{Ar}), 130.8 (C^{Ar}), 130.1 (C^{Ar}), 128.9 (C^{Ar}), 128.2 (C^{Ar}), 128.2 (C^{Ar}), 128.0 (C^{Ar}), 127.6 (C^{Ar}), 127.3 (C^{Ar}), 126.5 (C^{Ar}), 125.1 (C^{Ar}), 124.7 (C^{Ar}), 45.5 (CH_2^{Leu}), 42.0 (CH_2^{Lys}), 37.1 (CH_2^{Gln}), 35.9 (CH_2^{Lys}), 33.0 (CH_2^{Lys}), 30.4 (CH^{Leu}), 29.3 (CH_2^{Gln}), 28.8 (CH_2^{Lys}), 22.5 (CH_3^{Leu}) ppm.

HPLC (Nucleodur, ESI$^+$): t_R = 15.28 min; *m/z*: 429 [M^++H], 451 [M^++Na]; λ_{max} = 210, 230, 294 nm.

HRMS (DI-EI): calcd (*m/z*) for [M^+]: 428.2828; found: 428.2786.

9.3.3.7 (*E*)-3-(3-(4-(1,3-Dioxoisoindolin-2-yl)butyl)-3''-isobutyl-[1,1':4',1''-terphenyl]-2'-yl)acrylamide (41c)



41c

Compound **41c** was prepared according to procedure 9.2.4.1 from 88 mg (*E*)-3-(4-bromo-3'-(4-(1,3-dioxoisoindolin-2-yl)butyl)-[1,1'-biphenyl]-2-yl)acrylamide (**39c**) (0.17 mmol, 1.0 eq), 55 mg 2-(3-isobutylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**4f**) (0.21 mmol, 1.2 eq), 54 mg CsF (0.36 mmol, 2.0 eq) and 4 mg $PdCl_2$(dppf)·DCM (5 µmol, 3 mol%) in 10 mL absolute, degassed 1,2-DME at 80°C. The aryl-aryl coupling was completed after 15 h and purification by flash column chromatography (9.5 g SiO_2, 17x1.5 cm, cyclohexane/EtOAc = 1/1, R_f = 0.25) afforded product **41c** as a pale yellow solid.
Yield: 90 mg (95%), pale yellow solid, $C_{37}H_{36}N_2O_3$ [556.69 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84-7.81 (m, 3 H; H^{Phth}, CH), 7.70-7.62 (m, 4 H; H^{Phth}, H^{Ar}), 7.47-7.30 (m, 5 H; H^{Ar}), 7.19-7.15 (m, 4 H; H^{Ar}), 6.44 (d, ^3J (H,H) = 15.8 Hz, 1 H; CH), 5.71 (bs, 2 H; $CONH_2$), 3.72 (t, ^3J (H,H) = 6.2 Hz, 2 H; CH_2^{Lys}), 2.71 (t, ^3J (H,H) = 6.4 Hz, 2 H; CH_2^{Lys}), 2.57 (d, ^3J (H,H) = 7.1 Hz, 2 H; CH_2^{Leu}), 2.01-1.90 (m, 1 H; CH^{Leu}), 1.74-1.72 (m, 4 H; CH_2^{Lys}), 0.95 (d, ^3J (H,H) = 6.6 Hz, 6 H; CH_3^{Leu}) ppm.

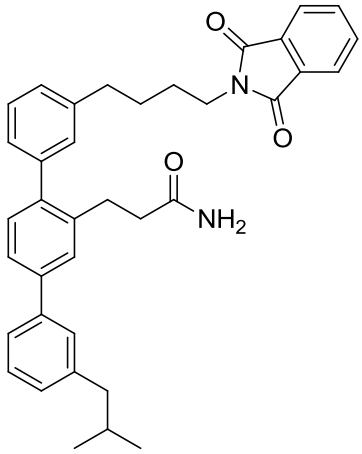
^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 168.7 (C_q; $C{=}O^{Phth}$), 168.1 (C_q; $CONH_2$), 142.5 (C_q; C^{Ar}), 142.2 (C_q; C^{Ar}), 141.7 (C_q; C^{Ar}), 141.5 (CH), 140.9 (C_q; C^{Ar}), 140.2 (C_q; C^{Ar}), 139.8 (C_q; C^{Ar}), 134.0 (C^{Phth}), 133.3 (C_q; C^{Ar}), 132.3 (C_q; C^{Phth}), 131.1 (C^{Ar}), 130.1 (C^{Ar}), 128.8 (C^{Ar}),

128.6 (C^{Ar}), 128.5 (C^{Ar}), 128.5 (C^{Ar}), 128.1 (C^{Ar}), 127.9 (C^{Ar}), 127.5 (C^{Ar}), 125.8 (C^{Ar}), 124.6 (C^{Ar}), 123.3 (C^{Phth}), 121.7 (CH), 45.7 (CH_2^{Leu}), 38.0 (CH_2^{Lys}), 35.5 (CH_2^{Lys}), 30.4 (CH^{Leu}), 28.8 (CH_2^{Lys}), 28.2 (CH_2^{Lys}), 22.6 (CH_3^{Leu}) ppm.

m.p.$^{exp.}$ = 63-67°C.

HRMS (DI-EI): calcd (*m*/*z*) for [M^+]: 506.2726; found: 556.2740.

9.3.3.8 3-(3-(4-(1,3-Dioxoisoindolin-2-yl)butyl)-3''-isobutyl-[1,1':4',1''-terphenyl]-2'-yl)-propanamide (19c)



19c

In a 50 mL two-neck round-bottom flask with two argon-inlets 75 mg (*E*)-3-(3-(4-(1,3-dioxo-isoindolin-2-yl)butyl)-3''-isobutyl-[1,1':4',1''-terphenyl]-2'-yl)acrylamide (**41c**) (0.13 mmol, 1.0 eq) were dissolved in 10 mL MeOH and 8 mg $Pd(OH)_2/C$ (10 wt%) were added to the pale yellow solution.* After ensuring hydrogen atmosphere, by evacuating and back-flushing with hydrogen gas (3x), the reaction mixture was stirred for 1.5 d at room temperature. Due to slow conversion additional 8 mg $Pd(OH)_2/C$ (10 wt%) were added and after further 2 d of stirring at room temperature, the catalyst was filtered off (3x3 cm SiO_2, eluent: MeOH).† The solvent was removed under reduced pressure and compound **19c** was isolated as a pale yellow solid. The product was used in the next step without further purification.

Yield: 70 mg (96%), pale yellow solid, $C_{37}H_{38}N_2O_3$ [558.71 g/mol].

TLC: R_f = 0.33 (cyclohexane/EtOAc = 4/6).

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

† The catalyst was filtered off using a pad of Celite® or SiO_2 under inert conditions and eluted with MeOH. The hydrogenation catalyst was washed with H_2O and stored in a glass bottle covered with water.

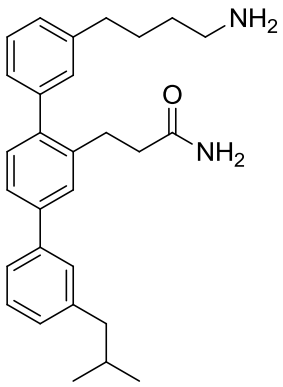
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83-7.79 (m, 2 H; H^{Phth}), 7.72-7.68 (m, 2 H; H^{Phth}), 7.55-7.28 (m, 7 H; H^{Ar}), 7.18-7.13 (m, 4 H; H^{Ar}), 5.46 (bs, 1 H; $CONH_2$), 5.36 (bs, 1 H; $CONH_2$), 3.72 (t, ^{3}J (H,H) = 6.2 Hz, 2 H; CH_2^{Lys}), 3.04 (t, ^{3}J (H,H) = 8.0 Hz, 2 H; CH_2^{Gln}), 2.72 (t, ^{3}J (H,H) = 6.3 Hz, 2 H; CH_2^{Lys}), 2.55 (d, ^{3}J (H,H) = 7.2 Hz, 2 H; CH_2^{Leu}), 2.34 (t, ^{3}J (H,H) = 8.0 Hz, 2 H; CH_2^{Gln}), 2.00-1.86 (m, 1 H; CH^{Leu}), 1.73-1.71 (m, 4 H; CH_2^{Lys}), 0.95 (d, ^{3}J (H,H) = 6.6 Hz, 6 H; CH_3^{Leu}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 174.7 (C_q; $CONH_2$), 168.7 (C_q; $C{=}O^{Phth}$), 142.4 (C_q; C^{Ar}), 142.2 (C_q; C^{Ar}), 141.4 (C_q; C^{Ar}), 140.9 (C_q; C^{Ar}), 140.8 (C_q; C^{Ar}), 140.6 (C_q; C^{Ar}), 138.6 (C_q; C^{Ar}), 134.1 (C^{Phth}), 132.2 (C_q; C^{Phth}), 130.8 (C^{Ar}), 129.3 (C^{Ar}), 128.7 (C^{Ar}), 128.5 (C^{Ar}), 128.4 (C^{Ar}), 128.3 (C^{Ar}), 128.0 (C^{Ar}), 127.4 (C^{Ar}), 126.8 (C^{Ar}), 125.2 (C^{Ar}), 124.6 (C^{Ar}), 123.4 (C^{Phth}), 45.7 (CH_2^{Leu}), 38.0 (CH_2^{Lys}), 37.1 (CH_2^{Gln}), 35.4 (CH_2^{Lys}), 30.4 (CH^{Leu}), 29.4 (CH_2^{Gln}), 28.7 (CH_2^{Lys}), 28.3 (CH_2^{Lys}), 22.6 (CH_3^{Leu}) ppm.

m.p.$^{exp.}$ = 48-50°C.

HRMS (DI-EI): calcd (*m*/*z*) for [M^+]: 558.2883; found: 558.2925.

9.3.3.9 3-(3-(4-Aminobutyl)-3''-isobutyl-[1,1':4',1''-terphenyl]-2'-yl)propanamide (1f)



1f

In a 25 mL round-bottom flask 58 mg 3-(3-(4-(1,3-dioxoisoindolin-2-yl)butyl)-3''-isobutyl-[1,1':4',1''-terphenyl]-2'-yl)propanamide (**19c**) (0.10 mmol, 1.0 eq) were dissolved in 4 mL MeOH. After adding 50 µL $H_2NNH_2{\cdot}H_2O$ (52 mg, 1.04 mmol, 10.0 eq) the colorless solution was stirred for 3 d until full conversion was monitored by TLC, followed by evaporating the solvent under reduced pressure. Flash column chromatography (5.5 g SiO_2, 15x1 cm, MeOH, R_f = 0.08) afforded compound **1f** as a pale yellow oil.

Yield: 34 mg (79%), pale yellow oil, $C_{29}H_{36}N_2O$ [428.61 g/mol].

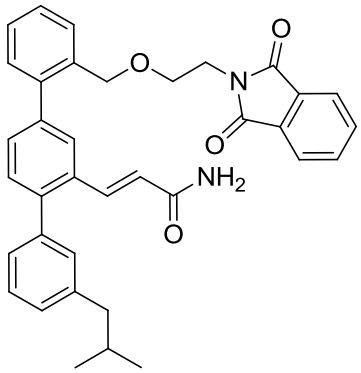
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (bs, 1 H; H^{Ar}), 7.47-7.22 (m, 6 H; H^{Ar}), 7.15-7.10 (m, 4 H; H^{Ar}), 5.77 (bs, 1 H; $CONH_2$), 5.63 (bs, 1 H; $CONH_2$), 2.99 (t, ^3J (H,H) = 8.1 Hz, 2 H; CH_2^{Gln}), 2.68-2.63 (m, 4 H; CH_2^{Lys}), 2.52 (d, ^3J (H,H) = 7.2 Hz, 2 H; CH_2^{Leu}), 2.28 (t, ^3J (H,H) = 8.1 Hz, 2 H; CH_2^{Gln}), 2.06 (bs, 2 H; NH_2), 1.96-1.81 (m, 1 H; CH^{Leu}), 1.71-1.61 (m, 2 H; CH_2^{Lys}), 1.49-1.39 (m, 2 H; CH_2^{Lys}), 0.91 (d, ^3J (H,H) = 6.6 Hz, 6 H; CH_3^{Leu}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 174.8 (C_q; $CONH_2$), 142.4 (C_q; C^{Ar}), 142.4 (C_q; C^{Ar}), 141.3 (C_q; C^{Ar}), 141.0 (C_q; C^{Ar}), 140.8 (C_q; C^{Ar}), 140.6 (C_q; C^{Ar}), 138.7 (C_q; C^{Ar}), 130.7 (C^{Ar}), 129.4 (C^{Ar}), 128.7 (C^{Ar}), 128.5 (C^{Ar}), 128.3 (C^{Ar}), 128.2 (C^{Ar}), 128.0 (C^{Ar}), 127.4 (C^{Ar}), 126.7 (C^{Ar}), 125.2 (C^{Ar}), 124.6 (C^{Ar}), 45.7 (CH_2^{Leu}), 41.9 (CH_2^{Lys}), 37.0 (CH_2^{Gln}), 35.6 (CH_2^{Lys}), 32.5 (CH_2^{Lys}), 30.4 (CH^{Leu}), 29.3 (CH_2^{Gln}), 28.6 (CH_2^{Lys}), 22.6 (CH_3^{Leu}) ppm.

HPLC (Nucleodur, ESI^+): t_R = 16.60 min; *m/z*: 429 [M^++H], 451 [M^++Na]; λ_{max} = 210, 230, 294 nm.

HRMS (DI-EI): calcd (*m*/*z*) for [M^+]: 428.2828; found: 428.2852.

