D I P L O M A R B E I T

SELECTIVE SEQUENTIAL CROSS-COUPLING REACTIONS ON IMIDAZOLE TOWARDS NEURODAZINE AND ANALOGS

AUSGEFÜHRT AM INSTITUT FÜR

ANGEWANDTE SYNTHESECHEMIE
DER TECHNISCHEN UNIVERSITÄT WIEN

UNTER ANLEITUNG VON

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WIEN, 21.MÄRZ 2011

Danksagung

Zuerst gilt mein Dank Prof. Marko D. Mihovilovic, der es mir ermöglich hat, die vorliegende Diplomarbeit in seiner Gruppe auszuführen.
Außerdem möchte ich meinem Betreuer Dr. Michael Schnürch danken, der immer die Zeit aufgebracht hat um meine Probleme anzuhören, immer einen guten Rat für mich hatte und sich stundenlang für mich mit der LC-MS herumgeärgert hat.

Ich möchte mich bei Prof. Erwin Rosenberg für die schnellen Messungen der HR-MS Proben und bei Dr. Hametner für die Messung der anscheinend niemals enden wollenden NMR-Spektren auf der 400 MHz Maschine bedanken.

Ein riesengroßes Dankeschön geht natürlich an meine Kollegen im Stockwerk, die mir das Leben während der Diplomarbeit versüßt haben: Finki (danke für die Musik und das Fortgehen und alle möglichen Erlebnisse während des ganzen Studiums), Max (mit dir ist alles immer abwechslungsreich: diskutieren, Taxi fahren, auf einen Spritzer gehen, Prüfungen machen, Präparate nachmachen, …), Laurin (immer für einen Tipp bereit und immer ein guter Gesprächspartner und danke für all die NMRs), Moumita (thanks for always helping me, especially with the NMRs), Navid (du bist so smart, das wirft mich um!), Schöni (immer bei einem neuen HPLC-Abenteuer dabei), Maria & Kathi S. (immer für Klatsch&Tratsch bereit!), Anna (danke für all die „interessanten“ Gesprächsthemen, vor allem beim Mittagessen), Johanna (meine Banknachbarin, die immer für einen kleinen Tratsch verfügbar war), wie auch an Alex, Andrej, Birgit M., Birgit W., David, Farooq, Ghobi, Kathi B., Maria, Naseem, Saima, Sonja, Stefan, Thomas F., Thomas L., Valentin. Außerdem möchte ich mich auch bei Florian Untersteiner bedanken, der nicht nur all meine Computerprobleme gelöst hat sondern auch meinen kleinen Tiefs mit Schokolade, Wein und guten Gesprächen entgegengekommen ist. Es hat mir echt Spaß gemacht mit euch allen zusammenzuarbeiten.

Mein größter Dank geht an meine Eltern Bojan und Susanna sowie an meine Geschwister Alex und Krissi, die mich immer unterstützt und gefördert haben und ohne deren Hilfe das Studium nicht möglich gewesen wäre. Ich habs geschafft!
Ein spezielles Danke geht auch an Lucia, für die vielzähligen und aufbauenden „Wir-schaffen-das-und-werden-auch-noch-mit-dem-Studium-fertig“-Gespräche!

Mes plus profonds remerciements sont adressés à Séb pour son amour, son soutien et sa patience infinie.

Key

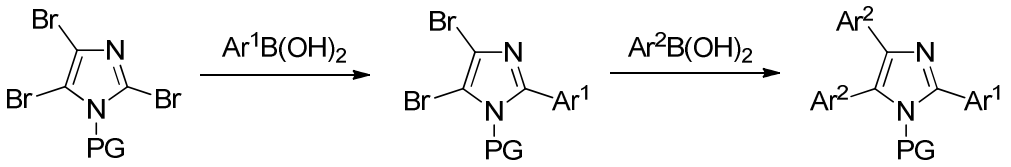
All compounds prepared in this thesis are numbered in bold Arabic numbers. Compounds unknown to the literature are additionally underlined. General structures and compounds presented as literature examples are numbered in bold Roman numbers.
Literature citations are indicated by superscript Arabic numbers.

Abstract

The aim of this diploma thesis was to develop a facile protocol for the synthesis of 2,4,5-triarylated imidazoles from easily available tribromoimidazole using a Suzuki-Miyaura cross-coupling method. Initially, tribromoimidazole had to be protected for the cross-coupling reactions, and three different and orthogonal *N*-protecting groups were investigated.

In the first step, a (hetero)arylboronic acid was coupled in 2-position of the imidazole, in line with the general reactivity at this heterocyclic system, to obtain N-protected 2-aryl-4,5-dibromoimidazole.

The subsequent selective cross-coupling in 5-position could not be achieved even after an elaborate screening of reaction conditions; this is in marked contrast to the previously investigated thiazole system. Consequently, the cross-coupling in 4- and 5-position of imidazole was performed simultaneously (Scheme 1).



Scheme 1

With this protocol, the precursor for Neurodazine (Figure 1), a molecule with reported properties as cell-differentiation promoter for neurogenesis, was synthesized and a novel total synthesis of the target compound could be established within 3 follow-up steps.

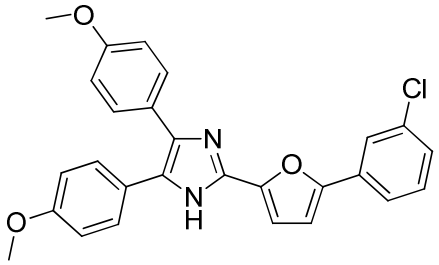


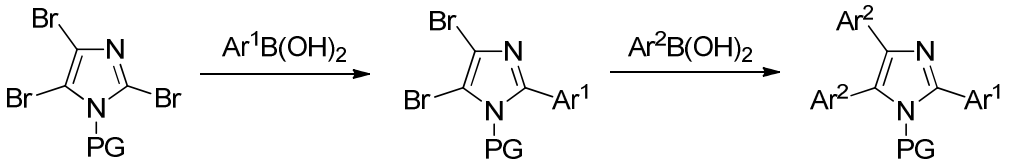
Figure 1

Furthermore, a one-pot protocol was developed for the synthesis of 2,4,5-triarylated imidazoles.

Deutsche Kurzfassung

Das Ziel der vorliegenden Diplomarbeit war die Entwicklung eines vielseitig anwendbaren Syntheseprotokolls von 2,4,5-triarylierten Imidazolen ausgehend von dem einfach erhältlichen Tribromimidazol unter Einsatz von Suzuki-Miyaura Kreuzkupplungsreaktionen. Die dargelegte Synthesesequenz nutzt Tribromimidazol als Ausgangsmaterial, wobei drei verschiedene orthogonale Schutzgruppen am Stickstoff untersucht wurden, um diese Reaktionen am Imidazol durchführen zu können.

Als erster Schritt wurde eine (Hetero)Arylboronsäure in die 2-Position des Imidazols gekuppelt um N-geschützte 2-Aryl-4,5-dibromoimidazole zu erhalten; die Regioselektivität dieses Schrittes ist konsistent mit der generellen Reaktivität des heterocyclischen Systems.
Die nachfolgende Kreuzkupplung in 5-Position des Imidazols konnte nicht selektiv durchgeführt werde, trotz eines ausführlichen Screenings verschiedener Konditionen, was in krassem Gegensatz zu Vorstudien an entsprechenden Thiazolen steht. Daher wurde die Kreuzkupplung in 4- und 5-Position des Imidazols gleichzeitig ausgeführt (Schema 1).



Schema 1

Mit diesem Protokoll wurde auch die Vorstufe von Neurodazin (Abbildung 1), für welches zelldifferenzierende Eigenschaften hinsichtlich neurogener Aktivität berichtet wurden, hergestellt und mittels drei weiterer Stufen eine neue Syntheseroute zu diesem Zielprodukt eröffnet werden.

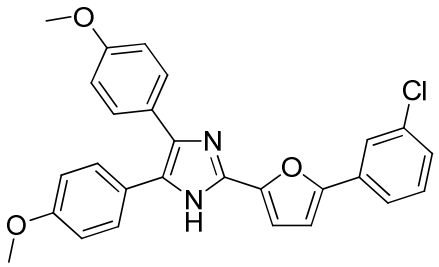


Abbildung 1

Schließlich konnte die Kupplungsstrategie in ein generelles Ein-Topf-Verfahren zur Herstellung von 2,4,5-triarylierten Imidazolen ausgeweitet werden.

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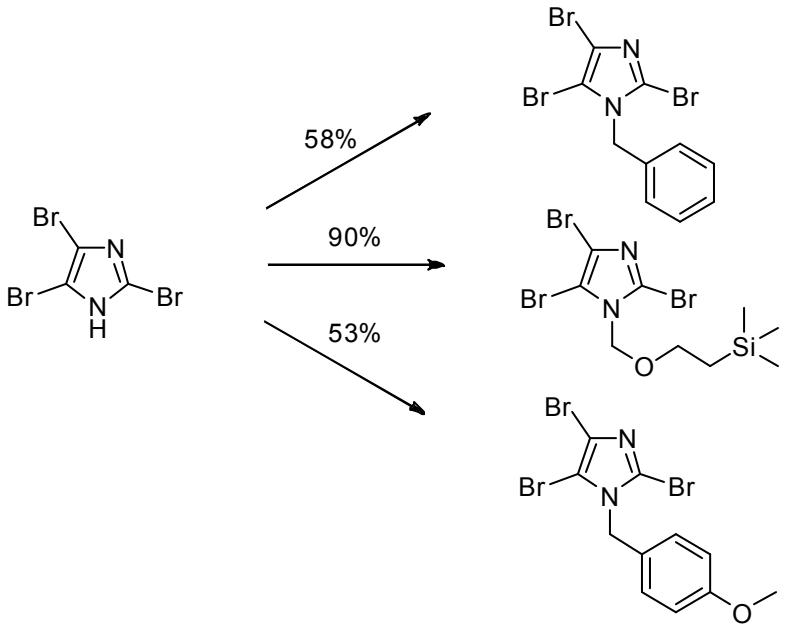
General Schemes

Synthesis of Coupling Partners



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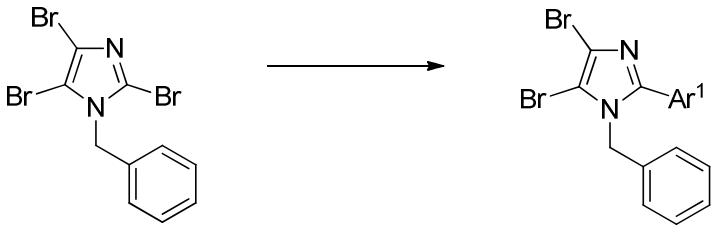

3 **8-12**

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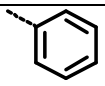
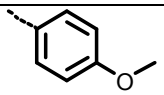
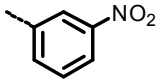
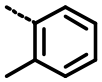
8		81%
9		77%
10		55%
11		79%
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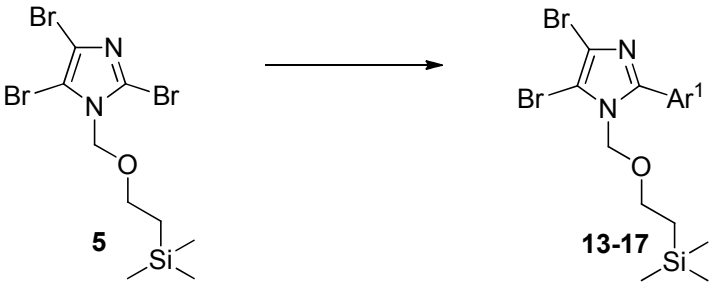

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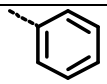
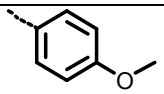
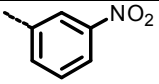
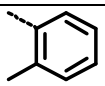
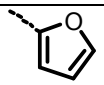
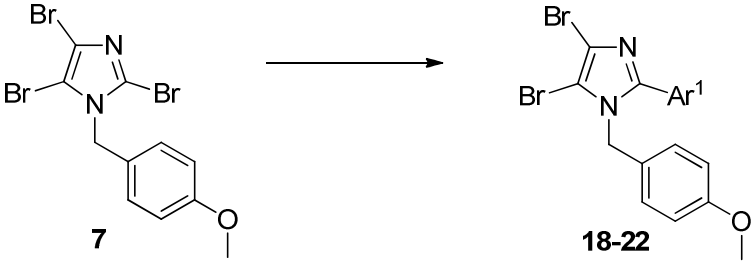
13		72%
14		74%
15		65%
16		42%
17		31%



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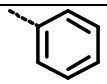
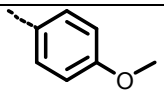
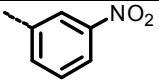
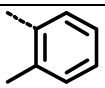
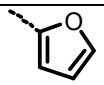
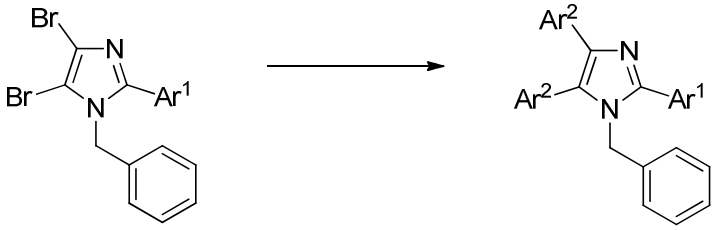
18		74%
19		77%
20		63%
21		59%
22		35%



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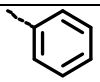
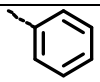
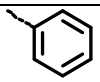
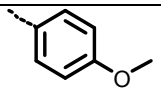
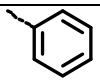
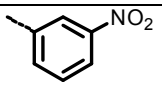
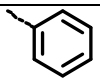
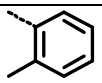
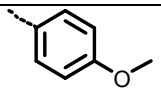
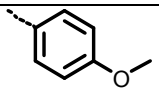
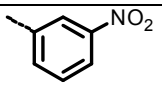
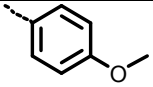
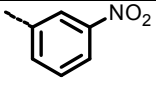
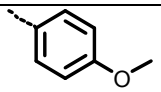
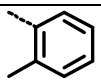
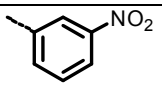
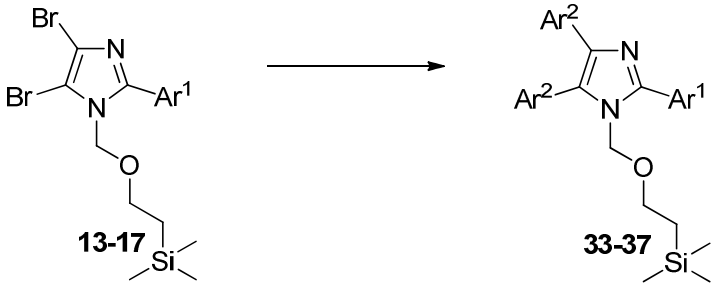
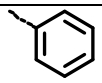
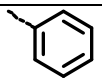
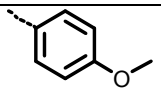
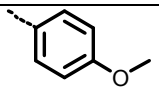
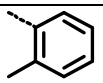
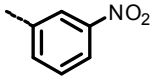
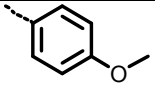
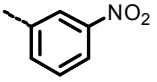
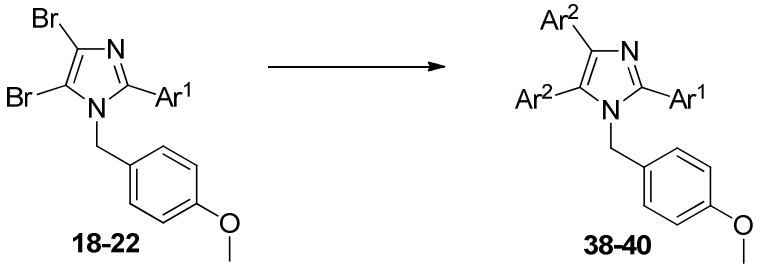
23			79%
24			85%
25			55%
26			37%
27			81%
28			60%
29			32%
30			85%
31			59%
32			39%



Compound	Ar^1	Ar^2	Yield
33			91%
34			67%
35			11%
36			53%
37			74%



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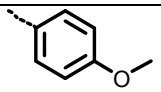
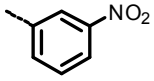
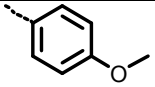
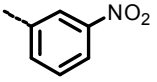
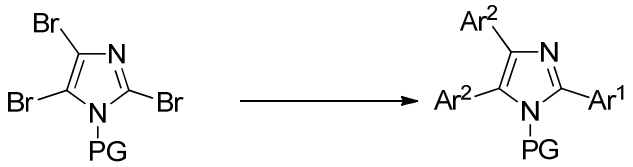
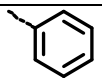
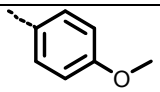
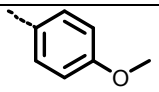
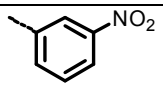
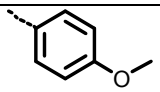
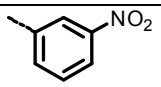
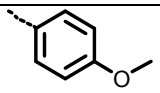
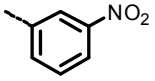
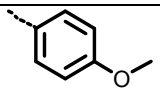
38			53%
39			92%
40			42%

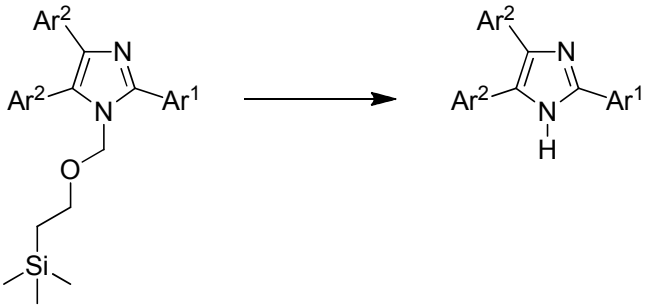
One-Pot Protocol



Compound	PG	Ar^1	Ar^2	Yield
24	Bn			80%
28	Bn			73%
34	SEM			25%*
36	SEM			58%
39	PMB			48%*

* minor contaminations by impurities

Deprotection



Compound	Ar^1	Ar^2	Yield
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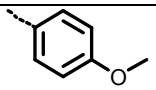
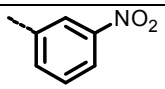
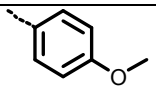
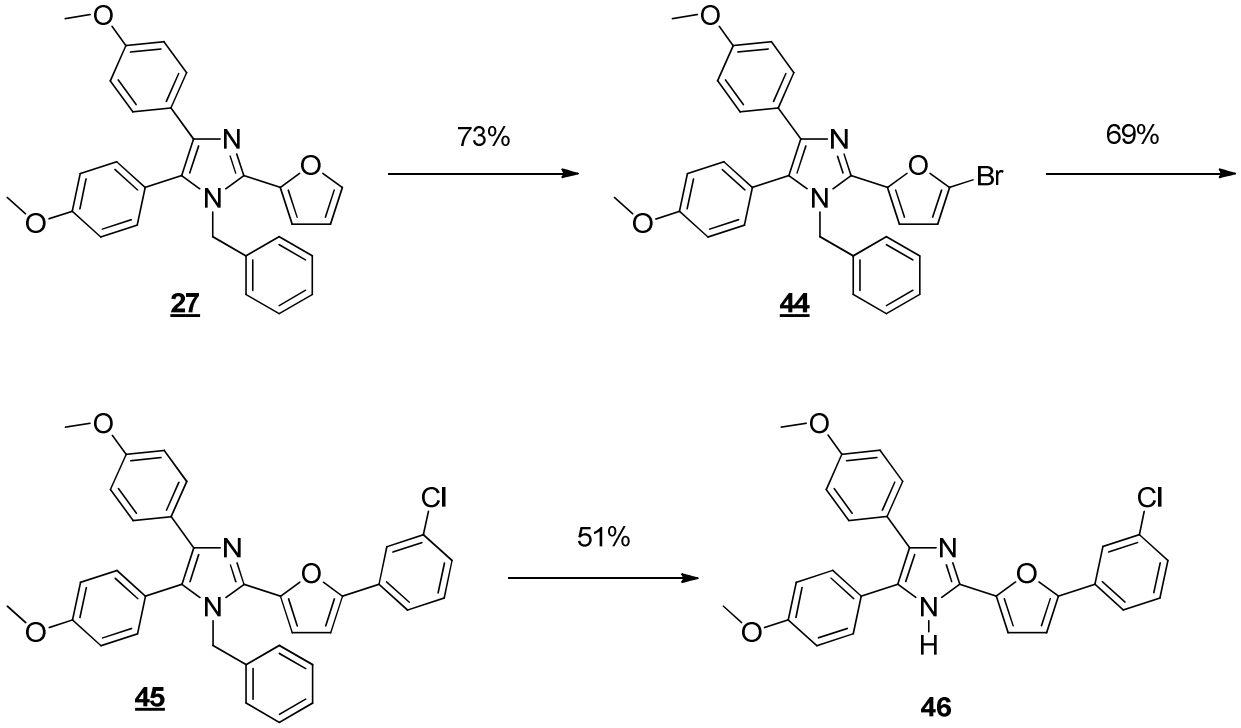
42			40%
43			56%

Synthesis of Neurodazine



1 Introduction

1.1. Imidazole

Imidazole[1] is an aromatic five-membered heterocycle which possesses a pyrrole-like N-atom in position 1 and a pyridine-like nitrogen in position 3. The name according to the Hantzsch-Widman nomenclature is 1,3-diazole. The imidazole ring is planar and forms an almost regular pentagon.

Its aromaticity is due to the π-electronic sextet which is formed by two electrons (lone pair) from the pyrrole-like N-atom, and one electron each from the pyridine-like N-atom as well as the three C-atoms. This sextet is largely delocalized over the five ring atoms. Hence, imidazole belongs to the group of π-excessive heterocycles. Figure 2 shows the electron densities in the molecule.

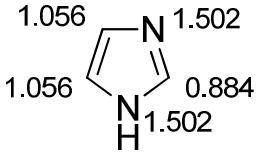
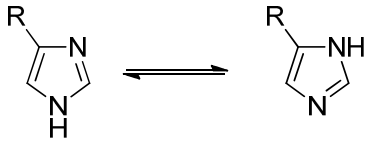


Figure 2

Imidazoles are amphoterical. They can react as a base with a pK_b value of 7. On the other hand, imidazole can also react as an acid. The pK_a value of imidazole is 14.52 and therefore greater than the pK_a value of ethanol (pK_a = 16).[2] Because of this amphotheric behavior the slightly acidic H can be transferred between the two N-atoms in 1- and 3-position. If the imidazole ring is substituted in 4-position, this tautomerism leads to isomerization to the 5-substituted compound (Scheme 2).

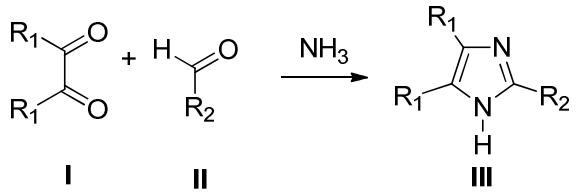


Scheme 2

Electrophilic attack occurs on the N-atoms of imidazole. Alkylation, acylation, sulfonation, and silylation are known reactions. The reaction of a haloalkane with imidazole leads to 1-alkylimidazole which can further react to 1,3-dialkylimidazolium salts. These salts form an important group of ionic liquids. Imidazole can be halogenated on the carbon atoms using

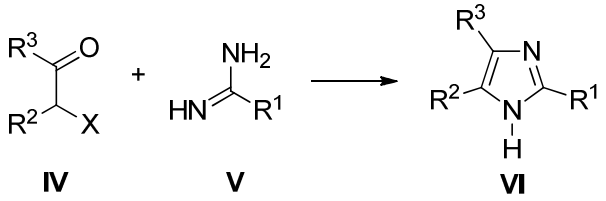
sulfuryl chloride, bromine, or iodine. Also azo-coupling can occur in 2-position of the imidazole under basic conditions. However, nitration and sulfonation proceed very slowly due to formation of imidazolyl cations under acidic conditions. Electrophiles attack preferably in 4-position. Nucleophilic substitution proceeds very slowly and exclusively at 2-position.

Imidazole can be synthesized by several strategies. An early approach is represented by cyclo-condensation of 1,2-dicarbonyl compounds **I** with ammonia and an aldehyde **II** to form imidazole derivatives (Scheme 3).[3-4]



Scheme 3

α–Halo ketones **IV** can be reacted with amidines **V** in a Hantzsch-like reaction in order to obtain imidazoles with different substituents in 4- and 5-position as shown in Scheme 4.[5]



Scheme 4

1.2. Imidazole Containing Natural Products and Bioactive Compounds

The imidazole ring is a common motif in natural products and bioactive compounds. One of the most important natural products derived from imidazole is the amino acid histidine **VII** (Figure 3).[6] This amino acid is present in many proteins and plays an important role in the structure and the binding functions of haemoglobin. The decarboxylation of histidine leads to histamine **VIII**,[7] a neurotransmitter which is involved in allergic reactions.

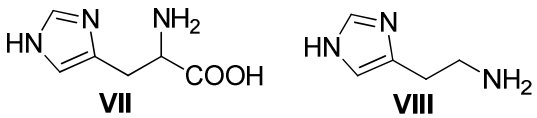


Figure 3

Purines are another example which contain the imidazole ring fused to pyrimidine. The two purines adenine **IX** and guanine **X** are two of the four building blocks of DNA that are responsible for base pairing (Figure 4).

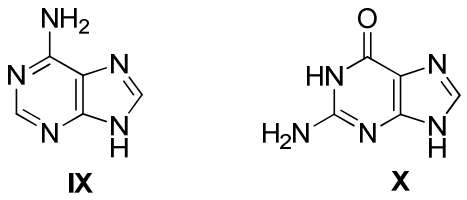


Figure 4

Substituted imidazoles are also interesting building blocks in bioactive compounds. Amongst others, they belong to the class of azole antifungals. Ketoconazole **XI**,[8] miconazole **XII**[9] and clotrimazole **XIII**[10] are three examples of this group (Figure 5). The mode of action is the inhibition of the enzyme lanosterol 14 α-demethylase which converts lanosterol to ergosterol.[11] The lack of ergosterol leads to destruction of the fungal membrane and thus to the inhibition of fungal growth.

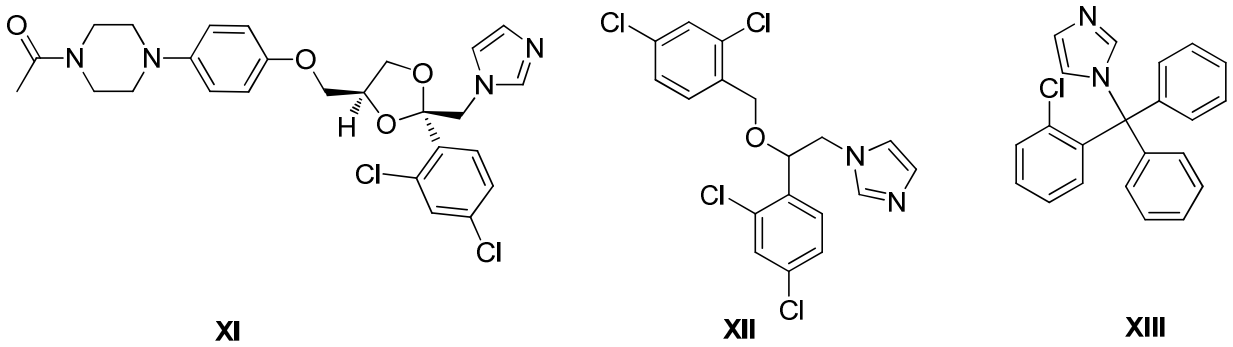
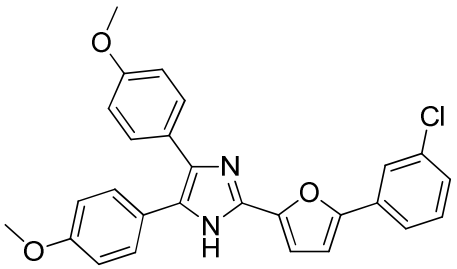


Figure 5

Another bioactive compound with cell-differentiating properties is neurodazine **XIV** (Figure 6). Recently, it was reported[12] that treatment of C2C12 mouse myoblast cells (progenitor cells of muscle cells) with neurodazine resulted in development of cells which have certain properties of neurons. Neuronal marker proteins were found to be up-regulated, however also skeletal muscle specific markers remained highly expressed. So it seems that an incomplete transformation from a muscle cell to a neuron was observed. The particular properties of neurodazine were found during a neurogenesis screening of approximately 300 imidazole derivatives. The trans-differentiation of one specified cell type into another is highly attractive

due to several reasons. On one hand, transplant rejection can be avoided by treating patients suffering from neurodegenerative diseases such as Alzheimer or Parkinson with their own tissues. On the other hand, the use of specified cell tissues would circumvent the use of embryonic stem cells for the treatment and therefore circumvent the ethical discussion about this method.

