Multiple Functionalizations of Selected *N*-Heterocycles By Palladium-Catalyzed Cross-Coupling Reactions

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Abstract

The presented dissertation deals with the multiple functionalization of several *N*-heterocycles via palladium-catalyzed cross-coupling reactions. In this regard, different polyalkynylated, polyalkenylated and polyarylated pyridine, pyrazine and naphthyridine derivatives were synthesized. The exploration of site-selectivity of the reactions of initial halogenated pyridines was of particular interest. Absorption and emission spectroscopy was used to analyze the photophysical properties of the polyalkynylated compounds. Further, the electrochemical investigation of polyalkynylated pyrazines was carried out to validate the results gained by photophysical studies.

In addition, various *N*-phenyl diarylpyrrols were synthesized by “ligand-free” palladium-catalyzed C–H activation. The role of the reaction medium was investigated and a probable mechanism was proposed.

Zusammenfassung

Die vorliegende Dissertation beschäftigt sich mit der mehrfachen Funktionalisierung verschiedener *N*-Heterozyklen mittels Palldadium katalysierter Kreuzkupplungsreaktionen. In diesem Zusammenhang wurden verschiedene polyalkinylierte, polyalkenylierte und polyarylierte Pyridin-, Pyrazin- und Naphthyridinderivate hergestellt. Die Untersuchung der Regioselektivität der Reaktionen von halogenierten Pyridinen war dabei von besonderem Interesse. Absorptions- und Emissionsspektroskopie wurde zur Analyse der optischen Eigenschaften der synthetisierten polyalkinylierten Verbindungen eingesetzt. Außerdem wurden polyalkinylierte Pyrazine mittels elektrochemischer Methoden untersucht, um die Ergebnisse der photophysikalischen Messungen zu bestätigen.

Des Weiteren wurden verschiedene *N*-Phenyl-diarylpyrrole durch „ligandenfreie“ Palladium katalysierte C–H Aktivierung synthetisiert. Die Rolle des Reaktionsmediums wurde studiert und ein möglicher Mechanismus postuliert.

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List of Abbreviations

[M^+]	molecular ion peak
[Pd]	palladium complex
abs	absorbtion
AIE	aggreagation-induced emmision
Ac	acetyl
Ad	adamantyl
aq.	aqueous
Ar	aryl
ATPase	adenosinetriphosphatase
Boc	*tert*-butyloxycarbonyl
Bu	butyl
cata*CX*ium A	di(1-adamantyl)-*n*-butylphosphine
cf.	confer (compare)
C_2MIM	1-ethyl-3-methylimidazolium
COSY	correlation spectroscopy
COX	cyclooxygenase
Cy	cyclohexyl
dba	dibenzylideneacetone
DCB	dichlorobenzene
DCM	dichloromethane
DMAc	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1’-bis(diphenylphosphino)ferrocene
DSC	differential scanning calorimetry
E	peak potential
e.g.	exempli gratia (for example)

EA	electron affinity
EI	electron ionization
equiv.	equivalent
ER	estrogen receptor
ESI	electrospray ionization
Et	ethyl
eV	electron volt
GC	gas chromatography
GP	general procedure
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectroscopy
i.e.	id est (that is)
IP	ionization potential
i-Pr	isopropyl
IR	infrared spectroscopy
J	coupling constant
L	ligand
LCD	liquid crystal display
LED	light-emitting diode
LUMO	lowest unoccupied molecular orbital
m/z	mass-to-charge ratio
Me	methyl
mp	melting point
MS	mass spectrometry
NHE	normal hydrogen electrode
NLO	nonlinear optical materials
NMP	*N*-methyl-2-pyrrolidone
NOESY	nuclear Overhauser enhancement spectroscopy
OAc	acetate
OAE	oligo(aryleneethynylene)
ORTEP	Oak Ridge thermal-ellipsoid plot

OTf	triflate (trifluoromethanesulfonate)
PAE	poly(aryleneethynylene)
PEG	polyethylene glycol
Ph	phenyl
Piv	pivalate
PLED	polymer light-emitting diode
POM	polarized optical microscopy
PPh_3	triphenylphosphine
Pr	propyl
QPhos	pentaphenyl-1'-(di-*tert*-butylphosphino)ferrocene
R	organic rest
R-M	organometallic compound
R-X	organohalide
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TBA	tetrabutylammonium
t-Bu	tertiary butyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
X	halide
XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
δ	chemical shift
ε	extinction coefficient
ϕ	fluorescence quantum yield
λ	wavelength

1. General Introduction

1.1 Background

Application of catalysis as a technique has revolutionized the field of organic chemistry giving rise to the science not only in academic but also in industrial level.

The concept of catalysis is known to mankind for many centuries, and a good example of that is the production of alcoholic beverages with yeast. The term itself was first introduced only in 1836 by Berzelius who referred to catalysts as substances being able to ʻʻ*awake affinities that are asleep at this temperature by their mere presence and not by their own affinity*ʼʼ.[1] Three decades after, Ostwald gave the well-known definition of a catalyst as a ʻʻ*substance that increases the rate of the chemical reaction without itself being consumed*ʼʼ.[2] Since then the field of catalysis had undergone an incredible development with many transformations being discovered.

The history of catalysis development can be conditionally represented by four milestone phases during each significant contributions to the specific fields of chemical industry were made (Figure 1).[3]

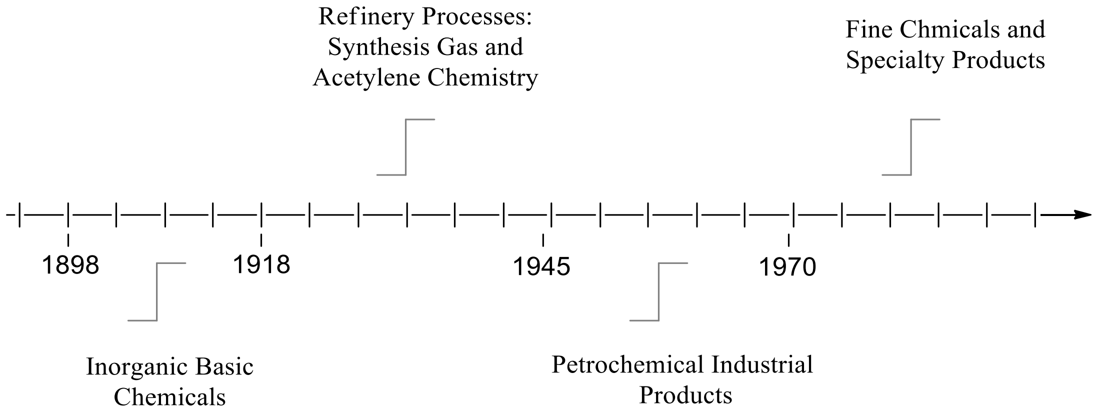


Figure 1. Historical timeline of catalysis development in chemical manufacturing.

In recent 50 years, thirteen scientists were awarded five Nobel Prizes collectively for their outstanding research on homogeneous transition metal catalysis only. In particular, the awards were granted for the distinguished contributions in polymerization (Ziegler and Natta 1963), sandwich compounds (Wilkinson and Fischer 1973), asymmetric catalysis (Knowles, Noyori and Sharpless 2001), metathesis (Chauvin, Grubbs and Schrock 2005), and cross-coupling reactions (Heck, Negishi and Suzuki 2010).[4]

Nowadays, many industrial productions including chemicals, petroleum, agriculture, pharmaceuticals, and electronics strongly depend on catalysis. In fact, the use of it is so demanded that at least 80% of all chemical processes at some stage involve catalysts.[3]

The use of catalytic processes gives several advantages among which are cost reduction, energy saving, reaction selectivity, and diminishment of byproducts. Therefore, the implementation of catalysts is obviously essential for the optimization of many established procedures. Moreover, utilization of renewable sources and the use of harmless reaction media creates a significant potential for the development of environmentally friendly and sustainable procedures, which makes catalysis an important component of green chemistry.