9.3.3.10 (*E*)-3-(2''-((2-(1,3-Dioxoisoindolin-2-yl)ethoxy)methyl)-3-isobutyl-[1,1':4',1''-terphenyl]-2'-yl)acrylamide (41d)



41d

Compound **41d** was prepared according to procedure 9.2.4.1 from 100 mg (*E*)-3-(4-bromo-3'-isobutyl-[1,1'-biphenyl]-2-yl)acrylamide (**39d**) (0.28 mmol, 1.0 eq), 136 mg 2-(2-((2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)oxy)ethyl)isoindoline-1,3-dione (**2c**) (0.33 mmol, 1.2 eq), 85 mg CsF (0.56 mmol, 2.0 eq) and 7 mg $PdCl_2$(dppf)·DCM (9 µmol, 3 mol%) in 12 mL absolute, degassed 1,2-DME at 80°C. The aryl-aryl coupling was completed within 16 h and after flash column chromatography (9 g SiO_2, 18x1.5 cm, cyclohexane/EtOAc = 45/55, R_f = 0.30), product **41d** was isolated as a pale yellow solid.
Yield: 133 mg (85%), colorless solid, $C_{36}H_{34}N_2O_4$ [558.67 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82-7.71 (m, 6 H; H^{Phth}, H^{Ar}, CH), 7.46 (d, ^{3}J (H,H) = 7.2 Hz, 1 H; H^{Ar}), 7.36-7.33 (m, 6 H; H^{Ar}), 7.19-7.16 (m, 3 H; H^{Ar}), 6.63 (d, ^{3}J (H,H) = 15.5 Hz, 1 H; CH), 6.52 (bs, 1 H; $CONH_2$, overlapping), 5.69 (bs, 1 H; $CONH_2$), 4.45 (s, 2 H; CH_2^{Lys}), 3.94 (t, ^{3}J (H,H) = 5.1 Hz, 2 H; CH_2^{Lys}), 3.76 (t, ^{3}J (H,H) = 5.1 Hz, 2 H; CH_2^{Lys}), 2.53 (d, ^{3}J (H,H) = 7.1 Hz, 2 H; CH_2^{Leu}), 1.99-1.88 (m, 1 H; CH^{Leu}), 0.95 (d, ^{3}J (H,H) = 6.5 Hz, 6 H; CH_3^{Leu}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 168.7 (C_q; $C{=}O^{Phth}$), 168.2 (C_q; $CONH_2$), 142.1 (C_q; C^{Ar}), 141.9 (C_q; C^{Ar}), 141.8 (C_q; C^{Ar}), 141.6 (CH), 139.8 (C_q; C^{Ar}), 139.6 (C_q; C^{Ar}), 134.7 (C_q; C^{Ar}), 134.2 (C^{Phth}), 132.6 (C_q; C^{Ar}), 132.1 (C_q; C^{Phth}), 130.8 (C^{Ar}), 130.6 (C^{Ar}), 130.4 (C^{Ar}), 130.4 (C^{Ar}), 130.3 (C^{Ar}), 128.6 (C^{Ar}), 128.3 (C^{Ar}), 128.2 (C^{Ar}), 127.9 (C^{Ar}), 127.7 (C^{Ar}), 127.4 (C^{Ar}), 123.5 (C^{Phth}), 121.1 (CH), 71.5 (CH_2^{Lys}), 67.0 (CH_2^{Lys}), 45.6 (CH_2^{Leu}), 38.1 (CH_2^{Lys}), 30.4 (CH^{Leu}), 22.6 (CH_3^{Leu}) ppm.

m.p.$^{exp.}$ = 61-67°C.

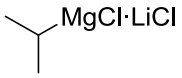
HRMS (DI-EI): calcd (*m*/*z*) for [M^+]: 558.2559; found: 558.2518.*

* HRMS (DI-EI) spectrum also showed degradation fragments because of decomposition during heating process.

9.4 Synthesis of Teraryls using the Triflate Approach

9.4.1 Synthesis of Pyridine-Based Building Blocks A and C

9.4.1.1 Isopropylmagnesium chloride lithium chloride solution (*i*PrMgCl·LiCl) (52)



52

A flame dried 250 mL two-neck round-bottom flask with reflux condenser (with argon-inlet) was charged with 7.34 g magnesium turnings (0.30 mol, 1.2 eq) and heated in vacuo with a heat gun for 5 min on maximum power level. After cooling to room temperature, 30 mL absolute, degassed THF were added and the mixture was sonicated for 10 min. 23.20 mL 2-chloropropane (19.93 g, 0.25 mol, 1.0 eq) were added *via* syringe under inert conditions. After activation by heating, the strong exothermic reaction was kept between 55°C and 60°C by intensive ice cooling. If the reaction did not start by heating, a small crystal of iodine was added without stirring to initiate the reaction at a localized position. After the Grignard formation had started, the suspension was diluted with 85 mL absolute, degassed THF (overall 115 mL, $c^{calcd} \approx 2.2$M). After decay of the exothermic reaction, the mixture was heated for ~1 h at 80°C, stirred overnight at room temperature and finally filtered under inert conditions using a Schlenk filtration funnel. A titration according to procedure 9.4.1.2 was performed to obtain the concentration of the isopropylmagnesium chloride. The pale brown filtered Grignard solution was added to 9.93 g ground and vacuum dried (120°C/6 h) lithium chloride (0.23 mmol, 1.0 eq, based on the formed Grignard). After stirring for 12 h at room temperature, the *i*PrMgCl·LiCl solution (**52**) was titrated again using the following procedure.[*,[79]]

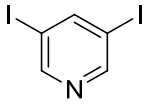
9.4.1.2 Titration of isopropylmagnesium chloride lithium chloride solution (*i*PrMgCl·LiCl) (52)

A flame dried amber glass 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 calculated concentration of this stock solution (c^{calcd} = 0.99M) was used as reference for the titration of *i*PrMgCl·LiCl solution (**52**).

[*] The *i*PrMgCl·LiCl solution was stored under an atmosphere of argon at -28°C.
[†] 2-Butanol, Sigma-Aldrich 294810, anhydrous, 99.5%.

In a Schlenk-flask ~2-5 mg *N*-phenyl-4-phenylazoaniline were dissolved in 2.0 mL stock solution and the Grignard solution was added dropwise under inert conditions. The equivalence point was indicated by a sharp color change from yellow-orange to deep red. To ensure a precise titration a triple determination was performed. The titration was carried out before every use of the Grignard solution.[*,†]

9.4.1.3 3,5-Diiodopyridine (49b)



49b

In a flame dried 250 mL Schlenk-flask 7.27 g 3,5-dibromopyridine (**49a**) (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*'-dimethylethylenediamine (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 with 50 mL saturated NH_4Cl solution and the deep blue aqueous phase was extracted with DCM (4x70 mL), after filtration. The combined yellow organic layers were dried over Na_2SO_4, filtered and concentrated to dryness. The golden crude product (9.23 g, 91%) was recrystallized from 235 mL EtOH. As alternative purification method small amounts could be sublimated by 110-120°C at 0.01 torr.[§,[110]]

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

TLC: R_f = 0.68 (cyclohexane/EtOAc = 9/1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.75 (d, ^4J (H,H) = 1.3 Hz, 2 H; H^{Py}), 8.35 (t, ^4J (H,H) = 1.8 Hz, 1 H; H^{Py}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 154.3 (C^{Py}), 151.7 (C^{Py}), 94.0 (C_q; C^{Py}) ppm.

[*] According to Sigma-Aldrich titration method "Titrimetric analysis of Organolithium compounds and Grignard reagents".
[†] If the concentration of the active Grignard had decreased by more than a half, the reaction time of the metal-halide exchange was dramatically prolonged.
[‡] Commercially available CuI was washed with THF using a Soxhlet extractor before use. After drying in vacuo CuI was stored in a freezer under an atmosphere of argon.
[§] Starting from 3,5-dichloropyridine, no conversion was observed under same conditions.

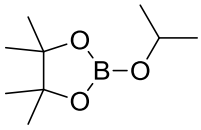
GC-MS (EI, 70 eV; MP_50_S): t_R = 5.66 min; *m/z* (%): 331 (100) [M^+], 204 (46) [M^+−I], 77 (17) [M^+−I_2].

m.p.$^{exp.}$ = 166-168°C (m.p.$^{lit.}$ = 170-172°C).[111]

sublim.$^{exp.}$ = 100-110°C, 0.01 torr (sublim.$^{lit.}$ = 110-120°C, 0.01 torr).[110]

Analytical data are in accordance with those reported.[111]

9.4.1.4 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (PinBO*i*Pr) (54a)



54a

A flame dried and argon-flushed 100 mL two-neck round-bottom flask, equipped with argon-inlet, was charged with 6.92 g pinacol (58.6 mmol, 1.0 eq) and 13.50 mL triisopropyl borate (11.00 g, 58.5 mmol, 1.0 eq). After stirring for 2 h at 68°C, the formed 2-propanol was removed under inert conditions in vacuo at room temperature (~15 mbar). Compound **54a** was isolated by fractionated distillation (b.p.$^{1.4}$ = 30°C) as a colorless liquid.*,[79,112]
Yield: 4.75 g (44%), colorless liquid, $C_9H_{19}BO_3$ [186.06 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.32 (sept, ^3J (H,H) = 6.1 Hz, 1 H; CH), 1.24 (s, 12 H; CH_3^{BPin}), 1.19 (d, ^3J (H,H) = 6.1 Hz, 6 H; CH_3) ppm.†

^{13}C NMR (76 MHz, $CDCl_3$): δ = 82.6 (C_q; C^{BPin}), 67.5 (CH), 24.7, (CH_3^{BPin}), 24.5 (CH_3) ppm.†

GC-MS (EI, 70 eV; MP_50_S): t_R = 3.94 min; *m/z* (%): 186 (1) [M^+], 171 (100) [M^+−CH_3], 129 (33) [M^+−C_4H_9].

b.p.$^{exp.}$ = 30°C, 1.4 torr, (b.p.$^{lit.}$ = 52°C, 9.0 torr).[113]

Analytical data are in accordance with those reported.[112]

* The purchased 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (PinBO*i*Pr) (Aldrich 417149, 98%) can also be used without further purification.
† NMR data also showed signals for the condensation product 2,2'-oxybis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane ($(PinB)_2O$) and 2-propanol.

9.4.1.5 Representative procedure for the first metal-halide exchange

A flame dried and argon-flushed 100 mL two-neck round-bottom flask, equipped with argon-inlet, was charged with 3,5-diiodopyridine (**49b**) (1.0 eq) and absolute, degassed THF was added until a clear solution was achieved at room temperature (c ≈ 0.2M). The colorless solution was cooled to -78°C and *i*PrMgCl·LiCl solution (**52**) (1.05 eq) was added in one portion. After degassing, the pale yellow solution was stirred at -78°C until full conversion (1.5-2 h) was detected by GC-MS. The metal-halide exchange was monitored by GC-MS, after quenching a small aliquot of the reaction mixture with saturated NH_4Cl solution and extracted with DCM. After quantitative conversion, the corresponding electrophile was added and the reaction mixture was allowed to warm to room temperature after 30 min at -78°C and kept stirring until full conversion was detected by GC-MS. The reaction mixture was quenched with saturated NH_4Cl solution, extracted with DCM (5×20 mL) and dried over Na_2SO_4. After filtration, the solvent was removed in vacuo using a rotary evaporator and the yellow or orange oil was purified by flash column chromatography (short SiO_2-column, 4x4 cm, eluents are mentioned).[79]

9.4.1.6 Representative procedure for the formation of 3-(chloromethyl)-5-iodopyridine derivatives from the corresponding pyridine-3-yl-methanols

A 50 mL round-bottom flask with reflux condenser was charged with the corresponding pyridine-3-yl-methanol. After cooling to -12°C, freshly distilled $SOCl_2$ was added and the mixture was stirred at indicated temperature. In some cases DCM was added to ensure complete dissolution of the formed pyridinium-salt. The chlorination was monitored by GC-MS, after quenching a small aliquot of the reaction mixture with saturated Na_2CO_3 solution and extracted with DCM. After quantitative conversion, the $SOCl_2$ was distilled off and the crude product was quenched with saturated Na_2CO_3 solution. The aqueous phase (pH ~8) was extracted with DCM (4x20 mL) and the combined organic layers were washed with brine (1x15 mL). The pale yellow or reddish organic phase was dried over Na_2SO_4 and after filtration, the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (short SiO_2-column, 4x4 cm, eluents are denoted).

9.4.1.7 Representative procedure for the second metal-halide exchange

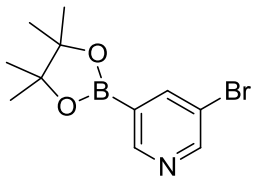
A flame dried and argon-flushed 50 mL two-neck round-bottom flask, equipped with argon-inlet, was charged with the corresponding 3-(chloromethyl)-5-iodopyridine derivative (1.0 eq) and absolute, degassed THF (c ≈ 0.2M) was added. The solution was cooled to -78°C

and *i*PrMgCl·LiCl solution (**52**) (1.1 eq) was added in one portion. After degassing, the solution was stirred at -78°C until full conversion was detected by GC-MS (~2 h). The GC-samples were prepared by quenching a small aliquot of the reaction mixture with saturated NH_4Cl solution and extracted with DCM. PinBO*i*Pr (**54a**) (1.15 eq) was added and the reaction mixture was allowed to warm to room temperature and kept stirring until full conversion (~1 h) was detected by GC-MS. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with DCM (4×25 mL). The combined organic layers were washed with brine (1x15 mL) and dried over Na_2SO_4. After filtration, the solvent was removed in vacuo using a rotary evaporator and the crude product was used in the next step without further purification, due to instability on SiO_2.[79]

9.4.1.8 Representative procedure for the dechlorination of the corresponding 3-(chloromethyl)-5-(BPin)-pyridines

In a 250 mL round-bottom flask 1.0 eq of the corresponding 3-(chloromethyl)5-(BPin)-pyridine derivatives was dissolved in a ~1.0M DCM/glacial acetic acid (21 eq) solution. After addition of zinc dust (<10 µm, equivalents are denoted), the green suspension was stirred at mentioned conditions, monitored by GC-MS analysis. The GC-samples were prepared by quenching a small aliquot of the reaction mixture with saturated Na_2CO_3 solution and extracted with DCM followed by filtration. After quantitative conversion the reaction mixture was quenched with saturated Na_2CO_3 solution, extracted with DCM (4×20 mL) and washed with brine (1x20 mL). The combined organic layers were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the pale yellow or orange, oily crude product was purified by Kugelrohr-distillation (temperature and pressure are mentioned).

9.4.1.9 3-Bromo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (50a)



50a

A flame dried and argon-flushed 250 mL two-neck round-bottom flask, equipped with argon inlet, was charged with 2.45 g 3,5-dibromopyridine (**49a**) (10.34 mmol, 1.0 eq) and 80 mL absolute, degassed THF were added. The colorless solution was cooled to -78°C and 23.80 mL *i*PrMgCl·LiCl solution (**52**) (13.09 mmol, 0.55M, 1.3 eq) were added in one portion. After degassing, the pale yellow solution was stirred at -78°C for 2.5 h followed by 2.13 mL PinBOiPr (**54a**) (1.94 g, 10.44 mmol, 1.0 eq). The reaction mixture was allowed to warm to room temperature after 30 min at -78°C and kept stirring overnight (~15 h). The reaction mixture was quenched with a small amount of saturated NH_4Cl solution, extracted with DCM (3×35 mL) and the combined organic layers were dried over Na_2SO_4. After filtration, the solvent was removed in vacuo using a rotary evaporator and the pale yellow, oily crude product was purified by flash column chromatography (25 g SiO_2, 5x4 cm, cyclohexane/EtOAc = 2/1, R_f = 0.28, tailing, CAM).