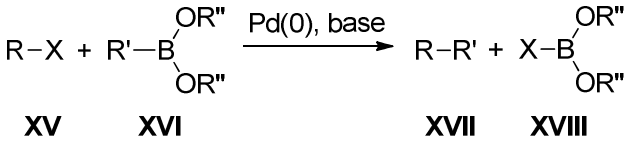


XIV

Figure 6

1.3. The Suzuki-Miyaura Cross-Coupling Reaction

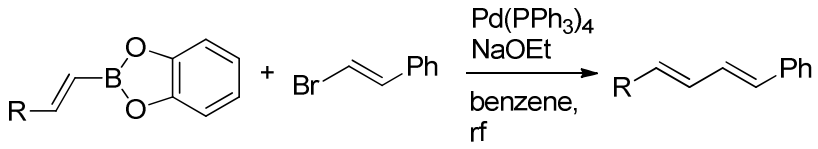
The Suzuki-Miyaura reaction represents the palladium-catalyzed cross-coupling reaction of an organoboron compound **XVI** with a halide or pseudohalide **XV** (for example triflates) in the presence of base as generalized in Scheme 5.[13] This coupling reaction has become a powerful and common tool for the formation of C-C bonds. It displays several advantages in comparison to other Pd-catalyzed cross-coupling reactions such as mild conditions, water stability, high functional group tolerance, low catalyst loadings, non-toxic intermediates, and facile separation of inorganic boron compounds.



XV **XVI** **XVII** **XVIII**

Scheme 5

The first Pd-catalyzed C-C cross-coupling reaction involving organoboranes was reported in 1979 by Suzuki et al.[14] The reaction of (*E*)-1-alkenyl-1,3,2-benzodioxaboroles **XIX** with 1-alkenyl halides **XX** in the presence of catalytic $Pd(PPh_3)_4$ and base resulted in the stereoselective formation of the conjugated *E*-diene **XXI** (Scheme 6).



XIX **XX** **XXI**

Scheme 6

Two years later, the first method was reported to prepare biaryls via the cross-coupling reaction between arylboron compounds and aryl halides.[15] Since then, various modifications of the reaction conditions have been published. Nevertheless, a combination of $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$ and aq. sodium carbonate in dimethoxyethane works satisfactorily in many cases and these conditions are widely applied.

Mainly iodides and bromides are used as electrophiles for the cross-coupling reaction with organoboron compounds. Additionally, it was discovered that also triflates can be used as leaving groups in cross-coupling reactions.[16] The use of chlorides requires more specialized catalytic systems with bulky and electron rich ligands due to low reactivity of the precursors.[17] The order of reactivity of halides and triflate is: I>Br>OTf>>Cl.

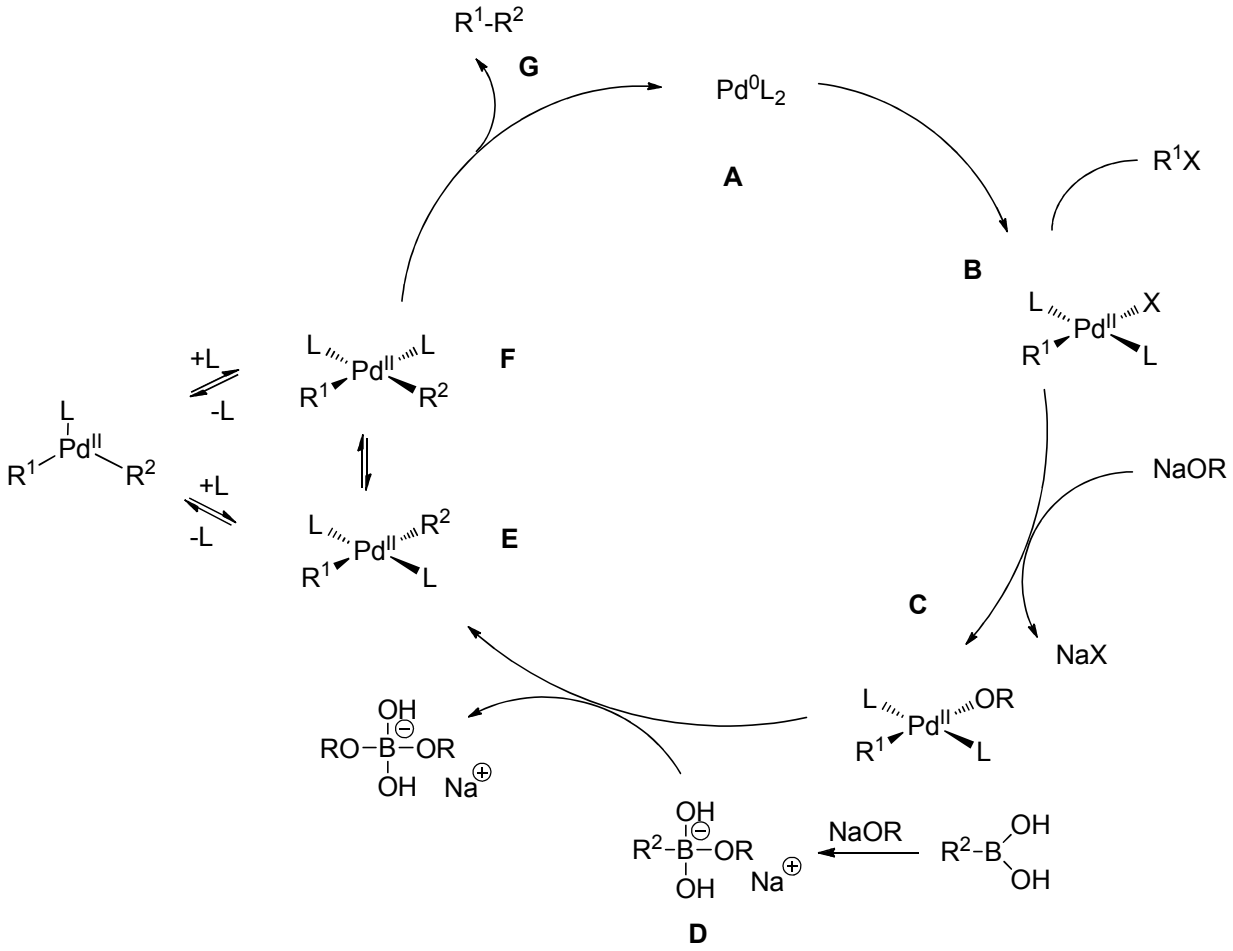
The substrate scope with respect to organoboron compounds is broad ranging from alkylborons,[18] 1-alkenyl[19] and 1-alkynylborons,[20] to aryl and heteroaryl[21] boron compounds. The cross-coupling to alkyl halides represents a challenging problem. On one hand, oxidative addition of an alkyl halide to the Pd(0) complex is very slowly; in addition, fast β-hydride elimination from alkylpalladium intermediates can occur.[22]

The most common organoboron compounds applied in Suzuki-Miyaura reactions are boronic acids. Moreover, boronic acid esters and trifluoroborates[23] can be used for cross-coupling reactions as well as easily accessible trialkylboranes.[24]

Recent developments of new catalysts also allow cross-coupling reactions involving less reactive tosylates and mesylates[25] as well as alkyl halides.[26]

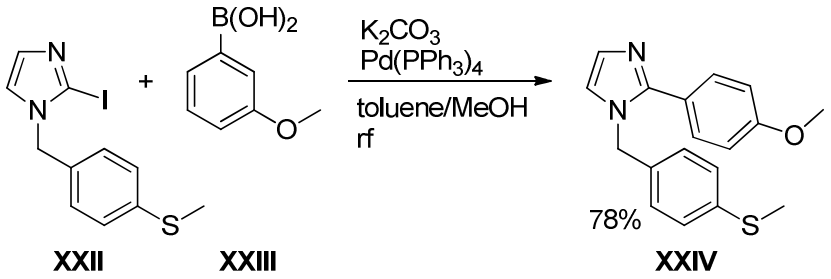
A broad range of catalysts have already been employed for the Suzuki-Miyaura protocol.[27-28] However, phosphine-based ligands are generally used as they are stable upon prolonged heating. Even chiral ligands have been developed for enantioselective cross-coupling.[29]

Scheme 7 outlines the catalytic cycle of the reaction. Oxidative addition of an organo halide to Pd(0) complex **A** generates an organopalladium-halide complex **B**. The halide in the organopalladium-halide complex **B** is then replaced by base to give intermediate **C**. Then complex **C** undergoes transmetallation with an activated organoboron compound **D**. Cis-trans isomerization can occur on the diorgano-palladium complex **E**. Only the resulting cis-complex **F** undergoes reductive elimination to form a product **G** and to regenerate the catalytically active Pd(0) species **A**.



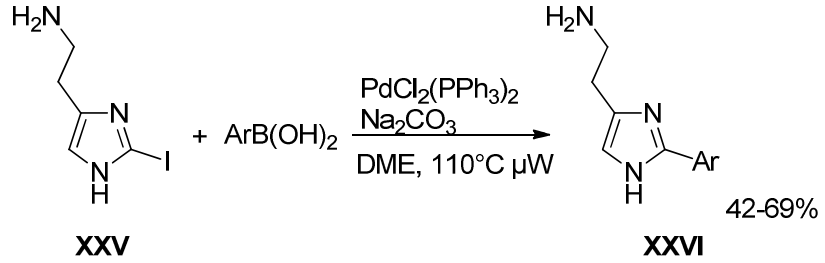
Scheme 7

The Suzuki-Miyaura cross-coupling reaction is a common and well-established tool in the arylation of monohalogenated imidazoles. Erker et al.[30] reported the cross-coupling of 3-methoxyphenylboronic acid **XXIII** in 2-position of *N*-substituted imidazoles **XXII** (Scheme 8).



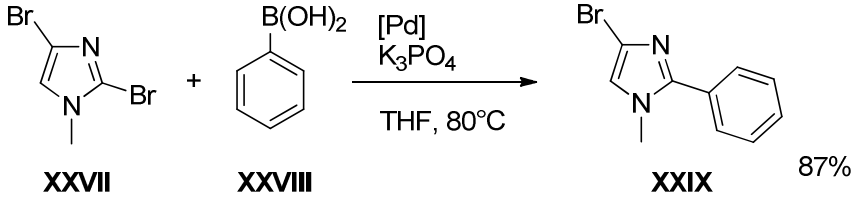
Scheme 8

Thomas et al.[31] reported the synthesis of substituted 2-phenylhistamines **XXVI** via a microwave promoted Suzuki-Miyaura cross-coupling in the same year (Scheme 9).



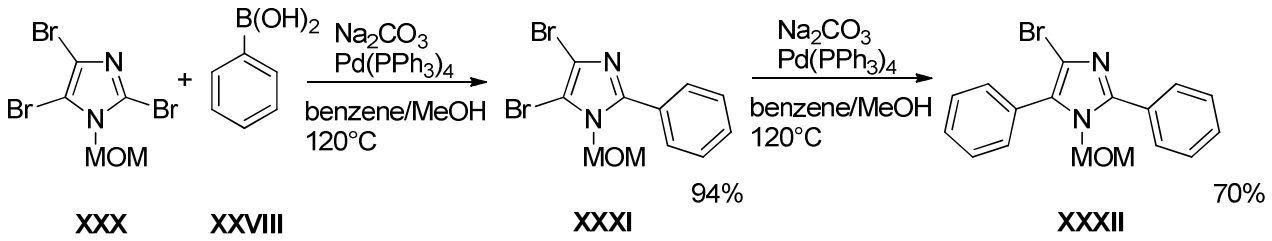
Scheme 9

Strotman et al.[32] disclosed a regioselective arylation of 2,4-dibromoimidazoles **XXVII** in 2-position (Scheme 10).



Scheme 10

Ohta et al.[33] reported regioselective arylation in 2- and 5-positions on 2,4,5-tribromoimidazole **XXX** (Scheme 11).

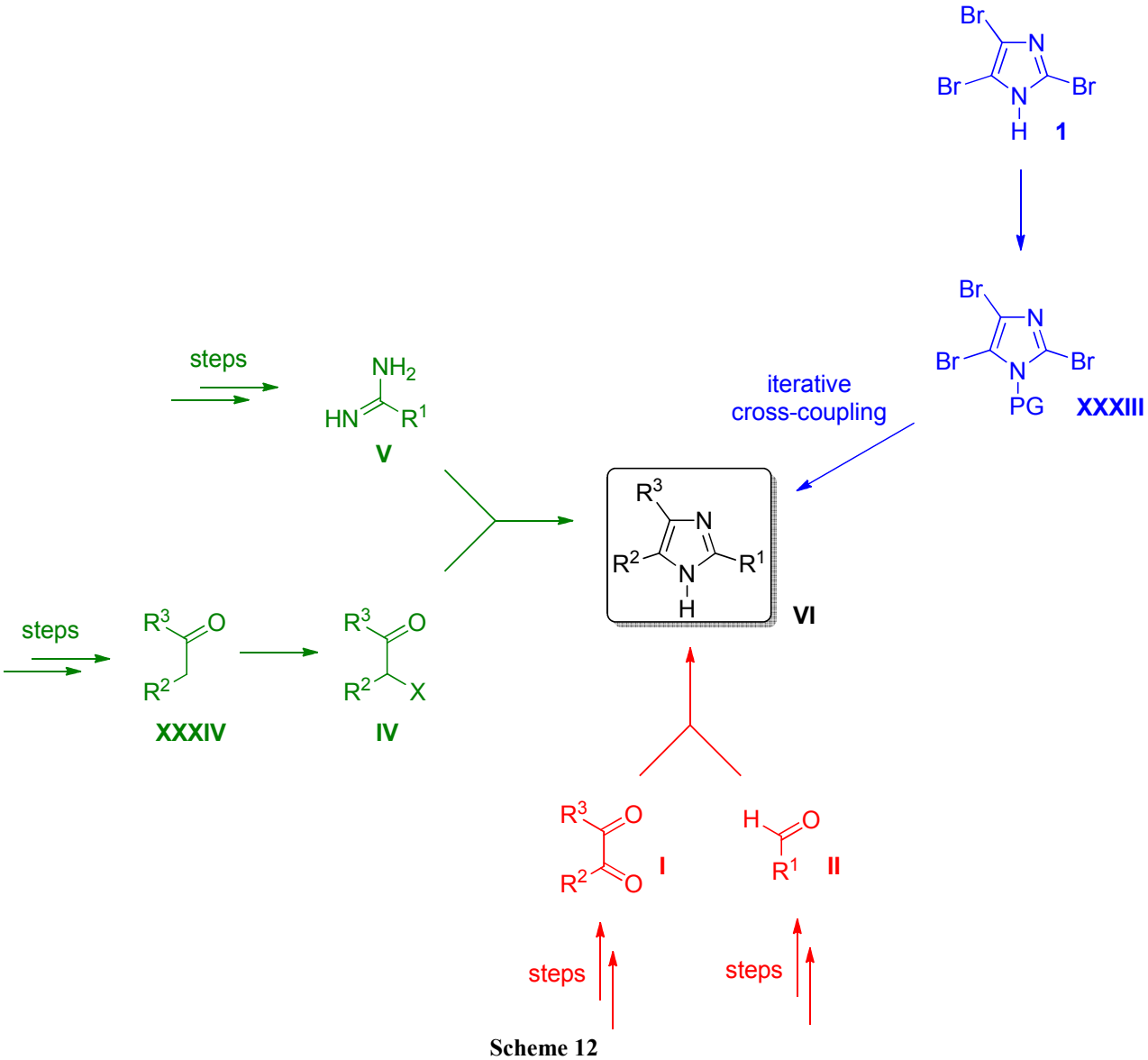


Scheme 11

However, no selective cross-coupling sequence in all three positions of 2,4,5-tribromoimidazole has been reported, so far.

1.4. Objective

The selected bioactive compounds discussed in section 1.2 demonstrate why substituted imidazoles are considered to be interesting building blocks and often act as structural motifs in synthetic bioactive compounds.



Scheme 12

As already described in section 1.1 a common strategy for the synthesis of substituted imidazoles is the cyclo-condensation of 1,2-dicarbonyl compounds **I** with ammonia and an aldehyde **II** (Scheme 12 red, section 1.1). This is definitely an attractive method for the synthesis of one or a small collection of products as well as for production in large scale.

Recently, Singh et al.[34] synthesized various 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted compounds with this protocol. In this publication easily available benzil was mainly used as 1,2-diketon. However, when e.g. a library of differently substituted imidazoles is envisaged this method becomes very elaborate: For each substitution pattern the corresponding 1,2-dicarbonyl compounds **I** and aldehydes **II** have to be prepared separately. Another problem occurs in the synthesis of 1-substituted imidazoles starting from α-haloketones **IV** and amidines **V** (Scheme 12 green, section 1.1). In this case, the 4- and 5-positions of the imidazole ring are not equal any more and the use of unsymmetrically substituted ketones (Scheme 3) would lead to a mixture of regioisomeric products which are difficult to separate.

Under these circumstances transition-metal catalyzed cross-coupling reactions represent an attractive alternative. By applying this methodology it becomes possible to decorate a simple imidazole building block in a stepwise manner to ultimately obtain a wide range of target compounds with different substituents (Scheme 12 blue).

Cross-coupling reactions on mono- or di-halogenated imidazoles are a common and well-studied tool for C-C bond formation in the synthesis of mono-arylated imidazoles.[30-31] Selective cross-coupling reactions on 2,4-dihaloimidazoles or 2,5-dihaloimidazoles also have been reported.[32,35]

Furthermore, cross-coupling reactions on tri-halogenated imidazoles in 2- and 5-position have been reported, previously.[33] However, triarylation of imidazole in 2-, 4-, and 5-position using a Pd-catalyzed cross-coupling protocol has never been demonstrated, so far.

In our group, analog studies on selective cross-coupling reactions on the tribromothiazole were already performed. Selectivity between the positions 2, 4 and 5 could be obtained and also a one-pot protocol was developed.[36-37]

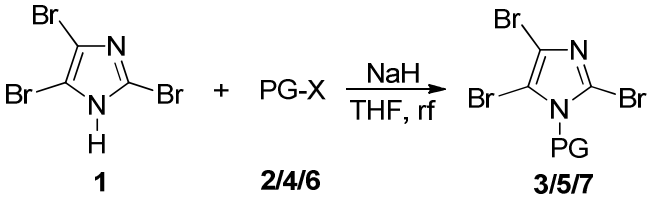
Therefore, it was the major aim of this thesis to synthesize 2,4,5-triarylated imidazoles starting from the easily accessible substrate tribromoimidazole by sequential selective Suzuki-Miyaura cross-coupling reactions.

2 Results and Discussion

2.1. Synthesis of Coupling Partners

Before starting our investigations regarding sequential cross-coupling reactions on imidazole, suitable starting materials had to be prepared. Preliminary tests in our group have shown that cross-coupling reactions cannot be performed on unprotected imidazoles. Consequently, the tribromoimidazole coupling precursor has to be protected. Several different protecting groups with orthogonal properties were selected for further investiations: the benzyl group (Bn) is usually cleaved under reductive conditions, whereas the 4-methoxybenzyl group (PMB) usually requires acidic (TFA) or oxidative conditions (DDQ). Moreover (2-(trimethyl-silyl)ethoxy)methyl (SEM) was used as a protecting group which needs tetrabutylammonium fluoride for deprotection. Hence, the different protecting groups require different conditions for deprotection. This assures that an appropriate protecting group can be chosen depending on the variation of substituents at the arylboronic acids. Tert-butyloxycarbonyl (Boc) was also considered as a protecting group in order to change electronic properties on the imidazole ring. In contrast to Ohta et al. we did not consider methoxymethyl (MOM) as protecting group due to the high toxicity of the required MOMCl reagent.

2.1.1. *N*-Protected 2,4,5-Tribromo-1*H*-imidazole

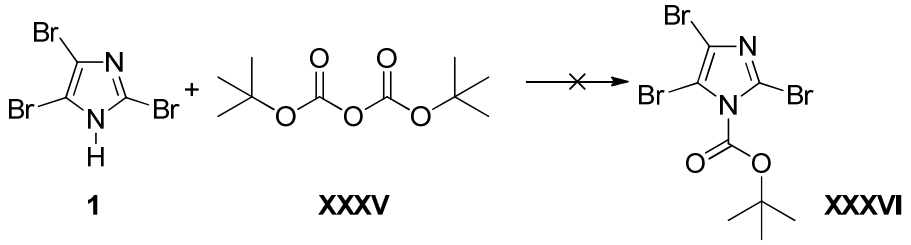


Scheme 13

N-Protected 2,4,5-tribromo-1*H*-imidazoles **3/5/7** were synthesized according to a protocol developed in our group (Scheme 13). 2,4,5-Tribromoimidazole **1** was deprotonated with NaH at 0°C under argon atmosphere upon liberation of H_2. In the next step the formed imidazole anion reacted with the corresponding halide (benzyl bromide **2**, 2-(trimethylsilyl)-ethoxymethyl chloride **4**, or 4-methoxybenzyl chloride **6**) under reflux within 1-6 hours. After workup and purification the protected products bearing Bn, SEM, or PMB were isolated with 58%, 90%, and 53% yield, respectively.

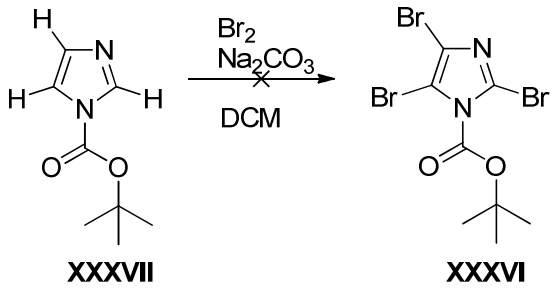
2.1.2. 1-(tert-Butyloxycarbonyl)-2,4,5-tribromo-1*H*-imidazole

Preparation of the title compound was attempted by introducing the Boc group in 2,4,5-tribromoimidazole as well as by bromination of 1-(tert-butyloxycarbonyl)-imidazole.



Scheme 14

First, the solvent- and catalyst free protocol for the protection of imidazole from Jia[38] et al. was applied (Scheme 14). 2,4,5-Tribromoimidazole **1** (1 equivalent) was placed in a 6 mL vial and 1 equivalent Boc-anhydride **XXXV** was added dropwise under stirring. After the addition was completed the mixture could not be stirred anymore as the solid was not dissolved in the liquid but the liquid was absorbed. No conversion could be observed. The mixture was grinded in a mortar in order to start the reaction employing mechanochemistry, however, no conversion could be observed. Therefore, the mixture was dissolved in dry dichloromethane but still no reaction could be observed after a few hours of stirring. Hence, triethylamine was added as a base to deprotonate tribromoimidazole but also this did not promote the reaction. The reason for this might be that the Boc-group is too sterically demanding to fit in between the two bromine atoms. So the nucleophilic attack of the tribromoimidazole anion to the partially positively charged carbonyl group of the Boc-anhydride is sterically not feasible.



Scheme 15

As the introduction of the Boc group was not successful on 2,4,5-tribromoimidazole, the bromination of Boc-protected imidazole was attempted. A procedure for the tribromination of unprotected imidazole reported by Balaban[39] et al. was used for that purpose (Scheme 15).

Boc-protected imidazole **XXXVII** was dissolved in dry dichloromethane. Na_2CO_3 was added as base to quench the formed HBr and to avoid deprotection of the Boc group under acidic conditions. Then, a solution of bromine in dry dichloromethane was added to the reaction mixture. After one hour stirring at room temperature the starting material was fully converted according to TLC. Unfortunately, the desired product **XXXVI** was not formed but only decomposition to unidentified products was observed.

2.2. Establishment of Reaction Monitoring

In initial experiments in our group[36] Suzuki-Miyaura cross-coupling reactions on 2,4,5-tribromothiazole were monitored by thin layer chromatography (TLC) using mixtures of light petroleum and ethyl acetate as eluent. Unfortunately, already initial cross-coupling experiments on tribromoimidazoles showed that in this case the R_f-values of substrates and products were too close together and a different way to monitor the reactions had to be established. Initially, different polar phases for TLC were used such as ethyl acetate, isopropanol, THF, acetone, and tert-butylmethylether in combination with toluene and light petroleum as non-polar phase. But none of these combinations could improve the separation of substrate and product on TLC.

At a later stage, some more eluents for TLC were tested and it was found that dichloromethane/methanol (200:1) was a good eluent to separate substrates and products from cross-coupling reactions on imidazole. It was used successfully for the reaction monitoring of cross-coupling reactions.

In order to find also a method for quantitative analysis, gas chromatography (GC) was considered for reaction monitoring. Therefore, it was necessary to measure references to determine the peak of the starting material. With this method, consumption of starting material can be observed but it is time-consuming since all of the products are rather polar and have high boiling points which made long GC-runs (about 40 minutes) necessary. Furthermore, it was found that some of the 2,5-diarylated-4-bromoimidazoles – mainly those containing nitro-functions – and most of the 2,4,5-triarylated imidazoles were insufficiently volatile for GC analysis, at all. Additionally, boronic acids cannot be detected on GC. All these facts made the analysis of reaction selectivity extremely difficult. In order to determine if a cross-coupling reaction is selective in 5-position of the 2-aryl-4,5-dibromoimidazole, it is not only necessary to monitor starting material consumption and product (2,5-diaryl-4-

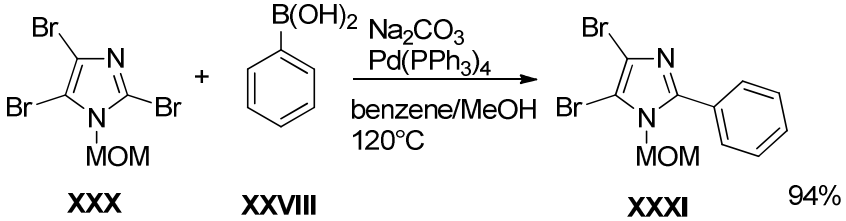
bromoimidazole) formation but also the possible formation of 2,4,5-triarylimidazoles. Therefore, GC could only be used in the monitoring of starting material consumption, but it is limited in the tracking of (by-)product formation. In conclusion, GC was not suitable for selectivity studies on tribromoimidazole.

As mentioned above, boronic acids cannot be detected on GC. As the boronic acid is often the limiting part in cross-coupling reactions due to decomposition at high temperature we were looking for a method which can detect starting material and boronic acid in order to determine the consumption of both substrates and to adjust the amount of boronic acid. As the most obvious choice, we tested reversed phase HPLC for reaction monitoring. Initially, we used the reversed phase column LiChrospher 100-RP18-5µ (4.6x150mm) with acetonitrile/water (70:30) as eluent. Again, samples of starting material had to be measured first as references for further investigations. With this method, the consumption of boronic acid could be measured but there were some problems concerning 2,4,5-tribromoimidazole. Obviously, the compound's UV absorption is so high that even small amounts led to a significant absorption peak. Therefore it was difficult to determine complete and also nearly complete consumption of starting material. Interestingly, this problem disappeared with the use of another column that is specific for the separation of polyhalogenated compounds (Phenomenex Kinetex PFP column, 2.6µ, 100x4.6mm). A gradient of acetonitrile/water (0.1% TFA) was used to wash possible triarylated imidazoles and triphenylphosphine out of the column. Comparing to GC it is less time-consuming as a single run requires only 15 minutes (with an UHPLC which became available during this thesis, one run could be reduced to 4 minutes). Moreover substrate and boronic acid could be monitored and there is no limitation in the polarity of the products. Unfortunately, some problems were encountered regarding identification of peaks. Retention times varied considerably no matter how long the column was preconditioned. In some cases differences in retention times of one minute were observed for the same compound measured on two different days. Therefore it became difficult to determine substrate and product peaks reliably. Moreover, it is not the best method for monitoring reaction selectivity. Several new compounds can be formed (e.g. mono-, di- or tri-arylated imidazoles, and various debrominated compounds) in the cross-coupling reaction and hence several new peaks can and did occur. Unfortunately, using HPLC as sole analytical method does not allow unequivocal assignment of peaks to certain products. Hence, HPLC is also not 100% suitable for monitoring reaction selectivity.