Throughout the evolution of catalysis, transition metals have come to play a critical role in organic synthesis by inducing the development of a large number of transition metal-catalyzed reactions.[5][6]

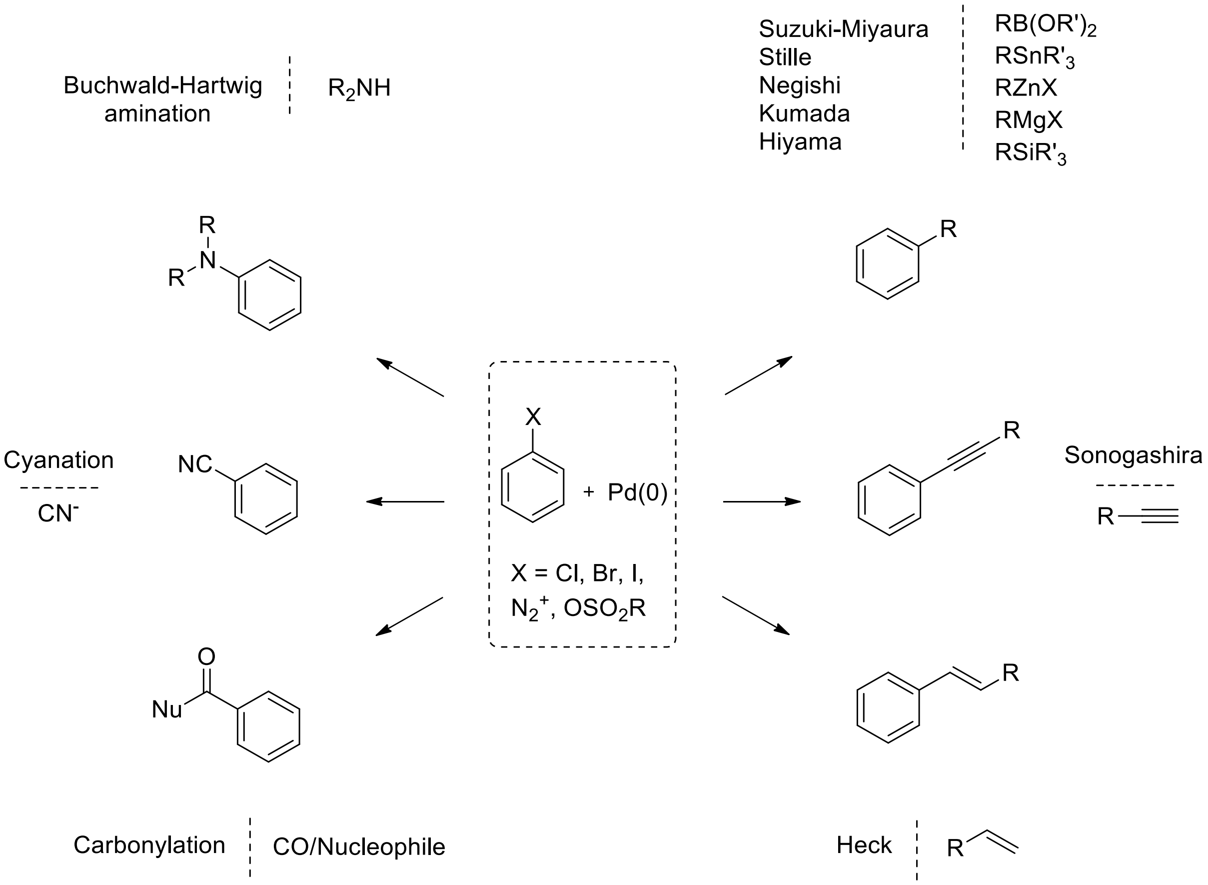
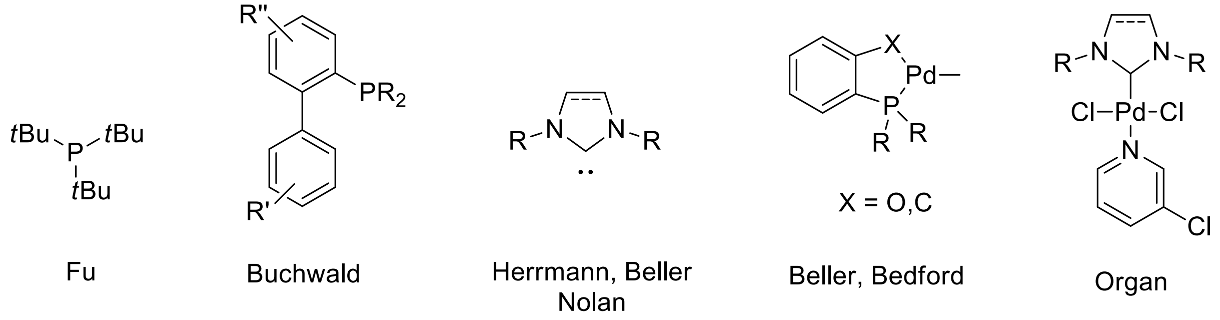


Figure 2. Functionalization of ArX via different Pd-catalyzed cross-coupling reactions.

As such, outstanding examples are cross-coupling reactions.[7] Among them, palladium-catalyzed cross-coupling reactions represent one of the most convenient and practical methods for the construction of carbon-carbon and carbon-heteroatom bonds.[8] Those reactions are highly efficient and versatile affording the synthesis of biologically active compounds including pharmaceuticals, agrochemicals, and materials such as polymers, liquid crystals, as well as materials for light-emitting devices.[9]

Despite the fact that palladium has a relatively high price, it still predominantly prevails over other transition metals due to a number of advantages.[10] Particularly, palladium catalysts often show high activity making possible the conversion of less reactive substrates[11] and provide performance at comparably low temperatures.[12] Furthermore, palladium catalysts are relatively stable towards oxygen and moisture, they provide certain kinds of reaction selectivity features and offer broad versatility in terms of functional group tolerance.[13] Considering those advantages, a wide range of palladium-catalyzed cross-couplings have been established.[7,14,15]

These reactions generally start with the generation of Pd(0) complex, followed by the oxidative addition of organic electrophile (typically aryl or vinyl halide), transmetallation of the second coupling partner, and reductive elimination to regenerate the catalyst and form the desired product. It is worth noting that aryl electrophiles with electron withdrawing substituents are more reactive in the oxidative addition step due to their lower activation barriers.[16] And often the main limitation for these reactions is the requirement to apply aryl bromides, triflates or iodides instead of less reactive aryl chlorides. However, application of bulky and electron-rich ligands, such as bulky trialkylphosphines, has proven to facilitate the oxidative addition processes of less reactive aryl halides (e.g. electron-rich aryl chlorides).[8,17,18]



Fu

Buchwald

Herrmann, Beller
Nolan

Beller, Bedford

Organ

Figure 3. Examples of different sterically demanding ligand frameworks.[7]

Moreover, sterically demanding ligands also enhance the rates of reductive elimination step by the relief of steric congestion.[19] In this regard, the design and implementation of new ancillary ligand frameworks stay in the focus of organic chemists.

Over the last decades, the development of a powerful repertoire of transition metal-catalyzed protocols has opened the way for the synthesis of new targets that were inconceivable earlier. Highly substituted aromatics bearing aryl, alkenyl and alkynyl moieties are among those targets.

This kind of systems is very interesting given their structural features. On the one hand, aromatic groups are considered to be essential pharmacophores in medicinal chemistry and drug development. As an example, a review in 2007 showed that more than 75% of recent phase III and marketed pharmaceuticals had at least one aryl functionality.[20] And on the other hand, these molecules have extended conjugation making them potentially useful for optical and electronic applications e.g. semiconductors, nonlinear optical media, liquid crystals as well as sensors.[21]

1.2 Research Goal and Objectives

During recent years, palladium-catalyzed cross-coupling reactions of polyhalogenated heterocycles have gained significant importance. Palladium-catalyzed cross-coupling protocols such as Suzuki and Sonogashira reactions offer mild, little energy consuming, and environmentally friendly procedures towards the synthesis of highly substituted aromatic scaffolds that are not readily accessible by other methods. It should be emphasized that the utilization of aryl chlorides is rather challenging due to its poor reactivity. On the other hand, the implementation of chlorides is beneficial in terms of cost efficiency and availability of materials. In this regard, the development of new efficient methods for the synthesis of polysubstituted aromatics starting from aryl chlorides is of significant practical importance.

The aim of the work is to extend the scope of palladium-catalyzed cross-coupling reactions as tools for the synthesis of multifunctionalized aromatics including polyaryl, polyalkenyl and polyalkynyl naphthyridines, pyridines and pyrazines.

The objectives that are chosen towards the achievement of the abovementioned goal are as follows:

- the usage of polychlorinated heterocycles as starting materials, since they are (i) less costly and more available in both laboratory and industrial scale as well as (ii) less reactive and thus more challenging;
- the investigation of site-selectivity of the cross-coupling reactions on tetrachlorinated pyridines to be able to finetune the substitution pattern;
- the development of optimal reaction conditions for the efficient synthesis of products, and the synthesis of a range of products for the purpose of studying the scope of the reactions;
- the investigation of photophysical and electrochemical properties of polyconjugated products

Although there are several reports on cross-coupling reactions of aromatic systems, only little is known about multiple functionalizations of polychlorinated six-membered heterocycles. In this context, presented research is expected to be contributive in terms of enriching the knowledge on the subject of multiple functionalizations of perchlorinated pyridines and pyrazine.