Yield: 482 mg (16%), pale yellow oil, $C_{11}H_{15}BBrNO_2$ [283.96 g/mol].[*,[114]]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.82 (d, ^4J (H,H) = 1.2 Hz, 1 H; H^{Py}), 8.72 (d, ^4J (H,H) = 2.5 Hz, 1 H; H^{Py}), 8.18 (dd, ^4J (H,H) = 2.3 Hz, ^4J (H,H) = 1.4 Hz, 1 H; H^{Py}), 1.34 (s, 12 H; CH_3^{BPin}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 153.4 (C^{Py}), 153.1 (C^{Py}), 144.7 (C^{Py}), 121.1 (C_q; C^{Py}), 84.8 (C_q; C^{BPin}), 25.0 (CH_3^{BPin}) ppm.[†]

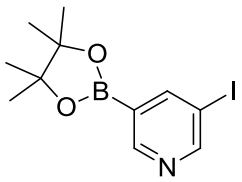
GC-MS (EI, 70 eV; MP_50_S): t_R = 6.30 min; *m/z* (%): 285 (37) [M^+], 283 (39) [M^+], 270 (97) [M^+−CH_3], 268 (100) [M^+−CH_3], 186 (47) [$C_5H_4BBrNO^+$], 184 (48) [$C_5H_4BBrNO^+$].

Analytical data are in accordance with those reported; in literature [D_6]DMSO was used.[114]

[*] In literature a colorless solid was obtained; m.p.$^{lit.}$ = 60°C

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

9.4.1.10 3-Iodo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (50b)



50b

A flame dried and argon-flushed 250 mL two-neck round-bottom flask, equipped with argon-inlet, was charged with 1.26 g 3,5-diiodopyridine (**49b**) (3.81 mmol, 1.0 eq) and 50 mL absolute, degassed THF were added. The colorless solution was cooled to -78°C and 2.44 mL *i*PrMgCl·LiCl solution (**52**) (3.81 mmol, 1.56M, 1.0 eq) were added in one portion. After degassing, the pale yellow solution was stirred at -78°C for 2.5 h and 930 µL PinBO*i*Pr (**54a**) (848 mg, 4.56 mmol, 1.2 eq) were added. The reaction mixture was allowed to warm to room temperature after 30 min at -78°C and kept stirring until full conversion (1.5 h) was achieved. The reaction mixture was quenched with small amount of saturated NH_4Cl solution, extracted with EtOAc (2x25 mL), DCM (2×20 mL) and dried over Na_2SO_4. After filtration, the solvent was removed in vacuo using a rotary evaporator and the pale yellow solid was purified by sublimation (50°C, $1 \cdot 10^{-3}$ mbar).[*,79]

Yield: 240 mg (19%), colorless solid, $C_{11}H_{15}BINO_2$ [330.96 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.87 (d, ^4J (H,H) = 2.0 Hz, 1 H; H^{Py}), 8.84 (bs, 1 H; H^{Py}), 8.38 (d, ^4J (H,H) = 1.9 Hz, 1 H; H^{Py}), 1.34 (s, 12 H; CH_3^{BPin}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 157.6 (C^{Py}), 153.3 (C^{Py}), 150.6 (C^{Py}), 93.9 (C_q; C^{Py}), 84.8 (C_q; C^{BPin}), 25.0 (CH_3^{BPin}) ppm.[†]

GC-MS (EI, 70 eV; MP_50_S): t_R = 6.65 min; *m/z* (%): 331 (77) [M^+], 316 (100) [M^+-CH_3], 232 (51) [$C_5H_4BINO^+$].

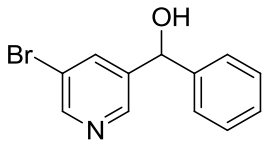
m.p.$^{exp.}$ = 64-66°C (m.p.$^{lit.}$ = 70.9-73.2°C).[79]

Analytical data are in accordance with those reported.[79]

[*] Dramatically lower yields where obtained using the purification method reported in literature (recrystallization from DCM).[79]

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

9.4.1.11 (5-Bromopyridin-3-yl)(phenyl)methanol (55a)



55a

Compound **55a** was prepared according to procedure 9.4.1.5 from 3.00 g 3,5-dibromopyridine (**49a**) (12.66 mmol, 1.0 eq) in 20 mL absolute, degassed THF, 6.59 mL *i*PrMgCl·LiCl solution (**52**) (12.65 mmol, 1.92M, 1.0 eq) and 1.54 mL benzaldehyde (**53a**) (1.61 g, 15.17 mmol, 1.2 eq). The metal-halide exchange was completed after 2 h. The crude product was purified by flash column chromatography (150 g SiO_2, 21x3.5 cm, cyclohexane/EtOAc = 3/1, R_f = 0.15, CAM) to achieve compound **55a** as a pale yellow oil.
Yield: 3.16 g (95%), pale yellow, highly viscous oil, $C_{12}H_{10}BrNO$ [264.12 g/mol].

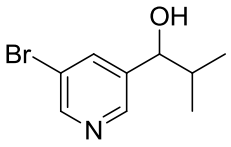
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.45 (d, ^4J (H,H) = 2.0 Hz, 1 H; H^{Py}), 8.42 (d, ^4J (H,H) = 1.2 Hz, 1 H; H^{Py}), 7.89 (t, ^4J (H,H) = 1.7 Hz, 1 H; H^{Py}), 7.40-7.28 (m, 5 H; H^{Ar}), 5.81 (s, 1 H; CH), 3.32 (bs, 1 H; OH) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 149.5 (C^{Py}), 146.1 (C^{Py}), 142.6 (C_q; C^{Ar}), 141.4 (C_q; C^{Py}), 137.0 (C^{Py}), 129.1 (C^{Ar}), 128.5 (C^{Ar}), 126.7 (C^{Ar}), 121.0 (C_q; C^{Py}), 73.6 (CH) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 7.19 min; *m/z* (%): 265 (97) [M^+], 263 (100) [M^+], 248 (4) [M^+−HO], 246 (5) [M^+−HO], 184 (31) [M^+−Br], 167 (14) [M^+−HBrO], 158 (75) [$C_{10}H_8NO^+$], 107 (39) [$C_7H_7O^+$].

Analytical data are in accordance with those reported.[115]

9.4.1.12 1-(5-Bromopyridin-3-yl)-2-methylpropan-1-ol (55b)



55b

Compound **55b** was prepared according to procedure 9.4.1.5 from 2.65 g 3,5-dibromopyridine (**49a**) (11.19 mmol, 1.0 eq) in 20 mL absolute, degassed THF, 5.90 mL *i*PrMgCl·LiCl solution (**52**) (11.33 mmol, 1.92M, 1.0 eq) and 1.30 mL isobutyraldehyde (**53b**) (1.03 g, 14.28 mmol, 1.3 eq). The metal-halide exchange was completed after 1.5 h.

The crude product was purified by flash column chromatography (91 g SiO_2, 20x4 cm, cyclohexane/EtOAc = 5/2, R_f = 0.24, CAM) to achieve compound **55b** as a pale yellow, highly viscous oil.

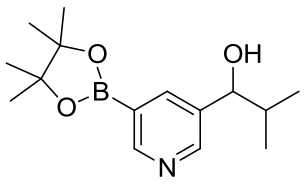
Yield: 2.21 g (86%), pale yellow oil, $C_9H_{12}BrNO$ [230.10 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.50 (d, ^4J (H,H) = 2.1 Hz, 1 H; H^{Py}), 8.36 (d, ^4J (H,H) = 1.5 Hz, 1 H; H^{Py}), 7.84 (t, ^4J (H,H) = 1.8 Hz, 1 H; H^{Py}), 4.43 (d, ^3J (H,H) = 6.3 Hz, 1 H; C*H*-OH), 2.99 (bs, 1 H; OH), 1.99-1.88 (m, 1 H; CH), 0.95 (d, ^3J (H,H) = 6.7 Hz, 3 H; CH_3), 0.84 (d, ^3J (H,H) = 6.8 Hz, 3 H; CH_3) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 149.6 (C^{Py}), 146.3 (C^{Py}), 141.2 (C_q; C^{Py}), 137.1 (C^{Py}), 120.9 (C_q; C^{Py}), 76.6 (CH-OH), 35.4 (CH), 18.8 (CH_3), 17.7 (CH_3) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 5.94 min, *m/z* (%): 231 (20) [M^+], 229 (20) [M^+], 188 (96) [M^+−C_3H_7], 186 (100) [M^+−C_3H_7].

9.4.1.13 2-Methyl-1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)propan-1-ol (56b)



56b

In a flame dried and argon-flushed 25 mL Schlenk-flask 269 mg 3,5-diiodopyridine (**49b**) (0.81 mmol, 1.0 eq) were dissolved in 4 mL absolute, degassed THF. At -78°C 680 µL *i*PrMgCl·LiCl solution (**52**) (0.82 mmol, 1.20M, 1.0 eq) were added to the colorless reaction mixture. After degassing, the pale yellow solution was stirred at -78°C for 2.5 h and 180 µL PinBO*i*Pr (**54a**) (164 mg, 0.88 mmol, 1.1 eq) were added. The colorless solution was stirred for 1.5 h at -78°C and after warming to room temperature for further 1.5 h. Subsequently, the second metal-halide exchange was performed by adding additional 1.00 mL *i*PrMgCl·LiCl solution (**52**) (1.20 mmol, 1.20M, 1.5 eq) and after stirring for 2.5 h at -78°C 190 µL isobutyraldehyde (**53b**) (150 mg, 2.08 mmol, 2.5 eq) were added. The reaction mixture was stirred overnight in the dry ice/acetone mixture, followed by addition of 4 mL saturated NH_4Cl solution. The aqueous phase was extracted with DCM (3x20 mL) and dried over

Na_2SO_4. After filtration and removing the solvent under reduced pressure, the crude product was recrystallized from 2 mL *n*-pentane, yielding product **56b** as a colorless solid.*

Yield: 32 mg (14%), colorless solid, $C_{15}H_{24}BNO_3$ [277.17 g/mol].

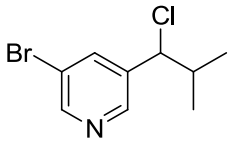
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.79 (s, 1 H; H^{Py}), 8.54 (s, 1 H; H^{Py}), 8.02 (s, 1 H; H^{Py}), 4.41 (d, ^3J (H,H) = 6.6 Hz, 1 H; C*H*-OH), 2.93 (bs, 1 H; OH), 2.04-1.90 (m, 1 H; CH), 1.34 (s, 12 H; CH_3^{BPin}), 0.98 (d, ^3J (H,H) = 6.6 Hz, 3 H; CH_3), 0.81 (d, ^3J (H,H) = 6.8 Hz, 3 H; CH_3) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 154.1 (C^{Py}), 150.3 (C^{Py}), 140.8 (C^{Py}), 138.5 (C_q; C^{Py}), 84.4 (C_q; C^{BPin}), 77.7 (CH-OH), 35.3 (CH), 25.0 (CH_3^{BPin}), 19.0 (CH_3), 18.0 (CH_3) ppm.†

GC-MS (EI, 70 eV; MP_50_S): t_R = 7.10 min; *m/z* (%): 277 (2) [M^+], 262 (3) [M^+-CH_3], 234 (100) [$M^+-C_3H_7$].

m.p.$^{exp.}$ = 57-58°C.

9.4.1.14 3-Bromo-5-(1-chloro-2-methylpropyl)pyridine (59b´)



59b´

In a flame dried 50 mL two-neck round-bottom flask with argon-inlet 463 mg 1-(5-bromo-pyridin-3-yl)-2-methylpropan-1-ol (**55b**) (2.01 mmol, 1.0 eq) were dissolved in 5 mL freshly distilled $SOCl_2$. The pale yellow solution was stirred at 80°C overnight (~17 h) and the reaction mixture was quenched with 16 mL saturated Na_2CO_3 solution at 0°C. The aqueous phase was extracted with DCM (4x30 mL) and the combined organic layers were dried over Na_2SO_4. After filtration and removing the solvent under reduced pressure, compound **59b´** was isolated as a colorless oil after flash column chromatography (48 g SiO_2, 25x2.5 cm, cyclohexane/EtOAc = 20/1, R_f = 0.10).

Yield: 396 mg (79%), colorless oil, $C_9H_{11}BrClN$ [248.55 g/mol].

* HRMS (EI) gave no unambiguous results because of decomposition during heating process.
† Signal for the quaternary *ipso*-pyridine carbon (C_q; C^{Py}) at the boronic acid pinacol ester function was not observed.

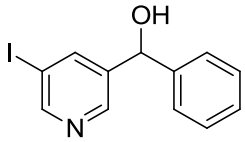
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.61 (bs, 1 H; H^{Py}), 8.47 (bs, 1 H; H^{Py}), 7.89 (t, ^4J (HH) = 1.9 Hz, 1 H; H^{Py}), 4.64 (d, ^3J (H,H) = 7.2 Hz, 1 H; CH-Cl), 2.30-2.14 (m, 1 H; CH), 1.09 (d, ^3J (H,H) = 6.6 Hz, 3 H; CH_3), 0.92 (d, ^3J (H,H) = 6.7 Hz, 3 H; CH_3) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 150.3 (C^{Py}), 146.7 (C^{Py}), 138.6 (C_q; C^{Py}), 138.0 (C^{Py}), 120.9 (C_q; C^{Py}), 66.5 (CH-Cl), 36.6 (CH), 20.0 (CH_3), 19.1 (CH_3) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 5.81 min, *m/z* (%): 251 (9) [M^+], 249 (36) [M^+], 247 (29) [M^+], 209 (25) [$C_6H_5BrClN^+$], 207 (100) [$C_6H_5BrClN^+$], 205 (75) [$C_6H_5BrClN^+$].

HRMS (EI): calcd (*m*/*z*) for [M^+]: 246.9763; found: 246.9782.

9.4.1.15 (5-Iodopyridin-3-yl)(phenyl)methanol (58a)



58a

Compound **58a** was prepared according to procedure 9.4.1.5 from 1.78 g 3,5-diiodopyridine (**49b**) (5.38 mmol, 1.0 eq) in 22 mL absolute, degassed THF, 3.38 mL *i*PrMgCl·LiCl solution (**52**) (5.65 mmol, 1.67M, 1.05 eq) and 534 µL benzaldehyde (**53a**) (557 mg, 5.25 mmol, 1.0 eq). The metal-halide exchange was completed after 1.5 h. The crude product was purified by flash column chromatography (cyclohexane/EtOAc = 3/1, R_f = 0.21, CAM) to achieve compound **58a** as a colorless, highly viscous oil.
Yield: 1.62 g (99%), colorless, highly viscous oil, $C_{12}H_{10}INO$ [311.12 g/mol].