At this time, a liquid chromatography mass spectrometry system (LC-MS) became available at our institute. As a HPLC method suitable for cross-coupling reactions on imidazole was already developed (see above), it only had to be adjusted to the requirements of the LC-MS system. With this method reactions could be monitored concerning consumption of starting material, formation of product, and reaction selectivity in a qualitative way. Until now it seems to represent the only way of monitoring reaction selectivity for cross-coupling reactions on imidazole in a reliable and reproducible fashion although reliable quantification was not possible. An equimolar mixture of N-benzyl 2-phenyl-4,5-dibromoimidazole **8**, 2,5-diphenyl-4-bromoimidazole **23a** and 2,4,5-triphenylimidazole **23** were prepared and measured on LC-MS to investigate the quantification of this method. However, the ratio of the integrals of these three peaks was about 1:20:200 instead of 1:1:1. It seems as if the N-benzyl 2,4,5-triphenylimidazole **23** ionizes 200fold stronger in the mass spectrometer and therefore gives a 200fold stronger signal than the substrate **8**. Even the product **23a** gave a 20fold stronger signal, which is also due to the differences in ionization. The exact calculation of a correction factor was impossible as the ratio of the three integrals were varying between two measurements.

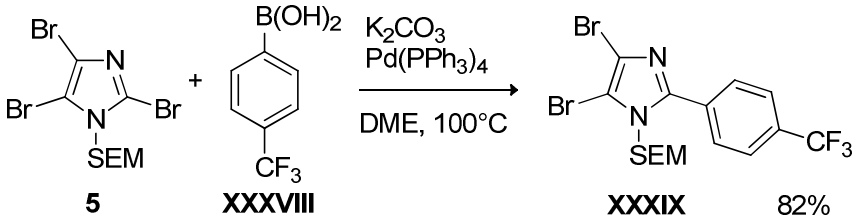
2.3. Selective Cross-Coupling in 2-Position

First, it was attempted to react benzyl-protected 2,4,5-tribromoimidazole **3** with boronic acid in the most activated 2-position. Initially, 5mol% of $Pd(PPh_3)_4$ were used as catalyst with 3 equivalents of 2 M aq. potassium carbonate solution as base and toluene as solvent. Boronic acid was used in slight excess (1.1 equivalents) as it shows decomposition at higher temperature to some extent. These conditions resulted in good yields but demand long reaction times (48h). Therefore, other conditions were tried to decrease the reaction time while maintaining the selectivity. Ohta et al.[33] published a protocol for the cross-coupling in 2-position of 2,4,5-tribromoimidazole **XXX** using benzene/methanol (5:1) as solvent and 2M aq. sodium carbonate as base (Scheme 16).



Scheme 16

Huang et al.[40] published another protocol for the cross-coupling on SEM-protected tribromoimidazole **5** using DME as solvent and potassium carbonate as base (Scheme 17).



5 **XXXVIII** **XXXIX** 82%

Scheme 17

These three conditions were tested on the benzyl and SEM protected-2,4,5-tribromoimidazoles **3** and **5** with phenylboronic acid as aryl donor. Ohta's conditions were slightly changed, by using the less toxic toluene instead of benzene. Moreover a modification from Ohta's condition was also tested changing the amount of catalyst from 10 to 5mol% and changing the base from sodium to potassium carbonate.

In Table 1 the results of screening these four conditions are summarized. The yields of all entries are varying from 53-81% except for entry 4 (only 31%) which can be explained by loss of the product during the purification as a part of the product was spilled. However, reaction times differ strongly between the different solvent/base systems. Using SEM as a protecting group always resulted in shorter reaction times. Regarding the solvent, toluene required the longest reaction times of 47 and 29 hours with benzyl and SEM as protecting groups, respectively (entries 1 and 2). The use of DME as solvent and potassium carbonate as base resulted in somewhat decreased reaction times (over night reactions, entry 7 and 8). Using toluene/methanol as solvent and sodium carbonate as base shortened the reaction times to two hours for both protecting groups (entries 3 and 4). However, using the modified Ohta protocol (entry 5 and 6), the reaction is completed in five hours and the yields are the highest for benzyl and SEM protected substrates.

Table 1

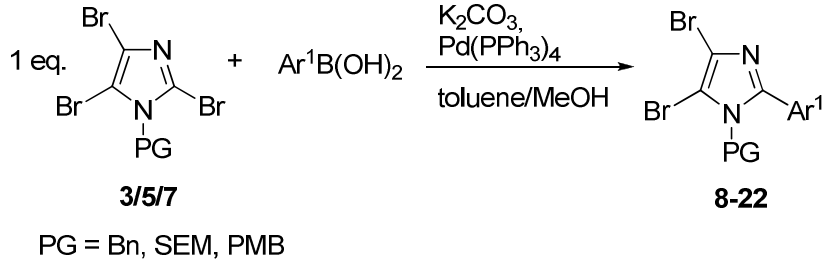
Entry	PG	Catalyst	Base	Solvent	Temp.	Time	Yield[a]
1	Bn	5 mol% $Pd(PPh_3)_4$	3 eq. K_2CO_3	Toluene	100°C	47 h	66%
2	SEM					29 h	67%
3	Bn	10 mol% $Pd(PPh_3)_4$	1 eq. Na_2CO_3	Toluene/ MeOH	120°C	2 h	53%
4	SEM					2 h	31%[b]
5	Bn	5 mol% $Pd(PPh_3)_4$	1 eq. K_2CO_3	Toluene/ MeOH	120°C	5 h	81%
6	SEM					5 h	72%
7	Bn	3 mol% $Pd(PPh_3)_4$	1.7 eq. K_2CO_3	DME	100°C	<22 h	56%
8	SEM					<22 h	71%

[a] isolated yield

[b] part of product spilled during purification

As entries 5 and 6 showed highest yields with acceptable reaction times, these conditions became the protocol of choice for the cross-coupling in 2 position.

With this protocol a variety of protected 2-aryl-4,5-dibromo-1*H*-imidazoles **8-22** was synthesized (Scheme 18, Table 2).

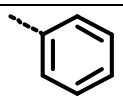
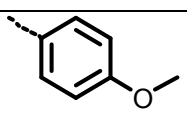


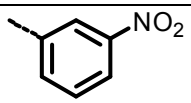
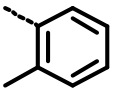
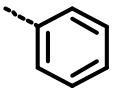
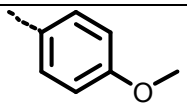
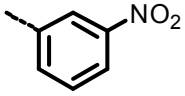
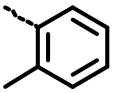
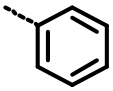
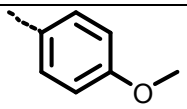
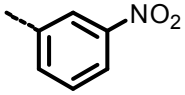
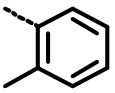
3/5/7 **8-22**

PG = Bn, SEM, PMB

Scheme 18

Table 2

Compound	PG	Ar^1	Equivalents	Yield[a]
8	Bn		1.2	81%
9	Bn		1.1	77%

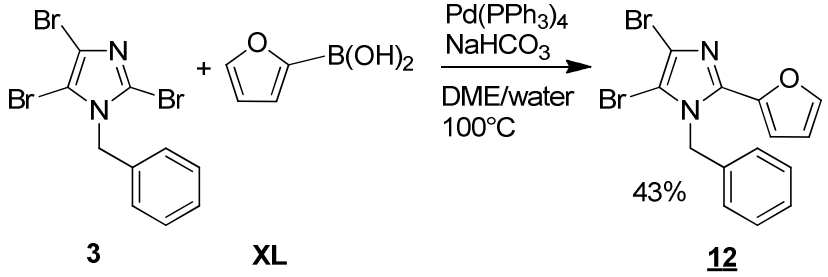
10	Bn		1.1	55%
11	Bn		1.3	79%
13	SEM		1.1	72%
14	SEM		1.1	74%
15	SEM		1.2	65%
16	SEM		1.1	42%
18	PMB		1.1	74%
19	PMB		1.1	77%
20	PMB		1.1	63%
21	PMB		1.1	59%

[a] isolated yield

All reactions were finished within a few hours (reaction monitoring by TLC). For some reactions, additional 0.1-0.2 equivalents boronic acid had to be added to complete consumption of imidazole starting material (compound **8**, **11**, **15**). Yields are usually good for coupling with arylboronic acids (55-81%). Only in the case of compound **16** a yield significantly below 60% was observed, which may be attributed to steric hindrance of the o-tolylboronic acid (however, the corresponding example employing benzyl as protecting group gave a good 79% yield of compound **11**). In general, the protecting group has no major influence on the yields of the cross-coupling process. For example, cross-coupling reaction using phenyl boronic acid resulted in 81, 72 and 74% yield using benzyl (compound **8**), SEM (compound **13**), and PMB (compound **18**) as protecting groups respectively. Hence, they are all suitable for the cross-coupling reactions on tribromoimidazole. Both electron with-drawing

(NO_2, compounds **10**, **15** and **20**) and electron-donating (OMe, compounds **9**, **14** and **19**) substituents on the phenyl ring were accepted in the cross-coupling reaction as well as the sterically demanding o-tolylboronic acid (compound **11**, **16** and **21**).

The cross-coupling of 2-furylboronic acid **XL** with *N*-protected 2,4,5-tribromoimidazole was more complicated. It is known that 2-furylboronic acid is not very stable. As the reaction was performed at 120°C, furylboronic acid decomposed very quickly. Hence, overall more equivalents of boronic acid had to be added to the reaction to compensate. Moreover, it is known in our group that cross-coupling of 2-furylboronic acid in 2-position on tribromothiazole demands different conditions than other boronic acids. Therefore, these conditions already developed in our group[36] were used for the cross-coupling of 2-furylboronic acid: DME/water (3:1) was used as a solvent, $NaHCO_3$ as base and $Pd(PPh_3)_4$ as catalyst (Scheme 19). Altogether 4.1 equivalents of 2-furanboronic acids were used before the reaction was stopped. The reaction resulted in 43% yield.



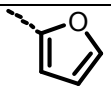
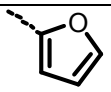
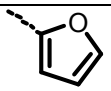
Scheme 19

Another problem was the reaction monitoring. First, the reaction was monitored by TLC but the R_f-values of the starting material and the product are the same. Moreover consumption/decomposition of the furylboronic acid could not be detected. Therefore, HPLC was used but also here it turned out that substrate and product have the same retention time. Also the UHPLC system could not resolve the two peaks. Therefore, the reaction was stopped after employing about 4 equivalents of 2-furylboronic acid in portions due to economical reasons.

Nevertheless, in order to develop a simple one-pot protocol, the reaction was also performed using the same conditions as for the other *N*-protected 2-aryl-4,5-dibromoimidazoles (Table 2) using Na_2CO_3 as base, $Pd(PPh_3)_4$ as catalyst and toluene/MeOH as solvent. In this manner, protected 2-furyl-4,5-dibromoimidazole was synthesized with the three different protecting

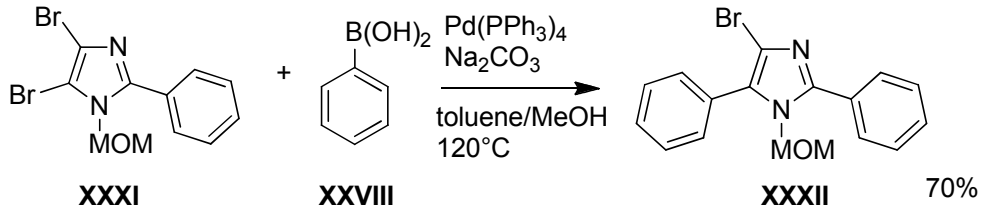
groups (Table 3). Overall 3.6 equivalents of 2-furylboronic acid were used. The reaction resulted in 25-35% yield.

Table 3

Compound	PG	Ar[1]	Equivalents	Yield
12	Bn		3.6	25%
17	SEM		3.6	31%
22	PMB		3.6	35%

2.4. Selective Cross-Coupling in 5-Position

The next step was to perform cross-coupling reactions in 5-position, if possible with high selectivity relative to position 4. In the literature there is only the publication by Ohta et al.[33] that claimed to obtain selectivity for the Suzuki-Miyaura cross-coupling in 5-position of a 4,5-dibromoimidazole (see section 1.3). When coupling phenylboronic acid with 1-methoxy-methyl-2-phenyl-4,5-dibromo-1*H*-imidazole **XXXI** they obtained 1-methoxymethyl-2,5-diphenyl-4-bromo-1*H*-imidazole **XXXII** in 70% yield after 10h (Scheme 20).

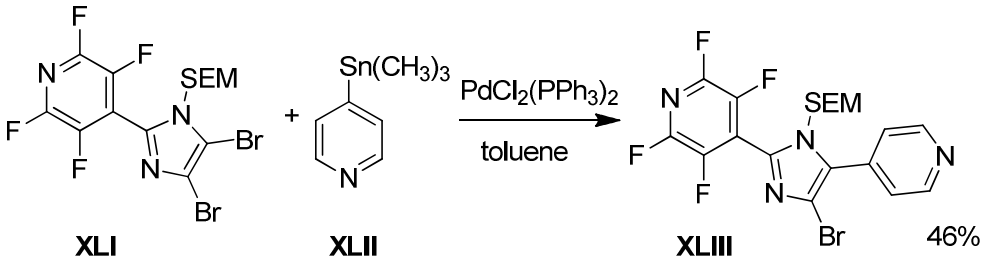


XXXI **XXVIII** **XXXII**

Scheme 20

As methyl chloromethyl ether is a highly toxic compound, we decided not to use this protecting group in this work. Using the benzyl protected analog, we could not repeat the results of Ohta and only 30% of impure product could be obtained due to an unselective reaction.

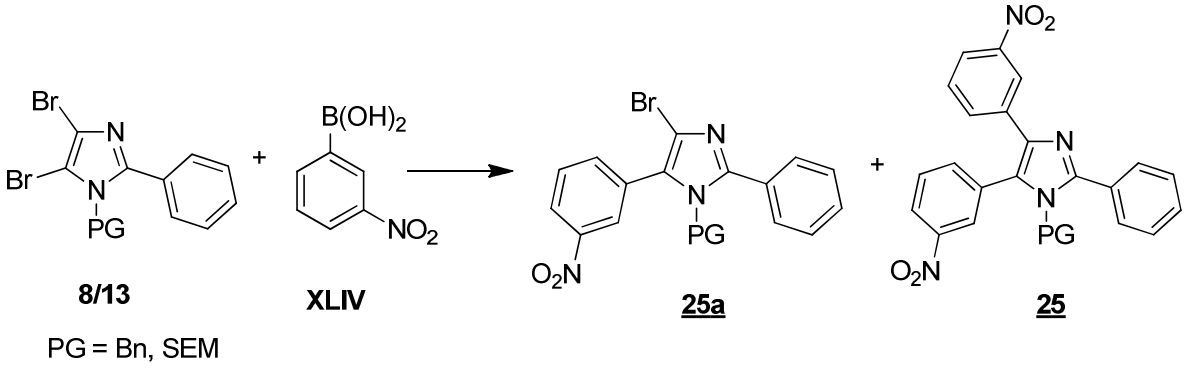
Another report from Revesz et al.[41] claimed a regioselective Stille reaction in 5-position of a 4,5-dibromoimidazole **XLI** (Scheme 21) with 46% yield.



Scheme 21

Therefore, a Stille coupling with 1.4 equivalents of tributyl(phenyl)stannane and 1-benzyl-2-phenyl-4,5-dibromo-1*H*-imidazole **8** using 5 mol% $Pd(PPh_3)_4$ as catalyst and toluene as solvent was performed. A yield of 42% could be obtained but there were also 45% yield of bis-coupled byproduct.

Various reaction conditions were applied in order to obtain selectivity between position 4 and 5. Benzyl and SEM protected-2-phenyl-4,5-dibromo-1*H*-imidazoles **8** and **13** were used as starting materials. 3-Nitrophenylboronic acid **XLIV** was chosen as coupling partner since then the products and starting materials were easily separable. Initially, DME/water (3:1) was used as solvent employing potassium carbonate as base and $Pd(PPh_3)_4$ as catalyst. Additionally, the modified conditions already used for coupling in 2-position from Ohta and the conditions from Huang were used (see section 2.3). The results are summarized in Table 4. In all cases a considerable amount of byproduct could be isolated, which was identified as protected 2-phenyl-4,5-di(3-nitrophenyl)imidazole **25** (Scheme 22). According to LC-MS, this byproduct is already formed very early in the reaction. As soon as the 2,5-diarylated product is formed this reacts further to the triarylated product making a selective transformation impossible.



Scheme 22

When the SEM protected 2-phenyl-4,5-dibromoimidazole **13** is used, the ratio of product to byproduct is approximately 2:1 (entries 2, 4 and 6). No trend is visible for benzyl protected 2-phenyl-4,5-dibromoimidazole. Following conditions according to entry 3 the product yield is very low and the ratio of product : byproduct is 1:1. Overall, the reaction is not selective for the 5-position under these three conditions since the electronic and hence also reactivity difference between position 4 and 5 is very small. Therefore, the reaction rate of the formation of diarylated and triarylated imidazole is also very similar.

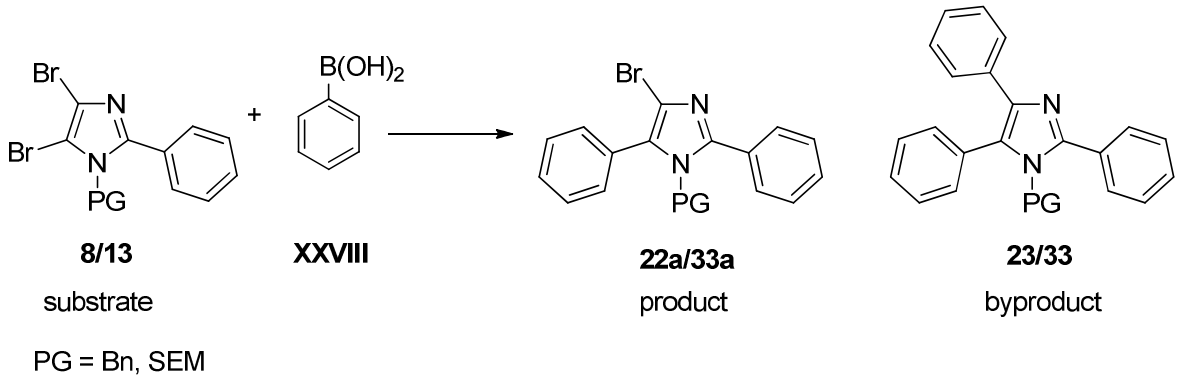
Table 4

Entry	PG	Catalyst	Base	Solvent	Temp.	Yield[a] product	Yield[a] byproduct
1	Bn	5 mol% $Pd(PPh_3)_4$	3 eq. K_2CO_3	Toluene	100°C	43%	35%
2	SEM					38%	17%
3	Bn	5 mol% $Pd(PPh_3)_4$	1 eq. K_2CO_3	Toluene/ MeOH	120°C	17%	16%
4	SEM					43%	24%
5	Bn	3 mol% $Pd(PPh_3)_4$	1.7 eq. K_2CO_3	DME	100°C	42%	17%
6	SEM					41%	25%

[a] isolated yield

2.4.1. Selectivity Screenings

To further explore possibilities to improve the selectivity between positions 4 and 5 a series of different reaction conditions was screened and monitored by LC-MS. All of the following screening conditions were tested on the cross-coupling reaction of phenylboronic acid to *N*-protected 2-phenyl-4,5-dibromoimidazoles **8** and **13** (Scheme 23).



Scheme 23

Using LC-MS for analysis, the presence of several compounds in the reaction mixture could be detected and assigned due to their mass spectra and characteristic isotope- and fragmentation patterns (Figure 7 and Figure 8). The identified peak with the lowest retention time was triphenylphosphine oxide, then debrominated substrate **XLV** (protected monobromoimidazole) followed by substrate **8** or **13**. Then there were often two signals with the mass spectrum and characteristic isotope- and fragmentation pattern of the product but with different retention times which can be explained by two regioisomeres of product **22a/33a** and **XLVI** where coupling occurs initially in 4- or in 5-position. The peak with the lower retention time is the 5-arylated product **22a/33a** (assigned via retention time comparison with isolated product). In a few cases also debrominated product **XLVII** could be detected at higher retention times. The last identified peak was the triarylated product **23** or **33**. This peak was always very broad. For the selectivity screening only the peak of the substrate, the product and the byproduct (triarylated imidazole) were considered as the other peaks are generally very small.

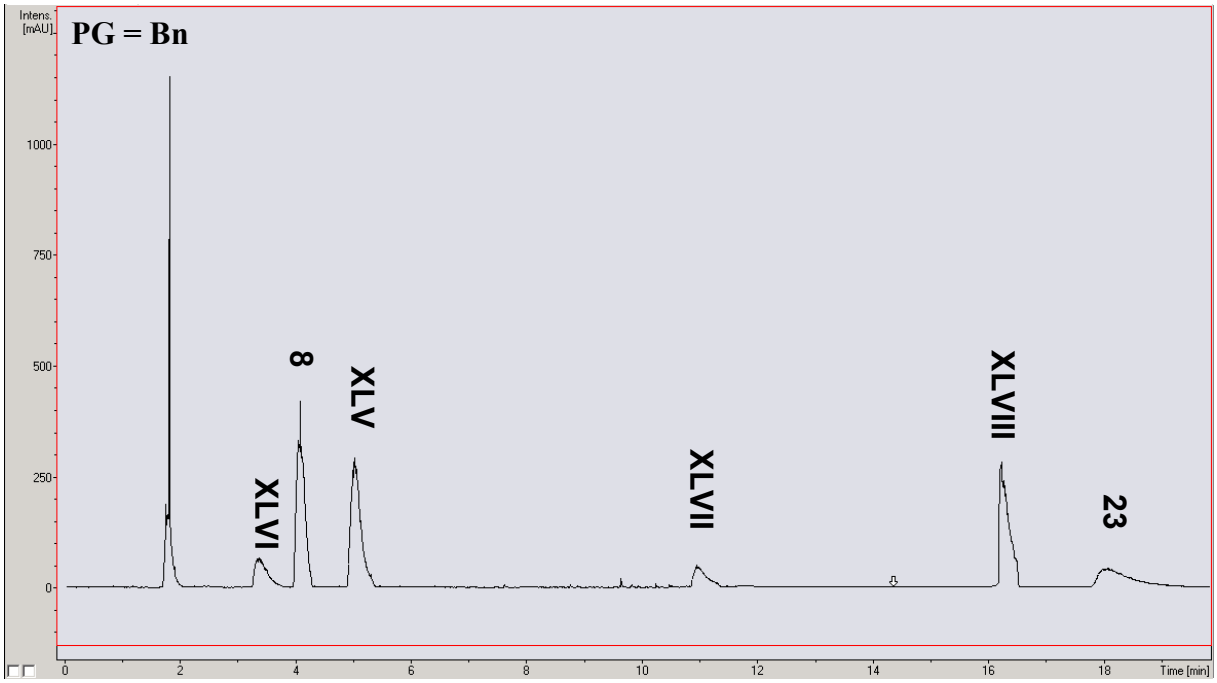


Figure 7

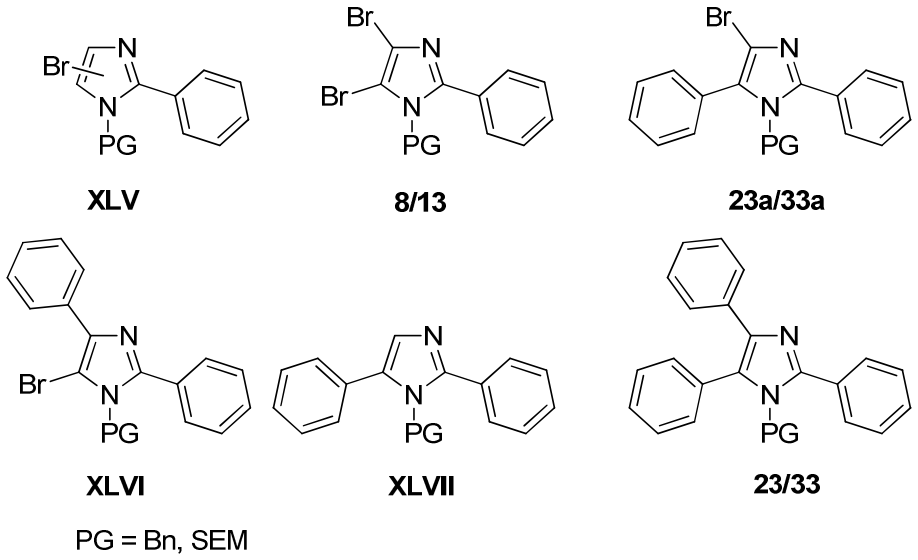
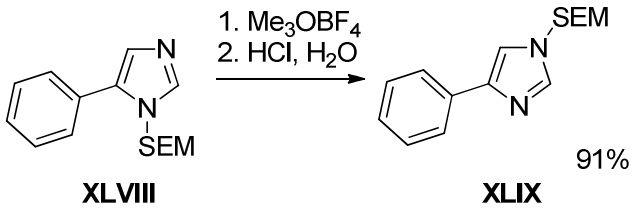


Figure 8

Nevertheless, the results obtained from LC-MS could not be analyzed quanititatively as it turned out that peaks cannot be integrated without extensive calibration efforts (see section 2.1). Therefore, the following selectivity studies could only be analyzed in a qualitative way providing rough trends regarding potentially more selective conditions.

First, Ohta's conditions were screened on different temperatures (r.t. and 60°C) to investigate if cross-coupling in 4-position already occurs at low temperature. After 6 hours, considerable amounts of byproduct **23** were formed in both cases. In the same manner also the conditions using DME/water (3:1) as solvent and $NaHCO_3$ as base were investigated under room temperature, 60°C and 120°C. At room temperature the starting material consumption is very slow and also in this case, byproduct **23** is formed already from the beginning in significant amounts. At 120°C the reaction proceeds more quickly but the amounts of byproduct **23** are significantly higher.

So far, all screenings were performed on 1-benzyl-4,5-dibromo-2-phenyl-1*H*-imidazole **8**. The same temperature screenings were also carried out on SEM protected 2-phenyl-4,5-dibromoimidazoles **13** to investigate the influence of the protecting group on the selectivity Using Ohta's conditions two peaks with different retention times were observed, both with the mass and the isotope and fragmentation pattern of the product **33a**. This time it was difficult to assign the peaks to the corresponding regioisomers since the two peaks have a ratio of about 1:1. Moreover, in one measurement one peak is higher than the other and in the next measurement the situation changes. As the eluent is slightly acidic, it is possible that the SEM group migrates between the two imidazole nitrogen atoms on the column. Such a SEM shift was already exploited in literature in direct arylation reactions of imidazole (Scheme 24).[42]



XLVIII **XLIX**

Scheme 24

Therefore, the two peaks were considered to belong to the desired product. At room temperature the reaction proceeds very slowly but also here the byproduct can be detected from the beginning.

Using DME/water as solvent and $NaHCO_3$ as base gave slight improvements for the inhibition of byproduct formation on the SEM protected substrate. The peak of the byproduct **33** is never as significant as in the other screenings, but still it is obtained from the beginning.

In all experiments so far $Pd(PPh_3)_4$ was used as catalyst; in the next step the reaction was performed in presence of $Pd(OAc)_2$ at room temperature in the absence of any ligand which should be a catalyst with lower activity possibly favoring a selective reaction. However, the reaction proceeded even faster with the ligand-free catalyst and byproducts **23** and **33** were formed instantly.

Another approach to increase selectivity by decreasing reactivity of reagents was the use of boronic ester instead of the acid as such esters are known to be less reactive. Unfortunately, also under such conditions formation of byproducts could not be avoided.

One selectivity run was also performed with 1-(4-methoxybenyzl)-2-phenyl-4,5-dibromoimidazole **7** using phenylboronic acid for the cross-coupling reaction under Ohta's conditions. As it was anticipated, also in this reaction protected triphenylimidazole was formed from the beginning, since the methoxy group in 4-position of the benzyl group has no significant influence on the electron distribution in the imidazole ring.