In addition to conventional methods, C–H activation reaction of *N*-phenyl pyrrole with aryl halides is chosen to be investigated in the context of the synthesis of multifuncionallized *N*-heterocycles. The objectives are as follows:

- studying the direct double arylation reaction under phosphine ligand-free conditions using an ionic salt as an environmentally benign reaction medium;
- exploring scope and limitations of the reaction
- proposing a possible reaction mechanism.

The achievement of the set goal is believed to enhance the knowledge in the field of C–H activations and add to the understanding of the mechanism of ligand-free palladium-catalyzed arylation reactions in ammonium salts.

2. Polyfunctionalized Arenes with Extended Conjugation

History of aromatic compounds has begun in 1825 when Faraday isolated benzene from the condensed phase of pyrolyzed whale oil. In 1861 Loschmidt first proposed benezen's cyclic planar structure[22] which was fully understood only 70 years after with the emerging of Hückel's theory[23] and the theory of resonance.[24] From the synthetic perspective, the starting point in the chemistry of aromatic compounds was probably the synthesis of aspirin, acetylsalicylic acid which was successfully commercialized by Bayer in 1900.[25] Prior to that polycycles like naphthalene, phenanthrene, pyrene and fluoranthene were isolated from coal-tar and other petroleum products. In this regard, efforts of Graebe and Glaser greatly contributed to hydrocarbon diversity existing at that time and spread light in potential future topologies.[26] From that time on, an immense number of various reactions were used to synthesize different aromatic systems including ones with extended aromaticity.[27]

Aromatic compounds with extended conjugation attracted a lot of attention due to their practical relevance in material sciences, design of molecular devices as well as in biological processes.[28] Mono and polycyclic aromatic hydrocarbons can serve as industrial polymers,[29] dyes and fluorescent materials[30] and liquid crystals.[31] Moreover, given their specific electronic properties such compounds have been very useful in the preparation of organic conductors,[32] solar cells,[33] photo- and electroluminescent devices,[34] optically active poymers[35] and non-linear optical (NLO) materials.[36]

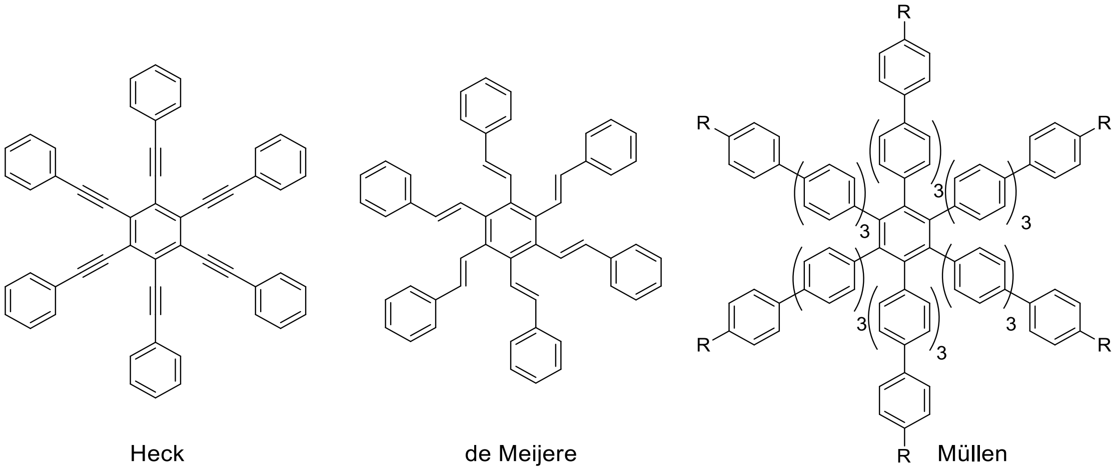


Figure 4. Star-shaped structures introduced by Heck, de Meijere and Müllen.[28]

Conjugated aromatic molecules with acetylenic scaffolds have similar applications. This applies to both linear and branched structures. Acetylene moieties are structurally rigid and have good electronic communication which allows this molecule to show promising optical and electronic features. Arylene ethynylene based oligomers, dendrimers or polymers are now commonly accepted to be one of the most important semiconducting organic materials.[21]

Shape-persistent acetylenic molecules can be useful in the preparation of tubular superstructures, two-dimensional networks, hosts for molecular recognition and adaptable systems able to conform to the external stimuli.[21]

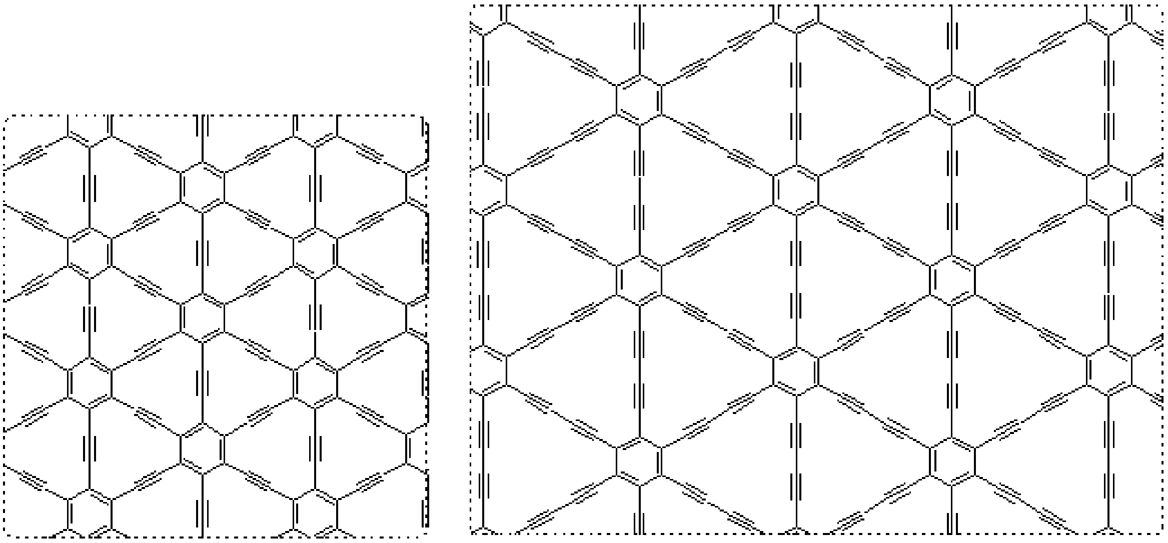


Figure 5. 2D carbon networks graphyne (left) and graphdiyne (right).

Carbon network graphyne[37] having an equal number of sp and sp^2 carbons and its analog graphdiyne[38] where acetylene linkages are replaced by butadyine units, were calculated to exhibit non-linear optical properties. They are considered as novel allotropes of carbon.

Star-shaped polyalkynylated arenes have also great potential to be implemented in the areas of optics and electronics.[39,40] After the first synthesis of hexaethynyl benzene[41] using Sonogashira reaction, similar polyalkynylated compounds with different cores like thiophene,[42] pyrrole,[43] cyclobutadiene,[44] ferrocene[45] were also reported.

There are different methods for the synthesis of polyfunctionalized aromatic structures, and cross-coupling reactions are among the most convenient tools used for that purpose as such scaffolds are often not easily accessible by other methods.[27] In continuation, C–H activation is another very attractive and relatively less mature approach for multiple functionalizations.