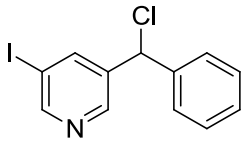
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.64 (d, ^4J (H,H) = 1.5 Hz, 1 H; H^{Py}), 8.48 (d, ^4J (H,H) = 1.1 Hz, 1 H; H^{Py}), 8.09 (bs, 1 H; H^{Py}), 7.38-7.31 (m, 5 H; H^{Ar}), 5.80 (s, 1 H; CH), 2.94 (bs, 1 H; OH) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 154.3 (C^{Py}), 146.3 (C^{Py}), 142.8 (C^{Py}), 142.5 (C_q; C^{Ar}), 141.6 (C_q; C^{Py}), 129.1 (C^{Ar}), 128.6 (C^{Ar}), 126.7 (C^{Ar}), 93.6 (C_q; C^{Py}), 73.61 (CH) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 7.52 min; *m/z* (%): 311 (100) [M^+], 294 (3) [M^+−OH], 234 (8) [M^+−C_6H_5], 204 (14) [M^+−C_7H_7O].

HRMS (EI): calcd (*m*/*z*) for [M^+]: 310.9807; found: 310.9822.

9.4.1.16 3-(Chloro(phenyl)methyl)-5-iodopyridine (59a)



59a

Compound **59a** was prepared according to procedure 9.4.1.6 from 1.52 g (5-iodopyridin-3-yl)(phenyl)methanol (**58a**) (4.89 mmol, 1.0 eq) in 5 mL $SOCl_2$. After stirring at room temperature for 1.5 h and removing the $SOCl_2$ by distillation, the crude product was purified by flash column chromatography (cyclohexane/EtOAc = 7/1, R_f = 0.35, CAM). Compound **59a** was isolated as a pale brown, highly viscous oil.

Yield: 1.47 g (91%), pale brown, highly viscous oil, $C_{12}H_9ClIN$ [329.56 g/mol].

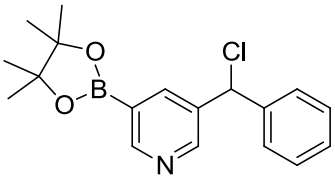
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.76 (d, ^4J (H,H) = 1.8 Hz, 1 H; H^{Py}), 8.57 (d, ^4J (H,H) = 1.8 Hz, 1 H; H^{Py}), 8.12 (t, ^4J (H,H) = 1.7 Hz, 1 H; H^{Py}), 7.40-7.36 (m, 5 H; H^{Ar}), 6.05 (s, 1 H; CH) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 154.9 (C^{Py}), 147.1 (C^{Py}), 144.1 (C^{Py}), 139.3 (C_q; C^{Ar}), 139.2 (C_q; C^{Py}), 129.2 (C^{Ar}), 129.0 (C^{Ar}), 127.8 (C^{Ar}), 93.4 (C_q; C^{Py}), 60.6 (CH) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 7.38 min; *m/z* (%): 329 (10) [M^+], 294 (100) [M^+−Cl], 167 (55) [M^+−ClI].

HRMS (EI): calcd (*m*/*z*) for [M^+]: 328.9468; found: 328.9450.

9.4.1.17 3-(Chloro(phenyl)methyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-pyridine (60a)



60a

Compound **60a** was prepared according to procedure 9.4.1.7 from 1.43 g 3-(chloro(phenyl)methyl)-5-iodopyridine (**59a**) (4.34 mmol, 1.0 eq) in 20 mL absolute, degassed THF, 2.87 mL *i*PrMgCl·LiCl solution (**52**) (4.79 mmol, 1.67M, 1.1 eq) and 1.02 mL PinBO*i*Pr (**54a**) (930 mg, 5.00 mmol, 1.15 eq). The second metal-halide exchange was

completed after 1.5 h and the crude product was used in the next step without further purification.

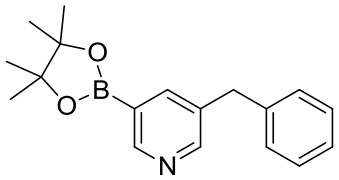
Yield: 1.56 g (109%, crude), reddish oil, $C_{18}H_{21}BClNO_2$ [329.63 g/mol].

TLC: R_f = 0.20 (cyclohexane/EtOAc = 6/4, CAM).

GC-MS (EI, 70 eV; MP_50_S): t_R = 8.14 min; *m/z* (%): 329 (1) [M^+], 294 (100) [M^+−Cl], 194 (32) [M^+−$C_6H_{12}ClO$].

HRMS (EI): calcd (*m/z*) for [M^+]: 329.1357; found: 329.1358.

9.4.1.18 3-Benzyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (51a)



51a

Compound **51a** was prepared according to procedure 9.4.1.8 from 1.43 g 3-(chloro(phenyl)methyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**60a**) (4.34 mmol, 1.0 eq) in 100 mL DCM (c ≈ 0.9M, with regard to glacial acetic acid), 5.21 mL glacial acetic acid (5.47 g, 91.0 mmol, 21.0 eq) and 425 mg zinc dust (6.50 mmol, 1.5 eq). The dechlorination was completed after 2 h at room temperature. After Kugelrohr-distillation (175°C, $7 \cdot 10^{-3}$ mbar) product **51a** was isolated as a colorless solid.

Yield: 891 mg (84%, over two steps), colorless solid, $C_{18}H_{22}BNO_2$ [295.18 g/mol].

TLC: R_f = 0.08 ($EtOAc/NEt_3$ = 1/1000, tailing, CAM).

^{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.*

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

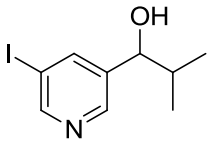
GC-MS (EI, 70 eV; MP_50_S): t_R = 7.71 min; *m/z* (%): 295 (97) [M^+], 280 (100) [M^+−CH_3], 238 (55) [M^+−C_4H_{13}], 194 (80) [M^+−$C_6H_{13}O$].

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.

9.4.1.19 1-(5-Iodopyridin-3-yl)-2-methylpropan-1-ol (58b)



58b

Compound **58b** was prepared according to procedure 9.4.1.5 from 1.78 g 3,5-diiodopyridine (**49b**) (5.38 mmol, 1.0 eq) in 22 mL absolute, degassed THF, 3.38 mL *i*PrMgCl·LiCl solution (**52**) (5.64 mmol, 1.67M, 1.05 eq) and 540 µL isobutyraldehyde (**53b**) (427 mg, 5.92 mmol, 1.1 eq). The metal-halide exchange was completed after 3 h. The crude product was purified by flash column chromatography (cyclohexane/EtOAc = 3/1, R_f = 0.24, CAM) to obtain product **58b** as a pale yellow, highly viscous oil.
Yield: 1.38 g (95%), pale yellow, highly viscous oil, $C_9H_{12}INO$ [277.10 g/mol].

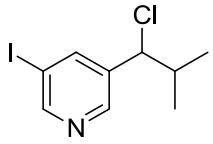
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.69 (d, ^4J (H,H) = 1.9 Hz, 1 H; H^{Py}), 8.43 (d, ^4J (H,H) = 1.6 Hz, 1 H; H^{Py}), 8.05 (t, ^4J (H,H) = 1.7 Hz, 1 H; H^{Py}), 4.41 (d, ^3J (H,H) = 6.3 Hz, 1 H; C*H*-OH), 2.62 (bs, 1 H; OH), 2.00-1.89 (m, 1 H; CH), 0.96 (d, ^3J (H,H) = 6.7 Hz, 3 H; CH_3), 0.86 (d, ^3J (H,H) = 6.8 Hz, 3 H; CH_3) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 154.3 (C^{Py}), 146.5 (C^{Py}), 143.0 (C^{Py}), 141.4 (C_q; C^{Py}), 93.5 (C_q; C^{Py}), 76.7 (CH-OH), 35.4 (CH), 18.9 (CH_3), 17.7 (CH_3) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 6.30 min; *m/z* (%): 277 (25) [M^+], 234 (100) [M^+−C_3H_7], 107 (9) [M^+−C_3H_7I].

HRMS (EI): calcd (*m*/*z*) for [M^+]: 276.9964; found: 276.9965.

9.4.1.20 3-(1-Chloro-2-methylpropyl)-5-iodopyridine (59b)



59b

Compound **59b** was prepared according to procedure 9.4.1.6 from 1.23 g 1-(5-iodopyridin-3-yl)-2-methylpropan-1-ol (**58b**) (4.44 mmol, 1.0 eq) in 5 mL $SOCl_2$. Quantitative conversion was detected after stirring under reflux overnight. Purification by flash column chromatography (cyclohexane/EtOAc = 5/1, R_f = 0.50) afforded compound **59b** as a highly viscous, pale yellow oil.

Yield: 1.11 g (85%), pale yellow, highly viscous oil, $C_9H_{12}ClIN$ [295.55 g/mol].

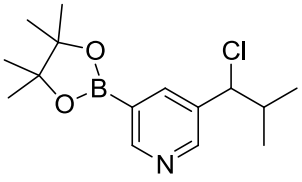
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.76 (d, ^4J (H,H) = 1.6 Hz, 1 H; H^{Py}), 8.50 (d, ^4J (H,H) = 1.6 Hz, 1 H; H^{Py}), 8.07 (t, ^4J (H,H) = 1.8 Hz, 1 H; H^{Py}), 4.60 (d, ^3J (H,H) = 7.2 Hz, 1 H; CH-Cl), 2.27-2.15 (m, 1 H; CH), 1.08 (d, ^3J (H,H) = 6.6 Hz, 3 H; CH_3), 0.92 (d, ^3J (H,H) = 6.7 Hz, 3 H; CH_3) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 155.0 (C^{Py}), 146.9 (C^{Py}), 143.8 (C^{Py}), 138.9 (C_q; C^{Py}), 93.3 (C_q; C^{Py}), 66.5 (CH-Cl), 36.6 (CH), 20.1 (CH_3), 19.1 (CH_3) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 6.19 min; *m/z* (%): 295 (77) [M^+], 260 (8) [M^+−Cl], 253 (100) [M^+−C_3H_6], 252 (18) [M^+−C_3H_7].

HRMS (EI): calcd (*m*/*z*) for [M^+]: 294.9625; found: 294.9626.

9.4.1.21 3-(1-Chloro-2-methylpropyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-pyridine (60b)



60b

Compound **60b** was prepared according to procedure 9.4.1.7 from 1.11 g 3-(1-chloro-2-methylpropyl)-5-iodopyridine (**59b**) (3.76 mmol, 1.0 eq) in 4 mL absolute, degassed THF, 2.47 mL *i*PrMgCl·LiCl solution (**52**) (4.12 mmol, 1.67M, 1.1 eq) and 950 µL PinBO*i*Pr (**54a**)

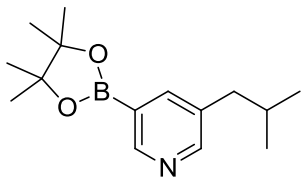
(866 mg, 4.66 mmol, 1.2 eq). The second metal-halide exchange was completed after 3 h and the crude product was used in the next step without further purification.

Yield: 1.22 g (110%, crude), orange-brown oil, $C_{15}H_{23}BClNO_2$ [295.61 g/mol].

GC-MS (EI, 70 eV; MP_50_S): t_R = 7.03 min; *m/z* (%): 295 (47) [M^+], 280 (96) [M^+-CH_3], 260 (47) [M^+-Cl], 252 (100) [$M^+-C_3H_7$].

HRMS (EI): calcd (*m/z*) for [M^+]: 295.1513; found: 295.1535.

9.4.1.22 3-Isobutyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (51b)



51b

Compound **51b** was prepared according to procedure 9.4.1.8 from 1.19 g 3-(1-chloro-2-methylpropyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**60b**) (4.03 mmol, 1.0 eq) in 100 mL DCM (c ≈ 1.0M, with regard to glacial acetic acid), 5.75 mL glacial acetic acid (6.03 g, 0.10 mol, 25.0 eq) and 1.31 g zinc dust (20.03 mmol, 5.0 eq). The dechlorination was completed after 20 h at 40°C. After Kugelrohr-distillation (100°C, $3\cdot10^{-2}$ mbar) compound **51b** was isolated as a colorless solid.

Yield: 583 mg (56%, over two steps), colorless solid, $C_{15}H_{24}BNO_2$ [261.17 g/mol].

TLC: R_f = 0.12 (cyclohexane/EtOAc = 2/8, tailing, CAM).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.77 (d, ^4J (H,H) = 1.3 Hz, 1 H; H^{Py}), 8.46 (d, ^4J (H,H) = 2.2 Hz, 1 H; H^{Py}), 7.88 (bs, 1 H; H^{Py}), 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, $CDCl_3$): δ = 152.3 (C^{Py}), 151.8 (C^{Py}), 143.4 (C^{Py}), 136.5 (C_q; C^{Py}), 84.4 (C_q; C^{BPin}), 42.4 (CH_2), 30.2 (CH), 25.0 (CH_3^{BPin}), 22.4 (CH_3) ppm.*

GC-MS (EI, 70 eV; MP_50_S): t_R = 6.55 min; *m/z* (%): 261 (63) [M^+], 246 (100), [M^+-CH_3], 218 (44) [$M^+-C_3H_7$], 204 (40) [$M^+-C_4H_9$], 162 (72) [$M^+-C_7H_{15}$].

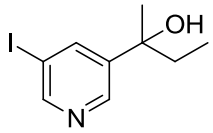
* Signal for the quaternary *ipso*-pyridine carbon (C_q; C^{Py}) at the boronic acid pinacol ester function was not observed.

m.p.$^{exp.}$ = 75-77°C.

b.p.^{KRD} = 100°C, $3 \cdot 10^{-2}$ mbar.

HRMS (EI): calcd (*m*/*z*) for [M^+]: 261.1903; found: 261.1884.

9.4.1.23 2-(5-Iodopyridin-3-yl)butan-2-ol (58c)



58c

Compound **58c** was prepared according to procedure 9.4.1.5 from 2.51 g 3,5-diiodopyridine (**49b**) (7.59 mmol, 1.0 eq) in 30 mL absolute, degassed THF, 6.64 mL *i*PrMgCl·LiCl solution (**52**) (7.57 mmol, 1.14M, 1.0 eq) and 2.05 mL 2-butanone (**53c**) (1.65 g, 22.9 mmol, 3.0 eq). The metal-halide exchange was completed after 4.5 h. Because of its instability on silica gel (formation of the corresponding elimination-product), the crude product was used in the next step without further purification.

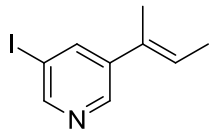
Yield: 2.07 g (99%, crude), yellow-orange, highly viscous oil, $C_9H_{12}INO$ [277.10 g/mol].