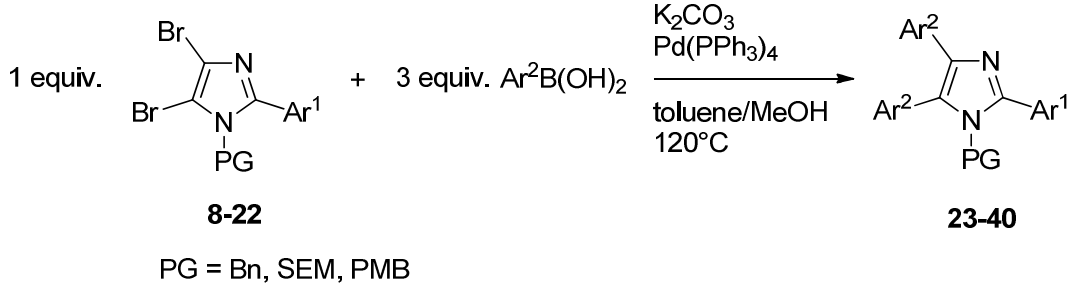
In summary, the byproduct could always be detected even at low conversions. Neither modifying the solvent, the temperature, nor the catalyst improved the regioselectivity of the transformation (summary in Table 5). Neither the benzyl-, the SEM, nor the PMB protecting group could influence the electronic distribution in the imidazole ring. Obviously, reaction rates of substrate and product are too similar to obtain any selectivity. Unfortunately, the tert-butyloxycarbonyl group (Boc) could not be installed, which would have a significant influence on the electron density distribution of the imidazole ring.

Table 5

Conditions					PG
Phenylboronic acid	Toluene/MeOH	Na_2CO_3	$Pd(PPh_3)_4$	**r.t.**	Bn
					SEM
Phenylboronic acid	Toluene/MeOH	Na_2CO_3	$Pd(PPh_3)_4$	**60°C**	Bn
					SEM
Phenylboronic acid	DME/H_2O	$NaHCO_3$	$Pd(PPh_3)_4$	**r.t.**	Bn
					SEM
Phenylboronic acid	DME/H_2O	$NaHCO_3$	$Pd(PPh_3)_4$	**60°C**	Bn
					SEM
Phenylboronic acid	DME/H_2O	$NaHCO_3$	$Pd(PPh_3)_4$	**120°C**	Bn
					SEM
Phenylboronic acid	Toluene/MeOH	Na_2CO_3	**$Pd(OAc_2)$**	r.t.	Bn
					SEM
Phenylboronic ester	Toluene/MeOH	Na_2CO_3	$Pd(PPh_3)_4$	60°C	Bn
					SEM
Phenylboronic ester	DME/H_2O	$NaHCO_3$	$Pd(PPh_3)_4$	60°C	Bn
					SEM
Phenylboronic acid	Toluene/MeOH	Na_2CO_3	$Pd(PPh_3)_4$	r.t.	**PMB**

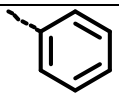
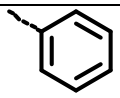
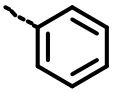
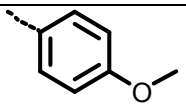
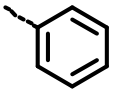
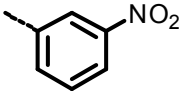
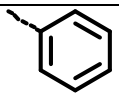
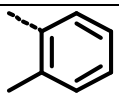
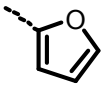
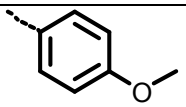
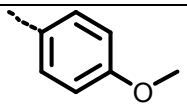
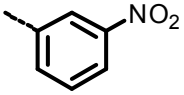
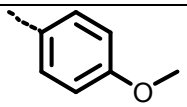
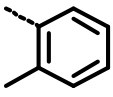
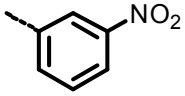
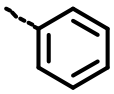
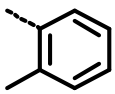
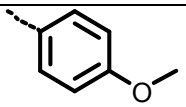
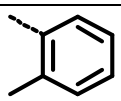
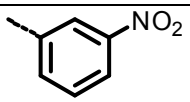
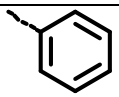
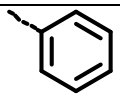
2.5. Simultaneous Cross-Coupling in 4- and 5-Position

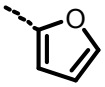
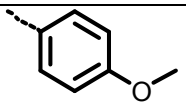
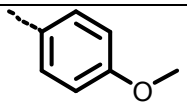
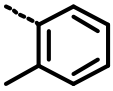
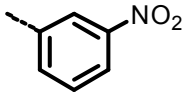
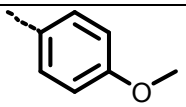
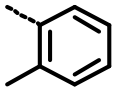
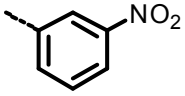
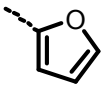
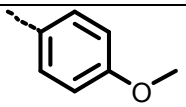
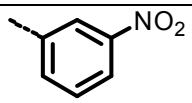
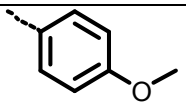
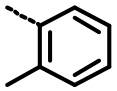
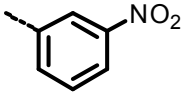
Since selective cross-coupling could not be achieved in 5-position and, hence, formation of 2,4,5-triarylated imidazoles with three different substituents was not possible, conversion of *N*-protected-2-aryl-4,5-dibromoimidazoles **8-22** to triarylated compounds was studied in a one step protocol with the same aryl substituents in positions 4 and 5. Thus, *N*-protected 2-aryl-4,5-dibromoimidazoles **8-22** were reacted with 3 equivalents of boronic acid. The same conditions as for the first coupling step were chosen since all three coupling steps should be combined in a one-pot protocol at a later stage. So, 2 M aq. potassium carbonate was used as base, $Pd(PPh_3)_4$ as catalyst, and toluene/methanol (5:1) as solvent (Scheme 25). The reaction was monitored by TLC. If the reaction was not complete within a few hours, more equivalents of boronic acid were added. The results of this coupling step are displayed in Table 6.



Scheme 25

Table 6

Compound	PG	Ar^1	Ar^2	Equiv.	Yield[a]
23	Bn			3	79%
24	Bn			3	85%
25	Bn			3	55%
26	Bn			3	37%[b]
27	Bn			3	81%
28	Bn			3	60%
29	Bn			3	32%[b]
30	Bn			3	85%
31	Bn			3	59%[b]
32	Bn			3.5	39%
33	SEM			3	91%

34	SEM			3	67%
35	SEM			5	11%[b]
36	SEM			3	53%
37	SEM			6	74%
38	PMB			6	53%
39	PMB			3	92%
40	PMB			3	42%

[a] isolated yield

[b] additionally purified by preparative HPLC

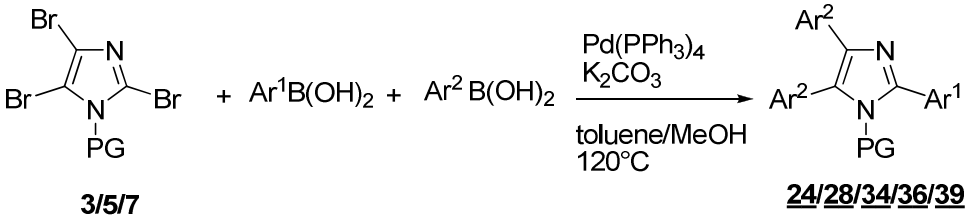
In general the yields were between 50 and 90%. Neither the protecting group nor the aryl substituent in 2-position had a significant influence on the yield. For example, *N*-protected 2,4,5-triphenylimidazole (compounds **23** and **33**) was synthesized in 79% and 91% using benzyl and SEM as protecting groups, respectively. Electron withdrawing (NO_2) as well as electron donating (OMe) substituents were accepted on the arylboronic acids and did not influence the yield. However, m-nitrophenylboronic acid gave lower yields of 39% and 42%, respectively, using starting materials carrying benzylic PGs (compounds **32** and **40**). Coupling reactions with sterically demanding o-tolylboronic acid (compounds **26**, **29** and **35**) did not proceed exclusively to the desired products but resulted in a mixture of protected 2,5-diaryl-4-bromoimidazole and protected 2,4,5-triarylated product. This can be attributed to steric hindrance between two neighboring o-tolyl groups. In two cases (compounds **26** and **29**) this mixture was not detected on TLC since the R_f-values were equal. In the case of compound **35**, two spots were visible on TLC for the product mixture but the difference in R_f-values was too small for separation by flash column chromatography; hence preparative HPLC had to be employed. Unfortunately, the mass recovery rate of preparative HPLC was only around 70% which partially contributes to the observed low yields.

Also compound **31** had to be purified by preparative HPLC as some impurities could not be separated from the product by flash column chromatography, but the yield was still satisfactory.

Most importantly, the synthesis of Neurodazine precursors (compounds **27**, **34** and **38**) resulted in 81%, 67% and 53% yields using benzyl, SEM, and PMB as protecting groups, respectively. Hence, synthesis of Neurodazine via this cross-coupling approach was feasible and will be discussed in section 2.8.

2.6. One-Pot Procedure

In a next step, a one-pot procedure was developed for the synthesis of *N*-protected 2,4,5-triarylated imidazoles starting from *N*-protected tribromoimidazoles. As the reaction conditions for the coupling steps in 2- and in 4/5-positions are the same, the handling of the procedure was very simple. Reactions were conducted using 5mol% of $Pd(PPh_3)_4$ and 4 equiv. of 2 M aq. potassium carbonate solution in toluene/methanol (5:1) as solvent. In the first step, 1.1 equiv. of boronic acid was reacted with protected tribromoimidazole **3**, **5** or **7**. When the consumption of the substrate was completed according to TLC, 3 equiv. of another boronic acid were added to the reaction solution (Scheme 26). Five compounds were synthesized using this protocol (Table 7).



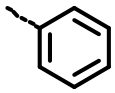
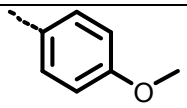
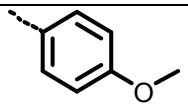
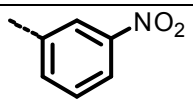
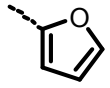
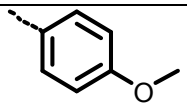
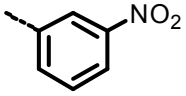
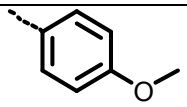
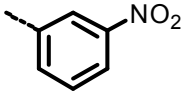
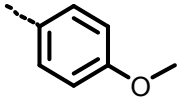
3/5/7

24/28/34/36/39

PG = Bn, SEM, PMB

Scheme 26

Table 7

Compound	PG	Ar^1	Ar^2	Yield[a]
24	Bn			80% (64%)
28	Bn			73% (46%)
34	SEM			25%[b] (21%)
36	SEM			58% (34%)
39	PMB			48%[c] (58%)

[a] isolated yield, in parentheses yields over two steps

[b] 10% impurity left

[c] 20% impurity left

In most of the cases the one-pot yield is significantly higher compared to the two step protocol. Two examples could not be purified completely by flash column chromatography and preparative TLC as the R_f-values of the product and the impurity were too similar. Another possibility would be the purification using preparative HPLC but as the mass recovery rate is only at 70%, the yields would have been significantly lower and comparison with the sequential cross-coupling protocol would have been impossible.

Compound **24** could be synthesized with 80% yield in one-pot while the sequential synthesis gave 64% yield. In the case of compound **28** the product was isolated with 73% yield in the one-pot synthesis, while the synthesis over two steps resulted in 46% yield. Also compound **36** shows a great improvement in the one-pot synthesis compared to a sequential sequence with isolation of intermediates. There, 58% yield could be obtained by the one-pot procedure while the yield over two steps is only 34%. In the case of compound **34**, the difference between the one-pot and the sequential procedure is marginal. Only 25% of the product could be isolated in the one-pot procedure. Moreover, 10% of unidentified impurity was still left according to NMR. The low yield might be due to the fact that the first coupling step using 2-furyl boronic acid causes a lot of problems (see section 2.4) due to the limited stability of 2-furylboronic acid. Compound **39** is the only example where the two step procedure resulted in

better yields (58%) than the one-pot procedure (48%). Moreover, 20% of impurity, which seems to be 1-(4-methoxybenzyl)-4-(4-methoxyphenyl)-2,5-(3-nitrophenyl)-imidazole **L** (Figure 9), could not be separated according to NMR.

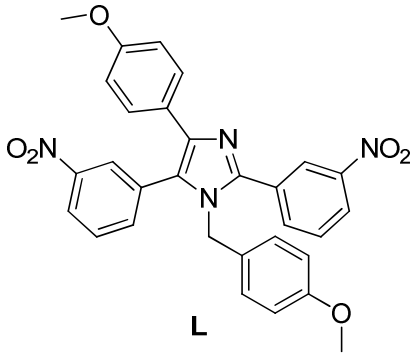


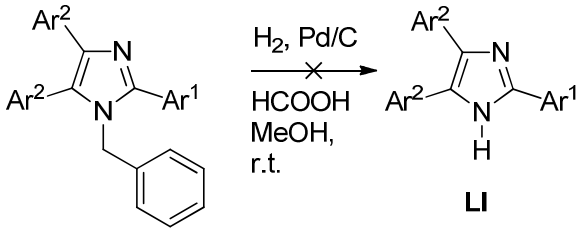
Figure 9

In summary, some products could also be obtained purely using a one-pot protocol and the yield could be increased. Nevertheless, this method often provokes big problems during the purification. Byproducts were formed that could not be removed by column chromatography. Only preparative HPLC could separate the byproduct from the product but this would result in a loss of yield because the mass recovery rate of preparative HPLC is only at 70%.

2.7. Deprotection of Triarylated Imidazoles

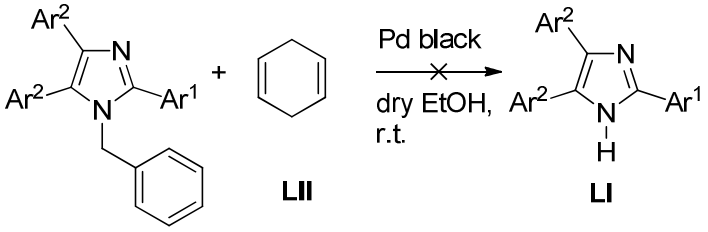
2.7.1. Deprotection of 1-Benzyl-2,4,5-triarylated imidazoles

Most commonly reductive conditions are applied to cleave a benzyl group (Scheme 27).[43] For that purpose, the substrate was dissolved in a 1:1 mixture of methanol/formic acid, 10w% Pd/C were added and the reaction vessel was purged with H_2 (~5 bar in a Schlenk-tube from ACE glass which can withstand up to 10 bar of pressure). No conversion could be detected by TLC over night. Therefore, more formic acid was added to end up with a 4:1 mixture of formic acid/methanol. This time hydrogenation was conducted in a Parr apparatus at 5bar H_2 pressure. No conversion could be detected after 4.5 hours.



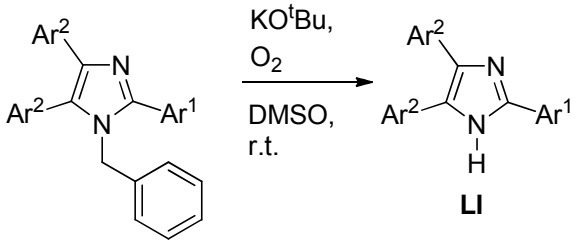
Scheme 27

Within the next experiment, the same protocol was used with formic acid as the sole solvent. After 4 hours in the Parr apparatus at 5 bar still no conversion could be detected.



Scheme 28

Next, another deprotection protocol by Felix et al.[44] was applied using transfer hydrogenation (Scheme 28). The substrate was dissolved in dry ethanol and 10w% of Pd black was added as catalyst. 1,4-Cyclohexadiene **LII** was added dropwise and the reaction was stirred at room temperature. No conversion could be detected by TLC over night.

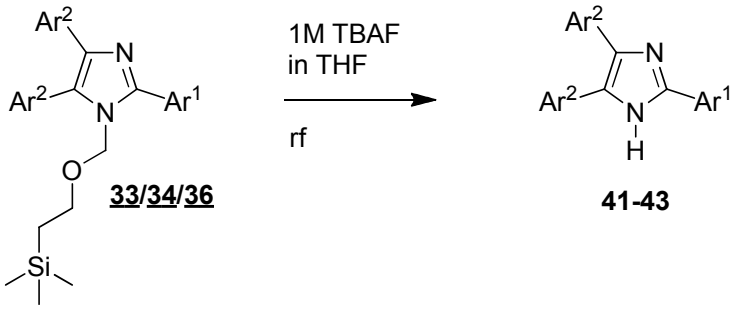


Scheme 29

In a next experiment, the oxidative deprotection protocol of Deaton-Rewoliski et al.[45] was used (Scheme 29). The substrate was dissolved in DMSO and a 1M solution of potassium *tert*-butoxide in THF was added dropwise. The solution immediately changed the color. Then oxygen was bubbled through the stirred reaction solution for 10-15 minutes at room temperature. The reaction was monitored with TLC and complete conversion was observed after a few hours. After work-up and purification the product was obtained.

A few compounds have been deprotected using this protocol but except in the case of the neurodazine precursor (see section 2.8.3) no product could be purified completely. Overall, no general method could be identified for the deprotection of triarylated benzyl protected imidazoles.

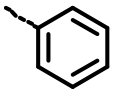
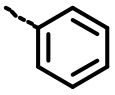
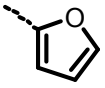
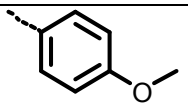
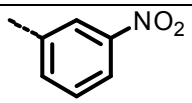
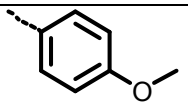
2.7.2. Deprotection of 1-((2-(Trimethylsilyl)ethoxy)methyl)-2,4,5-triarylated imidazoles



Scheme 30

The deprotection of 1-((2-(trimethylsilyl)ethoxy)methyl)-2,4,5-triarylated imidazoles was performed according to a procedure by Whitten et al.[46] (Scheme 30). The corresponding 1-((2-(trimethylsilyl)ethoxy)methyl)-2,4,5-triaryl-1*H*-imidazole **33**, **34** or **36** (1 equiv.) was dissolved in 5 equiv. of 1M tetrabutylammonium fluoride in THF in a 4 mL vial with stirring bar and a screw cap. The reaction was heated to reflux and monitored by TLC. After work-up and purification by preparative TLC the pure product was obtained. Three different triarylated imidazoles have been deprotected by this protocol. The substrates and yields are shown in Table 8.

Table 8

Compound	Ar^1	Ar^2	Scale	Yield
41			40mg	41%
42			8mg	40%
43			36mg	56%

The yields vary from 40% to 56%. The low yields can be explained by the small reaction scale as a loss of a few milligrams of product during work-up already drops the yield by several percent. However, these results should be improvable when carrying out the reactions in larger scale.

2.7.3. Deprotection of 1-(4-Methoxybenzyl)-2,4,5-triarylated imidazoles

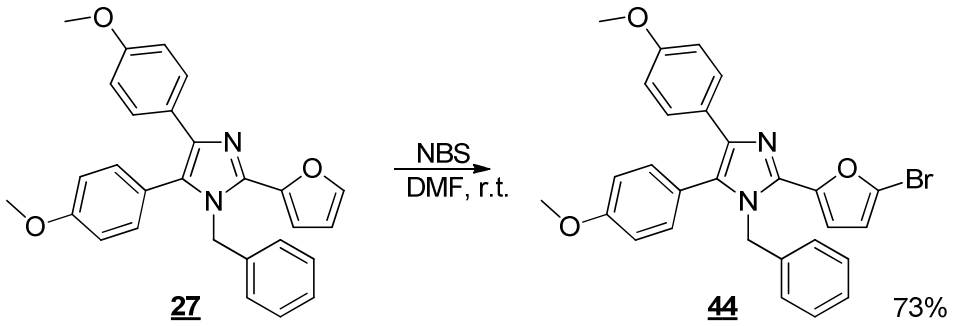
Only very limited literature precedence is available for deprotecton of the PMB group. Deprotection was first attempted following the standard literature procedure:[43] 1 equiv. of substrate was dissolved in pure trifluoroacetic acid and heated to 65°C for two hours. As no conversion could be detected, the solution was stirred at 80°C over night. Still, no conversion could be detected. Therefore, another protocol from Forbes et al.[47] was performed using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as oxidizing agent; 1 equiv. of substrate and 2.2 equiv. of DDQ were dissolved in toluene/H_2O and heated to 80°C. The reaction was stirred over night but no conversion could be detected. Neither of the protocols could cleave the protecting group.

In summary, best results in the deprotection step were obtained when cleaving the SEM group where all reactions gave the desired product. The benzyl group can be cleaved however not reductively but oxidatively. Unfortunately, purification problems occurred which could not be overcome so far. The PMB group could not be cleaved at all.

2.8. Synthesis of Neurodazine

To demonstrate the utility of the developed cross-coupling chemistry in the synthesis of an interesting target molecule, the synthesis of Neurodazine was completed starting from precursor **27**. It was envisioned to brominate the furan ring in position 5 to introduce a leaving group for a subsequent cross-coupling reaction with 3-chlorophenylboronic acid. Deprotection of the imidazole ring would then lead to Neurodazine.

2.8.1. Synthesis of 1-Benzyl-2-(5-bromofuran-2-yl)-4,5-di(4-methoxyphenyl)-1*H*-imidazole



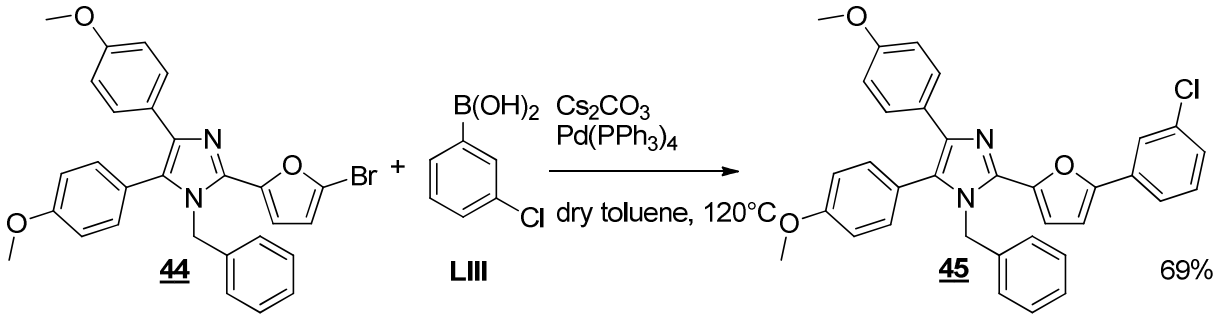
27 **44**

Scheme 31

1-Benzyl-2-(5-bromofuran-2-yl)-4,5-di(4-methoxyphenyl)-1*H*-imidazole **44** was synthesized according to a protocol developed in our group[36] in the synthetic sequence leading to thiazolo-

neurodazine (Scheme 31). 1-Benzyl-2-(2-furyl)-4,5-di(4-methoxyphenyl)-imidazole **27** was dissolved in 6 mL DMF and the solution was cooled to 0°C. N-Bromosuccinimide (1.1 equiv.) was added in portions and the reaction was allowed to warm to room temperature and stirred for 4 hours. After work-up and purification the product was obtained in 73% yield.

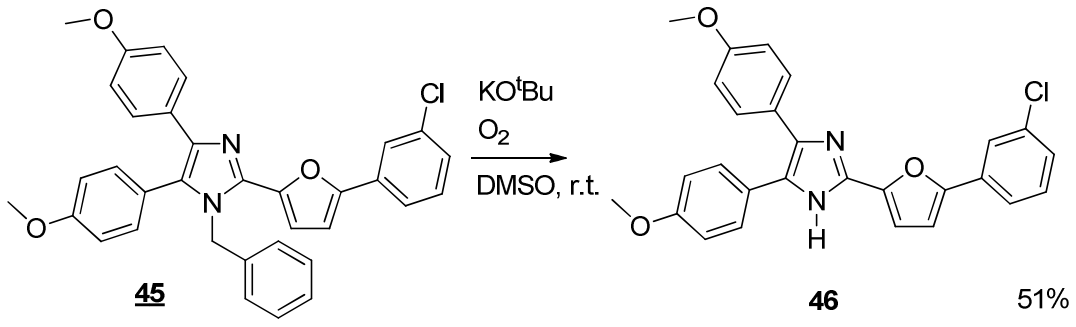
2.8.2. Synthesis of 1-Benzyl-2-(5-(3-chlorophenyl)furan-2-yl)-4,5-di(4-methoxyphenyl)-1*H*-imidazole



Scheme 32

1-Benzyl-2-(5-(3-chlorophenyl)furan-2-yl)-4,5-di(4-methoxyphenyl)-1*H*-imidazole **45** was synthesized according to a protocol developed in our group[36] (Scheme 32) for the synthesis of thiazolo-neurodazine. 1-Benzyl-2-(5-bromofuran-2-yl)-4,5-di(4-methoxyphenyl)-1H-imidazole **44**, 1.1 equiv. of 3-chlorphenylboronic acid **LIII**, 2 equiv. of cesium carbonate, 5mol% of $Pd(PPh_3)_4$ and 1.5 mL dry toluene were stirred in a 4 mL vial under argon atmosphere. The mixture was heated to 120°C for 4 hours. After work-up and purification the product was obtained in 69% yield.

2.8.3. Synthesis of 2-(5-(3-chlorophenyl)furan-2-yl)-4,5-di(4-methoxyphenyl)-1*H*-imidazole



Scheme 33

Benzyl deprotection of 2-(5-(3-chlorophenyl)furan-2-yl)-4,5-di(4-methoxyphenyl)-1*H*-imidazole was carried out according to a protocol by Deaton-Rewolinski et al.[45] (Scheme 33). 1-Benzyl-2-(5-(3-chlorophenyl)furan-2-yl)-4,5-di(4-methoxyphenyl)-1H-imidazole **45** was dissolved in 0.2 mL DMSO. 0.26 mL of a 1M potassium *tert*-butoxide solution in THF was added with a syringe. The color of the reaction solution changed from yellow to orange immediately. Oxygen was bubbled through the solution for 15 minutes. The reaction was stirred at room temperature for 1 hour. After work-up and purification product **46** was obtained in 51% yield.

2.9. Conclusion

Different protecting groups were used within this work. The protecting group does not influence the yields of the cross-coupling reactions. Still, SEM turned out to be the best protecting group as PMB could not be cleaved and deprotection of benzyl resulted in purification problems.

The selective cross-coupling step in 2-position resulted in good yields. A broad range of arylboronic acids are accepted in this reaction. Using 2-furylboronic acid for the cross-coupling was a challenging problem, as the boronic acid is very unstable. Moreover, the reaction monitoring posed a problem which could not be resolved.

No selectivity could be obtained for the cross-coupling step in 5-position after an elaborate condition screening. Therefore, the cross-coupling in 4- and 5-position of the imidazole was performed simultaneously. This reaction resulted in general in good yields. An exception is the use of 2-tolylboronic acid as aryldonor, which is too sterically demanding to be neighboring.

With this method, a critical Neurodazine precursor could be obtained which was converted to the bioactive target within 3 more steps.

Moreover, a one-pot protocol was developed for the synthesis of 2,4,5-triarylimidazoles starting from 2,4,5-tribromoimidazole. In general, the yields of the one-pot protocol were higher in comparison to the two step protocol. However, sometimes purification problems occurred.

3 Experimental Part

3.1. General Notes

Unless otherwise noted, chemicals were purchased from commercial suppliers and were used without further purification.

Chromatography

Flash column chromatography was performed on silica gel 60 from Merck (40-63µm). For thin layer chromatography (TLC) aluminium backed silica gel was used. For preparative TLC 20x20cm 1000µ thin layer chromatography plates were used. Signals were visualized with UV light (254nm).

HPLC

HPLC runs were performed on a Thermo Fisher Scientific Surveyor Plus using a Phenomenex Kinetex PFP column (2.6µ, 100x4.6mm). Detection was performed on a Thermo Finnigan PDA Plus photodiode array detector. The following method was applied:

- 5 minutes 50% H_2O (0.1%TFA)/50% MeCN
  1 minute 50% H_2O (0.1%TFA)/50% MeCN → 2% H_2O (0.1%TFA)/98% MeCN
  5 minutes 2% H_2O (0.1%TFA)/98% MeCN
  1 minute 2% H_2O (0.1%TFA)/98% MeCN → 50% H_2O (0.1%TFA)/50% MeCN
  5 minutes 50% H_2O (0.1%TFA)/50% MeCN
- flow rate: 1.5 mL/min
- column temperature: 35°C

Preparative HPLC

Preparative HPLC was performed on a Shimadzu LC-8A device with an SIL-10AP autosampler, SPD-20A detector and FRC-10A fraction collector. For separation the following conditions were used: column: Phenomenex Luna 10 µm RP18(2) 100A, 250 x 21.20 mm; Injection volume: 2 mL, Flow: 20 mL/min; Detection wavelength: 254 nm. The following method was applied:

10 minutes 60% MeOH/40% H_2O
30 minutes 60% MeOH/40% H_2O → 90% MeOH/10% H_2O

Lyophylizer

Compounds purified by preparative HPLC, were directly lyophilized using a LABCONCO FreeZone 2.5 lyophillizing system.