3. Palladium-Catalyzed Cross-Couplings

3.1 General Mechanism

With the exception of Heck reaction, Pd-catalyzed cross-couplings are generally proposed to have a similar catalytic cycle with distinctive steps that can be presented in a common simplified mechanism.[19] The active palladium(0) species is primarily formed in situ either by dissociation of two ligands derived from palladium(0)-type precatalyst or from the reduction of palladium(II) salts. Afterward, the oxidative addition of the organic electrophile Ar-X occurs onto the palladium(0) complex [L_nPd^0]. Initially, a *cis*-[$Pd^{II}ArXL_n$] complex is formed which undergoes isomerization to form a more stable *trans*-[$Pd^{II}ArXL_n$] complex. This phenomenon is called "transphobia" and is caused by a destabilizing interaction between mutually trans phosphorous donor and aryl ligands.[7]

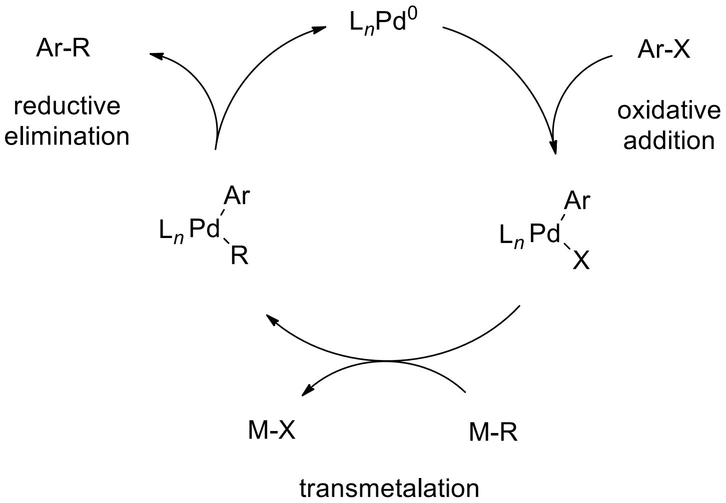


Figure 6. General simplified mechanism of Pd-catalyzed cross-couplings.

It is worth noting that aryl electrophiles with electron-withdrawing substituents are more reactive in the oxidative addition step increasing the rate (I > OTf ≥ Br ≫ Cl).[46] In the case of less reactive aryl halides (e.g. chlorides), the oxidative addition is the rate-determining step. Likewise, electron-rich phosphine-ligands facilitate this reaction due to their stabilizing effect of the oxidation state.[6] During the next step called transmetalation, the diorganopalladium(II) complex [$Pd^{II}ArRL_n$] is formed by the reaction of palladium(II) halide complex with the organometallic compound M-R. When very reactive aryl halides (e.g. iodides) are employed, this step is the one, which determines the rate of the reaction. The final step in the catalytic cycle is reductive elimination. In a fast and irreversible reaction, the coupling product Ar-R is formed and the active palladium(0) species is regenerated, which subsequently undergoes another catalytic cycle.

3.2 Sonogashira Reaction

In 1975, Sonogashira reported the synthesis of substituted alkynes under mild conditions in the presence of palladium catalyst and copper iodide acting as a co-catalyst.[47] Independently, Heck[48] and Cassar[49] also reported similar reactions, but those were not implying the use of copper salts and were requiring harsh conditions.

Sonogashira cross-coupling, which is a reaction between aryl or vinyl halides and terminal alkynes, is nowadays one of the most important and commonly used methods for the formation of sp^2-sp carbon-carbon bonds. This method is advantageous due to several factors including mild reaction conditions, selectivity and wide range of functional group tolerance. In addition, the solvents and the reagents do not need to be rigorously dried and the syntheses can be carried out on a large scale (>100 g). Sonogashira reaction can also be considered as the improved catalytic alternative to Castro-Stephens coupling. In this regard, stoichiometric amounts of shock-sensitive copper acetylides are avoided due to the application of catalytic amounts of copper co-catalyst.[50]

However, there are also several limitations. In particular, aryl chlorides and unreactive bulky substrates require harsh reaction conditions. Also, terminal alkynes are not stable towards high temperatures and generally undergo side reactions.

A large number of modifications have been made to improve reaction outcome in terms of efficiency, due to which the Sonogashira cross-coupling reaction has become essential for the synthesis of pharmaceuticals, natural products and advanced materials.[7,51,52]

A generally accepted mechanism assumes to include two independent catalytic cycles involving palladium and copper, respectively (Figure 7).

First, the active palladium(0) species [Pd^0L_2] is formed as described above. Next, the oxidative addition of the aryl or vinyl halide R^1-X to [Pd^0L_2] affords the palladium(II) adduct of the type [$Pd^{II}L_2R^1X$]. Oxidative addition is considered to be the rate-determining step for Sonogashira reaction. The intermediate subsequently undergoes transmetalation with the copper acetylide formed in cycle B to form [$Pd^{II}L_2R^1(C{\equiv}CR^2)$]. The last step is reductive elimination which leads to the formation of coupling product and regeneration of the active catalyst. In "copper-cycle" (B) π-alkyne copper complex is assumably being formed which increases the acidity of the acetylenic proton.

Similar to many other couplings, the overall efficiency in Sonogashira cross-coupling reactions depends on the choice of reaction components.[53] For example, the choice of the solvent can affect the yield of the reaction by increasing the solubility of catalysts, reactants, and products. Often, dimethylformamide, dimethylacetamide, *N*-methyl-2-pyrrolidone, toluene, and tetrahydrofuran are employed in Sonogashira reactions as solvents. Also, the use of water and benign media have been reported.[54] In some cases, like in original protocol, no solvent is required while employed amine (e.g. Et_3N) can serve as both base and solvent.[47]

As bases, Et_3N, Et_2NH, and i-Pr_2NH are commonly used, although piperidine, as well as pyrrolidine, are also utilized rather frequently.[55] The influence of bases in Sonogashira reactions have been studied and a general reactivity of bases was reported to have the following interrelationships: $n\text{-}BuNH_2 > Et_3N > i\text{-}Pr_2NH > Et_2NH > K_2CO_3$.[14,56]

For Sonogashira cross-coupling reactions $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ are the most often employed catalysts as they are advantageous in terms of air and temperature stability, solubility in various solvents and commercial availability. However, other catalysts with bidentate ligands like $Pd(dppe)Cl_2$ and $Pd(dppf)Cl_2$ have shown to be efficient too.[57] The development of electron-rich and sterically hindered phosphine ligands like SPos, $P(t\text{-}Bu)_3$, PCy_3, cata*CX*ium A, etc was a matter of more recent research focus. These ligands facilitate the cross-coupling reactions of less activated aryl chlorides, allow lowering the catalyst loadings and carry out the reaction under milder conditions.[18,58] Additionally, water-soluble phosphine ligands,[59] NHC ligands,[60] as well as heterogeneous catalysts[39] have been reported in Sonogashira cross-coupling reactions.[56]

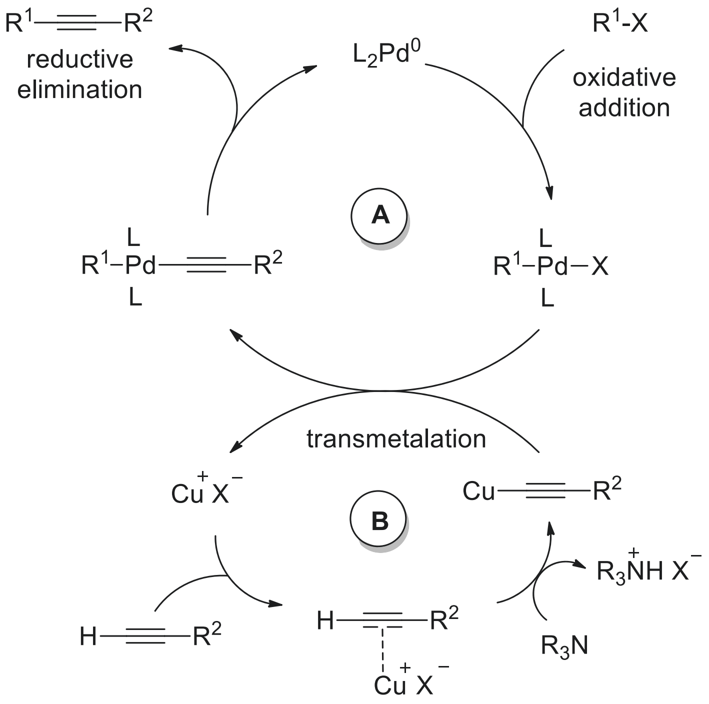
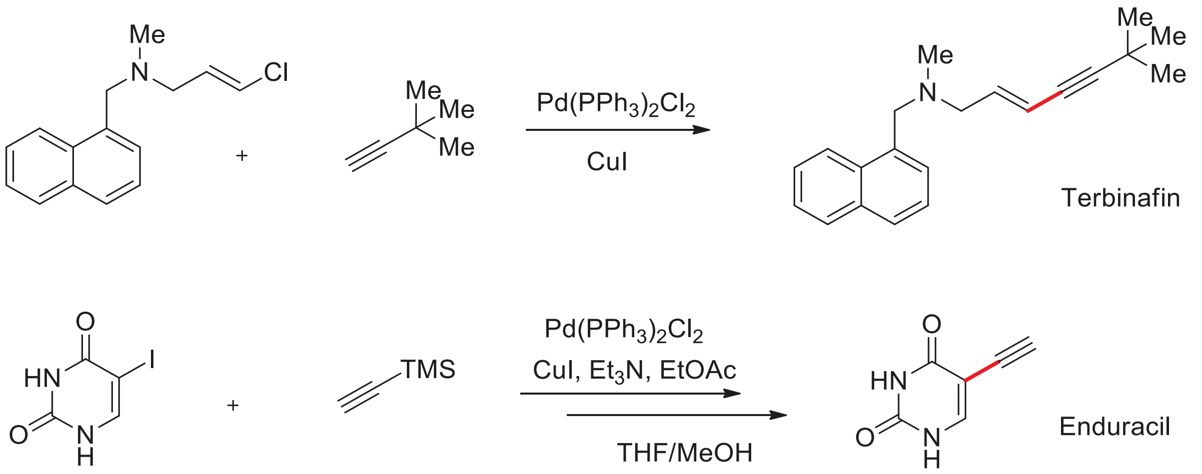