TLC: R_f = 0.35 (cyclohexane/EtOAc = 3/1, CAM).

GC-MS (EI, 70 eV; MP_50_S): t_R = 6.17 min; *m/z* (%): 277 (8) [M^+], 259 (54) [$M^+ - H_2O$], 248 (100) [$M^+ - C_2H_5$].

HRMS (EI): calcd (*m*/*z*) for [M^+]: 276.9964; found: 276.9989.

9.4.1.24 (*E*/*Z*)-3-(But-2-en-2-yl)-5-iodopyridine (61)



61

In a flame dried and argon-flushed Schlenk-flask 2.00 g 2-(5-iodopyridin-3-yl)butan-2-ol (**58c**) (7.22 mmol, 1.0 eq) were dissolved in 150 mL absolute DCM. After adding 1.00 mL concentrated H_2SO_4 (1.84 g, 18.76 mmol, 2.6 eq) the yellow solution was stirred at room temperature overnight. The reaction mixture was quenched with 100 mL saturated Na_2CO_3 solution and after extraction (DCM, 2x100 mL) of the aqueous phase (pH ~9) and washing

with brine (1x50 mL), the yellow combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness. Compound **61** was purified by flash column chromatography (45 g SiO_2, 32x2cm, cyclohexane/EtOAc = 10/1, R_f = 0.36, CAM) and was isolated as a pale yellow solid.*

Yield: 733 mg (39%, over two steps), pale yellow solid, $C_9H_{10}IN$ [259.09 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.65 (bs, 1 H; H^{Py}), 8.55 (bs, 1 H; H^{Py}), 7.98 (t, ^4J (H,H) = 1.8 Hz, 1 H; H^{Py}), 5.92 (dq, ^3J (H,H) = 6.8 Hz, ^4J (H,H) = 1.1 Hz, 1 H; CH), 2.00 (s, 3 H; CH_3), 1.81 (d, ^3J (H,H) = 6.8 Hz, 3 H; CH_3) ppm.

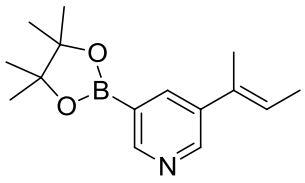
^{13}C NMR (76 MHz, $CDCl_3$): δ = 153.1 (C^{Py}), 145.4 (C^{Py}), 141.4 (C^{Py}), 135.6 (C_q; C^{Py}), 131.6 (C_q; C=CH), 126.2 (CH), 93.4 (C_q; C^{Py}), 15.2 (CH_3), 14.6 (CH_3) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 5.94 min; *m/z* (%): 259 (96) [M^+], 244 (17) [M^+-CH_3], 132 (17) [M^+-I], 117 (100) [M^+-CH_3I].

m.p.$^{exp.}$ = 43-45°C.

HRMS (EI): calcd (*m/z*) for [M^+]: 258.9858; found: 258.9872.

9.4.1.25 (*E*)-3-(But-2-en-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-pyridine (51c´)



51c´

Compound **51c´** was prepared according to procedure 9.4.1.7 from 565 mg (*E*)-3-(but-2-en-2-yl)-5-iodopyridine (**61**) (2.18 mmol, 1.0 eq) in 7 mL absolute, degassed THF, 3.73 mL *i*PrMgCl·LiCl solution (**52**) (4.36 mmol, 1.17M, 2.0 eq) and 950 µL PinBO*i*Pr (**54a**) (866 mg, 4.66 mmol, 2.1 eq). The second metal-halide exchange was completed after 4 h and compound **51c´** was isolated as a colorless solid by Kugelrohr-distillation (125°C, $4\cdot10^{-3}$ mbar).

Yield: 384 mg (68%), colorless solid, $C_{15}H_{22}BNO_2$ [259.15 g/mol].

* In the crude product also the *Z*-isomer was detected by GC-MS (*E*/*Z* = 9/1), but after flash column chromatography only the major isomer was detectable.

TLC: R_f = 0.21 (cyclohexane/EtOAc = 2/8, tailing, CAM).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.77 (s, 1 H; H^{Py}), 8.66 (s, 1 H; H^{Py}), 8.04 (bs, 1 H; H^{Py}), 5.92 (dq, ^3J (H,H) = 6.8 Hz, ^4J (H,H) = 1.3 Hz, 1 H; CH), 2.04 (s, 3 H; CH_3), 1.81 (dd, ^3J (H,H) = 6.9 Hz, ^4J (H,H) = 0.9 Hz, 3 H; CH_3), 1.35 (s, 12 H; CH_3^{BPin}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 152.7 (C^{Py}), 148.7 (C^{Py}), 139.6 (C^{Py}), 138.9 (C_q; C^{Py}), 132.6 (C_q; C=CH), 124.9 (CH), 84.4 (C_q; C^{BPin}), 25.0 (CH_3^{BPin}), 15.3 (CH_3), 14.5 (CH_3) ppm.*

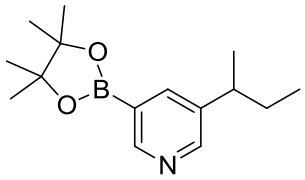
GC-MS (EI, 70 eV; MP_50_S): t_R = 6.86 min; *m/z* (%): 259 (100) [M^+], 244 (49) [M^+−CH_3], 202 (36) [M^+−C_4H_9], 160 (76) [M^+−C_7H_{15}], 144 (29) [M^+−$C_7H_{15}O$].

m.p.$^{exp.}$ = 71-72°C.

b.p.^{KRD} = 125°C, $4 \cdot 10^{-3}$ mbar.

HRMS (EI): calcd (*m*/*z*) for [M^+]: 259.1747; found: 259.1739.

9.4.1.26 3-(*sec*-Butyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (51c)



51c

Hydrogenation was performed utilizing a H-Cube™ at a pressure of 60 bar at 60°C with a 10% palladium on carbon powder cartridge (THS 01111). A solution of 38 mg 3-(but-2-en-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**51c´**) (0.15 mmol, 1.0 eq) in 3 mL MeOH (~0.05M) was used in continuous flow mode of 1.0 mL/min. After removing the solvent under reduced pressure, pure compound **51c** was isolated as a colorless oil.

Yield: 36 mg (92%), colorless, highly viscous oil, $C_{15}H_{24}BNO_2$ [261.17 g/mol].

TLC: R_f = 0.21 (cyclohexane/EtOAc = 2/8, tailing, CAM).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.77 (d, ^4J (H,H) = 1.5 Hz, 1 H; H^{Py}), 8.49 (d, ^4J (H,H) = 2.3 Hz, 1 H; H^{Py}), 7.85 (bs, 1 H; H^{Py}), 2.67-2.55 (m, 1 H; CH), 1.67-1.56 (m, 2 H; CH_2), 1.35

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

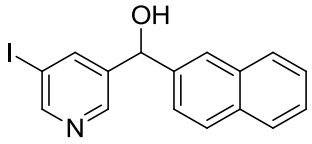
(s, 12 H; CH_3^{BPin}), 1.25 (d, ^3J (H,H) = 7.0 Hz, 3 H; CH_3), 0.82 (t, ^3J (H,H) = 7.4 Hz, 3 H; CH_3) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 153.3 (C^{Py}), 151.6 (C^{Py}), 141.8 (C_q; C^{Py}), 140.6 (C^{Py}), 84.3 (C_q; C^{BPin}), 39.4 (CH), 31.0 (CH_2), 25.0 (CH_3^{BPin}), 21.7 (CH_3), 12.3 (CH_3) ppm.*

GC-MS (EI, 70 eV; MP_50_S): t_R = 6.53 min; *m/z* (%): 261 (29) [M^+], 246 (27) [M^+−CH_3], 232 (100) [M^+−C_2H_5], 204 (11) [M^+−C_4H_9], 162 (23) [$C_9H_{13}BNO^+$].

HRMS (EI): calcd (*m/z*) for [M^+]: 261.1903; found: 261.1914.

9.4.1.27 (5-Iodopyridin-3-yl)(naphthalen-2-yl)methanol (58d)



58d

Compound **58d** was prepared according to procedure 9.4.1.5 from 2.03 g 3,5-diiodopyridine (**49b**) (6.13 mmol, 1.0 eq) in 25 mL absolute, degassed THF, 4.09 mL *i*PrMgCl·LiCl solution (**52**) (6.14 mmol, 1.50M, 1.0 eq) and 1.05 g 2-naphthaldehyde (**53d**) (6.72 mmol, 1.1 eq). The metal-halide exchange was completed after 2.5 h. After recrystallization of 2.47 g crude product (111%) from EtOAc/cyclohexane = 145/350, product **58d** was isolated as a colorless solid.

Yield: 1.50 g (68%), colorless solid, $C_{16}H_{12}INO$ [361.18 g/mol].

TLC: R_f = 0.15 (cyclohexane/EtOAc = 4/1, CAM).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.65 (s, 1 H; H^{Py}), 8.53 (s, 1 H; H^{Py}), 8.10 (s, 1 H; H^{Py}), 7.85-7.81 (m, 4 H; H^{Naph}), 7.54-7.48 (m, 2 H; H^{Naph}), 7.36 (dd, ^3J (H,H) = 8.5 Hz, ^4J (H,H) = 1.6 Hz, 1 H; H^{Naph}), 5.93 (s, 1 H; CH), 3.16 (bs, 1 H; OH) ppm.

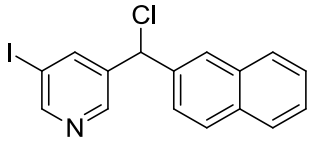
^{13}C NMR (76 MHz, $CDCl_3$): δ = 154.4 (C^{Py}), 146.5 (C^{Py}), 142.9 (C^{Py}), 141.5 (C_q; C^{Py}), 139.8 (C_q; C^{Naph}), 133.3 (C_q; C^{Naph}), 133.3 (C_q; C^{Naph}), 129.2 (C^{Naph}), 128.2 (C^{Naph}), 127.9 (C^{Naph}), 126.8 (C^{Naph}), 126.7 (C^{Naph}), 125.7 (C^{Naph}), 124.4 (C^{Naph}), 93.6 (C_q; C^{Py}), 73.7 (CH) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 9.60 min; *m/z* (%): 361 (43) [M^+], 344 (2) [M^+−OH], 129 (100) [$C_{10}H_9^+$].

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

HRMS (EI): calcd (*m*/*z*) for [M^+]: 360.9964; found: 360.9967.

9.4.1.28 3-(Chloro(naphthalen-2-yl)methyl)-5-iodopyridine (59d)



59d

Compound **59d** was prepared according to procedure 9.4.1.6 from 1.45 g (5-iodopyridin-3-yl)(naphthalen-2-yl)methanol (**58d**) (4.01 mmol, 1.0 eq) in 15 mL $SOCl_2$. After stirring for 5 h at room temperature, the $SOCl_2$ was distilled off under inert conditions and the crude product was recrystallized from 5 mL EtOAc. Compound **59d** was isolated as a colorless solid.

Yield: 1.13 g (74%), colorless solid, $C_{16}H_{11}ClIN$ [379.62 g/mol].

TLC: R_f = 0.46 (cyclohexane/EtOAc = 4/1, CAM).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.78 (s, 1 H; H^{Py}), 8.64 (s, 1 H; H^{Py}), 8.14 (s, 1 H; H^{Py}), 7.88-7.83 (m, 4 H; H^{Naph}), 7.53 (dd, ^3J (H,H) = 6.3 Hz, ^3J (H,H) = 3.3 Hz, 2 H; H^{Naph}), 7.44 (dd, ^3J (H,H) = 8.6 Hz, ^4J (H,H) = 1.8 Hz, 1 H; H^{Naph}), 6.22 (s, 1 H; CH) ppm.

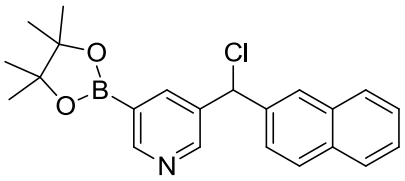
^{13}C NMR (76 MHz, $CDCl_3$): δ = 155.1 (C^{Py}), 147.3 (C^{Py}), 144.0 (C^{Py}), 139.0 (C_q; C^{Py}), 136.5 (C_q; C^{Naph}), 133.3 (C_q; C^{Naph}), 133.1 (C_q; C^{Naph}), 129.3 (C^{Naph}), 128.3 (C^{Naph}), 127.9 (C^{Naph}), 127.2 (C^{Naph}), 127.0 (C^{Naph}), 127.0 (C^{Naph}), 125.1 (C^{Naph}), 93.4 (C_q; C^{Py}), 61.0 (CH) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 9.29 min; *m/z* (%): 379 (19) [M^+], 344 (100) [M^+−Cl], 217 (46) [$C_6H_4IN^+$], 127 (6) [$C_{10}H_7^+$].

m.p.$^{exp.}$ = 108-110°C.

HRMS (EI): calcd (*m*/*z*) for [M^+]: 378.9625; found: 378.9643.

9.4.1.29 3-(Chloro(naphthalen-2-yl)methyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (60d)



60d

Compound **60d** was prepared according to procedure 9.4.1.7 from 1.14 g 3-(chloro(naphthalen-2-yl)methyl)-5-iodopyridine (**59d**) (3.00 mmol, 1.0 eq) in 15 mL absolute, degassed THF, 2.93 mL *i*PrMgCl·LiCl solution (**52**) (3.43 mmol, 1.17M, 1.14 eq) and 730 µL PinBO*i*Pr (**54a**) (666 mg, 3.58 mmol, 1.2 eq). The second metal-halide exchange was completed after 2 h and the highly viscous oil was used in the next step without further purification.

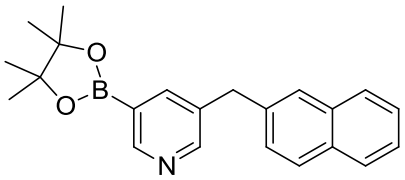
Yield: 971 mg (85%, crude), reddish brown oil, $C_{22}H_{23}BClNO_2$ [379.69 g/mol].

TLC: $R_f = 0.42$ (cyclohexane/EtOAc = 3/1).

GC-MS (EI, 70 eV; MP_100_L): $t_R = 8.59$ min; *m/z* (%): 379 (7) [M^+], 364 (1) [M^+-CH_3], 344 (100) [M^+-Cl], 217 (6) [$C_{12}H_{16}BNO_2^+$].

HRMS (EI): calcd (*m*/*z*) for [M^+]: 379.1515; found: 379.1518.