LC-MS

LC-MS runs were performed on a LC-MS system from Bruker with a Bruker HCT/esquire MS unit and an Agilent HPLC with an Agilent G1315D DAD detector. For HPLC chromatography a Phenomenex Kinetex PFP column (2.6µ, 100x4.6mm) was used. The following method was applied:

- 4 minutes 50% H_2O (0.1% HCOOH)/50% MeCN
  2 minutes 50% H_2O (0.1% HCOOH)/50% MeCN → 2% H_2O (0.1% HCOOH)/98% MeCN
  22 minutes 2% H_2O (0.1% HCOOH)/98% MeCN
  1 minute 2% H_2O (0.1% HCOOH)/98% MeCN → 50% H_2O (0.1%TFA)/50% MeCN
  6 minutes 50% H_2O (0.1% HCOOH)/50% MeCN
- flow rate: 1.0 ml/min
- column temperature: 35°C

HR-MS

HR-MS was carried out by E. Rosenberg at the Vienna University of Technology, Institute for Chemical Technologies and Analytics.

Analytical method:

All samples were analyzed by LC-IT-TOF-MS in only positive ion detection mode upon recording of MS and MS/MS spectra. For the evaluation in the following, only positive ionization spectra were used (where the quasi-molecular ion is the one of $[M+H]^+$ and the adduct is the one of $[M+Na]^+$), and further data or information were not taken into consideration.

Instrumental parameters:

Shimadzu Prominence HPLC, consisting of: solvent degassing unit (DGU-20 A3), binary gradient Pump (2 x LC-20AD), auto-injector (SIL-20A), column oven (CTO-20AC), control module (CBM-20A), and diode array detector (SPD-M20A).

MS System: Shimadzu IT-TOF-MS with electrospray interface.

Chromatography (parameters: Short_Col_PI_NI_MSonly):

Column: Phenomenex Prodigy ODS(3), 30 mm x 4.6 mm, 3 µm particles, operated at 40°C; Gradient: 0 min: 70% A, 30% B (1 min); linear gradient to 5 min to 10% A, 90% B (hold 4

min); at 9.01 min back to 70% A, 30% B, hold until 11.0 min);. A: MeOH, B: H_2O. Column flow: 0.5 mL/min; injection volume: 2 µl.

MS Parameters:

MS parameters as in autotune. Data recorded with detector voltage at autotune value. Scan range: 50-1000 amu for both, MS and MS/MS (PI) detection. ES ionization.

Melting points were determined using a Stanford Research Systems OptiMelt MPA100 or a Kofler-type Leica Galen III micro hot stage microscope and are uncorrected.

NMR-spectroscopy

NMR-spectra were recorded from either $CDCl_3$, DMSO-d6 or MeOD-d4 solutions on a Bruker AC 200 (200MHz) or a Bruker Avance Ultrashield (400MHz) spectrometer (as indicated) and chemical shifts are reported in ppm relative to the nominal residual solvent signals: $CDCl_3$: δ = 7.26 ppm (^{1}H), δ = 77.16 ppm (^{13}C); DMSO-d6: δ = 2.50 (^{1}H), δ = 39.52 (^{13}C); MeOD-d4: δ = 3.31 ppm (^{1}H), δ = 49.00 ppm (^{13}C);. DEPT-135 was used to aid in the multiplet assignment in the ^{13}C spectra.

Assignments for chemical shifts of C and H-atoms of more than one ring system are marked with ^{a}, ^{b}, ^{c}, ^{d} and ^{e} as explained in the following example (Figure 10). In the case of Neurodazine, the additional 3-chlorophenyl ring was marked with an f. Ambiguous assignments are marked with an asterisk.

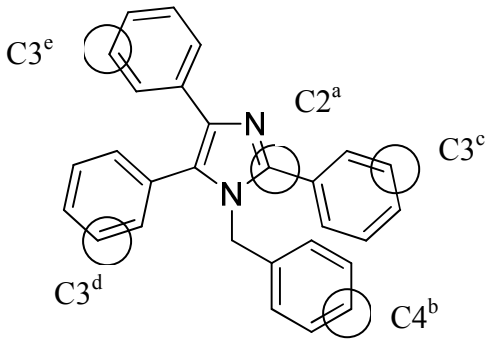


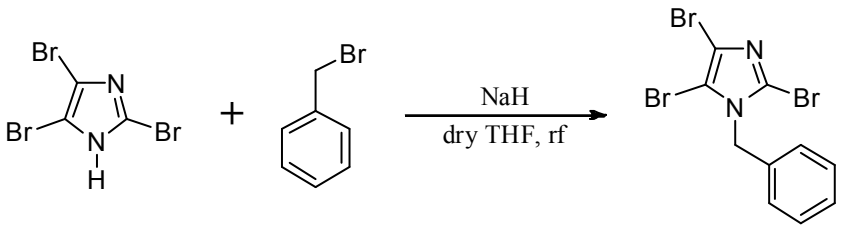
Figure 10

3.2. Abbreviations

DCM	Dichloromethane
DME	Dimethoxyethane
EtOAc	Ethyl acetate
equiv.	Equivalent
J	Coupling constant
LP	Light petroleum
MeOH	Methanol
M.p.	Melting point
PG	Protecting group
rf	Reflux
r.t.	Room temperature
THF	Tetrahydrofuran
TLC	Thin layer chromatography

3.3. Protection of Tribromoimidazole

3.3.1. 2,4,5-Tribromo-1-benzyl-1*H*-imidazole (3)



1 **2** **3**

$C_3HBr_3N_2$ M = 304.77

$C_{10}H_8Br_4N_2$ M = 475.80

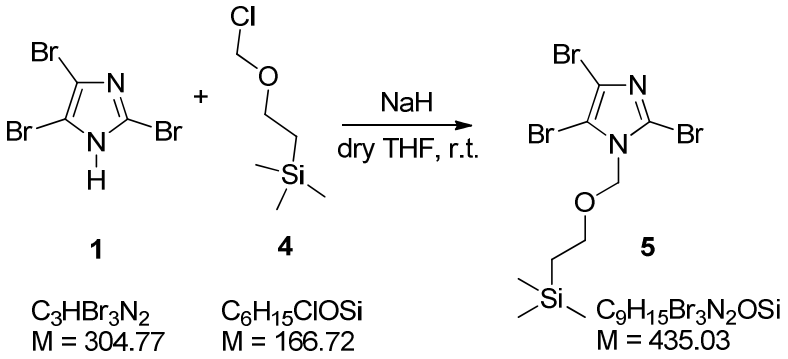
$C_{10}H_7Br_3N_2$ M = 394.89

A dry 500 mL three-necked flask equipped with a thermometer, a reflux condenser, a magnetic stir bar and a septum was flushed with argon. Dry THF (200 mL) was placed in the flask and NaH (2.16 g, 90 mmol, 3 equiv.) was added and suspended. The mixture was cooled to 0°C. Then, 2,4,5-tribromoimidazole (9.15 g, 30 mmol, 1 equiv.) was added in portions. The solution was warmed to room temperature and stirred for 30 minutes. Benzyl bromide (3.92 mL, 33 mmol, 1.1 equiv., $\rho = 1.438$ g/cm^3) was added dropwise and then the reaction solution was heated under reflux for 5 hours. Subsequently, the reaction mixture was poured into water

(100 mL). The aqueous solution was extracted three times with DCM. The combined organic layers were washed with water and dried over sodium sulfate. The solvent was evaporated and the crude product was purified by flash column chromatography (100 g silica gel, LP:EtOAc = 30:1).

Yield: 58% (6.83 g, 17.30 mmol)
Appearance: colorless solid
M.p.: 68-69°C (lit.[48]: 58-59°C)
TLC: 0.46 (LP:EtOAc = 10:1)
^{1}H NMR ($CDCl_3$, 200MHz): δ = 5.22 (s, 2H, CH_2), 7.09-7.19 (m, 2H, H3/5[b]), 7.31-7.41 (m, 3H, H2/4/6[b])
^{13}C NMR ($CDCl_3$, 50MHz): δ = 51.4 (t, CH_2), 105.8 (s, C5[a]), 117.2 (s, C4[a]), 118.8 (s, C2[a]), 126.9 (d, C2/6[b]), 128.5 (d, C4[b]), 129.1 (d, C3/5[b]), 134.1 (s, C1[b])

3.3.2. 2,4,5-Tribromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole (5)[35]

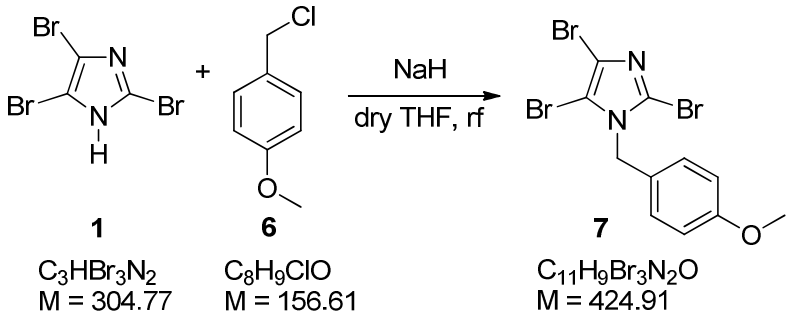


A dry 500 mL three-necked flask equipped with a thermometer, a reflux condenser, a magnetic stirring bar, and a septum was flushed with argon. Dry THF (200 mL) was placed in the flask and NaH (0.72 g, 30 mmol, 2 equiv.) was added and suspended. The mixture was cooled to 0°C before 2,4,5-tribromoimidazole (4.58 g, 15 mmol, 1 equiv.) was added in portions. The solution was warmed to room temperature and was stirred for 2 hours. 2-(Trimethylsilyl)-ethoxymethyl chloride (2.93 mL, 17 mmol, 1.1 equiv.) was added dropwise and then the solution was stirred at room temperature. After 1 hour the reaction was completed according to TLC. The reaction mixture was poured into water (100 mL). The aqueous solution was extracted three times with diethyl ether. The combined organic layers were washed with water and dried over sodium sulfate. The solvent was evaporated, a yellow

oil was obtained which was purified by flash column chromatography (50 g silica gel, LP:EtOAc = 10:1).

Yield: 90% (5.85 g, 13.45 mmol)
Appearance: colorless solid
M.p.: 58-60°C
TLC: 0.56 (LP:EtOAc = 10:1)
^{1}H NMR ($CDCl_3$, 200MHz): δ = 0.00 (s, 9H, $SiCH_3$), 0.93 (t, ^3J = 8.2 Hz, 2H, $SiCH_2$), 3.61 (t, ^3J = 8.2 Hz, 2H, OCH_2), 5.33 (s, 2H, NCH_2O)
^{13}C NMR ($CDCl_3$, 50MHz): δ = 1.3 (q, $SiCH_3$), 17.9 (t, $SiCH_2$), 67.4 (t, OCH_2), 76.0 (t, NCH_2O), 105.8 (s, C5[a]), 117.7 (s, C4[a]), 119.2 (s, C2[a])

3.3.3. 2,4,5-Tribromo-1-(4-methoxybenzyl)-1*H*-imidazole (7)



A dry 50 mL three-necked flask equipped with a thermometer, a reflux condenser, a magnetic stir bar and a septum was flushed with argon. Dry THF (12.5 mL) was placed in the flask and NaH (0.12 g, 4.8 mmol, 3 equiv.) was added and suspended. The mixture was cooled to 0°C before 2,4,5-tribromoimidazole (0.5 g, 1.6 mmol, 1 equiv.) was added in portions. The solution was warmed to room temperature and was stirred for 30 minutes. 4-Methoxybenzyl chloride (0.24 mL, 1.8 mmol, 1.1 equivalents, ρ = 1.154 g/cm^3) was added dropwise and then the solution was heated under reflux for 6 hours. The reaction mixture was poured into water (20 mL). The aqueous solution was extracted three times with DCM. The combined organic layers were washed with water and dried over sodium sulfate. The solvent was evaporated and the crude product was purified by flash column chromatography (50 g silica gel, LP:EtOAc = 30:1).

Yield: 53 % (0.37 g, 0.87 mmol)

Appearance: colorless solid

M.p.: 58-59°C (lit.[48]: 69-70°C)

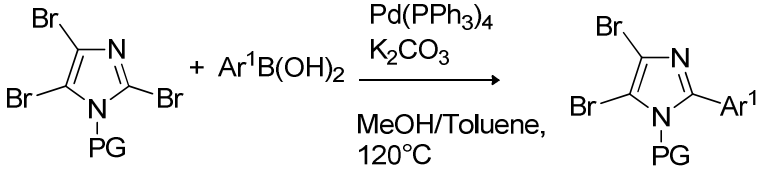
TLC: 0.34 (LP:EtOAc = 10:1)

^{1}H NMR ($CDCl_3$, 200MHz): δ = 3.79 (s, 3H, OCH_3), 5.14 (s, 2H, CH_2), 6.87 (d, ^3J = 8.6 Hz, 2H, H3/5[b]), 7.14 (d, ^3J = 8.6 Hz, 2H, H2/6[b])

^{13}C NMR ($CDCl_3$, 50MHz): δ = 51.0 (t, CH_2), 55.4 (q, OCH_3), 105.6 (s, C5[a]), 114.4 (d, C3/5[b]), 117.1 (s, C4[a]), 118.5 (s, C2[a]), 126.2 (s, C1[b]), 128.6 (d, C2/6[b]), 159.7 (s, C4[b])

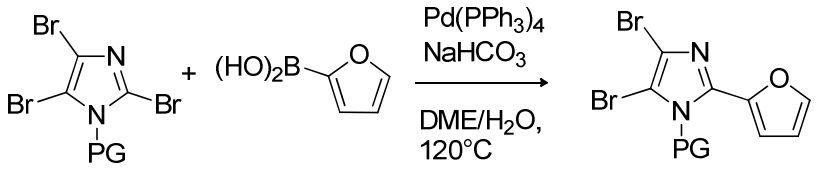
3.4. Suzuki-Miyaura Cross-Coupling Reaction

3.4.1. General Procedure A



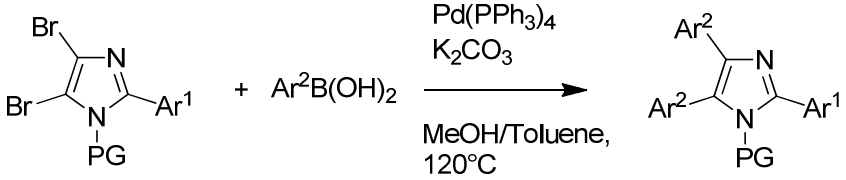
Protected-2,4,5-tribromo-1*H*-imidazole (1 equiv.), boronic acid (1.1 equiv.), a 2M solution of K_2CO_3 (1 equiv.), $Pd(PPh_3)_4$ (5 mol%), and MeOH/toluene (5:1) were placed in a 8 mL vial with a magnetic stirring bar and a screw cap with septum. The solution was purged with argon for 5 minutes. Then the septum screw cap was exchanged for a closed cap under argon flow, since caps with septum did not withstand the pressure built up during the reaction. The mixture was heated to 120°C in the heating block. The reaction was monitored by TLC and stopped when reaction control showed complete consumption of the starting material. If the reaction showed no further progress, additional equivalents of boronic acid were added until the reaction was completed. The reaction mixture was cooled to room temperature, filtered through a pad of Celite® and the solvent was evaporated. The residue was diluted with water and extracted with DCM. The combined organic layers were washed with water and dried over sodium sulfate. The solvent was evaporated and the desired product was obtained by flash column chromatography.

3.4.2. General Procedure B



Protected-2,4,5-tribromo-1*H*-imidazole (1 equiv.), 2-furylboronic acid (1.1 equiv.), $NaHCO_3$ (2.5 equiv.), $Pd(PPh_3)_4$ (5 mol%), and DME:H_2O (3:1) were placed in a 8 mL vial with a magnetic stirring bar and a screw cap with septum. The solution was purged with argon for 5 minutes. Then the septum screw cap was exchanged for a closed cap under argon flow, since caps with septum did not withstand the pressure built up during the reaction. The mixture was heated to 100°C in the heating block. If the reaction showed no further progress, additional equivalents of boronic acid were added. The addition of boronic acid was stopped when about 4 equivalents were already added. The reaction mixture was cooled to room temperature, filtered through a pad of Celite® and the solvent was evaporated. The residue was diluted with water and extracted with DCM. The combined organic layers were washed with water and dried over sodium sulfate. The solvent was evaporated and the desired product was obtained by flash column chromatography.

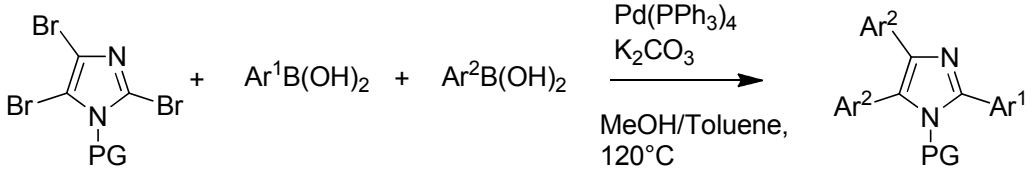
3.4.3. General Procedure C



Protected-2-aryl-4,5-tribromo-1*H*-imidazole (1 equiv.), boronic acid (3 equiv.), a 2M solution of K_2CO_3 (3 equiv.), $Pd(PPh_3)_4$ (5 mol%) and MeOH/toluene (5:1) were placed in a 4 mL vial with a magnetic stirring bar and a screw cap with septum. The solution was purged with argon for 5 minutes. Then the septum screw cap was exchanged for a closed cap under argon flow, since caps with septum did not withstand the pressure built up during the reaction. The mixture was heated to 120°C in the heating block. The reaction was monitored by TLC and stopped when reaction control showed complete consumption of the starting material. If the reaction showed no further progress, additional equivalents of boronic acid were added until

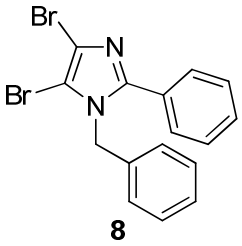
the reaction was completed. The reaction mixture was cooled to room temperature, filtered through a pad of Celite® and the solvent was evaporated. The residue was diluted with water and extracted with DCM. The combined organic layers were washed with water and dried over sodium sulfate. The solvent was evaporated and the desired product was obtained by flash column chromatography.

3.4.4. General Procedure D – One-Pot Protocol for the Formation of 2,4,5-Triarylated Imidazoles



Protected-2,4,5-tribromo-1*H*-imidazole (1 equiv.), boronic acid (1.1 equiv.), a 2M solution of K_2CO_3 (4 equiv.), $Pd(PPh_3)_4$ (5 mol%) and MeOH/toluene (5:1) were placed in a 4 mL vial with a magnetic stirring bar and a screw cap with septum. The solution was purged with argon for 5 minutes. Then the septum screw cap was exchanged for a closed cap under argon flow, since caps with septum did not withstand the pressure built up during the reaction. The mixture was heated to 120°C in the heating block. The reaction was monitored by TLC. If the reaction showed no further progress, additional equivalents of boronic acid were added until the reaction was completed. After complete consumption of the starting material, the second boronic acid (3 equiv.) was added. The reaction was stopped when reaction control showed complete consumption of the starting material. The reaction mixture was cooled to room temperature, filtered through a pad of Celite® and the solvent was evaporated. The residue was diluted with water and extracted with DCM. The combined organic layers were washed with water and dried over sodium sulfate. The solvent was evaporated and the desired product was obtained by flash column chromatography.

3.4.5. 1-Benzyl-4,5-dibromo-2-phenyl-1*H*-imidazole (8)



8

$C_{16}H_{12}Br_2N_2$
M = 392.09

Method: Prepared according to general procedure A starting from compound **3** (1 g, 2.53 mmol).

Boronic acid: Phenylboronic acid (0.37 g, 3.04 mmol, 1.2 equiv.); 1.1 equiv. added at the beginning, 0.1 equiv. added after 4 hours;

Amount of solvent: 6 mL

Time: 5 hours

Purification: flash column chromatography (150 g silica gel, DCM:MeOH = 200:1)

Yield: 81% (0.8 g, 2.05 mmol)

Appearance: pale yellow solid

M.p.: 91-92°C (lit.[49]: 91-93°C)

TLC: 0.39 (LP:EtOAc = 10:1)

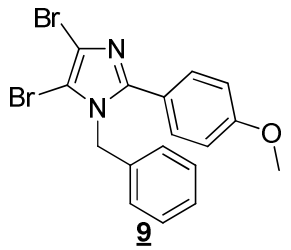
^{1}H NMR ($CDCl_3$, 200MHz): δ = 5.29 (s, 2H, CH_2), 6.97-7.07 (m, 2H, ArH), 7.29-7.53 (m, 8H, ArH)

^{13}C NMR ($CDCl_3$, 50MHz): δ = 50.3 (t, CH_2), 105.5 (s, C5[a]), 117.6 (s, C4[a]), 125.9 (d, C2/6[b]), 128.0 (d, C4[c]), 128.6 (d), 128.8 (d), 129.1 (d), 129.4 (s, C1[c]), 129.8 (d, C4[b]), 135.6 (s, C1[b]), 149.3 (s, C2[a])

LC-MS:

Main fragments: 415 (8), 393 (100, MH^+), 312 (18), 233 (13), 91 (3)

3.4.6. 1-Benzyl-4,5-dibromo-2-(4-methoxyphenyl)-1*H*-imidazole (9)



9

$C_{17}H_{14}Br_2N_2O$
M = 422.11

Method: Prepared according to general procedure A starting from compound **3** (500 mg, 1.27 mmol)

Boronic acid: 4-Methoxyphenylboronic acid (212 mg, 1.39 mmol, 1.1 equiv.)

Amount of solvent: 3 mL

Time: 7 hours

Purification: flash column chromatography (100 g silica gel, LP:EtOAc = 4:1)

Yield: 77% (412 mg, 0.98 mmol)

Appearance: colorless solid

M.p.: 117-121°C

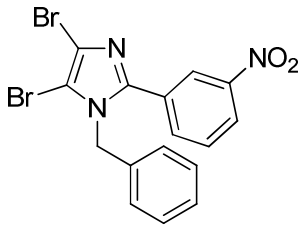
TLC: 0.25 (LP:EtOAc = 10:1)

^{1}H NMR ($CDCl_3$, 200MHz): δ = 3.81 (s, 3H, OCH_3), 5.26 (s, 2H, CH_2), 6.82-6.92 (m, 2H, H3/5^c), 6.97-7.07 (m, 2H, ArH), 7.29-7.45 (m, 5H, ArH)

^{13}C NMR ($CDCl_3$, 50MHz): δ = 50.4 (t, CH_2), 55.4 (q, OCH_3), 105.1 (s, C5^a), 114.3 (d, C3/5^c), 117.1 (s, C4^a), 121.7 (s,C1^c), 126.0 (d, C2/6^b), 128.1 (d, C4^b), 129.2 (d, C3/5^b), 130.2 (d, C2/6^c), 135.8 (s, C1^b), 149.3 (s, C2^a), 160.8 (s, C4^c)

HR-MS: $[M+H]^+$ m/z (predicted) = 420.9546, m/z (measured) = 420.9553, difference = 1.66 ppm

3.4.7. 1-Benzyl-4,5-dibromo-2-(3-nitrophenyl)-1*H*-imidazole (10)



10

$C_{16}H_{11}Br_2N_3O_2$

M = 437.09

Method: Prepared according to general procedure A starting from compound **3** (592.5 mg, 1.5 mmol).

Boronic acid: 3-Nitrophenylboronic acid (275 mg, 1.65 mmol, 1.1 equiv.)

Amount of solvent: 3.6 mL

Time: 3.5 hours

Purification: flash column chromatography (100 g silica gel, DCM:MeOH = 200:1)

Yield: 55% (357 mg, 0.82 mmol)

Appearance: yellow solid

M.p.: 96-100°C

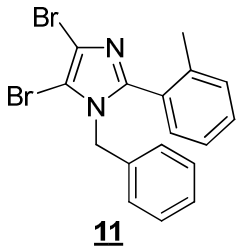
TLC: 0.23 (LP:EtOAc = 10:1)

^{1}H NMR (DMSO-d6, 200MHz): δ = 5.44 (s, 2H, CH_2), 7.02 (d, ^{3}J = 6.4 Hz, 2H, H2/6^{b}), 7.24-7.43 (m, 3H, H3/4/5^{b}), 7.70-7.81 (m, 1H, H5^{c}), 7.99 (d, ^{3}J = 7.8 Hz, 1H, H4^{c}), 8.24-8.34 (m, 2H, H2/6^{c})

^{13}C NMR (DMSO-d6, 50MHz): δ = 50.1 (t, CH_2), 107.5 (s, C5^{a}), 117.1 (s, C4^{a}), 122.9 (d, C2^{c}*), 124.2 (d, C4^{c}*), 125.8 (d, C2/6^{b}), 127.8 (d, C1^{b}), 129.0 (d, C3/5^{b}), 130.4 (s, C1^{c}), 130.6 (d, C5^{c}), 134.4 (d, C6^{c}), 135.6 (s, C1^{b}), 146.2 (s, C3^{c}), 147.9 (s, C2^{a})

HR-MS: $[M+H]^+$ m/z (predicted) = 435.9291, m/z (measured) = 435.9301, difference = 2.29 ppm

3.4.8. 1-Benzyl-4,5-dibromo-2-(2-tolyl)-1*H*-imidazole (<u>11</u>)



<u>11</u>

$C_{17}H_{14}Br_2N_2$
M = 406.11

Method: Prepared according to general procedure A starting from compound **3** (500 mg, 1.27 mmol)

Boronic acid: 2-Tolylboronic acid (223 mg, 1.64 mmol, 1.3 equiv.); 1.1 equiv. added at the beginning, 0.2 equiv. added after 4 hours;

Amount of solvent: 3 mL

Time: 6 hours

Purification: flash column chromatography (150 g silica gel, DCM:MeOH = 200:1)

Yield: 79% (403 mg, 0.99 mmol)

Appearance: yellow solid

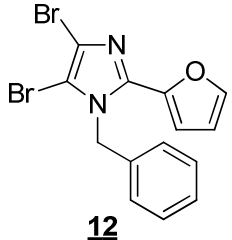
M.p.: 105-106°C

TLC: 0.44 (LP:EtOAc = 10:1)

^{1}H NMR ($CDCl_3$, 200MHz): δ = 2.11 (s, 3H, CH_3), 5.06 (s, 2H, CH_2), 6.83-6.94 (m, 2H, ArH), 7.13-7.42 (m, 7H, ArH)

^{13}C NMR ($CDCl_3$, 50MHz): δ = 19.7 (q, CH_3), 50.0 (t, CH_2), 104.1 (s, C5[a]), 116.8 (s, C4[a]), 125.8 (d, C4[c]), 126.8 (d, C2/6[b]), 128.1 (d, C4[b]), 128.8 (d, C3/5[b]), 129.3 (s, C2[c]), 130.2 (d), 130.3 (d), 130.7 (d), 135.4 (s, C1[b]), 138.7 (s, C1[c]), 148.5 (s, C2[a])

3.4.9. 1-Benzyl-4,5-dibromo-2-(2-furyl)-1*H*-imidazole (12)



12

$C_{14}H_{10}Br_2N_2O$

M = 382.05

Method: Prepared according to general procedure A starting from compound **3** (2 g, 5.06 mmol)

Boronic acid: 2-Furylboronic acid (2.04 g, 18.32 mmol, 3.6 equiv.); 1.1 equiv. added at the beginning, 0.5 equiv. added after 1 hour, 1 equiv. after 30 minutes, 1 equiv. after 15 minutes;

Amount of solvent: 12 mL

Time: 2 hours

Purification: flash column chromatography (300 g silica gel, LP:EtOAc = 10:1)

Yield: 25% (482 mg, 1.26 mmol)

Method: Prepared according to general procedure B starting from compound **3** (500 mg, 1.27 mmol)

Boronic acid: 2-Furylboronic acid (586 mg, 5.23 mmol, 4.1 equiv.); 1.1 equiv. added at the beginning, 1 equiv. added after 0.5 hour, 1 equiv. after 2 hours, 1 equiv. after 1 hour;

Amount of solvent: 4 mL

Time: 4 hours

Purification: flash column chromatography (50 g silica gel, LP:EtOAc = 6:1)

Yield: 43% (210 mg, 0.55 mmol)

Appearance: brown solid

M.p.: 109-116°C

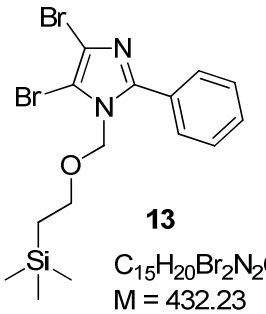
TLC: 0.38 (LP:EtOAc = 10:1)

^{1}H NMR ($CDCl_3$, 200MHz): δ = 5.52 (s, 2H, CH_2), 6.63 (dd, ^{3}J = 3.3 Hz, ^{3}J = 1.7 Hz, 1H, H4^{c}), 6.85 (d, ^{3}J = 3.5 Hz, 1H, H3^{c}), 7.05 (d, ^{3}J = 6.5 Hz, 2H, H2/6^{b}), 7.23-7.43 (m, 3H, H3/4/5^{b}), 7.79-7.86 (m, 1H, H5^{c})

^{13}C NMR ($CDCl_3$, 50MHz): δ = 49.9 (t, CH_2), 106.2 (s, C5^{a}), 110.9 (d, C3^{c} or C4^{c}), 111.9 (d, C3^{c} or C4^{c}), 117.0 (s, C4^{a}), 126.0 (d, C2/6^{b}), 127.7 (d, C4^{b}), 128.9 (d, C3/5^{b}), 135.8 (s, C1^{b}), 139.6 (s, C2^{a}), 143.4 (s, C2^{c}), 144.4 (d, C5^{c})

HR-MS: $[M+H]^+$ m/z (predicted) = 380.9233, m/z (measured) = 380.9252, difference = 4.99 ppm

3.4.10. 4,5-Dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-2-phenyl-1*H*-imidazole (13)[40]



13

$C_{15}H_{20}Br_2N_2OSi$

M = 432.23

Method: Prepared according to general procedure A starting from compound **5** (500 mg, 1.15 mmol)

Boronic acid: Phenylboronic acid (154 mg, 1.26 mmol, 1.1 equiv.)