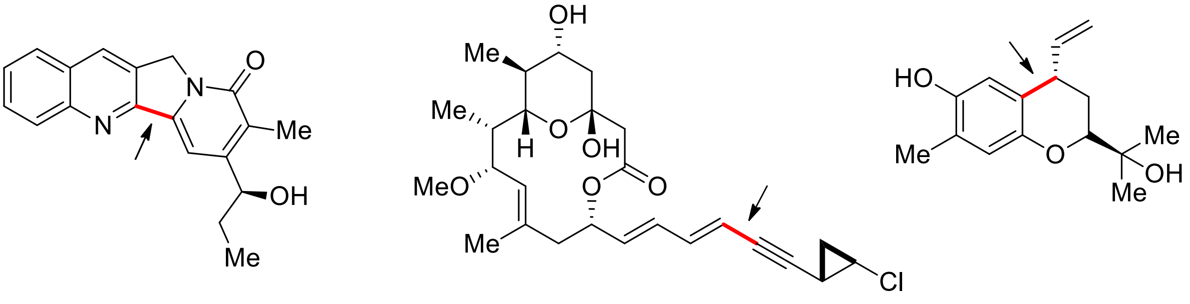
Figure 7. Proposed mechanism of copper co-catalyzed Sonogashira reaction.

The products of Sonogashira coupling reactions are widely used scaffolds in natural products, intermediates for various pharmaceuticals, agrochemicals, and materials with optical and electronic applications. Among the most important examples is the synthesis of Terbinafin, the active component of antimycotic drug Lamisil by Sandoz,[61] and synthesis of a dehydrogenase inactivator Enduracil by GlaxoSmithKline.[62]



Scheme 1. Synthesis of terbinafine and enduracil on an industrial scale by Sonogashira reaction.

Sonogashira reaction is also presented in the total synthesis of natural products. For example, for the total synthesis of mappicine, the introduction of the necessary acetylenic moiety was achieved by the Sonogashira coupling of the corresponding 2-chloroquinoline derivative with TMS-acetylene.[63] Likewise, alkynyl cyclopropane derivative was coupled with the corresponding dienyl iodide in the last step to provide callipeltoside aglycon in excellent yield.[64] For the synthesis of heliannane-type sesquiterpenoid (–)-heliannuol E the Sonogashira coupling was used for the reaction of unprotected propargyl alcohol with heavily functionalized aryl iodide.[65]



Mappicine

Callipeltoside aglycon

(–)-Heliannuol E

Figure 8. Natural products mappicine, callipeltoside aglycon and (–)-heliannuol E.[66]

The synthesis of linear polymers and oligomers consisting of sp^2- and sp-hybridized carbons via Sonogashira reactions have also been investigated because of interesting materials properties that products possess. Given their highly conjugated structure, poly(aryleneethynylene)s (PAEs) and corresponding oligomers (OAEs) can be considered as molecular wires due to their semiconducting properties.[67]

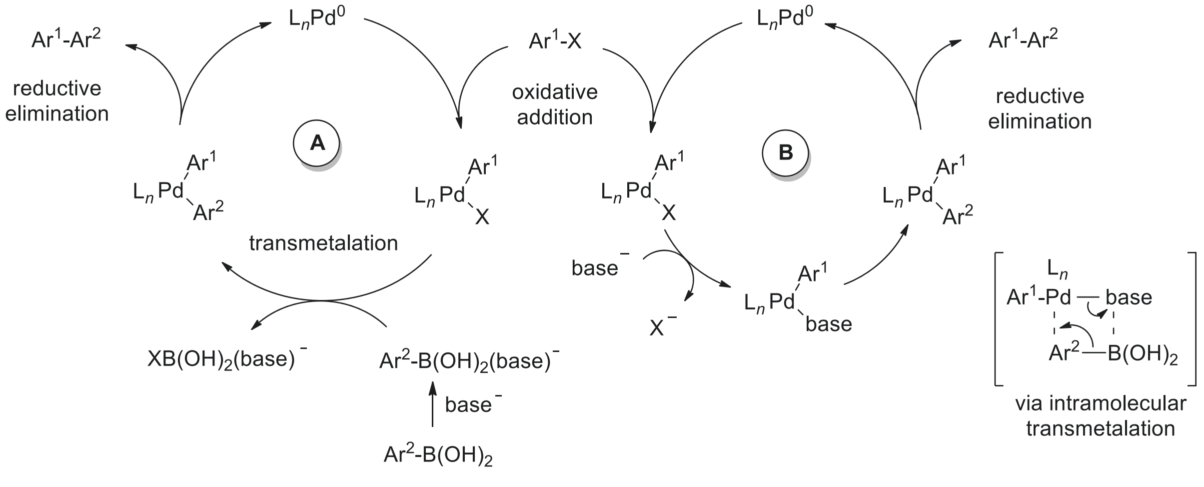
3.3 Suzuki-Miyaura Reaction

Initial report[68] by Suzuki and Miyaura dating back to 1979 is describing the reaction of 1-alkenylboranes with aryl halide in the presence of palladium catalyst. Nowadays, Suzuki-Miyaura reaction,[68,69] also known as Suzuki coupling, is a widely used method for the catalytic construction of carbon-carbon bonds. Typically, it is a palladium-catalyzed cross-coupling reaction of aryl halides or pseudo halides with boronic acids or esters.[7] This method has a number of advantages including mild reaction conditions, commercial availability of many boronic acids, stereo- and regioselectivity of the reactions as well as tolerance of starting materials towards a wide range of functional groups and towards the water.

There are also several challenges that need to be addressed. Among those is low reactivity of aryl chlorides, the formation of by-products like homo-coupling products due to solvent-dissolved oxygen, as well as side reactions like racemization of optically active compounds due to the presence of a base which is required for this reactions.

Suzuki-Miyaura reactions had a variety of improvements during the last decade, such as the expansion of the substrate scope, a better functional group tolerance and the use of more environmentally friendly procedures that involve green solvents, commercially available substrates and low catalyst loading.[70]

The most evident difference between Suzuki coupling and the rest of cross-coupling reactions is the role of a base generating a more reactive boronate anion being a good carbanion-transfer reagent (Figure 9, A).[56,71] Employed base otherwise can activate palladium(II) halide species to form more active palladium(II) base species (Figure 9, B).[7,14] The mechanistic investigation of the role of the base in the transmetalation step of the catalytic cycle of the Suzuki reaction has been reported by several research groups.[56,72]



X= halide or phseudohalide base= OH or OAlkyl

Figure 9. Proposed mechanism of transmetalation paths in Suzuki reaction.