9.4.1.30 3-(Naphthalen-2-ylmethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-pyridine (51d)



51d

Compound **51d** was prepared according to procedure 9.4.1.8 from 972 mg 3-(chloro(naphthalen-2-yl)methyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**60d**) (2.56 mmol, 1.0 eq) in 40 mL DCM (c ≈ 1.0M, with regard to glacial acetic acid), 2.20 mL glacial acetic acid (2.31 g, 38.47 mmol, 15.0 eq) and 252 mg zinc dust (3.85 mmol, 1.5 eq). The dechlorination was completed after less than 40 min at room temperature. After Kugelrohr-distillation (180°C, $1 \cdot 10^{-3}$ mbar) compound **51d** was isolated as a colorless solid.

Yield: 651 mg (63%, over two steps), colorless solid, $C_{23}H_{25}BNO_2$ [345.24 g/mol].

TLC: R_f = 0.08 (cyclohexane/EtOAc = 8/2, CAM).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.82 (d, ^4J (H,H) = 1.4 Hz, 1 H; H^{Py}), 8.60 (d, ^4J (H,H) = 2.3 Hz, 1 H; H^{Py}), 7.95 (bs, 1 H; H^{Py}), 7.82-7.76 (m, 3 H; H^{Naph}), 7.62 (s, 1 H; H^{Naph}), 7.47-7.43 (m, 2 H; H^{Naph}), 7.29 (dd, ^3J (H,H) = 8.5 Hz, ^4J (H,H) = 1.6 Hz, 1 H; H^{Naph}), 4.13 (s, 2 H; CH_2), 1.33 (s, 12 H; CH_3^{BPin}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 153.3 (C^{Py}), 152.3 (C^{Py}), 143.1 (C^{Py}), 137.5 (C_q; C^{Naph}), 135.8 (C_q; C^{Py}), 133.7 (C_q; C^{Naph}), 132.3 (C_q; C^{Naph}), 128.5 (C^{Naph}), 127.8 (C^{Naph}), 127.7 (C^{Naph}), 127.4 (C^{Naph}), 127.3 (C^{Naph}), 126.3 (C^{Naph}), 125.7 (C^{Naph}), 84.4 (C_q; C^{BPin}), 39.4 (CH_2), 25.0 (CH_3^{BPin}) ppm.*

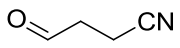
GC-MS (EI, 70 eV; MP_100_L): t_R = 7.79 min; *m/z* (%): 345 (100) [M^+], 330 (18) [M^+-CH_3], 245(40) [$M^+-C_6H_{12}O$], 218 (6) [$M^+-C_{10}H_7$].

m.p.$^{exp.}$ = 127-129°C.

b.p.^{KRD} = 180°C, $1\cdot10^{-3}$ mbar.

HRMS (EI): calcd (*m/z*) for [M^+]: 345.1904; found: 345.1938.

9.4.1.31 4-Oxobutanenitrile (53e)



53e

In a 250 mL two-neck round-bottom flask with argon-inlet 4.88 g 4,4-diethoxybutanenitrile (31.04 mmol, 1.0 eq) were mixed in degassed acetone (154 mL) and 6M HCl (62 mL). The colorless solution was stirred at -4°C 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 (~60 mL) was extracted with DCM (4×40 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 crude product as a colorless oil. After distillation (b.p.$^{1.7}$ = 56-58°C), compound **53e** was obtained as a colorless liquid.[116]

Yield: 1.92 g (74%), colorless liquid, C_4H_5NO [83.09 g/mol].

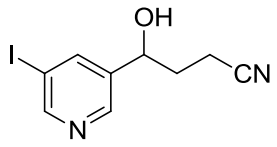
* Signal for the quaternary *ipso*-pyridine carbon (C_q; C^{Py}) at the boronic acid pinacol ester function was not observed.

^{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.

b.p.$^{exp.}$ = 56-58°C, 1.7 torr (b.p.$^{lit.}$ = 66-68°C, 2 torr).[117]

GC-MS (EI, 70 eV; MP_50_S): t_R = 3.17 min; *m/z* (%): 82 (4) [M^+−H], 54 (100) [M^+−CHO].

9.4.1.32 4-Hydroxy-4-(5-iodopyridin-3-yl)butanenitrile (58e)



58e

Compound **58e** was prepared according to procedure 9.4.1.5 from 2.81 g 3,5-diiodopyridine (**49b**) (8.49 mmol, 1.0 eq) in 30 mL absolute, degassed THF, 7.83 mL *i*PrMgCl·LiCl solution (**52**) (8.93 mmol, 1.14M, 1.05 eq) and 810 µL 4-oxobutanenitrile* (**53e**) (843 mg, 10.1 mmol, 1.2 eq). The metal-halide exchange was completed after 2 h. The crude product was purified by flash column chromatography (cyclohexane/EtOAc = 1/1, R_f = 0.20, CAM) to achieve compound **58e** as a highly viscous oil.

Yield: 2.04 g (83%), 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^{Py}), 8.49 (d, ^4J (H,H) = 1.7 Hz, 1 H; H^{Py}), 8.09 (t, ^4J (H,H) = 1.7 Hz, 1 H; H^{Py}), 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.

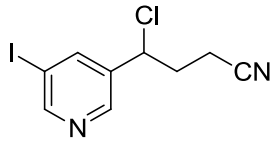
^{13}C NMR (76 MHz, $CDCl_3$): δ = 155.0 (C^{Py}), 145.7 (C^{Py}), 142.4 (C^{Py}), 141.2 (C_q; C^{Py}), 119.3 (C_q; CN), 93.8 (C_q; C^{Py}), 69.2 (CH), 34.3 (CH_2), 13.9 (CH_2) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 7.31 min; *m/z* (%): 288 (20) [M^+], 234 (100) [M^+−C_3H_4N].

HRMS (EI): calcd (*m/z*) for [M^+]: 287.9760; found: 287.9776.

* Density: 1.0409 g/cm^3.[118]

9.4.1.33 4-Chloro-4-(5-iodopyridin-3-yl)butanenitrile (59e)



59e

Compound **59e** was prepared according to procedure 9.4.1.6 from 1.79 g 4-hydroxy-4-(5-iodopyridin-3-yl)butanenitrile (**58e**) (6.21 mmol, 1.0 eq) in 20 mL $SOCl_2$ and 10 mL DCM. After stirring for 21 h at room temperature, the crude product was purified by flash column chromatography (37 g SiO_2, 8x3.5 cm, cyclohexane/EtOAc = 6/4, R_f = 0.38, CAM). Compound **59e** was isolated as a reddish brown, viscous oil.

Yield: 1.85 g (97%), reddish brown oil, $C_9H_8ClIN_2$ [306.53 g/mol].

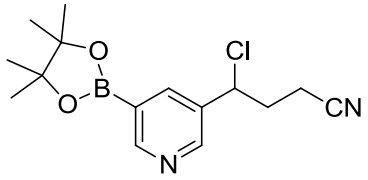
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.82 (d, ^4J (H,H) = 1.7 Hz, 1 H; H^{Py}), 8.59 (d, ^4J (H,H) = 1.7 Hz, 1 H; H^{Py}), 8.10 (t, ^4J (H,H) = 1.8 Hz, 1 H; H^{Py}), 4.95 (dd, ^3J (H,H) = 9.1 Hz, ^4J (H,H) = 5.3 Hz, 1 H; CH), 2.73-2.57 (m, 2 H; CH_2), 2.40-2.32 (m, 2 H; CH_2) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 156.1 (C^{Py}), 146.4 (C^{Py}), 143.1 (C^{Py}), 137.8 (C_q; C^{Py}), 118.0 (C_q; CN), 93.6 (C_q; C^{Py}), 57.5 (CH), 35.3 (CH_2), 15.4 (CH_2) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 7.09 min; *m/z* (%): 306 (97) [M^+], 271 (100) [M^+−Cl], 252 (58) [M^+−C_3H_4N].

HRMS (EI): calcd (*m*/*z*) for [M^+]: 305.9421; found: 305.9422.

9.4.1.34 4-Chloro-4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)butanenitrile (60e)



60e

Compound **60e** was prepared according to procedure 9.4.1.7 from 1.44 g 4-chloro-4-(5-iodopyridin-3-yl)butanenitrile (**59e**) (4.70 mmol, 1.0 eq) in 20 mL absolute, degassed THF, 4.40 mL *i*PrMgCl·LiCl solution (**52**) (5.10 mmol, 1.16M, 1.1 eq) and 1.10 mL PinBO*i*Pr (**54a**) (1.00 g, 5.39 mmol, 1.1 eq). The second metal-halide exchange was

completed after 2.5 h and the crude product was used in the next step without further purification.

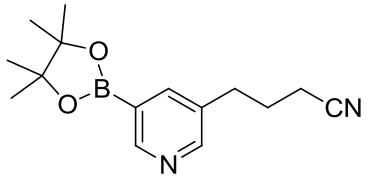
Yield: 1.37 g (95%, crude), pale yellow oil, $C_{15}H_{20}BClN_2O_2$ [306.60 g/mol].

TLC: R_f = 0.09 (cyclohexane/EtOAc = 3/7, CAM).

GC-MS (EI, 70 eV; MP_50_S): t_R = 7.74 min; *m/z* (%): 306 (9) [M^+], 291 (48) [M^+-CH_3], 271 (100) [M^+-Cl], 221 (30) [$M^+-C_6H_{13}$], 207 (68) [$M^+-C_5H_9NO$].

HRMS (EI): calcd (*m/z*) for [M^+-H]: 304.1264; found: 304.1273.

9.4.1.35 4-(5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)butanenitrile (51e)



51e

Compound **51e** was prepared according to procedure 9.4.1.8 from 1.36 g 4-chloro-4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)butanenitrile (**60e**) (4.44 mmol, 1.0 eq) in 90 mL DCM (c ≈ 1.1M, with regard to glacial acetic acid), 5.81 mL glacial acetic acid (6.09 g, 101.52 mmol, 22.9 eq) and 867 mg zinc dust (13.25 mmol, 3.0 eq). The dechlorination was completed after 5 h at room temperature. After Kugelrohr-distillation (150°C, $1 \cdot 10^{-3}$ mbar) compound **51e** was isolated as a colorless solid.

Yield: 809 mg (64%, over two steps), colorless solid, $C_{15}H_{21}BN_2O_2$ [272.15 g/mol].

TLC: R_f = 0.11 (EtOAc/MeOH = 4/1, CAM).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.82 (d, ^4J (H,H) = 1.3 Hz, 1 H; H^{Py}), 8.53 (d, ^4J (H,H) = 2.3 Hz, 1 H; H^{Py}), 7.93 (bs, 1 H; H^{Py}), 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^{Py}), 151.4 (C^{Py}), 142.7 (C^{Py}), 134.8 (C_q; C^{Py}), 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.*

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

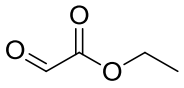
GC-MS (EI, 70 eV; MP_50_S): t_R = 7.44 min; *m/z* (%): 272 (28) [M^+], 257 (59) [M^+-CH_3], 187 (41) [$M^+-C_6H_{13}$], 173 (100) [$M^+-C_5H_9NO$].

m.p.$^{exp.}$ = 55-57°C.

b.p.^{KRD} = 150°C, $1\cdot10^{-3}$ mbar.

HRMS (EI): calcd (*m/z*) for [M^+-H]: 271.1620; found: 271.1633.

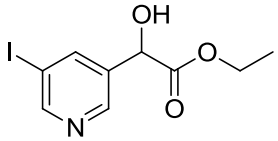
9.4.1.36 Ethyl 2-oxoacetate (53f)



53f

Ethyl glyoxylate as technical grade in toluene (50% concentration) was purchased from Aldrich (50705). Toluene was distilled off under inert conditions using a Vigreux column distillation. After addition of 500 mg P_2O_5 to the colorless residue (~10 g, colorless oil), the monomeric ethyl glyoxylate (**53f**) was isolated by fractionated distillation (b.p.^{13} = 102°C) as slightly yellow liquid. The monomer **53f** was stored in a freezer under an atmosphere of argon and was used within the next 24 h.[119]

9.4.1.37 Ethyl 2-hydroxy-2-(5-iodopyridin-3-yl)acetate (58f)



58f

Compound **58f** was prepared according to procedure 9.4.1.5 from 3.01 g 3,5-diiodopyridine (**49b**) (9.10 mmol, 1.0 eq) in 35 mL absolute, degassed THF, 10.60 mL *i*PrMgCl·LiCl solution (**52**) (12.19 mmol, 1.15M, 1.3 eq) and 1.80 mL ethyl 2-oxoacetate* (**53f**) (1.97 g, 19.30 mmol, 2.1 eq). The metal-halide exchange was completed after 1.5 h and after Kugelrohr-distillation (150°C, $8\cdot10^{-3}$ mbar) compound **58f** was isolated as a pale yellow-orange oil.

Yield: 2.35 g (84%), pale yellow-orange, highly viscous oil, $C_9H_{10}INO_3$ [307.09 g/mol].

TLC: R_f = 0.22 (cyclohexane/EtOAc = 3/1, CAM).

* Density: 1.094 g/cm^3.[120]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.79 (d, ^4J (H,H) = 1.9 Hz, 1 H; H^{Py}), 8.65 (d, ^4J (H,H) = 1.7 Hz, 1 H; H^{Py}), 8.16 (t, ^4J (H,H) = 1.6 Hz, 1 H; H^{Py}), 5.17 (s, 1 H; CH), 4.36-4.16 (m, 2 H; CH_2), 3.19 (bs, 1H; OH), 1.26 (t, ^3J (H,H) = 7.1 Hz, 3 H; CH_3) ppm.

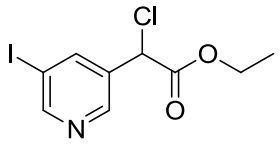
^{13}C NMR (76 MHz, $CDCl_3$): δ = 172.4 (C_q; $COOCH_3$), 155.2 (C^{Py}), 146.5 (C^{Py}), 142.8 (C^{Py}), 136.2 (C_q; C^{Py}), 93.4 (C_q; C^{Py}), 70.1 (CH), 63.2 (CH_2), 14.2 (CH_3) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 6.55 min; *m/z* (%): 307 (15) [M^+], 262 (1) [$M^+-C_2H_5O$], 234 (100) [$M^+-C_3H_5O_2$], 204 (9) [$C_5H_3IN^+$].

b.p.^{KRD} = 150°C, $8\cdot10^{-3}$ mbar.

HRMS (EI): calcd (*m/z*) for [M^+]: 306.9706; found: 306.9731.