Amount of solvent: 3 mL

Time: 5 hours

Purification: flash column chromatography (75 g silica gel, LP:EtOAc = 20:1)

Yield: 72% (358 mg, 0.83 mmol)

Appearance: colorless solid

M.p.: 76-79°C

TLC: 0.33 (LP:EtOAc = 10:1)

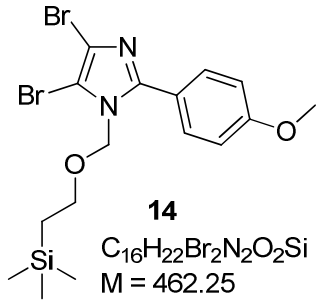
^{1}H NMR ($CDCl_3$, 200MHz): δ = 0.08 (s, 9H, $SiCH_3$), 0.95 (t, ^3J = 8.2 Hz, 2H, $SiCH_2$), 3.65 (t, ^3J = 8.2 Hz, 2H, OCH_2), 5.31 (s, 2H, NCH_2O), 7.41-7.51 (m, 3H, ArH), 7.72-7.83 (m, 2H, ArH)

^{13}C NMR ($CDCl_3$, 50MHz): δ = 1.3 (q, $SiCH_3$), 18.0 (t, $SiCH_2$), 67.0 (t, OCH_2), 74.7 (t, NCH_2O), 105.4 (s, C5[a]), 117.9 (s, C4[a]), 128.8 (d, C2/6[c]), 129.1 (d, C3/5[c]), 129.3 (s, C1[c]), 130.0 (d, C4[c]), 149.9 (s, C2[a])

LC-MS:

Main fragments: 455 (12), 433 (82, MH^+), 403 (17), 375 (100)

3.4.11. 4,5-Dibromo-2-(4-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole (14)[50]



14

$C_{16}H_{22}Br_2N_2O_2Si$

M = 462.25

Method: Prepared according to general procedure A starting from compound **5** (500 mg, 1.15 mmol)

Boronic acid: 4-Methoxyphenylboronic acid (192 mg, 1.26 mmol, 1.1 equiv.)

Amount of solvent: 3 mL

Time: 6.5 hours

Purification: flash column chromatography (100 g silica gel, LP:EtOAc = 7:1)

Yield: 74% (393 mg, 0.85 mmol)

Appearance: red brown solid

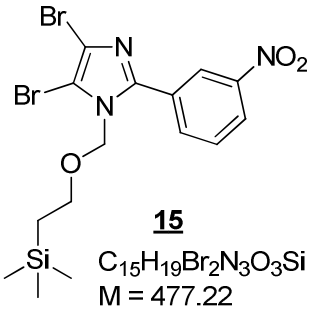
M.p.: 95-97°C

TLC: 0.31 (LP:EtOAc = 10:1)

^{1}H NMR ($CDCl_3$, 200MHz): δ = 0.00 (s, 9H, $SiCH_3$), 0.94 (t, ^3J = 8.3 Hz, 2H, $SiCH_2$), 3.65 (t, ^3J = 8.3 Hz, 2H, OCH_2), 3.83 (s, 3H, OCH_3), 5.26 (s, 2H, NCH_2O), 6.94 (d, ^3J = 8.7 Hz, 2H, H3/5^c), 7.79 (d, ^3J = 8.7 Hz, 2H, H2/6^c)

^{13}C NMR ($CDCl_3$, 50MHz): δ = -1.3 (q, $SiCH_3$), 18.0 (t, $SiCH_2$), 55.5 (q, OCH_3), 67.1 (t, OCH_2), 74.8 (t, NCH_2O), 105.0 (s, C5^a), 114.3 (s, C4^a), 117.0 (d, C3/5^c), 121.2 (s, C1^c), 130.6 (d, C2/6^c), 149.9 (s, C2^a), 161.1 (s, C4^c)

3.4.12. 4,5-Dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-2-(3-nitrophenyl)-1*H*-imidazole (<u>15</u>)



<u>15</u>

$C_{15}H_{19}Br_2N_3O_3Si$

M = 477.22

Method: Prepared according to general procedure A starting from compound **5** (500 mg, 1.15 mmol)

Boronic acid: 3-Nitrophenylboronic acid (230 mg, 1.38 mmol, 1.2 equiv.); 1.1 equiv. added at the beginning, 0.1 equiv. added after 5 hours;

Amount of solvent: 3 mL

Time: 6.5 hours

Purification: flash column chromatography (100 g silica gel, LP:EtOAc = 10:1)

Yield: 65% (355 mg, 0.74 mmol)

Appearance: yellow solid

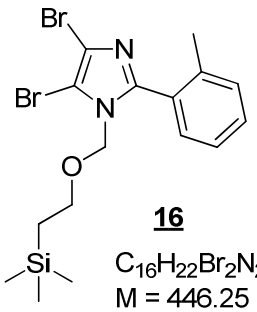
M.p.: 102-105°C

TLC: 0.21 (LP:EtOAc = 10:1)

^{1}H NMR ($CDCl_3$, 200MHz): δ = 0.03 (s, 9H, $SiCH_3$), 1.05 (t, ^3J = 8.3 Hz, 2H, $SiCH_2$), 3.78 (t, ^3J = 8.3 Hz, 2H, OCH_2), 5.33 (s, 2H, NCH_2O), 7.65 (t, ^3J = 8.0 Hz, 1H, H5^c), 8.17-8.33 (m, 2H, H4/6^c), 8.77 (t, ^3J = 1.8 Hz, 1H, H2^c)

^{13}C NMR ($CDCl_3$, 50MHz): δ = -1.3 (q, $SiCH_3$), 18.1 (t, $SiCH_2$), 67.4 (t, OCH_2), 74.8 (t, NCH_2O), 106.9 (s, C5^a), 118.4 (s, C4^a), 123.6 (d, C2^c), 124.5 (d, C4^c), 130.0 (d, C5^c), 130.8 (s, C1^c), 134.6 (d, C6^c), 147.3 (s, C3^c), 148.5 (s, C2^a)

3.4.13. 4,5-Dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-2-(2-tolyl)-1*H*-imidazole (**16**)



16

$C_{16}H_{22}Br_2N_2OSi$

M = 446.25

Method: Prepared according to general procedure A starting from compound **5** (200 mg, 0.46 mmol)

Boronic acid: 2-Tolylboronic acid (69 mg, 0.51 mmol, 1.1 equiv.)

Amount of solvent: 1.2 mL

Time: 5 hours

Purification: flash column chromatography (50 g silica gel, LP:EtOAc = 30:1)

Yield: 42% (86 mg, 0.19 mmol)

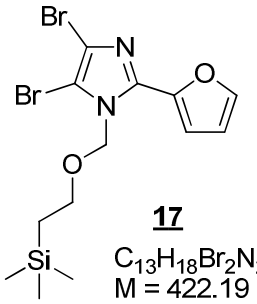
Appearance: brown oil

TLC: 0.40 (LP:EtOAc = 10:1)

^{1}H NMR ($CDCl_3$, 200MHz): δ = 0.00 (s, 9H, $SiCH_3$), 0.85 (t, ^3J = 8.3 Hz, 2H, $SiCH_2$), 2.29 (s, 3H, Ar-CH_3), 3.41 (t, ^3J = 8.3 Hz, 2H, OCH_2), 5.16 (s, 2H, NCH_2O), 7.24-7.48 (m, 4H, ArH)

^{13}C NMR ($CDCl_3$, 50MHz): δ = -1.4 (q, $SiCH_3$), 17.8 (t, $SiCH_2$), 19.9 (q, Ar-CH_3), 66.7 (t, OCH_2), 74.5 (t, NCH_2O), 104.0 (s, C5[a]), 117.3 (s, C4[a]), 125.8 (d), 128.9 (s, C2[c]), 130.2 (d), 130.70 (d), 130.74 (d), 138.6 (s, C1[c]), 148.9 (s, C2[a])

3.4.14. 4,5-Dibromo-2-(2-furyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole (**17**)



17

$C_{13}H_{18}Br_2N_2O_2Si$

M = 422.19

Method: Prepared according to general procedure A starting from compound **5** (500 mg, 1.15 mmol)

Boronic acid: 2-Furylboronic acid (463 mg, 4.14 mmol, 3.6 equiv.); 1.1 equiv. added at the beginning, 0.5 equiv. added after 1 hour, 1 equiv. after 30 minutes, 1 equiv. after 15 minutes;

Amount of solvent: 3 mL

Time: 2 hours

Purification: flash column chromatography (100 g silica gel, LP:EtOAc = 10:1)

Yield: 31% (149 mg, 0.35 mmol)

Appearance: brown solid

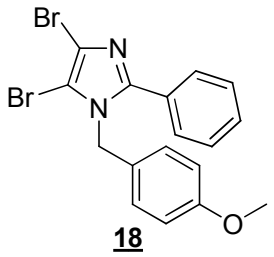
M.p.: 73-76°C

TLC: 0.49 (LP:EtOAc = 10:1)

^{1}H NMR ($CDCl_3$, 200MHz): δ = -0.04 (s, 9H, $SiCH_3$), 0.90 (t, ^3J = 8.2 Hz, 2H, $SiCH_2$), 3.60 (t, ^3J = 8.2 Hz, 2H, OCH_2), 5.56 (s, 2H, NCH_2O), 6.53 (dd, ^3J = 1.8 Hz, ^3J = 3.5 Hz, 1H, H4^c), 7.02 (d, ^3J = 3.5 Hz, 1H, H3^c), 7.53 (d, ^3J = 1.8 Hz, 1H, H5^c)

^{13}C NMR ($CDCl_3$, 50MHz): δ = -1.3 (q, $SiCH_3$), 17.9 (t, $SiCH_2$), 66.9 (t, OCH_2), 75.0 (t, NCH_2O), 105.4 (s, C5^a), 111.8 (d, C3^c or C4^c), 111.9 (d, C3^c or C4^c), 118.2 (s, C4^a), 140.7 (s, C2^a), 143.7 (d, C5^c), 144.0 (s, C2^c)

3.4.15. 4,5-Dibromo-1-(4-methoxybenzyl)-2-phenyl-1*H*-imidazole (<u>18</u>)



<u>18</u>

$C_{17}H_{14}Br_2N_2O$
M = 422.11

Method: Prepared according to general procedure A starting from compound **7** (100 mg, 0.24 mmol)

Boronic acid: Phenylboronic acid (32 mg, 0.26 mmol, 1.1 equiv.)

Amount of solvent: 0.6 mL

Time: 5 hours

Purification: flash column chromatography (50 g silica gel, LP:EtOAc = 10:1)

Yield: 74% (74 mg, 0.17 mmol)

Appearance: pale yellow solid

M.p.: 98-102°C

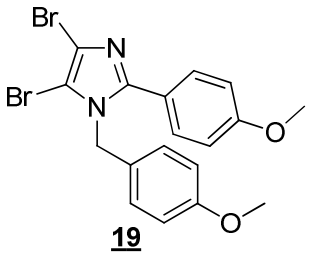
TLC: 0.32 (LP:EtOAc = 10:1)

^{1}H NMR ($CDCl_3$, 200MHz): δ = 3.79 (s, 3H, OCH_3), 5.22 (s, 2H, CH_2), 6.81-6.99 (m, 4H, H2/3/5/6^b), 7.31-7.54 (m, 5H, H2-6^c)

^{13}C NMR ($CDCl_3$, 50MHz): δ = 49.9 (t, CH_2), 55.4 (q, OCH_3), 105.4 (s, C5^a), 114.5 (d, C3/5^b), 117.5 (s, C4^a), 127.4 (d, C3/5^c), 127.6 (s, C1^b), 128.75 (d, C2/6^b or C2/6^c), 128.83 (d, C2/6^b or C2/6^c), 129.6 (s, C1^c), 129.8 (d, C4^c), 149.2 (s, C2^a), 159.3 (s, C4^b)

HR-MS: $[M+H]^+$ m/z (predicted) = 420.9546, m/z (measured) = 420.9547, difference = 0.24 ppm

3.4.16. 4,5-Dibromo-2-(4-methoxyphenyl)-1-(4-Methoxybenzyl)-1*H*-imidazole (19)



19

$C_{18}H_{16}Br_2N_2O_2$
M = 452.14

Method: Prepared according to general procedure A starting from compound **7** (100 mg, 0.24 mmol).

Boronic acid: 4-Methoxyphenylboronic acid (39 mg, 0.26 mmol, 1.1 equiv.)

Amount of solvent: 0.6 mL

Time: 5 hours

Purification: flash column chromatography (50g silica gel, LP:EtOAc = 10:1)

Yield: 77% (82 mg, 0.18 mmol)

Appearance: yellow oil

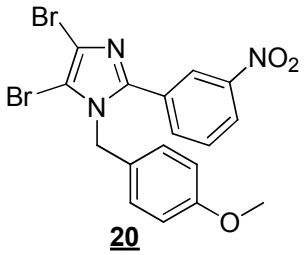
TLC: 0.19 (LP:EtOAc = 10:1)

^{1}H NMR ($CDCl_3$, 200MHz): δ = 3.79 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 5.18 (s, 2H, CH_2), 6.79-7.00 (m, 6H, ArH), 7.33-7.45 (m, 2H, H2/6^c)

^{13}C NMR ($CDCl_3$, 50MHz): δ = 49.8 (t, CH_2), 55.38 (q, OCH_3), 55.43 (q, OCH_3), 104.8 (s, C5^a), 114.2 (d, C3/5^c), 114.5 (d, C3/5^b), 117.2 (s, C4^a), 122.0 (s, C1^c), 127.3 (d, C2/6^b), 127.8 (s, C1^b), 130.2 (d, C2/6^c), 149.2 (s C2^a), 159.3 (s, C4^b), 160.7 (s, C4^c)

HR-MS: $[M+H]^+$ m/z (predicted) = 450.9651, m/z (measured) = 450.9670, difference = 4.21 ppm

3.4.17. 4,5-Dibromo-1-(4-methoxybenzyl)-2-(3-nitrophenyl)-1*H*-imidazole (<u>20</u>)



<u>20</u>

$C_{17}H_{13}Br_2N_3O_3$
M = 467.11

Method: Prepared according to general procedure A starting from compound **7** (200 mg, 0.47 mmol)

Boronic acid: 3-Nitrophenylboronic acid (86 mg, 0.52 mmol, 1.1 equiv.)

Amount of solvent: 1.2 mL

Time: 6 hours

Purification: flash column chromatography (75 g silica gel, LP:EtOAc = 10:1)

Yield: 63% (138 mg, 0.29 mmol)

Appearance: brown oil

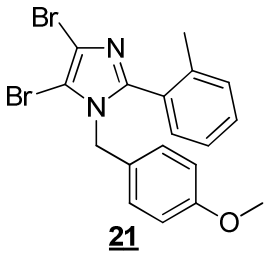
TLC: 0.15 (LP:EtOAc = 10:1)

^{1}H NMR ($CDCl_3$, 200MHz): δ = 3.80 (s, 3H, OCH_3), 5.27 (s, 2H, CH_2), 6.82-7.01 (m, 4H, H2/3/5/6^b), 7.57 (t, ^3J = 8.2 Hz, 1H, H5^c), 7.85 (d, ^3J = 7.7 Hz, 1H, H2^c), 8.25 (d, ^3J = 8.2 Hz, 1H, ArH, H4^c), 8.32-8.39 (m, 1H, ArH, H6^c)

^{13}C NMR ($CDCl_3$, 50MHz): δ = 50.3 (t, CH_2), 55.5 (q, OCH_3), 107.3 (s, C5^a), 114.8 (d, C3/5^b), 118.2 (s, C4^a), 123.4 (d, C2^c), 124.3 (d, C4^c), 126.8 (s, C1^b), 127.3 (d, C2/6^b), 130.0 (d, C5^c), 131.1 (s, C1^c), 134.4 (d, C6^c), 146.4 (s, C3^c), 148.4 (s, C2^a), 159.7 (s, C4^b)

HR-MS: $[M+Na]^+$ m/z (predicted) = 487.9216, m/z (measured) = 487.9229, difference = 2.66 ppm

3.4.18. 4,5-Dibromo-1-(4-methoxybenzyl)-2-(2-tolyl)-1*H*-imidazole (21)



21

$C_{18}H_{16}Br_2N_2O$
M = 436.14

Method: Prepared according to general procedure A starting from compound **7** (200 mg, 0.47 mmol).

Boronic acid: 2-Tolylboronic acid (70 mg, 0.52 mmol, 1.1 equiv.)

Amount of solvent: 1.2 mL

Time: 6 hours

Purification: flash column chromatography (75 g silica gel, LP:EtOAc = 10:1)

Yield: 59% (121 mg, 0.28 mmol)

Appearance: brown oil

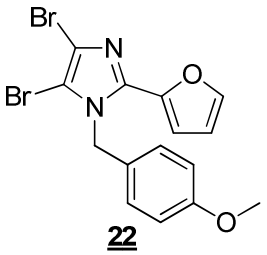
TLC: 0.36 (LP:EtOAc = 10:1)

^{1}H NMR ($CDCl_3$, 200MHz): δ = 1.97 (s, 3H, Ar-CH_3), 3.73 (s, 3H, OCH_3), 5.03 (s, 2H, CH_2), 6.72-6.79 (m, 4H, H2/3/5/6^b), 7.14-7.49 (m, 4H, H3-6^c)

^{13}C NMR ($CDCl_3$, 50MHz): δ = 19.5 (q, Ar-CH_3), 50.3 (t, CH_2), 55.7 (q, OCH_3), 105.8 (s, C5^a), 115.0 (d, C3/5^b), 116.5 (s, C4^a), 127.0 (d), 128.5 (s, C1^b), 129.4 (d, C2/6^b), 130.2 (s, C1^c), 131.3 (d), 131.6 (d), 131.7 (d), 139.9 (s, C2^c), 149.9 (s, C2^a), 160.9 (s, C4^b)

HR-MS: $[M+H]^+$ m/z (predicted) = 434.9702, m/z (measured) = 434.9707, difference = 1.15 ppm

3.4.19. 4,5-Dibromo-2-(2-furyl)-1-(4-methoxybenzyl)-1*H*-imidazole (22)



22

$C_{15}H_{12}Br_2N_2O_2$
M = 412.08

Method: Prepared according to general procedure A starting from compound **7** (400 mg, 0.94 mmol)

Boronic acid: 2-Furylboronic acid (379 mg, 3.39 mmol, 3.6 equiv.); 1.1 equiv. added at the beginning, 0.5 equiv. added after 1 hour, 1 equiv. after 30 minutes, 1 equiv. after 15 minutes;

Amount of solvent: 2.4 mL

Time: 2 hours

Purification: flash column chromatography (200 g silica gel, LP:EtOAc = 9:1)

Yield: 35% (136 mg, 0.33 mmol)

Appearance: dark brown oil

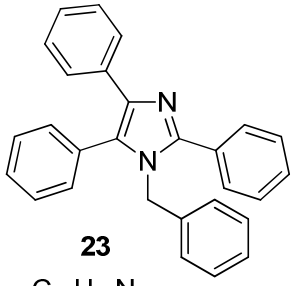
TLC: 0.25 (LP:EtOAc = 10:1)

^{1}H NMR ($CDCl_3$, 200MHz): δ = 3.75 (s, 3H, OCH_3), 5.42 (s, 2H, CH_2), 6.42-6.52 (m, 1H, H4^c), 6.77-6.87 (m, 3H, ArH), 7.02 (d, ^3J = 8.7 Hz, 2H, H2/6^b), 7.42-7.52 (m, 1H, H5^c)

^{13}C NMR ($CDCl_3$, 50MHz): δ = 50.0 (t, CH_2), 55.3 (q, OCH_3), 105.5 (s, C5^a), 110.9 (d, C3^c or C4^c), 111.8 (d, C3^c or C4^c), 114.3 (d, C3/5^b), 117.8 (s, C4^a), 127.3 (s, C1^b), 127.9 (d, C2/6^b), 140.0 (s, C2^a), 143.2 (d, C5^c), 144.3 (s, C2^c), 159.3 (s, C4^b)

HR-MS: $[M+H]^+$ m/z (predicted) = 410.9338, m/z (measured) = 410.9326, difference = -2.92 ppm

3.4.20. 1-Benzyl-2,4,5-triphenyl-1*H*-imidazole (23)



23

$C_{28}H_{22}N_2$
M = 386.49

Method: Prepared according to general procedure C starting from compound **8** (100 mg, 0.26 mmol).

Boronic acid: Phenylboronic acid (93 mg, 0.77 mmol, 3 equiv.)

Amount of solvent: 0.6 mL

Time: 3 hours

Purification: flash column chromatography (50 g silica gel, LP:EtOAc = 5:1)

Yield: 79% (79 mg, 0.20 mmol)

Appearance: colorless solid

M.p.: 157-160°C (lit.[51]: 157-159°C)

TLC: 0.56 (LP:EtOAc = 5:1)

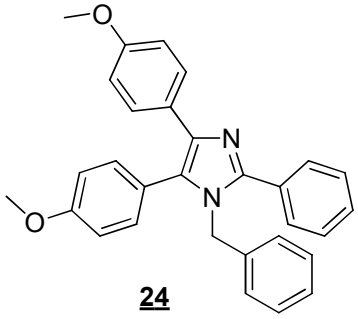
^{1}H NMR (DMSO-d6, 200MHz): δ = 5.15 (s, 2H, CH_2), 6.63-6.85 (m, 2H, ArH), 6.97-7.94 (m, 18H, ArH)

^{13}C NMR (DMSO-d6, 50MHz): δ = 47.6 (t, CH_2), 125.6 (d), 126.1 (d), 126.2 (d), 126.4 (d), 127.1 (d), 128.1 (d), 128.48 (d), 128.53 (d), 128.8 (d), 128.9 (d), 130.1 (s), 130.5 (s), 130.7 (s), 130.8 (d), 134.5 (s, C1^b), 136.8 (s), 137.3 (s), 147.0 (s, C2^a)

LC-MS:

Main fragments: 409 (3), 387 (100, MH^+), 296 (10)

3.4.21. 1-Benzyl-4,5-di(4-methoxyphenyl)-2-phenyl-1*H*-imidazole (24)



24

$C_{30}H_{26}N_2O_2$
M = 446.54

Method: Prepared according to general procedure C starting from compound **8** (100 mg, 0.26 mmol).

Boronic acid: 4-Methoxyphenylboronic acid (116 mg, 0.77 mmol, 3 equiv.)

Amount of solvent: 0.6 mL

Time: 4 hours

Purification: flash column chromatography (50 g silica gel, LP:EtOAc = 4:1)

Yield: 85% (97 mg, 0.22 mmol)

Method: Prepared according to general procedure D starting from compound **3** (100 mg, 0.26 mmol)

Boronic acid 1: Phenylboronic acid (34 mg, 0.28 mmol, 1.1 equiv.)

Boronic acid 2: 4-Methoxyphenylboronic acid (115 mg, 0.76 mmol, 3 equiv.)

Amount of solvent: 0.6 mL

Time: 3 hours for the first coupling step, 4.5 hours for the second coupling step

Purification: flash column chromatography (50 g silica gel, LP:EtOAc = 7:1)

Yield: 89% (102 mg, 0.23 mmol)

Appearance: brown oil

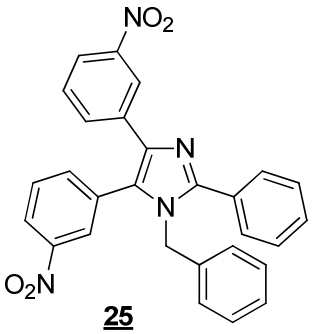
TLC: 0.28 (LP:EtOAc = 5:1)

^{1}H NMR (MeOD-d4, 200MHz): δ = 3.65 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 5.05 (s, 2H, CH_2), 6.60-7.65 (m, 18H, ArH)

^{13}C NMR (MeOD-d4, 50MHz): δ = 49.1 (t, CH_2), 55.6 (q, OCH_3), 55.7 (q, OCH_3), 114.6 (d), 115.3 (d), 123.7 (s, C5[a]), 127.0 (d, C2/6[b]), 128.0 (s, C4[a]), 128.4 (d), 129.4 (d, C3/5[b]), 129.6 (d), 129.7 (d, C2/6[c]), 130.3 (d, C3/5[c]), 130.4 (d), 130.7 (s), 131.8 (s), 133.5 (d), 138.8 (s), 138.9 (s), 149.2 (s, C2[a]), 160.0 (s), 161.4 (s)

HR-MS: $[M+H]^+$ m/z (predicted) = 447.2067, m/z (measured) = 447.2085, difference = 4.02 ppm

3.4.22. 1-Benzyl-4,5-di(3-nitrophenyl)-2-phenyl-1*H*-imidazole (25)



25

$C_{28}H_{20}N_4O_4$
M = 476.48

Method: Prepared according to general procedure C starting from compound **8** (100 mg, 0.26 mmol).

Boronic acid: 3-Nitrophenylboronic acid (128 mg, 0.77 mmol, 3. equiv.)

Amount of solvent: 0.6 mL

Time: 3 hours

Purification: flash column chromatography (15 g silica gel, DCM:MeOH = 200:1)

Yield: 56% (68 mg, 0.14 mmol)

Appearance: yellow solid

M.p.: 159-161°C

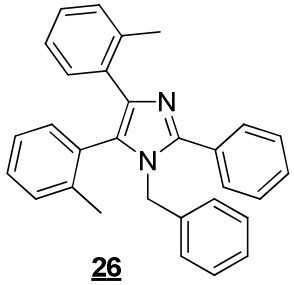
TLC: 0.28 (LP:EtOAc = 5:1)

^{1}H NMR (DMSO-d6, 200MHz): δ = 5.23 (s, 2H, CH_2), 6.68-6.87 (m, 2H, ArH), 7.08-7.27 (m, 3H, ArH), 7.43-7.61 (m, 4H, ArH), 7.64-7.84 (m, 5H, ArH), 8.03 (d, ^3J= 8.10 Hz, 1H, ArH), 8.15 (s, 1H, ArH), 8.26-8.41 (m, 2H, ArH)

^{13}C NMR (DMSO-d6, 50MHz): δ = 48.2 (t, CH_2), 120.3 (d), 121.2 (d), 124.0 (d), 125.4 (d), 125.9 (d), 127.4 (d), 128.6 (d), 128.8 (d), 128.9 (s), 129.3 (d), 130.0 (s), 130.8 (d), 131.4 (s), 131.9 (d), 135.6 (s), 136.7 (s), 137.5 (d), 148.1 (s), 148.5 (s)

HR-MS: $[M+Na]^+$ m/z (predicted) = 499.1377, m/z (measured) = 499.1398, difference = 4.21 ppm

3.4.23. 1-Benzyl-2-phenyl-4,5-di(2-tolyl)-1*H*-imidazole (26)



26

$C_{30}H_{26}N_2$

M = 414.54

Method: Prepared according to general procedure C starting from compound **8** (100 mg, 0.26 mmol)

Boronic acid: 2-Tolylboronic acid (104.1 mg, 0.77 mmol, 3 equiv.)