The implementation of organoboron compounds as coupling partners makes Suzuki reaction beneficial due to the high tolerance of those compounds towards a wide range of functional groups, stability towards air, humidity, user-friendliness and synthetic accessibility. Suzuki coupling proves to be advantageous also in terms of certain types of selectivity control features it provides including the regio-,[73] stereo-,[74] and chemo-selectivity.[75]

Different solvents, bases, and catalytic systems can be used in Suzuki couplings varying the outcome of the reactions. Solvent effects on palladium-catalyzed cross-coupling reactions, and in particular Suzuki reaction has been studied.[76] These reactions are mainly done in organic solvents such as tetrahydrofuran, dimethylformamide, dioxane, toluene, and acetonitrile. Suzuki couplings have also been performed in environmentally friendly media e.g. water,[77] ionic liquids,[78] and polyethylene glycols[79] offering a more benign choice in comparison to classical solvents.[56]

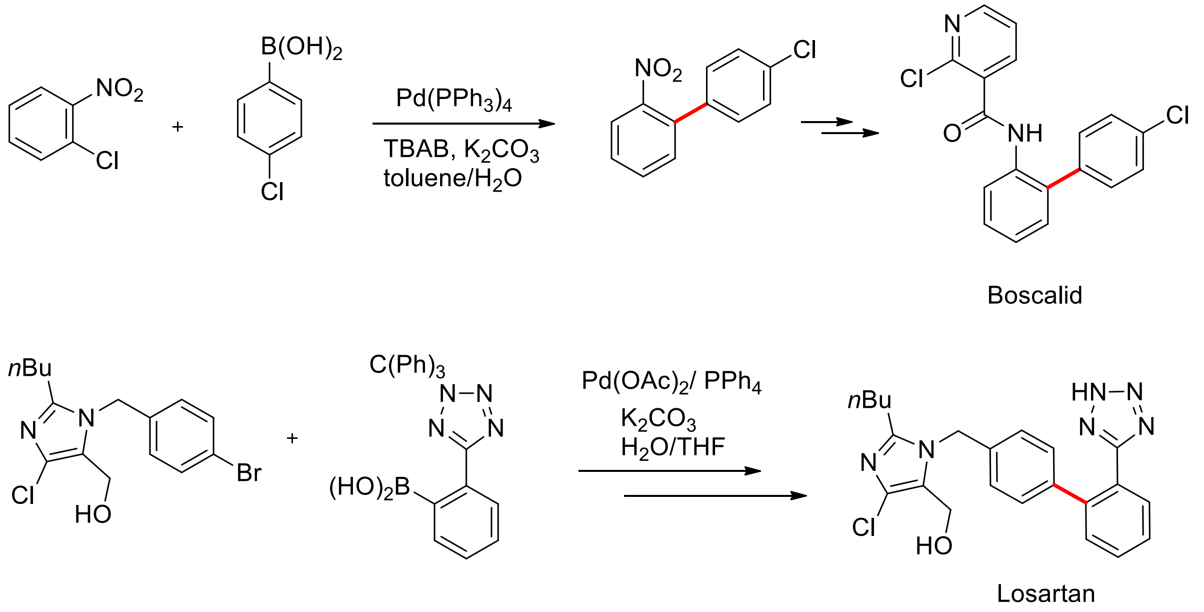
Often, carbonates, bicarbonates, phosphates, and alkoxylates of alkali metals are applied as bases. While less sterically hindered boronic acids can be efficiently converted into the product using weak bases, the conversion of sterically demanding arylboronic acids typically requires stronger bases.[14,80] With this regard, the influence of different bases on selected model reactions has been studied.[71,81] It has been shown that there is a strong correlation between the size of the cation and the reaction rate. Namely, larger-sized cations increase the rate and the yield of the Suzuki cross-coupling reactions.[56,82]

The choice of the catalyst is a crucial factor in the productivity of Suzuki couplings. Typically, Pd(0) precatalysts such as $Pd(PPh_3)_4$ as well as in situ catalysts like $PdCl_2$, $Pd(OAc)_2$ and $Pd_2(dba)_3$ in the presence of phosphine ligands are implemented.[83] Not only the above-mentioned catalysts but also palladium nanoparticles,[84] palladium catalysts supported on inorganic solids[85] and polymers[86] were successfully applied to form cross-coupling products.[56]

The rate of palladium-catalyzed cross-coupling reactions is enhanced by the presence of bulky and electron-rich phosphine ligands.[87] In recent years, numerous new ligands have been designed and synthesized to increase the catalyst efficiency, selectivity, and reaction scope.[8,88] Examples of those ligands are $P(t\text{-Bu})_3$,[89] QPhos,[90] cata*CX*ium A,[91] as well as biaryl phosphine ligands XPhos and SPhos.[92] Those allow the transformation of aryl and heteroaryl chlorides with low catalyst loadings even at room temperature. By the manipulations in the substitution pattern of ligands, it is possible to tune the catalyst in order to operate a target-oriented synthesis.[56,87]

Most of the palladium-catalyzed coupling reactions make use of easily available starting materials allowing more efficient and selective synthesis of functionalized arenes and heteroarenes compared to non-catalytic pathways. In the last decade, several palladium-catalyzed coupling reactions have been implemented into the industrial manufacture of pharmaceuticals, agrochemicals and fine chemicals. Additionally, these reactions proved to be useful in the synthesis of materials with optical and electronic applications.[10] Among palladium-catalyzed cross-coupling reactions, Suzuki reaction is probably one of the most widespread tools used in chemical manufacture. The range of its applications varies from the synthesis of natural products and intermediates for various biologically active compounds to the preparation of photo- and electroactive organic materials.[10]

An outstanding example of implementation of the Suzuki reaction in the industry is the synthesis of fungicide Boscalid. This procedure allowed annual production volume of Boscalid in more than 1000 tons a decade after it has been patented by BASF.[93] Another example is the synthesis of the angiotensin II receptor antagonist Losartan. Developed by Merk, this methodology made a possible avoiding a number of drawbacks associated with previously described syntheses.[94]



Scheme 2. Synthesis of Boscalid and Lozartan on an industrial scale by Suzuki reaction.

Suzuki cross-coupling is also represented in the total synthesis of many natural compounds. Examples include the synthesis of proteosome inhibitor TMC-95A,[95] antitumor compound epothilone A[96] and polyene antibiotic myxalamide A.[97] Similarly, the total synthesis of oximidine II was accomplished by intramolecular Suzuki-type cross-coupling of a corresponding alkenyl bromide and alkenyl potassium trifluoroborate.[98]

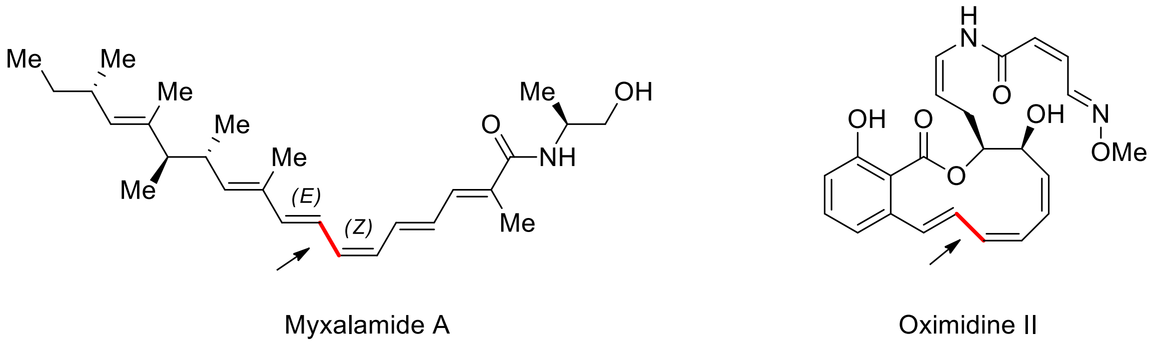


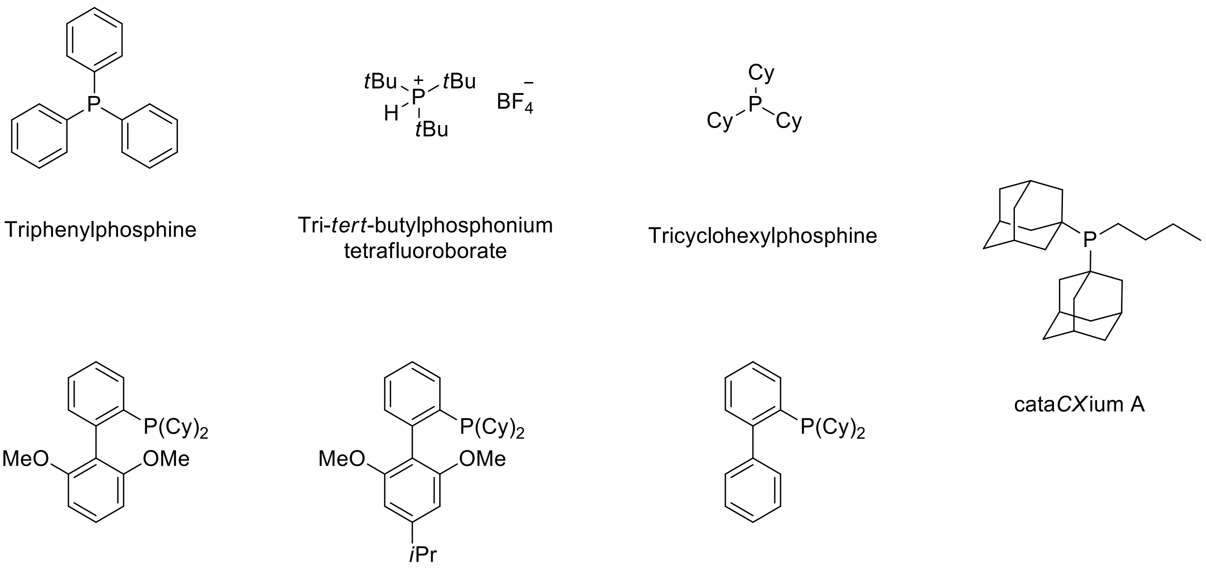
Figure 10. Natural products myxalamide A and oximidine II.[66]

3.4 Overview of the Phosphine Ligands

In this work, different palladium precursors as well as sterically demanding and electron-rich phosphine ligands were employed for reactions. With an exception of PPh_3, catalytically active species were generated in situ from palladium precursors and ligands in a ratio of 1 : 2, respectively. As a source of PPh_3, common catalysts such as $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ were applied. In all the other cases phosphine ligands were employed with precursors $Pd(OAc)_2$, $PdCl_2(CH_3CN)_2$, $Pd(dba)_2$ or $Pd_2(dba)_3$ to generate palladium(0) species by in situ reduction.