9.4.1.38 Ethyl 2-chloro-2-(5-iodopyridin-3-yl)acetate (59f)



59f

Compound **59f** was prepared according to procedure 9.4.1.6 from 1.47 g ethyl 2-hydroxy-2-(5-iodopyridin-3-yl)acetate (**58f**) (4.79 mmol, 1.0 eq) in 10 mL $SOCl_2$. Complete conversion was detected after 1 h. The $SOCl_2$ was distilled off and the residue was quenched with absolute EtOH. Compound **59f** was isolated after flash column chromatography (32 g SiO_2, 6.5x4 cm, cyclohexane/EtOAc = 8/2, R_f = 0.43) as a highly viscous, pale yellow oil.
Yield: 1.44 g (92%), pale yellow, highly viscous oil, $C_9H_9ClINO_2$ [325.53 g/mol].

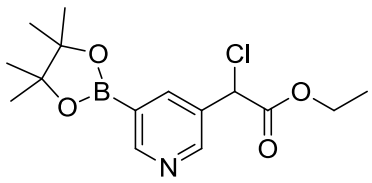
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.83 (d, ^4J (H,H) = 1.5 Hz, 1 H; H^{Py}), 8.62 (d, ^4J (H,H) = 1.4 Hz, 1 H; H^{Py}), 8.23 (t, ^4J (H,H) = 1.9 Hz, 1 H; H^{Py}), 5.27 (s, 1 H; CH), 4.31-4.17 (m, 2 H; CH_2), 1.28 (t, ^3J (H,H) = 7.1 Hz, 3 H; CH_3) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 167.3 (C_q; $COOCH_3$), 156.4 (C^{Py}), 147.3 (C^{Py}), 144.1 (C^{Py}), 133.8 (C_q; C^{Py}), 93.4 (C_q; C^{Py}), 63.3 (CH), 55.5 (CH_2), 14.1 (CH_3) ppm.

GC-MS (EI, 70 eV; MP_50_S): t_R = 6.57 min; *m/z* (%): 325 (25) [M^+], 252 (100) [$M^+-C_3H_5O_2$], 125 (14) [$C_6H_4ClN^+$].

HRMS (EI): calcd (*m/z*) for [M^+]: 324.9366; found: 324.9390.

9.4.1.39 Ethyl 2-chloro-2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)-acetate (60f)



60f

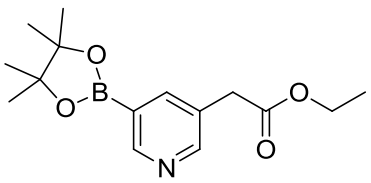
Compound **60f** was prepared according to procedure 9.4.1.7 from 1.24 g ethyl 2-chloro-2-(5-iodopyridin-3-yl)acetate (**59f**) (3.81 mmol, 1.0 eq) in 10 mL absolute, degassed THF, 2.04 mL *i*PrMgCl·LiCl solution (**52**) (4.18 mmol, 2.05M, 1.1 eq) and 930 µL PinBO*i*Pr (**54a**) (848 mg, 4.56 mmol, 1.2 eq). The second metal-halide exchange was completed after 3 h. Because of the formed isopropanol during the reaction, an inseparable mixture of the desired ethylester (Et) and the isopropylester (*i*Pr) (7/3) was analyzed by GC-MS. The crude product mixture was used in the next step without further purification.

Yield: 1.23 g (98%, crude), red orange oil, $C_{15}H_{21}BClNO_4$ [325.60 g/mol].

GC-MS (EI, 70 eV; MP_50_S): t_R^{Et} = 7.36 min; *m/z* (%): 325 (10) [M^+], 310 (23) [M^+-CH_3] 296 (1) [$M^+-C_2H_5$], 252 (100) [$M^+-C_3H_5O_2$]; t_R^{iPr} = 7.39 min; *m/z* (%): 339 (2) [M^+], 296 (4) [$M^+-C_3H_7$], 280 (2) [$M^+-C_3H_7O$], 252 (100) [$M^+-C_4H_7O_2$].

HRMS (EI) ethylester: calcd (*m*/*z*) for [M^+]: 325.1255; found: 325.1260; isopropylester: calcd (*m*/*z*) for [M^+]: 339.1412; found: 339.1436.

9.4.1.40 Ethyl 2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)-acetate (51f)



51f

Compound **51f** was prepared according to procedure 9.4.1.8 from 1.14 g ethyl 2-chloro-2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)acetate (**60f**) (3.45 mmol, 1.0 eq) (mixture of ethyl- and isopropylester, 7/3) in 60 mL DCM (c ≈ 0.4M, with regard to glacial acetic acid), 1.40 mL glacial acetic acid (1.47 g, 24.48 mmol, 7.1 eq) and 429 mg zinc dust (6.56 mmol, 1.9 eq). The dechlorination was completed in less than 2 h at room temperature.

After Kugelrohr-distillation (135°C, $7 \cdot 10^{-2}$ mbar) compound **51f** was isolated as a mixture of ethyl- and isopropylester (6/4).

Yield: 739 mg (71%, over two steps), colorless oil, $C_{15}H_{22}BNO_4$ [291.15 g/mol].

TLC: $R_f = 0.25$ (MeOH/EtOAc = 8/2, tailing).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.84 (bs, 1 H; H^{Py}), 8.58 (d, ^4J (H,H) = 2.3 Hz, 1 H; H^{Py}), 7.99 (bs, 1 H; H^{Py}), 5.01 (sept, ^3J (H,H) = 6.2 Hz, 0.3 H; $CH(CH_3)_2$), 4.15 (q, ^3J (H,H) = 7.1 Hz, 1.4 H; CH_2CH_3), 3.60 (s, 1.4 H; Py-CH_2^{Et}), 3.57 (s, 0.6 H; Py-CH_2^{iPr}), 1.34 (s, 12 H; CH_3^{BPin}), 1.25 (t, ^3J (H,H) = 7.1 Hz, 2.1 H; CH_2CH_3), 1.22 (d, ^3J (H,H) = 6.3 Hz, 1.8 H; $CH(CH_3)_3$) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 170.8 (C_q; $C{=}O^{Et}$), 170.4 (C_q; $C{=}O^{iPr}$), 154.1 (C^{Py}), 152.6 (C^{Py}), 143.3 (C^{Py}), 129.5 (C_q; $C^{Py(iPr)}$), 129.3 (C_q; $C^{Py(Et)}$), 84.4 (C_q; C^{BPin}), 68.8 (CH^{OiPr}), 61.3 (CH_2CH_3), 38.9 (Py-CH_2^{iPr}), 38.6 (Py-CH_2^{Et}), 25.0 (CH_3^{BPin}), 21.9 ($CH(CH_3)_2$), 14.3 (CH_2CH_3) ppm.*

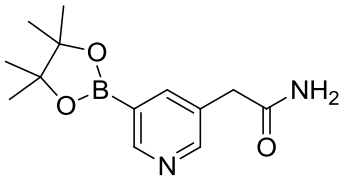
GC-MS (EI, 70 eV; MP_50_S): t_R^{Et} = 7.11 min; *m/z* (%): 291 (60) [M^+], 276 (100) [M^+-CH_3], 262 (21) [$M^+-C_2H_5$], 248 (29) [$M^+-C_3H_9$], 231 (61) [$M^+-C_3H_8O$], 218 (97) [$M^+-C_3H_5O_2$]; t_R^{iPr} = 7.15 min; *m/z* (%): 305 (19) [M^+], 290 (21) [M^+-CH_3], 262 (11) [$M^+-C_3H_7$], 231 (6) [$M^+-C_4H_{10}O$], 218 (100) [$M^+-C_4H_7O_2$], 203 (22) [$M^+-C_5H_{10}O_2$].

b.p.^{KRD} = 135°C, $7 \cdot 10^{-2}$ mbar.

HRMS (EI) ethylester: calcd (*m*/*z*) for [M^+]: 291.1645; found: 291.1669; isopropylester: calcd (*m*/*z*) for [M^+]: 305.1801; found: 305.1834.

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

9.4.1.41 2-(5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)acetamide (51g)



51g

A 15 mL "Ace pressure tube®, front seal" (Aldrich Z181099) with a "Duro-Silicone O-ring" was charged with 101 mg of compound mixture **51f** (0.35 mmol, 1.0 eq), 6 mg KCN (0.09 mmol, 26 mol%) and 7 mL of ammonia solution (7M in MeOH). The flask was sealed and the mixture was stirred at 50°C for 9 days. The solvent was evaporated in vacuo and the crude product was purified by Kugelrohr-distillation (185°C, $1 \cdot 10^{-2}$ mbar) to afford a colorless solid.

Yield: 62 mg (69%), colorless 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^{Py}), 8.61 (s, 1 H; H^{Py}), 8.03 (s, 1 H; H^{Py}), 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^{Py}), 151.9 (C^{Py}), 143.9 (C^{Py}), 130.4 (C_q; C^{Py}), 84.6 (C_q; C^{BPin}), 40.2 (CH_2), 25.0 (CH_3^{BPin}) ppm.*

GC-MS (EI, 70 eV; MP_50_S): t_R = 7.63 min; *m/z* (%): 262 (43) [M^+], 247 (70) [M^+-CH_3], 203 (80) [$M^+-C_2H_5NO$], 163 (100) [$C_8H_{10}BNO_2^+$], 146 (9) [$C_7H_5BNO_2^+$], 119 (50) [$C_7H_5NO^+$].

m.p.$^{exp.}$ = 174-179°C.

b.p.^{KRD} = 185°C, $1 \cdot 10^{-2}$ mbar.

HRMS (EI): calcd (*m/z*) for [M^+]: 262.1491; found: 262.1501.

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

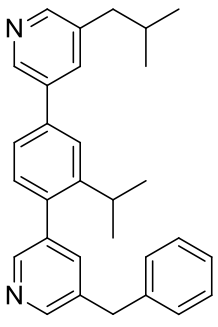
9.4.2 Synthesis of Teraryls

9.4.2.1 Representative procedure for the synthesis of teraryls using the triflate approach by consecutive double Suzuki-coupling

A flame dried two-neck round-bottom flask with argon-inlet was charged with 1.0-1.05 eq of the corresponding boronic acid pinacol ester **51**, 2.0 eq CsF* and 5 mol% $PdCl_2$(dppf)·DCM. After drying in vacuo, a solution of 1.0 eq trifluoromethanesulfonate **45**[73] in absolute, degassed 1,2-DME was added. After additional degassing, the reaction mixture was stirred at 80°C until full conversion was detected by TLC. The typically brown suspension was filtered through a pad of SiO_2 (3x2 cm, eluents are denoted) and the filtrate was concentrated to dryness using a rotary evaporator.

Another flame dried two-neck round-bottom flask with argon-inlet was charged with 1.0-1.2 eq of the second pyridine-based boronic acid pinacol ester **51**, 2.0-3.0 eq cesium carbonate (Cs_2CO_3)* and 5-7.5 mol% $PdCl_2$(dppf)·DCM. After drying in vacuo, a solution of the previously prepared crude intermediate (4-(pyridin-3-yl)phenyl trifluoromethanesulfonate derivative) in 5 mL absolute, degassed 1,2-DME were added. After additional degassing, the reaction mixture was stirred at 80°C overnight. The typically black suspension was filtered through a pad of SiO_2 (3x2 cm, eluent: 100 mL MeOH) and after concentrating to dryness, the crude product was purified by flash column chromatography. To obtain highly pure substrate, the product was purified by semi-preparative HPLC.

9.4.2.2 3-Benzyl-5-(4-(5-isobutylpyridin-3-yl)-2-isopropylphenyl)pyridine (1g)



1g

Compound **1g** was prepared according to procedure 9.4.3.1 from 72 mg 3-isobutyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**51b**) (0.28 mmol, 1.0 eq), 83 mg CsF (0.55 mmol, 2.0 eq), 11 mg $PdCl_2$(dppf)·DCM (13 µmol, 5 mol%) and 108 mg 4-iodo-2-iso-

* CsF and Cs_2CO_3 were dried overnight at 60°C in vacuo prior to use.

propylphenyl trifluoromethanesulfonate[73] (**45a**) (0.27 mmol, 1.0 eq) in 4 mL absolute, degassed 1,2-DME. After 7 h the brown suspension was filtered through a pad of SiO_2 (3x2 cm, eluent: 100 mL EtOAc) and the filtrate was concentrated to dryness (115 mg, 104%, crude, cyclohexane/EtOAc = 7/3, R_f = 0.47).

The second Suzuki-coupling was performed with 85 mg 3-benzyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**51a**) (0.29 mmol, 1.05 eq), 191 mg Cs_2CO_3 (0.59 mmol, 2.0 eq), 11 mg $PdCl_2$(dppf)·DCM (13 µmol, 5 mol%) and 115 mg of the previously prepared crude intermediate (0.29 mmol, 1.0 eq) in 5 mL absolute, degassed 1,2-DME. A quantitative conversion was confirmed by TLC (cyclohexane/EtOAc = 7/3, R_f = 0.23) after stirring at 80°C overnight and the black suspension was filtered through a pad of SiO_2 (3x2 cm, eluent: 100 mL MeOH). The crude product was purified by flash column chromatography (30 g SiO_2, 18x2.5 cm, cyclohexane/EtOAc = 8/2, R_f = 0.21) to achieve compound **1g** as a grey, highly viscous oil (96 mg, 83%).* After preparative HPLC† product **1g** was isolated as a colorless, highly viscous oil.

Yield: 54 mg (47%), colorless, 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; MP_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) [$M^+-C_5H_{13}$].

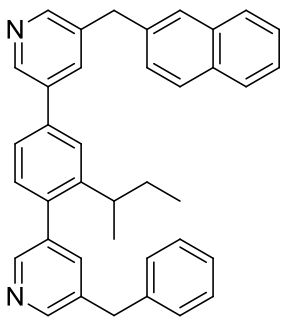
* Analytical HPLC indicated a product purity ≥ 90%.

† MeOH/water gradient with 1.0% (v/v) HCOOH at a flow rate of 15.0 mL/min: 0.0 min: 72% MeOH const., 0.0-7.0 min: 75% MeOH lin. gradient, 7.0-14.0 min.: 75% MeOH const., 14.0-14.5 min: 100% MeOH lin. gradient, 14.5-20.0 min: 100% MeOH const., 20.0-20.5 min: 72% MeOH lin. gradient, 20.5-25.0 min: 72% MeOH const.

HPLC (Nucleodur, ESI^+): t_R = 13.62 min; *m/z*: 421 [M^++H], 443 [M^++Na]; λ_{max} = 252, 281, 309 nm.*

HRMS (DI-EI): calcd (*m/z*) for [M^+]: 420.2566; found: 420.2557.