Amount of solvent: 0.6 mL

Time: 4 hours

Purification: flash column chromatography (50 g silica gel, LP:EtOAc = 4:1), followed by preparative HPLC

Yield: 37% (39 mg, 0.09 mmol)

Appearance: brown oil

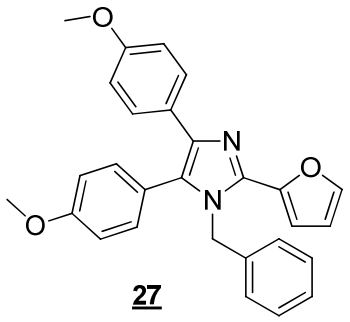
TLC: 0.53 (LP:EtOAc = 5:1)

^{1}H NMR (MeOD-d4, 200MHz): δ = 1.73 (s, 3H, Ar-CH_3), 2.30 (s, 3H, Ar-CH_3), 5.21 (d, ^3J = 16.0 Hz, 1H, CH_2), 5.11 (d, ^3J = 16.0 Hz, 1H, CH_2), 6.51-6.70 (m, 2H, H2/6^c), 6.90-7.32 (m, 11H, ArH), 7.39-7.58 (m, 3H, ArH), 7.61-7.79 (m, 2H, ArH)

^{13}C NMR (MeOD-d4, 50MHz): δ = 19.8 (q, Ar-CH_3), 20.7 (q, Ar-CH_3), 49.7 (t, CH_2), 126.3 (d), 126.8 (d), 127.5 (d, C2/6^b), 128.5 (d), 128.7 (d), 129.4 (d, C3/5^b), 129.9 (d, C2/6^c), 130.0 (d), 130.4 (d, C3/5^c), 130.5 (s), 131.3 (d), 131.4 (d), 131.6 (d), 131.7 (s), 131.8 (s), 132.8 (d), 135.1 (s), 139.8 (s), 140.3 (s), 149.6 (s, C2^a)

HR-MS: $[M+H]^+$ m/z (predicted) = 415.2169, m/z (measured) = 415.2176, difference = 1.69 ppm

3.4.24. 1-Benzyl-2-(2-furyl)-4,5-di(4-methoxyphenyl)-1*H*-imidazole (27)



27

$C_{28}H_{24}N_2O_3$

M = 436.50

Method: Prepared according to general procedure C starting from compound **12** (200 mg, 0.52 mmol).

Boronic acid: 4-Methoxyphenylboronic acid (238 mg, 1.57 mmol, 3 equiv.)

Amount of solvent: 1.2 mL

Time: 4 hours

Purification: flash column chromatography (100 g silica gel, LP:EtOAc = 2:1)

Yield: 81% (184 mg, 0.42 mmol)

Appearance: brown solid

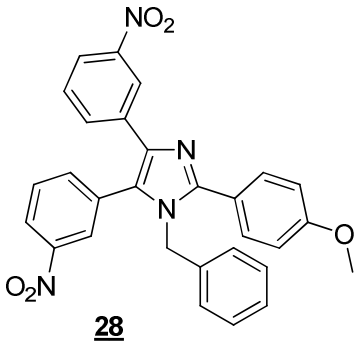
M.p.: 67-70°C

TLC: 0.28 (LP:EtOAc = 5:1)

^{1}H NMR (MeOD-d4, 200MHz): δ = 3.70 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 5.26 (s, 2H, CH_2), 6.47-6.54 (m, 1H, H4^c), 6.65-7.45 (m, 14H, ArH), 7.54-7.61 (m, 1H, H5^c)

^{13}C NMR (MeOD-d4, 50MHz): δ = 49.2 (t, CH_2), 55.6 (q, OCH_3), 55.7 (q, OCH_3), 111.5 (d), 112.6 (d), 114.6 (d), 115.4 (d), 123.0 (s, C5^a), 126.9 (d, C2/6^b), 127.7 (s), 128.4 (d), 129.5 (d, C3/5^b), 129.7 (d), 130.9 (s), 133.5 (d), 138.6 (s), 139.3 (s), 140.2 (s, C2^a), 144.5 (d, C5^c), 145.9 (s, C2^c), 160.1 (s), 161.5 (s)

3.4.25. 1-Benzyl-2-(4-methoxyphenyl)-4,5-di(3-nitrophenyl)-1*H*-imidazole (28)



28

$C_{29}H_{22}N_4O_5$
M = 506.51

Method: Prepared according to general procedure C starting from compound **9** (100 mg, 0.24 mmol).

Boronic acid: 3-Nitrophenylboronic acid (119 mg, 0.71 mmol, 3 equiv.)

Amount of solvent: 0.6 mL

Time: 5 hours

Purification: flash column chromatography (20 g silica gel, LP:EtOAc = 5:1)

Yield: 60% (73 mg, 0.14 mmol)

Method: Prepared according to general procedure D starting from compound **3** (100 mg, 0.26 mmol).

Boronic acid 1: 4-Methoxyphenylboronic acid (42 mg, 0.28 mmol, 1.1 equiv.)

Boronic acid 2: 3-Nitrophenylboronic acid (254 mg, 1.52 mmol, 6 equiv.)

Amount of solvent: 0.6 mL

Time: 6 hours for the first coupling step, 3 hours for the second coupling step

Purification: flash column chromatography (50 g silica gel, LP:EtOAc = 10:1)

Yield: 73% (94 mg, 0.18 mmol)

Appearance: yellow solid

M.p.: 149-151°C

TLC: 0.16 (LP:EtOAc = 5:1)

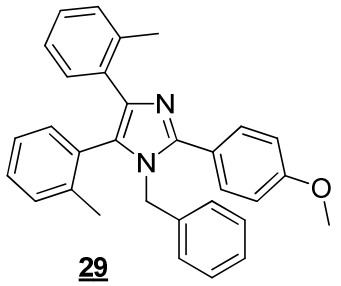
^{1}H NMR (DMSO-d6, 200MHz): δ = 3.80 (s, 3H, OCH_3), 5.20 (s, 2H, CH_2), 6.71-6.84 (m, 2H, ArH), 7.06 (d, ^3J = 8.7 Hz, 2H, H3/5^c), 7.12-7.28 (m, 3H, ArH), 7.50 (t, ^3J = 8.1 Hz, 1H, ArH), 7.59-7.81 (m, 5H, ArH), 8.01 (d, 1H, ArH), 8.13 (s, 1H, ArH), 8.23-8.38 (m, 2H, ArH)

^{13}C NMR (DMSO-d6, 50MHz): δ = 48.2 (t, CH_2), 55.3 (q, OCH_3), 114.2 (d, C3/5^c), 120.3 (d), 121.1 (d), 122.3 (s, C5^a), 124.0 (d), 125.4 (d), 125.8 (d,C2/6^b), 127.4 (d), 128.6 (d, C3/5^b),

130.0 (d), 130.2 (d, C2/6[c]), 130.8 (d), 131.6 (s), 131.9 (d), 135.4 (d), 135.7 (s), 136.8 (s), 137.5 (d), 148.0 (s), 148.1 (s), 148.5 (s), 160.0 (s, C4[c])

HR-MS: $[M+H]^+$ m/z (predicted) = 507.1663, m/z (measured) = 507.1686, difference = 4.53 ppm

3.4.26. 1-Benzyl-2-(4-methoxyphenyl)-4,5-di(2-tolyl)-1*H*-imidazole (29)



29

$C_{31}H_{28}N_2O$
M = 444.57

Method: Prepared according to general procedure C starting from compound **9** (100 mg, 0.24 mmol).

Boronic acid: 2-Tolylboronic acid (97 mg, 0.71 mmol, 3 equiv.)

Amount of solvent: 0.6 mL

Time: 4 hours

Purification: flash column chromatography (50 g silica gel, LP:EtOAc = 4:1), followed by preparative HPLC

Yield: 63% (66 mg, 0.15 mmol)

Appearance: colorless oil

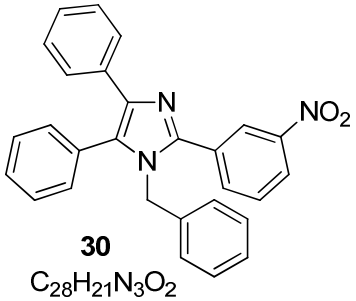
TLC: 0.35 (LP:EtOAc = 5:1)

^{1}H NMR (MeOD-d4, 200MHz): δ = 1.72 (s, 3H, Ar-CH_3), 2.29 (s, 3H, Ar-CH_3), 3.82 (s, 3H, OCH_3), 5.08 (d, ^3J = 16.1 Hz, 1H, CH_2), 5.18 (d, ^3J = 16.1 Hz, 1H, CH_2), 6.55-6.68 (m, 2H, H3/5[c]), 6.91-7.23 (m, 13H, ArH), 7.62 (d, ^3J = 8.9 Hz, 2H, H2/6[c])

^{13}C NMR (MeOD-d4, 50MHz): δ = 19.8 (q, Ar-CH_3), 20.7 (q, Ar-CH_3), 49.6 (t, CH_2), 55.8 (q, OCH_3), 115.3 (d, C3/5[c]), 124.0 (s, C5[a]), 126.3 (d), 126.8 (d), 127.5 (d, C2/6[b]), 128.5 (d), 128.6 (d), 129.4 (d, C3/5[b]), 123.0 (d), 130.7 (s), 131.26 (d), 131.30 (s), 131.4 (d), 131.6 (d), 131.8 (d, C2/6[c]), 132.8 (d), 135.3 (s), 138.2 (s), 138.4 (s), 139.8 (s), 140.1 (s), 149.6 (s, C2[a]), 162.0 (s, C4[c])

HR-MS: $[M+H]^+$ m/z (predicted) = 445.2274, m/z (measured) = 445.2282, difference = 1.80 ppm

3.4.27. 1-Benzyl-2-(3-nitrophenyl)-4,5-diphenyl-1*H*-imidazole (30)



30

$C_{28}H_{21}N_3O_2$

M = 431.49

Method: Prepared according to general procedure C starting from compound **10** (100 mg, 0.23 equiv.).

Boronic acid: Phenylboronic acid (84 mg, 0.69 mmol, 3 equiv.)

Amount of solvent: 0.6 mL

Time: 3 hours

Purification: flash column chromatography (50 g silica gel, LP:EtOAc = 4:1)

Yield: 85% (84 mg, 0.20 mmol)

Appearance: yellow solid

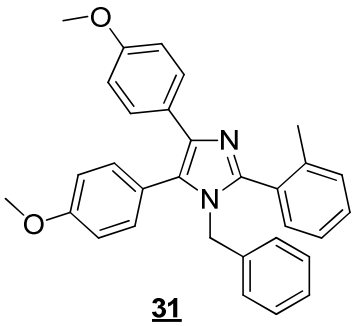
M.p.: 126-128°C (lit.[52]: 115-116°C)

TLC: 0.41 (LP:EtOAc = 5:1)

^{1}H NMR (DMSO-d6, 200MHz): δ = 5.23 (s, 2H, CH_2), 6.73-6.89 (m, 2H, ArH), 7.07-7.54 (m, 13H, ArH), 7.71 (t, ^3J = 8.0 Hz, 1H, H5^c), 8.13 (d, ^3J = 8.0 Hz, 1H, H4^c), 8.23 (dd, ^3J = 8.0 Hz, ^{4}J = 2.0 Hz, 1H, H6^c), 8.42-8.53 (m, 1H, H2^c)

^{13}C NMR (DMSO-d6, 50MHz): δ = 47.9 (t, CH_2), 122.8 (d, C2^c), 123.4 (d, C4^c), 125.7 (d), 126.2 (d), 126.5 (d), 127.3 (d), 128.2 (d), 128.6 (d), 129.0 (d), 130.1 (s), 130.3 (d), 130.8 (d), 131.3 (s, C5^c), 132.0 (s, C1^c), 134.1 (s, C6^c), 134.4 (d), 136.9 (s), 137.4 (s), 144.7 (s, C3^c), 147.8 (s, C2^a)

3.4.28. 1-Benzyl-4,5-di(4-methoxyphenyl)- 2-(2-tolyl)-1*H*-imidazole (31)



31

$C_{31}H_{28}N_2O_2$
M = 460.57

Method: Prepared according to general procedure C starting from compound **11** (100 mg, 0.25 mmol).

Boronic acid: 4-Methoxyphenylboronic acid (112 mg, 0.74 mmol, 3 equiv.)

Amount of solvent: 0.6 mL

Time: 3 hours

Purification: flash column chromatography (50 g silica gel, LP:EtOAc = 2:1), followed by preparative HPLC

Yield: 59% (66 mg, 0.14 mmol)

Appearance: brown oil

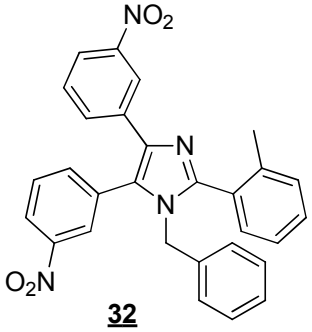
TLC: 0.28 (LP:EtOAc = 5:1)

^{1}H NMR (DMSO-d6, 200MHz): δ = 2.18 (s, 3H, Ar-CH_3), 3.68 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.91 (s, 2H, CH_2), 6.55-6.67 (m, 2H, ArH), 6.69-6.80 (m, 2H, H3/5^e), 6.86-6.97 (m, 2H, H3/5^d), 7.02-7.13 (m, 3H, ArH), 7.14-7.45 (m, 8H, ArH)

^{13}C NMR (DMSO-d6, 50MHz): δ = 19.9 (q, Ar-CH_3), 48.9 (t, CH_2), 55.6 (q, OCH_3), 55.7 (q, OCH_3), 114.6 (d), 115.5 (d), 123.9 (s, C5^a), 126.8 (d), 127.6 (d, C2/6^b), 128.1 (s), 128.4 (d), 129.3 (d), 129.4 (d), 129.6 (s), 130.9 (d), 131.5 (d), 131.6 (d), 133.6 (d), 138.2 (s), 139.9 (s), 148.5 (s, C2^a), 159.9 (s), 161.5 (s)

HR-MS: $[M+H]^+$ m/z (predicted) = 461.2224, m/z (measured) = 461.2237, difference = 2.82 ppm

3.4.29. 1-Benzyl-4,5-di(3-nitrophenyl)-2-(2-tolyl)-1*H*-imidazole (32)



32

$C_{29}H_{22}N_4O_4$
M = 490.51

Method: Prepared according to general procedure C starting from compound **11** (100 mg, 0.25 mmol)

Boronic acid: 3-Nitrophenylboronic acid (144 mg, 0.86 mmol, 3.5 equiv.); 3 equiv. added at the beginning, 0.5 equiv. added after 4 hours;

Amount of solvent: 0.6 mL

Time: 7 hours

Purification: flash column chromatography (50 g silica gel, LP:EtOAc = 5:1)

Yield: 39% (48 mg, 0.10 mmol)

Appearance: yellow oil

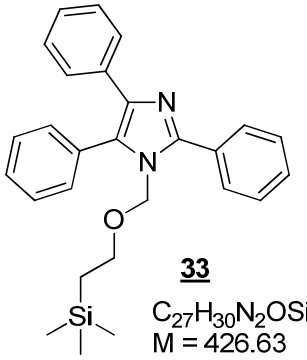
TLC: 0.33 (LP:EtOAc = 5:1)

^{1}H NMR (DMSO-d6, 200MHz): δ = 2.29 (s, 3H, Ar-CH_3), 5.01 (s, 2H, CH_2), 6.59-6.72 (m, 2H, ArH), 7.02-7.18 (m, 3H, ArH), 7.23-7.82 (m, 8H, ArH), 7.97-8.07 (m, 1H, ArH), 8.10-8.15 (m, 1H, ArH), 8.22-8.34 (m, 2H, ArH)

^{13}C NMR (DMSO-d6, 50MHz): δ = 20.0 (q, Ar-CH_3), 49.6 (t, CH_2), 122.5 (d), 122.6 (d), 125.1 (d), 126.9 (d), 127.1 (d), 127.7 (d), 128.8 (d), 129.6 (d), 130.6 (s), 130.8 (d), 131.4 (d), 131.68 (d), 131.74 (d), 131.8 (d), 133.0 (s), 133.8 (d), 136.6 (s), 137.4 (s), 138.5 (d), 139.9 (s), 149.7 (s, C2[a]), 150.0 (s), 150.6 (s)

HR-MS: $[M+H]^+$ m/z (predicted) = 491.1714, m/z (measured) = 491.1731, difference = 3.46 ppm

3.4.30. 1-((2-(Trimethylsilyl)ethoxy)methyl)-2,4,5-triphenyl-1*H*-imidazole (33)



33

$C_{27}H_{30}N_2OSi$
M = 426.63

Method: Prepared according to general procedure C starting from compound **13** (100 mg, 0.23 mmol)

Boronic acid: Phenylboronic acid (85 mg, 0.69 mmol, 3 equiv.)

Amount of solvent: 0.6 mL

Time: 4 hours

Purification: flash column chromatography (50 g silica gel, LP:EtOAc = 6:1)

Yield: 91% (90 mg, 0.21 mmol)

Appearance: colorless solid

M.p.: 67-70°C

TLC: 0.62 (LP:EtOAc = 5:1)

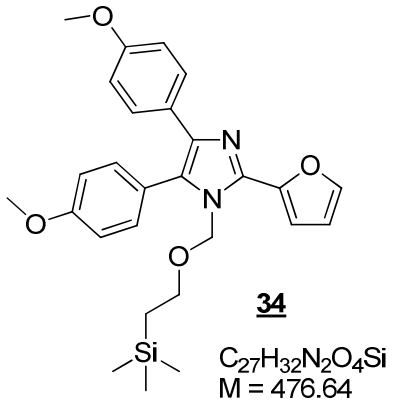
^{1}H NMR (DMSO-d6, 200MHz): δ = -0.10 (s, 9H, $SiCH_3$), 0.73 (t, ^3J = 8.2 Hz, 2H, $SiCH_2$), 3.20 (t, ^3J = 8.2 Hz, 2H, OCH_2), 5.06 (s, 2H, NCH_2O), 7.12-7.28 (m, 3H, ArH), 7.36-7.65 (m, 10H, ArH), 7.79-7.93 (m, 2H, ArH)

^{13}C NMR (DMSO-d6, 50MHz): δ = -1.4 (q, $SiCH_3$), 18.7 (t, $SiCH_2$), 67.0 (t, OCH_2), 74.3 (t, NCH_2O), 128.0 (d), 128.6 (d), 129.2 (d), 129.8 (d), 130.0 (d), 130.5 (d), 130.7 (d), 131.3 (s), 131.5 (s), 131.7 (s), 132.4 (d), 135.2 (s), 138.9 (s, C5[a]), 150.2 (s, C2[a])

LC-MS:

Main fragments: 427 (100, MH^+), 398 (15), 370 (25)

3.4.31. 2-(2-Furyl)-4,5-di-(4-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole (34)



34

$C_{27}H_{32}N_2O_4Si$
M = 476.64

Method: Prepared according to general procedure C starting from compound **17** (100 mg, 0.24 mmol).

Boronic acid: 4-Methoxyphenylboronic acid (108 mg, 0.71 mmol, 3 equiv.)

Amount of solvent: 0.6 mL

Time: 4 hours

Purification: flash column chromatography (50 g silica gel, LP:EtOAc = 3:1)

Yield: 67% (76 mg, 0.16 mmol)

Method: Prepared according to general procedure D starting from compound **5** (200 mg, 0.46 mmol).

Boronic acid 1: 2-Furylboronic acid (160 mg, 1.43 mmol, 1.1. equiv.)

Boronic acid 2: 4-Methoxyphenylboronic acid (210 mg, 1.38 mmol, 3 equiv.)

Amount of solvent: 1.2 mL

Time: 6 hours for the first coupling step, 2 hours for the second coupling step

Purification: flash column chromatography (100 g silica gel, LP:EtOAc = 5:1)

Yield: 25% (54 mg, 0.11 mmol)

Appearance: yellow brown oil

TLC: 0.25 (LP:EtOAc = 5:1)

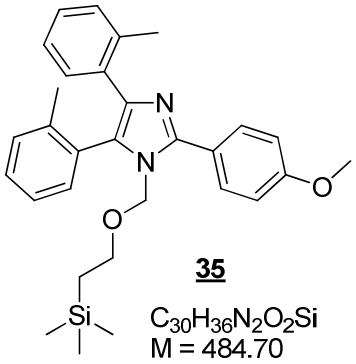
^{1}H NMR (MeOD-d4, 200MHz): δ = -0.07 (s, 9H, $SiCH_3$), 0.78 (t, ^3J = 8.1 Hz, 2H, $SiCH_2$), 3.35 (t, ^3J = 8.1 Hz, 2H, OCH_2), 3.75 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 5.34 (s, 2H, NCH_2O), 6.61-6.67 (m, 1H, H4^c), 6.74-6.83 (m, 2H, H3/5^e), 6.97-6.06 (m, 3H, ArH), 7.26-7.38 (m, 4H, ArH, H2/6$^{d/e}$), 7.70-7.75 (m, 1H, H5^c)

^{13}C NMR (MeOD-d4, 50MHz): δ = -1.4 (q, $SiCH_3$), 18.6 (t, $SiCH_2$), 55.6 (q, OCH_3), 55.8 (q, OCH_3), 67.1 (t, OCH_2), 74.1 (t, NCH_2O), 112.2 (d), 112.7 (d), 114.6 (d), 115.5 (d), 122.9 (s,

C4[a]), 127.5 (s), 129.8 (d), 130.7 (s), 133.9 (d), 139.0 (s, C5[a]), 140.6 (s, C2[a]), 144.8 (s, C2[c]), 145.8 (d, C5[c]), 160.2 (s), 161.7 (s)

HR-MS: $[M+H]^+$ m/z (predicted) = 477.2204, m/z (measured) = 477.2223, difference = 3.98 ppm

3.4.32. 2-(4-Methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-4,5-di(2-tolyl)-1*H*-imidazole (35)



35

$C_{30}H_{36}N_2O_2Si$
M = 484.70

Method: Prepared according to general procedure C starting from compound **14** (100 mg, 0.22 mmol)

Boronic acid: 2-Tolylboronic acid (147 mg, 1.08 mmol, 5 equiv.); 3 equiv. added at the beginning, 2 equiv. added after 4 hours;

Amount of solvent: 0.6 mL

Time: 6 hours

Purification: flash column chromatography (50 g silica gel, LP:EtOAc = 5:1), followed by preparative HPLC

Yield: 11% (28 mg, 0.04 mmol)

Appearance: yellow brown oil

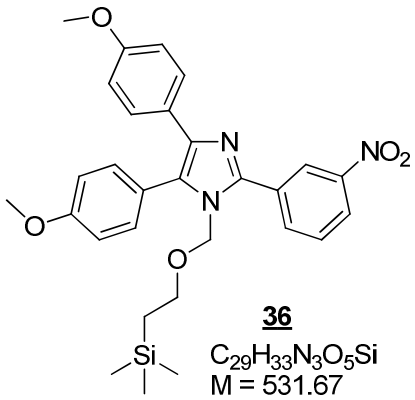
TLC: 0.52 (LP:EtOAc = 5:1)

^{1}H NMR (MeOD-d4, 200MHz): δ = -0.07 (s, 9H, $SiCH_3$), 0.76 (t, ^3J = 8.2 Hz, 2H, $SiCH_2$), 1.99 (s, 3H, Ar-CH_3), 2.28 (s, 3H, Ar-CH_3), 3.20 (t, ^3J = 8.2 Hz, 2H, OCH_2), 3.86 (s, 3H, OCH_3), 5.00 (d, ^3J = 10.5 Hz, 1H, NCH_2O), 5.19 (d, ^3J = 10.5 Hz, 1H, CH_2), 6.93-7.45 (m, 10H, ArH), 7.71-7.83 (m, 2H, H2/6[c])

^{13}C NMR (MeOD-d4, 50MHz): δ = -1.4 (q, $SiCH_3$), 18.7 (t, $SiCH_2$), 20.2 (q, Ar-CH_3), 20.7 (q, Ar-CH_3), 55.9 (q, OCH_3), 67.0 (t, OCH_2), 74.6 (t, NCH_2O), 115.2 (d, C3/5[c]), 123.6 (s, C4[a]), 126.3 (d), 126.8 (d), 128.8 (d), 130.2 (d), 130.5 (s), 131.2 (s), 131.3 (d), 131.4 (d), 131.6 (d), 131.8 (d, C2/6[c]), 133.3 (d), 135.1 (s), 138.3 (s), 139.8 (s), 140.0 (s), 150.0 (s, C2[a]), 162.2 (s, C4[c])

HR-MS: $[M+H]^+$ m/z (predicted) = 485.2619, m/z (measured) = 485.2641, difference = 4.53 ppm

3.4.33. 4,5-Di(4-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-2-(3-nitrophenyl)-1*H*-imidazole (<u>36</u>)



<u>36</u>

$C_{29}H_{33}N_3O_5Si$

M = 531.67

Method: Prepared according to general procedure C starting from compound **15** (50 mg, 0.11 mmol).

Boronic acid: 4-Methoxyphenylboronic acid (48 mg, 0.31 mmol, 3 equiv.)

Amount of solvent: 0.3 mL

Time: 4 hours

Purification: flash column chromatography (50 g silica gel, LP:EtOAc = 5:1)

Yield: 53% (30 mg, 0.07 mmol)

Method: Prepared according to general procedure D starting from compound **5** (100 mg, 0.23 mmol).

Boronic acid 1: 3-Nitrophenylboronic acid (42 mg, 0.25 mmol, 1.1 equiv.)

Boronic acid 2: 4-Methoxyphenylboronic acid (105 mg, 0.69 mmol, 3 equiv.)

Amount of solvent: 0.6 mL

Time: 6 hours for the first coupling step, 2 hours for the second coupling step

Purification: flash column chromatography (50 g silica gel, LP:EtOAc = 4:1)

Yield: 58% (71 mg, 0.13 mmol)

Appearance: yellow brown oil

TLC: 0.39 (LP:EtOAc = 5:1)

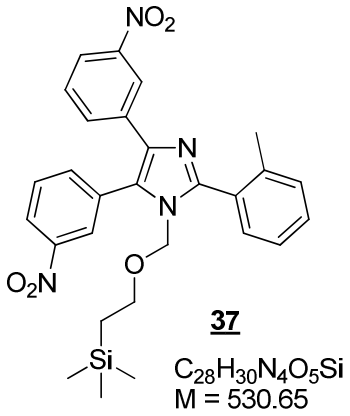
^{1}H NMR (MeOD-d4, 200MHz): δ = -0.01 (s, 9H, $SiCH_3$), 0.96 (t, ^3J = 8.3 Hz, 2H, $SiCH_2$), 3.41 (t, ^3J = 8.3 Hz, 2H, OCH_2), 3.74 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 5.01 (s, 2H, NCH_2O), 6.74 (d, ^3J = 8.6 Hz, 2H, H2/6^e), 7.01 (d, ^3J = 8.6 Hz, 2H, ArH, H2/6^d), 7.28-7.40

(m, 4H, H2/6$^{d/e}$), 7.76 (t, ^{3}J = 8.1 Hz, 1H, H5^{c}), 8.20-8.39 (m, 2H, H4/6^{c}), 8.74-8.81 (m, 1H, H2^{c})

^{13}C NMR (MeOD-d4, 50MHz): δ = -1.4 (q, $SiCH_3$), 18.8 (t, $SiCH_2$), 55.6 (q, OCH_3), 55.8 (q, OCH_3), 67.0 (t, OCH_2), 74.2 (t, NCH_2O), 114.7 (d), 115.5 (d), 123.0 (s, C4^{a}), 124.4 (d, C2^{c}), 124.9 (d, C4^{c}), 127.5 (s), 129.7 (d), 131.2 (d, C5^{c}), 131.7 (s), 132.9 (s), 133.6 (d), 136.0 (d, C6^{c}), 139.1 (s, C5^{a}), 147.1 (s, C2^{a}), 149.8 (s, C2^{c}), 160.3 (s), 161.8 (s)

HR-MS: $[M+H]^+$ m/z (predicted) = 532.2262, m/z (measured) = 532.2284, difference = 4.13 ppm

3.4.34. 1-((2-(Trimethylsilyl)ethoxy)methyl)-4,5-di(3-nitrophenyl)-2-(2-tolyl)-1*H*-imidazole (37)



37

$C_{28}H_{30}N_4O_5Si$
M = 530.65

Method: Prepared according to general procedure C starting from compound **16** (50 mg, 0.11 mmol).