In the context of gained results, SPhos and PCy_3 provided the best yields for the straightforward full arylation reactions of initial polychlorinated pyridines and pyrazine. Whereas XPhos has proven to be the most efficient ligand for multifold alkynylation reactions. Tetrafold alkenylation of pyrazine gave excellent yields when cata*CX*ium A was used.

In contrast, site-selectivity of the reactions was better controlled with the use of $Pd(PPh_3)_4$, which was applied for twofold functionalizations of starting pyridines.



Triphenylphosphine

Tri-*tert*-butylphosphonium tetrafluoroborate

Tricyclohexylphosphine

cata*CX*ium A

S-Phos

X-Phos

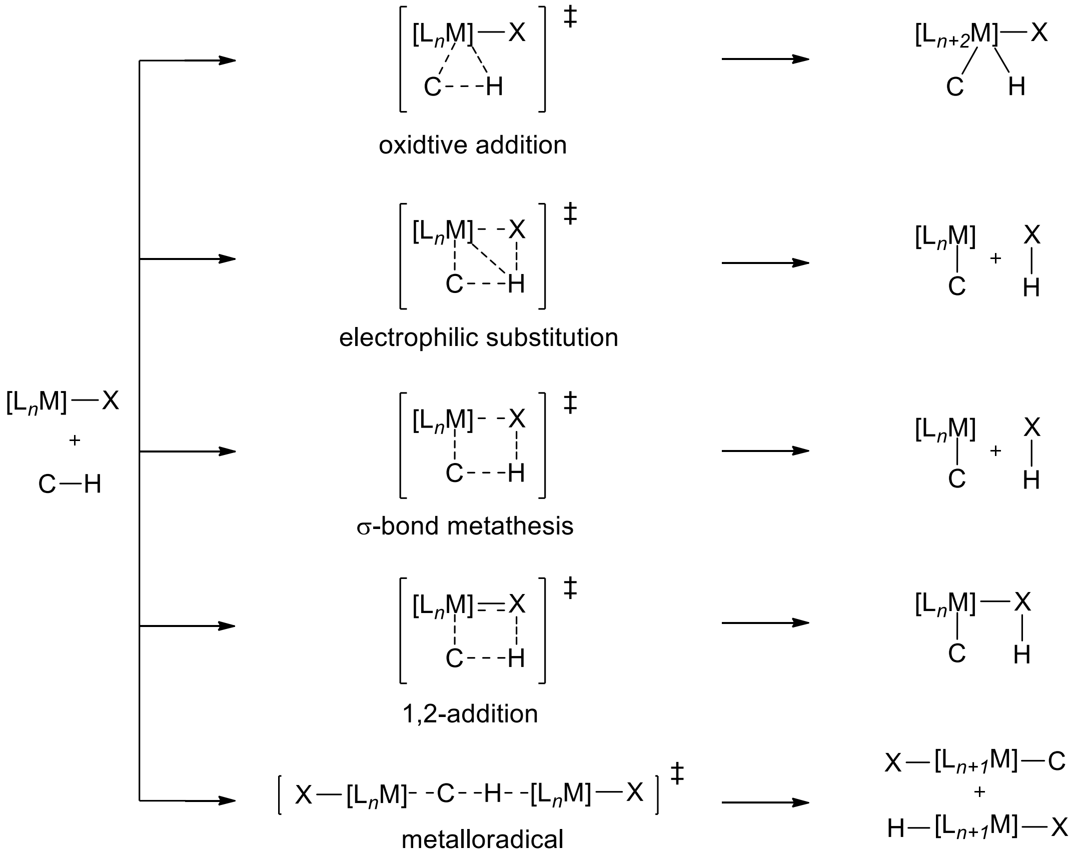
Cyclohexyl JohnPhos

Figure 11. Phosphine ligands used in this work.

4. C–H Activation

Palladium-catalyzed C–H activation reactions are highly valuable methods for the functionalization of aromatic and heteroaromatic compounds. In contrast to the conventional cross-couplings, C–H activation field is comparably less mature from an application point of view. These methods are highly attractive because they can proceed without any halide leaving group, just by using an oxidant.

Transition metal-catalyzed C–H activation methodology has been largely investigated after the first related paper was published in 1963.[99] Enormous possibilities of potential functionalizations of C–H bonds have triggered extensive research over the course of the recent two decades. Currently, C–H activation[100] is considered as an extremely powerful tool for the formation of carbon-carbon as well as carbon-heteroatom bonds prevailing over traditional routes in terms of atom economy, environmental impact and cost-efficiency.[101,102]

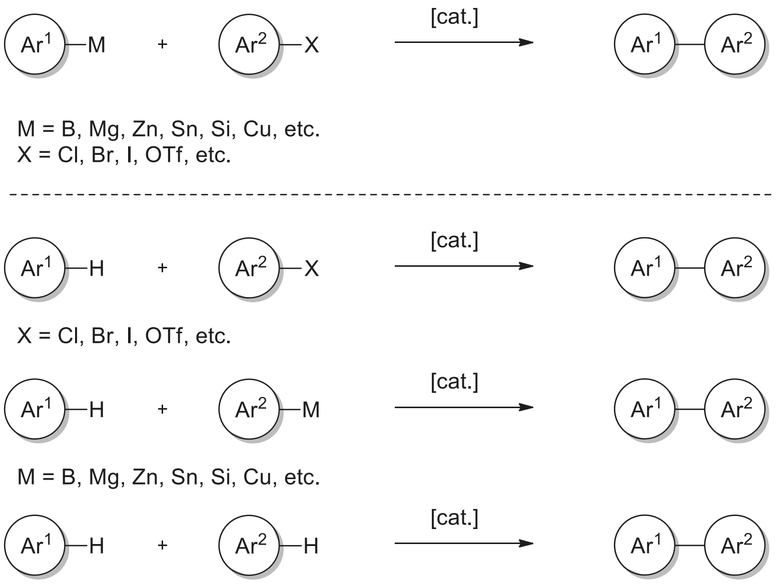


Scheme 3. Mechanisms of inner-sphere transition metal-mediated C–H bond cleavage.[103]

A number of different mechanistic pathways for transition metal-mediated carbon-hydrogen bond cleavage have been described to date.[104] Generally, those pathways are represented by inner- and outer-sphere mechanisms. In the case of inner-sphere mechanisms, a new [M–C] complex is formed, whereas outer-sphere mechanisms proceed without involving [M–C] species.[103]

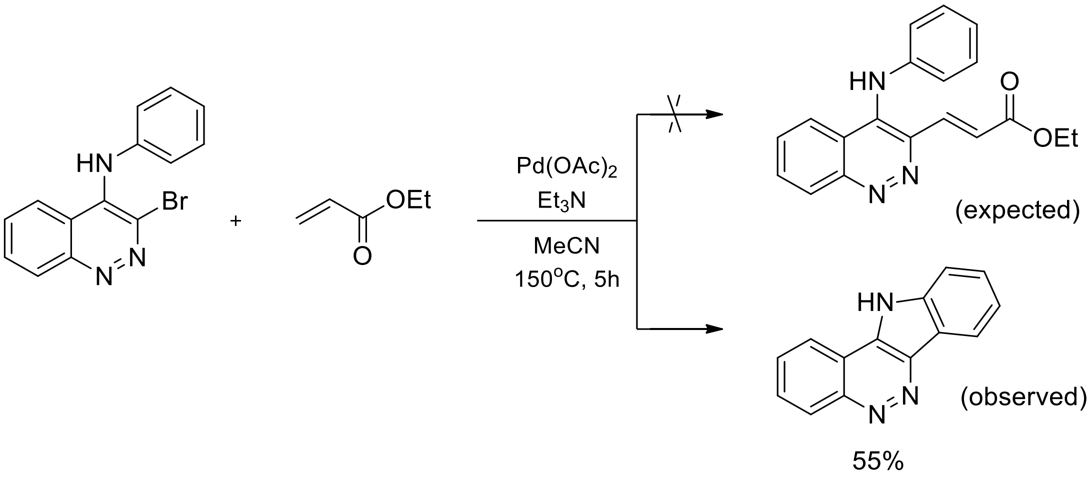
Within the first category, which implies the insertion of a transition metal, C–H bond cleavage may proceed through (i) oxidative addition,[105] (ii) electrophilic substitution,[106] (iii) σ-bond metathesis,[107] (iv) 1,2-addition[108] or (v) metalloradical activation.[109] Outer-sphere mechanisms that are relevant as further functionalization methods include (i) biomimetic oxidations[110] and (ii) metallocarbenoid/nitrenoid insertion.[111] Among listed pathways, transition metal-mediated C–H bond cleavage via oxidative addition and electrophilic substitution is the most common in synthetic transformations.