9.4.2.3 3-Benzyl-5-(2-(sec-butyl)-4-(5-(naphthalen-2-ylmethyl)pyridin-3-yl)phenyl)-pyridine (1h)



1h

Compound **1h** was prepared according to procedure 9.4.3.1 from 89 mg 3-(naphthalen-2-ylmethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**51d**) (0.26 mmol, 1.05 eq), 74 mg CsF (0.49 mmol, 2.0 eq), 10 mg $PdCl_2$(dppf)·DCM (12 µmol, 5 mol%) and 101 mg 2-(*sec*-butyl)-4-iodophenyl trifluoromethanesulfonate[73] (**45b**) (0.25 mmol, 1.0 eq) in 3 mL absolute, degassed 1,2-DME. After stirring overnight, the brown suspension was filtered through a pad of SiO_2 (3x2 cm, eluent: 100 mL cyclohexane/EtOAc = 1/1) and the filtrate was concentrated to dryness (132 mg, 106%, crude, cyclohexane/EtOAc = 3/1, R_f = 0.33).

The second Suzuki-coupling was performed with 87 mg 3-benzyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**51a**) (0.29 mmol, 1.2 eq), 159 mg Cs_2CO_3 (0.49 mmol, 3.0 eq), 10 mg $PdCl_2$(dppf)·DCM (12 µmol, 5 mol%) and 122 mg of the previously prepared intermediate (0.24 mmol, 1.0 eq) in 3 mL absolute, degassed 1,2-DME.

A quantitative conversion was confirmed by TLC (cyclohexane/EtOAc = 3/1, R_f = 0.14) after stirring at 80°C overnight and the black suspension was filtered through a pad of SiO_2 (3x2 cm, eluent: 100 mL MeOH). The crude product was purified by flash column chromatography (20 g SiO_2, 17x2 cm, cyclohexane/EtOAc = 1/1, R_f = 0.31) to achieve

* 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.

compound **1h** as a yellow, highly viscous oil. After preparative HPLC* product **1h** was isolated as a pale yellow, highly viscous oil.

Yield: 86 mg (66%), pale yellow, highly viscous oil, $C_{38}H_{34}N_2$ [518.69 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.75-8.27 (bm, 4 H; H^{Py}), 7.83-7.77 (m, 4 H; 3x H^{Naph}, H^{Py}), 7.69 (s, 1 H; H^{Naph}), 7.48-7.22 (m, 12 H; H^{Py}, 3x H^{Naph}, 5x H^{Phe}, 3x H^{Ar}, overlapping), 4.25 (s, 2 H; CH_2^{Naph}), 4.06 (s, 2 H; CH_2^{Phe}), 2.70-2.59 (m, 1 H; CH^{Ile}), 1.62-1.46 (m, 2 H; CH_2^{Ile}), 1.14 (d, ^3J (H,H) = 6.7 Hz, 3 H; CH_3^{Ile}), 0.65 (t, ^3J (H,H) = 7.2 Hz, 3 H; CH_3^{Ile}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 148.3 (C^{Py}), 147.9 (C^{Py}), 147.1 (C^{Py}), 146.6 (C_q; C^{Ar}), 145.6 (C^{Py}), 139.5 (C_q; C^{Phe}), 137.8 (C^{Py}), 137.8 (C_q; C^{Naph}), 137.7 (C_q; C^{Ar}, 2x C_q; C^{Py}), 137.0 (C_q; C^{Ar}, 2x C_q; C^{Py}), 135.7 (C^{Py}), 133.7 (C_q; C^{Naph}), 132.4 (C_q; C^{Naph}), 130.8 (C^{Ar}), 129.0 (C^{Phe}), 128.9 (C^{Phe}), 128.7 (C^{Naph}), 127.8 (C^{Naph}), 127.7 (C^{Naph}), 127.4 (C^{Naph}), 127.3 (C^{Naph}), 126.8 (C^{Phe}), 126.4 (C^{Naph}), 125.9 (C^{Naph}), 125.0 (C^{Ar}), 124.6 (C^{Ar}), 39.3 (CH_2^{Naph}), 39.0 (CH_2^{Phe}), 36.7 (CH^{Ile}), 31.3 (CH_2^{Ile}), 22.4 (CH_3^{Ile}), 12.3 (CH_3^{Ile}) ppm.

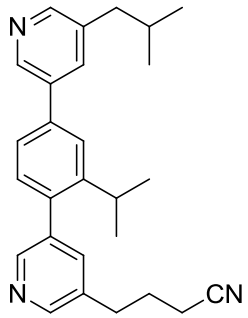
HPLC (Nucleodur, ESI^+): t_R = 8.66 min; *m/z*: 519 [M^++H]; λ_{max} = 235, 251, 281, 308 nm.†

HRMS (DI-EI): calcd (*m/z*) for [M^+]: 518.2722; found: 518.2718.

* MeOH/water gradient with 1.0% (v/v) HCOOH at a flow rate of 16 mL/min: 0.0 min: 84% MeOH const., 0.0-10.0 min: 91% MeOH lin. gradient, 10.0-13.0 min: 91% MeOH const., 13.0-13.5 min: 100% MeOH lin. gradient, 13.5-20.0 min: 100% MeOH const., 20.0-20.5 min: 84% MeOH lin. gradient, 20.5-25.0 min: 84% MeOH const.

† MeOH/water gradient with 1.0% (v/v) HCOOH at a flow rate of 1.0 mL/min: 0.0 min: 84% MeOH const., 0.0-10.0 min: 90% MeOH lin. gradient, 10.0-13.0 min: 90% MeOH const., 13.0-13.5 min: 100% MeOH lin. gradient, 13.5-19.0 min: 100% MeOH const., 19.0-19.5 min: 84% MeOH lin. gradient, 19.5-25.0 min: 84% MeOH const.

9.4.2.4 4-(5-(4-(5-Isobutylpyridin-3-yl)-2-isopropylphenyl)pyridin-3-yl)butanenitrile (1i)



1i

Compound **1i** was prepared according to procedure 9.4.3.1 from 139 mg 3-isobutyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**51b**) (0.53 mmol, 1.05 eq), 154 mg CsF (1.01 mmol, 2.0 eq), 21 mg $PdCl_2$(dppf)·DCM (26 µmol, 5 mol%) and 200 mg 4-iodo-2-isopropylphenyl trifluoromethanesulfonate[73] (**45a**) (0.51 mmol, 1.0 eq) in 3 mL absolute, degassed 1,2-DME. After stirring overnight at 80°C, the conversion was detected by GC-MS. Because of slow conversion the reaction mixture was stirred for further three days and the brown suspension was filtered through a pad of SiO_2 (3x2 cm, eluent: 100 mL EtOAc). Due to the long reaction time and high by-product concentration, the intermediate 4-(5-isobutylpyridin-3-yl)-2-isopropylphenyl trifluoromethanesulfonate was purified by flash column chromatography (10 g SiO_2, 15x1 cm, cyclohexane/EtOAc = 4/1, R_f = 0.18).

The second Suzuki-coupling was performed with 81 mg 4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)butanenitrile (**51e**) (0.30 mmol, 1.2 eq), 243 mg Cs_2CO_3 (0.75 mmol, 3.0 eq), 15 mg $PdCl_2$(dppf)·DCM (18 µmol, 7.2 mol%) and 100 mg of the previously prepared intermediate (0.25 mmol, 1.0 eq) in 3 mL absolute, degassed 1,2-DME.

A quantitative conversion was confirmed by TLC (cyclohexane/EtOAc = 1/2, R_f = 0.20) after stirring at 80°C overnight and the black suspension was filtered through a pad of SiO_2 (3x2 cm, eluent: 100 mL MeOH). The crude product was purified by flash column chromatography (10 g SiO_2, 16x1 cm, cyclohexane/EtOAc = 1/2, R_f = 0.20) to achieve compound **1i** as a pale brown, highly viscous oil (96 mg, 48%).[*] After preparative HPLC[†] product **1i** was isolated as a gray, highly viscous oil.

Yield: 93 mg (46%), gray, highly viscous oil, $C_{27}H_{31}N_3$ [397.56 g/mol].

[*] Analytical HPLC indicated a product purity ≥ 95%.

[†] MeOH/water gradient with 1.0% (v/v) HCOOH at a flow rate of 15.0 mL/min: 0.0 min: 48% MeOH const., 0.0-13.0 min: 72% MeOH lin. gradient, 13.0-17.5 min: 100% MeOH lin. gradient, 17.5-22.0 min: 100% MeOH const., 22.0-22.5 min: 48% MeOH lin. gradient, 22.5-25.0 min: 48% MeOH const.

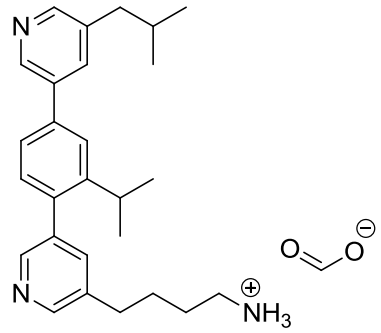
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.73-8.27 (m, 4 H; H^{Py}), 7.68 (s, 1 H; H^{Py}), 7.59 (s, 1 H; H^{Ar}), 7.49-7.44 (m, 2 H; H^{Ar}, H^{Py}), 7.25 (d, ^3J (H,H) = 7.0 Hz, 1 H; H^{Ar}, overlapping), 3.05-2.97 (m, 1 H; CH^{Val}), 2.87 (t, ^3J (H,H) = 7.2 Hz, 2 H; CH_2^{Lys}), 2.57 (d, ^3J (H,H) = 6.8 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.

HPLC (Nucleodur, ESI^+): t_R = 10.47 min; *m/z*: 398 [M^++H], 420 [M^++Na]; λ_{max} = 252, 281, 307 nm.*

HRMS (DI-EI): calcd (*m*/*z*) for [M^+]: 397.2518; found: 397.2516.

9.4.2.5 4-(5-(4-(5-Isobutylpyridin-3-yl)-2-isopropylphenyl)pyridin-3-yl)butan-1-ammonium formiate (1j)



1j

Hydrogenation was performed utilizing a H-Cube™ at a pressure of 80 bar at 70°C with a Raney-Nickel cartridge (THS 01112). A solution of 55 mg **1i** (0.14 mmol, 1.0 eq) in 8 mL MeOH/ammonia solution (35% ammonia in H_2O) (MeOH/ammonia = 125/5) was used in

* 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: 50% MeOH lin. gradient, 4.0-10.0 min.: 50% MeOH const., 10.0-10.5 min: 80% MeOH lin. gradient, 10.5-15.0 min: 80% MeOH const., 15.0-15.5 min: 30% MeOH lin. gradient, 15.5-25.0 min: 30% MeOH const.

continuous flow mode of 0.5 mL/min (~0.02M). After removing the solvent under reduced pressure, compound **1j** was purified by preparative HPLC.*

Yield: 54 mg (86%), colorless, 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.†

HPLC (Nucleodur, ESI^+): 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.

* 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.

† No signal for the carbon atom of the formiate function ($HCOO^-$) was observed.

‡ MeOH/water gradient with 1.0% (v/v) HCOOH at a flow rate of 1.0 mL/min: 0.0 min: 35% 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: 35% MeOH lin. gradient, 19.5-25.0 min: 35% MeOH const.

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11 Abbreviations

APT	attached proton test
°C	degree Celsius
$(i\text{Pr})_2\text{NH}$	diisopropylamine
µL	microliter
1,2-DME	1,2-dimethoxyethane
3-NOBA	3-nitrobenzyl alcohol
9-BBN	9-borabicyclo[3.3.1]nonane
Å	Ångström
ACN	acetonitrile
amu	atomic mass unit
Ar	phenyl
b	broad
$\text{B}(\text{O}i\text{Pr})_3$	triisopropyl borate
b.p.	boiling point
B_2Pin_2	bis(pinacolato)diboron
BHT	2,6-di-*tert*-butyl-4-methylphenol
BPin	boronic acid pinacol ester
c	concentration
calcd	calculated
CAM	cerium ammonium molybdate solution
CDCl_3	deuterated chloroform
cm	centimeter
COD	1,5-cyclooctadiene
const.	constant
C_q	quaternary carbon
δ	chemical shift
d	doublet
DCM	dichloromethane
dd	doublet of doublet
DEPT	distortionless enhancement by polarization transfer
DI	direct inlet
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide

dppf	1,1'-bis(diphenylphosphino)ferrocene
dq	doublet of quadruplet
dt	doublet of triplet
dtbpy	4,4'-di-*tert*-butyl-2,2'-bipyridine
ec	end-capped
EI	electron impact
eq	equivalence
ESI	electron spray ionization
Et_2O	diethyl ether
EtOAc	ethyl acetate
eV	electron Volt
exp.	experimental
FAB	fast atom bombardment
FT	Fourier transformation
GC-MS	gas chromatography – mass spectrometry
h	hour(s)
HBPin	4,4,5,5-tetramethyl-1,3,2-dioxaborolane
HMBC	heteronuclear multiple bond coherence
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	Hertz
*i*Pr	isopropyl
*i*PrMgCl·LiCl	isopropylmagnesium chloride lithium chloride solution
J	coupling constants
KNPhth	potassium phthalimide
KOAc	potassium acetate
KO*t*Bu	potassium *tert*-butoxide
KRD	Kugelrohr distillation
LAH	lithium aluminum hydride
lin.	linear
lit.	literature
λ_{max}	lamda max.
m	multiplet

M	mol/L
m	*meta*
m.p.	melting point
m/*z*	mass to charge ratio
M^+	molecular peak
MALDI	Matrix-assisted laser desorption/ionization
mbar	millibar
Me	methyl
MeOH	methanol
mg	milligram
MHz	mega Hertz
min	minute
mL	milliliter
mm	millimeter
MS	molecular sieve(s)
MS	mass spectrometry
MSD	mass sensitive detector
MTBE	methyl *tert*-butyl ether
Naph	naphthyl
NEt_3	triethylamine
NMR	nuclear magnetic resonance
NPhth	isoindoline-1,3-dione
o	*ortho*
p	*para*
PinBO*i*Pr	2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane
PinBOMe	2 methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane
PPI(s)	protein-protein-interaction(s)
ppm	parts per million
Pro	product
Py	pyridyl
q	quadruplet
quant.	quantitative
R_f	retardation factor
rt	room temperature

s	singlet
sept	septet
sec	secondary
sublim.	sublimation
t	triplet
THF	tetrahydrofuran
TLC	thin layer chromatography
t_R	retention time
UV	ultraviolet

Amino Acid Abbreviations

One letter code	Three letter code	Amino acid
A	Ala	Alanine
R	Arg	Arginine
N	Asn	Asparagine
D	Asp	Aspartic acid
C	Cys	Cysteine
E	Glu	Glutamic acid
Q	Gln	Glutamine
G	Gly	Glycine
H	His	Histidine
I	Ile	Isoleucine
L	Leu	Leucine
K	Lys	Lysine
F	Phe	Phenylalanine
M	Met	Methionine
P	Pro	Proline
S	Ser	Serine
T	Thr	Threonine
W	Trp	Tryptophan
Y	Tyr	Tyrosine
V	Val	Valine

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