Boronic acid: 3-Nitrophenylboronic acid (112 mg, 0.67 mmol, 6 equiv.); 3 equiv. added at the beginning, 3 equiv. added after 4 hours;

Amount of solvent: 0.3 mL

Time: 5 hours

Purification: flash column chromatography (50 g silica gel, LP:EtOAc = 7:1)

Yield: 74% (44 mg, 0.08 mmol)

Appearance: yellow oil

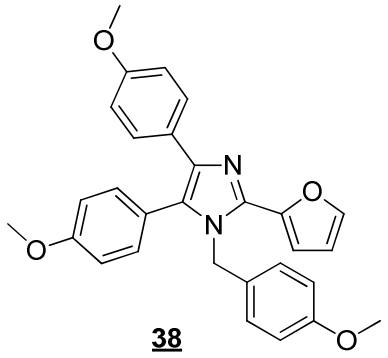
TLC: 0.43 (LP:EtOAc = 5:1)

^{1}H NMR (MeOD-d4, 200MHz): δ = -0.08 (s, 9H, $SiCH_3$), 0.78 (t, ^{3}J = 8.3 Hz, 2H, $SiCH_2$), 2.38 (s, 3H, Ar-CH_3), 3.25 (t, ^{3}J = 8.3 Hz, 2H, OCH_2), 5.01 (s, 2H, NCH_2O), 7.27-7.59 (m, 5H, ArH), 7.70-7.82 (m, 2H, ArH), 7.85-7.94 (m, 1H, ArH), 7.99-8.12 (m, 1H, ArH), 8.21-8.31 (m, 1H, ArH), 8.32-8.43 (m, 1H, ArH), 8.44-8.53 (m, 1H, ArH)

^{13}C NMR (MeOD-d4, 50MHz): δ = -1.5 (q, $SiCH_3$), 18.6 (t, $SiCH_2$), 20.2 (q, Ar-CH_3), 67.2 (t, OCH_2), 74.5 (t, NCH_2O), 122.9 (d), 125.1 (d), 126.9 (d), 127.0 (d), 129.6 (s, C4[a]), 130.2 (d), 130.8 (d), 131.5 (d), 131.7 (d), 131.8 (d), 132.6 (d), 134.2 (d), 136.5 (s), 137.5 (s), 138.5 (d), 140.1 (s, C5[a]), 149.8 (s, C2[a]), 150.1 (s), 150.7 (s)

HR-MS: $[M+H]^+$ m/z (predicted) = 531.2058, m/z (measured) = 531.2071, difference = 2.45 ppm

3.4.35. 2-(2-Furyl)-4,5-di(4-methoxyphenyl)-1-(4-methoxybenzyl)-1*H*-imidazole (**38**)



38

$C_{29}H_{26}N_2O_4$

M = 466.53

Method: Prepared according to general procedure C starting from compound **22** (40 mg, 0.11 mmol).

Boronic acid: 4-Methoxyphenylboronic acid (88 mg, 0.58 mmol, 6 equiv.); 3 equiv. added at the beginning, 3 equiv. added after 6 hours;

Amount of solvent: 0.3 mL

Time: 7 hours

Purification: flash column chromatography (25 g silica gel, LP:EtOAc = 2:1)

Yield: 53% (24 mg, 0.05 mmol)

Appearance: yellow oil

TLC: 0.19 (LP:EtOAc = 5:1)

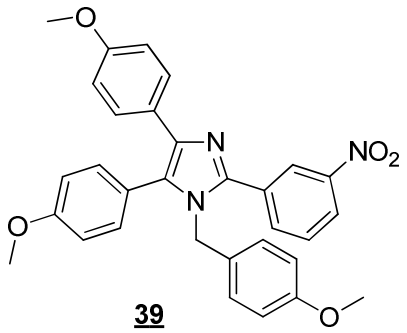
^{1}H NMR (MeOD-d4, 200MHz): δ = 3.71 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 5.22 (s, 2H, CH_2), 6.50-6.60 (m, 1H, H4[c]), 6.69-6.83 (m, 7H, ArH), 6.92 (d, ^3J = 8.7 Hz, 2H, H3/5[d]), 7.11 (d, ^3J = 8.7 Hz, 2H, H2/6[e]), 7.34 (d, ^3J = 8.7 Hz, 2H, H2/6[d]), 7.58-7.62 (m, 1H, H5[c])

^{13}C NMR (MeOD-d4, 50MHz): δ = 48.8 (t, CH_2), 55.6 (q, OCH_3), 55.8 (q, OCH_3), 111.6 (d), 112.6 (d), 114.6 (d, C3/5[b]), 115.0 (d), 115.4 (d), 123.2 (s, C4[a]), 127.8 (s), 128.4 (d,

C2/6[b]), 129.6 (d), 130.5 (s), 133.5 (d), 133.6 (d), 144.6 (d, C2[a]), 146.0 (s, C2[c]), 160.2 (s), 160.5 (s), 161.7 (s)

HR-MS: $[M+H]^+$ m/z (predicted) = 467.1965, m/z (measured) = 467.1977, difference = 2.57 ppm

3.4.36. 4,5-Di(4-methoxyphenyl)-1-(4-methoxybenzyl)-2-(3-nitrophenyl)-1*H*-imidazole (39)



39

$C_{31}H_{27}N_3O_5$

M = 521.56

Method: Prepared according to general procedure C starting from compound **20** (130 mg, 0.28 mmol).

Boronic acid: 4-Methoxyphenylboronic acid (127 mg, 0.84 mmol, 3 equiv.)

Amount of solvent: 0.6 mL

Time: 3.5 hours

Purification: flash column chromatography (50 g silica gel, LP:EtOAc = 5:1)

Yield: 43% (62 mg, 0.12 mmol)

Method: Prepared according to general procedure D starting from compound **7** (100 mg, 0.24 mmol).

Boronic acid 1: 3-Nitrophenylboronic acid (43 mg, 0.26 mmol, 1.1 equiv.)

Boronic acid 2: 4-Methoxyphenylboronic acid (107 mg, 0.71 mmol, 3 equiv.)

Amount of solvent: 0.6 mL

Time: 7 hours for the first coupling step, 3 hours for the second coupling step

Purification: flash column chromatography (50 g silica gel, LP:EtOAc = 3:1)

Yield: 48% (58 mg, 0.11 mmol)

Appearance: yellow oil

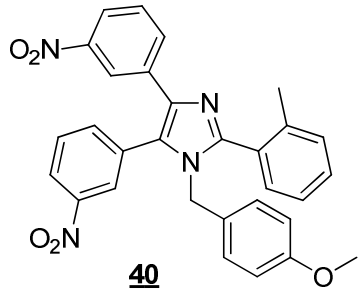
TLC: 0.18 (LP:EtOAc = 5:1)

^{1}H NMR (MeOD-d4, 200MHz): δ = 3.68 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 5.08 (s, 2H, CH_2), 6.63-6.84 (m, 6H, ArH), 6.91 (d, ^{3}J = 8.7 Hz, 2H, ArH), 7.18 (d, 3J = 8.7 Hz, 2H, H2/6^e), 7.38 (d, 3J = 8.8 Hz, 2H, H2/6^d), 7.64 (t, ^{3}J = 8.0 Hz, 1H, H5^c), 7.94-8.04 (m, 1H, H6^c), 8.18-8.32 (m, 1H, H4^c), 8.43 (t, ^{3}J = 1.8 Hz, 1H, H2^c)

^{13}C NMR (MeOD-d4, 50MHz): δ = 48.8 (t, CH_2), 55.6 (q, OCH_3), 55.7 (q, OCH_3), 55.8 (q, OCH_3), 114.6 (d, C3/5^b), 115.2 (d), 115.5 (d), 123.4 (s, C4^a), 124.7 (d, C2^c), 124.8 (d, C4^c), 127.8 (s), 128.3 (d, C2/6^b), 129.5 (d), 130.2 (s), 131.1 (d, C5^c), 131.8 (s), 133.5 (s), 133.6 (d), 135.9 (d, C6^c), 139.5 (s), 146.6 (s, C2^a), 149.6 (s, C3^c), 160.2 (s), 160.5 (s), 161.7 (s)

HR-MS: $[M+H]^+$ m/z (predicted) = 522.2023, m/z (measured) = 522.2043, difference = 3.83 ppm

3.4.37. 1-(4-Methoxybenzyl)-4,5-di(3-nitrophenyl)-2-(2-tolyl)-1*H*-imidazole (40)



40

$C_{30}H_{24}N_4O_5$

M = 520.54

Method: Prepared according to general procedure C starting from compound **21** (30 mg, 0.07 mmol).

Boronic acid: 3-Nitrophenylboronic acid (35 mg, 0.21 mmol, 3 equiv.)

Amount of solvent: 0.3 mL

Time: 5 hours

Purification: preparative TLC (LP:EtOAc = 3:1)

Yield: 92% (33 mg, 0.06 mmol)

Appearance: brown oil

TLC: 0.23 (LP:EtOAc = 5:1)

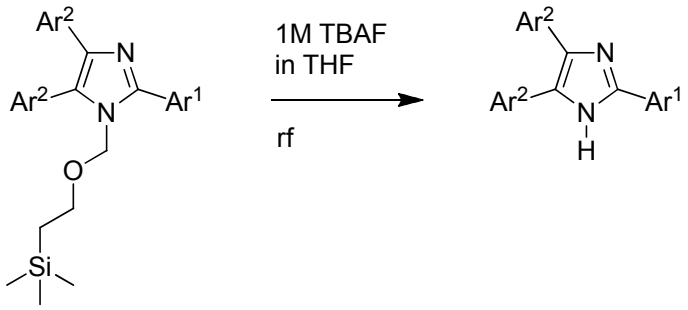
^{1}H NMR (DMSO-d6, 400MHz): δ = 2.27 (s, 3H, Ar-CH_3), 3.62 (s, 3H, OCH_3), 4.89 (s, 2H, CH_2), 6.51 (d, ^3J = 8.5 Hz, 2H, H3/5^b), 6.66 (d, ^3J = 8.5 Hz, 2H, H4/6^b), 7.26-7.57 (m, 5H, ArH), 7.65-7.85 (m, 3H, ArH), 7.97-8.05 (m, 1H, ArH), 8.16 (s, 1H, ArH), 8.27-8.37 (m, 2H, ArH)

^{13}C NMR (DMSO-d6, 100MHz): δ = 19.5 (q, $ArCH_3$), 47.4 (t, CH_2), 55.0 (q, OCH_3), 113.8 (d, C3/5^b), 120.2 (d), 121.0 (d), 123.9 (d), 125.4 (d), 125.8 (d), 127.6 (d, C2/6^b), 127.8 (s),

128.2 (s), 129.6 (d), 129.8 (s), 130.0 (d), 130.3 (d), 130.5 (d), 130.8 (d), 131.7 (s), 131.8 (d), 135.0 (s), 135.8 (s), 137.5 (d), 138.0 (s, C2[a]), 148.0 (s), 148.1 (s), 158.4 (s, C4[b])

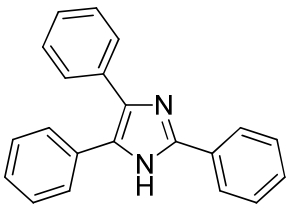
3.5. Deprotection of Triarylated Imidazoles

3.5.1. General Procedure E



1-((2-(Trimethylsilyl)ethoxy)methyl)-2,4,5-triaryl-1*H*-imidazole (1 equiv.) was dissolved in 5 equiv. of 1M KO^{t}Bu in THF in a 4 mL vial with stirring bar and a screw cap. The reaction was heated to 80°C and monitored by TLC (LP:EtOAc = 3:1). When the consumption of starting material was completed, the reaction solution was poured into water and extracted with DCM. The combined organic layers were washed with water and dried over sodium sulfate. The solvent was evaporated and the desired product was obtained by preparative TLC.

3.5.2. 2,4,5-Triphenyl-1*H*-imidazole (41)



41

$C_{21}H_{16}N_2$

M = 296.37

Method: Prepared according to general procedure E starting from compound **33** (40 mg, 0.09 mmol).

KO^{t}Bu: 0.47 mL 1M solution in THF (0.47 mmol)

Time: 3 hours

Purification: preparative TLC (LP:EtOAc = 3:1)

Yield: 41% (11 mg, 0.04 mmol)

Appearance: colorless solid

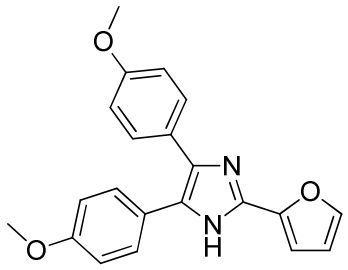
M.p.: 270-272°C (lit.[53]: 275°C)

TLC: 0.39 (LP:EtOAc = 3:1)

^{1}H NMR (DMSO-d6, 200MHz): δ = 7.14-7.60 (m, 13H, ArH), 8.01-8.13 (m, 2H, ArH), 12.69 (s, 1H, NH)

^{13}C NMR (DMSO-d6, 50MHz): δ = 125.2 (d), 126.5 (d), 127.1 (d), 127.8 (d), 128.2 (d), 128.3 (d), 128.5 (d), 128.69 (d), 128.71 (d), 130.3 (s), 131.1 (s), 135.2 (s), 137.1 (s), 145.5 (s, C2[a])

3.5.3. 2-Furyl-4,5-di(4-methoxyphenyl)-1*H*-imidazole (42)[54]



42

$C_{21}H_{18}N_2O_3$

M = 346.38

Method: Prepared according to general procedure E starting from compound **34** (8 mg, 0.02 mmol).

KO^{t}Bu: 0.10 mL 1M solution in THF (0.10 mmol)

Time: 4 hours

Purification: preparative TLC (LP:EtOAc = 1:1)

Yield: 40% (5 mg, 0.01 mmol)

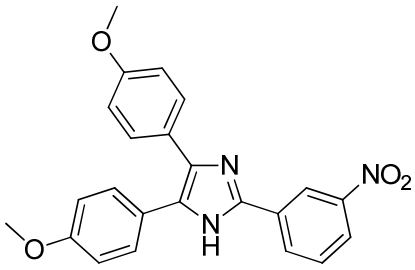
Appearance: pale yellow oil

TLC: 0.09 (LP:EtOAc = 1:1)

^{1}H NMR (DMSO-d6, 400MHz): δ = 3.74 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 6.61-6.64 (m, 1H, H4[c]), 6.87 (d, ^{3}J = 8.7Hz, 2H), 6.92 (d, ^{3}J = 3.4Hz, 1H, H3[c]), 6.99 (d, 3J = 8.7Hz, 2H), 7.38 (d, ^{3}J = 8.7Hz, 2H), 7.42 (d, ^{3}J = 8.7Hz, 2H), 7.76-7.79 (m, 1H, H5[c])

^{13}C NMR (DMSO-d6, 100MHz): δ = 55.5 (q, OCH_3), 55.6 (q, OCH_3), 107.5 (d), 112.3 (d), 114.1 (d), 114.6 (d), 123.7 (s, C4[a]), 126.9 (s), 128.1 (s), 128.6 (d), 130.1 (d), 136.7 (s), 138.4 (s), 143.3 (d, C5[c]), 146.3 (s, C2[c]), 158.4 (s), 159.2 (s)

3.5.4. 4,5-di(4-methoxyphenyl)-2-(3-nitrophenyl)-1*H*-imidazole (43)[55]



43

$C_{23}H_{19}N_3O_4$

M = 401.41

Method: Prepared according to general procedure E starting from compound **36** (36 mg, 0.07 mmol)

KO^{t}Bu: 0.40 mL 1M solution in THF (0.40 mmol)

Time: 4 hours

Purification: preparative TLC (LP:EtOAc = 1:1)

Yield: 56% (15 mg, 0.04 mmol)

Appearance: orange oil

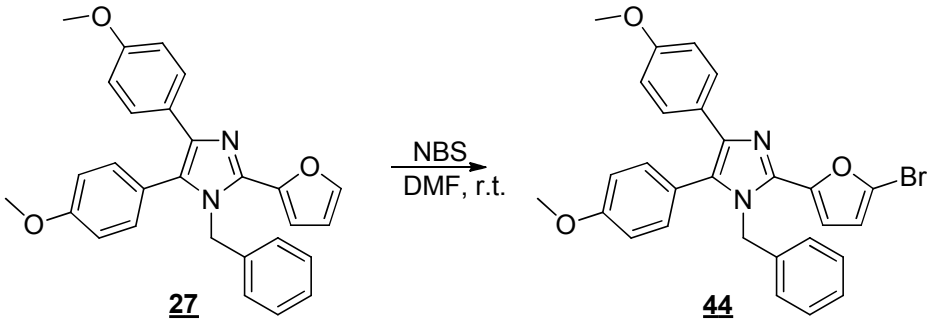
TLC: 0.209 (LP:EtOAc = 1:1)

^{1}H NMR (DMSO-d6, 400MHz): δ = 3.75 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 6.69 (d, ^{3}J = 8.7Hz, 2H), 7.02 (d, ^{3}J = 8.7Hz, 2H), 7.33-7.58 (m, 4H, H2/6$^{d/e}$), 7.76 (t, ^{3}J = 8.0Hz, 1H, H5^c), 8.19 (dd, ^{3}J = 8.0Hz, ^{4}J = 2.0Hz, 1H, H6^c), 8.48 (d, ^{3}J = 7.9Hz, 1H, H4^c), 8.89-8.97 (m, 1H, H2^c)

^{13}C NMR (DMSO-d6, 100MHz): δ = 55.0 (q, OCH_3), 55.2 (q, OCH_3), 113.7 (d), 114.2 (d), 119.2 (d, C2^c), 122.3 (d, C4^c), 123.1 (s, C4^a), 127.4 (s), 128.3 (d), 129.7 (d), 130.4 (d, C5^c), 131.0 (d, C6^c), 132.0 (s), 137.0 (s), 142.7 (s, C5^a), 148.4 (s, C2^a), 158.1 (s), 159.0 (s)

3.6. Synthesis of Neurodazine

3.6.1. 1-Benzyl-2-(5-bromofuran-2-yl)-4,5-di(4-methoxyphenyl)-1*H*-imidazole (44)



27
$C_{28}H_{24}N_2O_3$
M = 436.50

44
$C_{28}H_{23}BrN_2O_3$
M = 515.40

1-Benzyl-2-(2-furyl)-4,5-di(4-methoxyphenyl)-imidazole (110 mg, 0.25 mmol, 1 equiv.) was dissolved in DMF (6 mL) in a 8 mL vial with a magnetic stirring bar and a screw cap. The solution was cooled to 0°C. N-Bromosuccinimide (49 mg, 0.28 mmol, 1.1 equiv.) was added in portions and the reaction was warmed to room temperature. The reaction was stirred for 4 hours at room temperature. The reaction solution was poured into saturated aq. NH_4Cl solution (10 mL) and was extracted three times with ethyl acetate. The combined organic phases were washed with water and dried over sodium sulfate. The solvent was evaporated and the pure product was obtain by flash column chromatography (130 g silica gel, LP:EtOAc = 3:1).

Yield: 73% (95 mg, 0.18 mmol)

Appearance: yellow solid

M.p.: 95-99°C

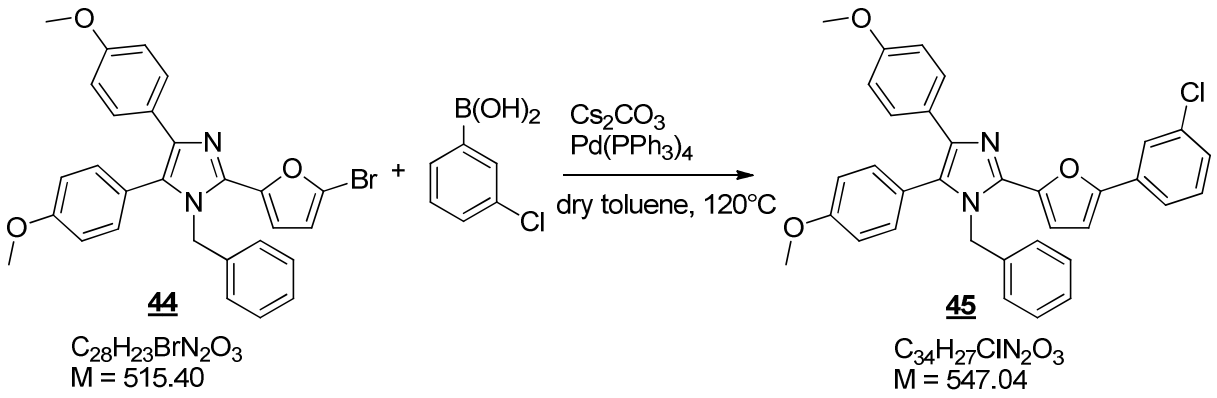
TLC: 0.26 (LP:EtOAc = 3:1)

^{1}H NMR (DMSO-d6, 200MHz): δ = 3.70 (s, 3H, OCH_3), 3.77 (s, 3H; OCH_3), 5.18 (s, 2H, CH_2), 6.60-7.05 (m, 8H, ArH), 7.13-7.48 (m, 7H, ArH)

^{13}C NMR (DMSO-d6, 50MHz): δ = 47.4 (t, CH_2), 55.0 (q, OCH_3), 55.1 (q, OCH_3), 111.9 (d, C4^c), 113.6 (d), 114.6 (d), 121.6 (s), 122.0 (s), 125.6 (d, C2/6^b), 126.7 (s), 127.3 (d, C3^c), 127.4 (d, C3/5^b), 128.6 (d), 129.4 (s), 132.2 (d), 136.9 (s), 137.1 (s), 146.8 (s, C2^c), 158.0 (s), 159.7 (s)

HR-MS: $[M+H]^+$ m/z (predicted) = 515.0965, m/z (measured) = 515.0974, difference = 1.75 ppm

3.6.2. 1-Benzyl-2-(5-(3-chlorophenyl)furan-2-yl)-4,5-di(4-methoxyphenyl)-1*H*-imidazole (45)



1-Benzyl-2-(5-bromofuran-2-yl)-4,5-di(4-methoxyphenyl)-1H-imidazole (60 mg, 0.12 mmol, 1 equiv.), 3-chlorphenylboronic acid (20 mg, 0.13 mmol, 1.1 equiv.), Cs_2CO_3 (76 mg, 0.23 mmol, 2 equiv.), $Pd(PPh_3)_4$ (6.7 mg, 5mol%), and dry toluene (1.5 mL) were placed in a 4 ml vial with a magnetic stirring bar and a screw cap with septum. The solution was purged with argon for 5 minutes. Then the septum screw cap was exchanged for a closed cap under argon flow, since caps with septum did not stand the pressure that is built up during the reaction. The mixture was heated to 120°C in the heating block. The reaction was monitored by TLC (LP:EtOAc = 3:1) and stopped after 4 hours when reaction control showed complete consumption of the starting material. The reaction mixture was cooled to room temperature, filtered through a pad of Celite® and the solvent was evaporated. The residue was diluted with water and extracted with DCM. The combined organic layers were washed with water and dried over sodium sulfate. The solvent was evaporated and the desired product was obtained by flash column chromatography (50 g silica gel, LP:EtOAC = 3:1).

Yield: 69% (44 mg, 0.08 mmol)

Appearance: yellow solid

M.p.: 67-69°C

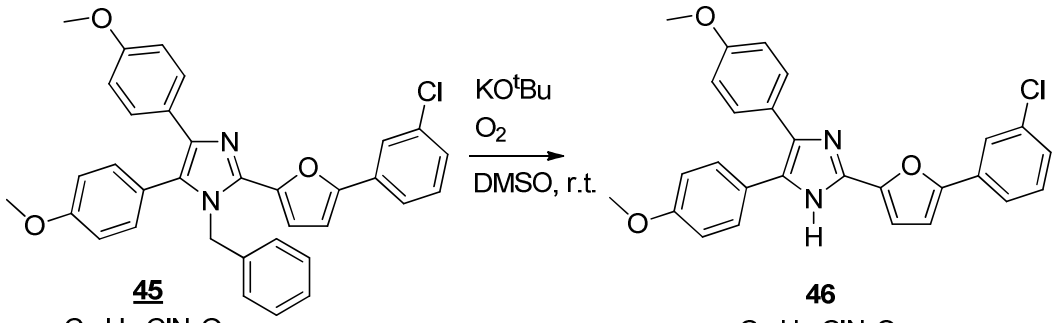
TLC: 0.19 (LP:EtOAc = 3:1)

^{1}H NMR (DMSO-d6, 200MHz): δ = 3.70 (s, 3H, OCH_3), 3.77 (s, 3H; OCH_3), 5.33 (s, 2H, CH_2), 6.76-7.05 (m, 8H, ArH), 7.13-7.53 (m, 11H, ArH)

^{13}C NMR (DMSO-d6, 50MHz): δ = 47.8 (t, CH_2), 55.0 (q, OCH_3), 55.2 (q, OCH_3), 109.2 (d), 111.8 (d), 113.6 (d), 114.6 (d), 121.7 (s, C4[a]), 122.0 (d), 122.8 (d), 125.2 (d), 126.8 (s), 127.1 (d), 127.4 (d), 128.7 (d), 129.4 (s), 130.7 (d), 131.5 (s), 132.2 (d), 133.8 (s, C3[f]), 137.4 (s), 137.6 (s), 137.9 (s), 145.4 (s, C2[c]), 151.4 (s, C5[c]), 158.0 (s), 159.7 (s)

HR-MS: $[M+H]^+$ m/z (predicted) = 547.1783, m/z (measured) = 547.1809, difference = 4.75 ppm

3.6.3. 2-(5-(3-Chlorophenyl)furan-2-yl)-4,5-di(4-methoxyphenyl)-1*H*-imidazole (46)[56]



45
$C_{34}H_{27}ClN_2O_3$
M = 547.04

46
$C_{27}H_{21}ClN_2O_3$
M = 456.92

1-Benzyl-2-(5-(3-chlorophenyl)furan-2-yl)-4,5-di(4-methoxyphenyl)-1H-imidazole (20 mg, 0.037 mmol, 1 equiv.) was dissolved in DMSO (0.2 mL) in a 4 mL vial with stir bar and a screw cap with septum. A 1M potassium *tert*-butoxide solution in THF (0.26 mL, 0.26 mmol) was added with a syringe. The solution changed from yellow to orange immediately. Oxygen was bubbled through the solution for 15 minutes. The reaction was stirred at room temperature for 1 hour. The solution was poured into saturated aq. NH_4Cl (1 mL) and extracted three times with ethyl acetate. The combined organic layers were washed with water and dried over sodium sulfate. The solvent was evaporated and the desired product was obtained by preparative TLC (LP:EtOAc = 1:1).

Yield: 51% (8.6 mg, 0.018 mmol)

Appearance: yellow oil

TLC: 0.17 (LP:EtOAc = 2:1)

^{1}H NMR (DMSO-d6, 400MHz): δ = 3.75 (s, 3H, OCH_3), 3.81 (s, 3H; OCH_3), 6.88 (d, ^3J = 8.9 Hz, 2H, ArH), 7.00-7.07 (m, 3H, ArH), 7.25 (d, ^3J = 3.7 Hz, 1H, ArH), 7.35-7.52 (m, 6H, ArH), 7.85 (d, ^3J = 8.2 Hz, 1H, ArH), 7.98-8.01 (m, 1H, ArH)

^{13}C NMR (DMSO-d6, 100MHz): δ = 55.5 (q, OCH_3), 55.7 (q, OCH_3), 109.4 (d), 109.9 (d), 114.1 (d), 114.6 (d), 122.7 (d), 123.5 (d), 123.6 (s), 127.3 (s), 127.7 (d), 127.9 (s), 128.6 (d), 130.4 (d), 131.2 (d), 132.6 (s), 134.3 (s, C3^f), 137.2 (s), 137.9 (s), 146.4 (s, C2^c), 151.3 (s, C5^c), 158.5 (s), 159.4 (s)

3.7. References

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