Due to the presence of reactive d-orbitals, there is a wide variety of transition metal catalysts used for the activation of carbon-hydrogen bonds, and palladium-based catalysts are, arguably, the most popular ones.[112] Given the importance of aryl moiety, C–H arylation represents the most significant and highly demanded methodology among all other transition metal-catalyzed C–H transformations.[113]



Scheme 4. Biaryl synthesis via conventional cross-couplings and C–H activation.[114]

The first palladium-catalyzed C–H arylation reaction was discovered in 1982 by Ames.[115] While studying various palladium-catalyzed reactions of 4-substituted-3-bromociannolines, he observed the formation of intramolecular C–H activation product, instead of expected Heck reaction (Scheme 5).

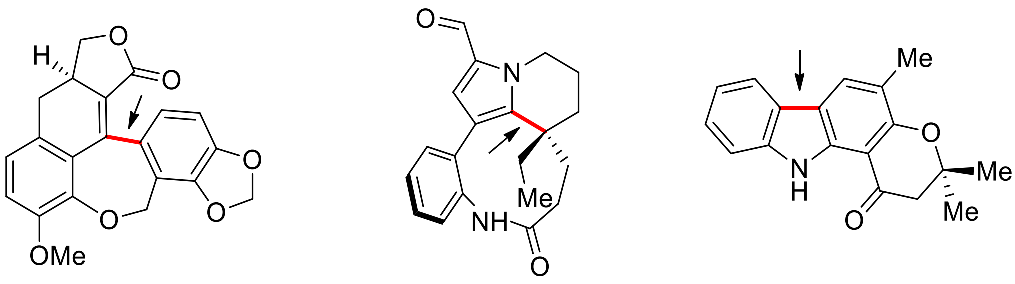


Scheme 5. Synthesis of benzofuro[3,2-*c*]cinnoline by C–H activation.[115,116]

Synthetic procedures based on functionalization of aromatic C–H bonds as an alternative to traditional cross-coupling reactions have gained much interest over recent years. In comparison to conventional cross-coupling reactions where stoichiometric amounts of both aryl halides and organometallic reagents are used as coupling partners, C–H arylation reactions represent a more promising option in terms of atom economy, cost-effectiveness and environmental impact. This method is advantageous also allowing the last-stage transformations of biologically relevant complex organic molecules.[117] Reduction or avoidance of the metallic side products is especially important in the pharmaceutical and agrochemical industry where undesired contamination is highly unwelcomed.

Several leading global pharmaceutical corporations proposed C–H activation reactions as one of the most perspective and sustainable strategies in the production of medicines.[20] In fact palladium-catalyzed C–H activation is used in the total synthesis of many biologically relevant molecules including anticancer agents (+)-linoxepin,[118] rhazinilam[119] together with its congener rhazinal,[120] and euchrestifoline[121] possessing potential antituberculosis activity.

However, there are challenges in the field of C–H activation chemistry. For example, the difficulties of selective functionalization of a targeted C–H bond preferentially over others should be addressed. Particularly, developments on catalyst-controlled regioselectivity and stereoselectivity of a C–H activation via ligand design would be a significant step forward in the field. In addition, reducing catalyst loading would be another aspect of development.[116]



(+)-Linoxepin Rhanizal Euchrestifoline

Figure 12. Natural products (+)-linoxepin, rhazinal and euchrestifoline.

Further developments in this field would have a significant impact on our abilities to manipulate organic molecules. Thereby it will most likely have an immediate impact not only on medicinal chemistry to process routes for the synthesis of active pharmaceutical ingredients, but also for the synthesis of crop protecting agents, fluorescent dyes and building blocks for organic conductors. A better sustainability and environmental compatibility is another important driving force for the development of this field.

5. Multiple Sonogashira Reactions of Polychlorinated Pyridines and Pyrazine

Being the most prominent method for the alkynylation of sp^2-carbon atoms, the Sonogashira reaction is currently used almost in all fields of organic chemistry. Its applications range from the total synthesis of natural products to the synthesis of new materials (*cf.* Chapter 3.2).[14,52,122]

Given the practical importance in the areas of optics and electronics, a number of different heavily substituted arenes and heteroarenes bearing alkynyl moieties have been synthesized. Those molecules can be used as discotic liquid crystals,[40,123] nonlinear optical materials[124] and scaffolds for dendritic molecules.[125] It should be mentioned that there are only a few reports on the synthesis of polyalkynylated six-membered heterocycles.[126]

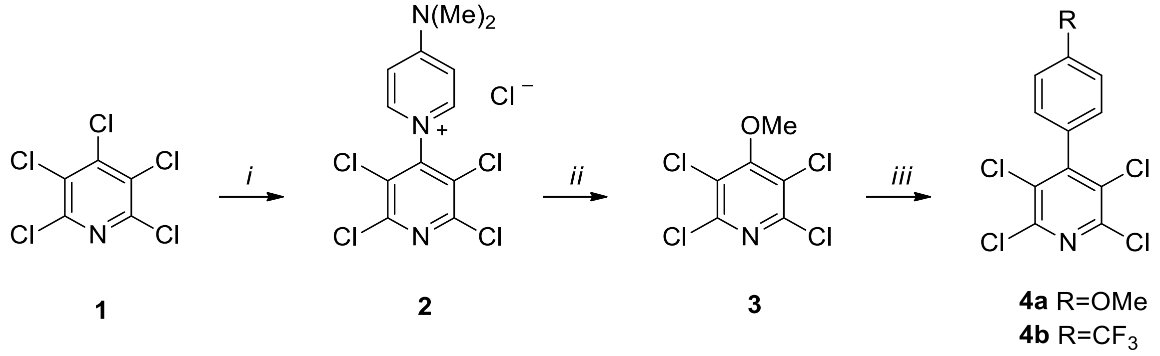
In this chapter, multiple functionalizations of polychlorinated pyridines and pyrazine by palladium-catalyzed Sonogashira reactions will be discussed together with the results of photophysical and electrochemical investigations.

5.1 Synthesis of 2,3,5,6-tetraalkynyl-4-(4-aryl)pyridines

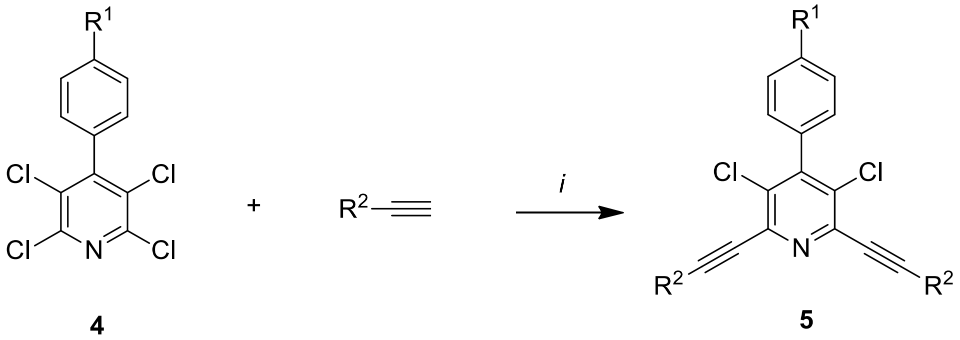
5.1.1 Site-selective alkynylation of 2,3,5,6-tetrachloro-4-(aryl)pyridines

Sonogashira reaction is a very powerful tool for the synthesis of fine chemicals, natural products and other materials, especially when applied in a site-selective manner. Due to the electronic changes induced by the heteroatom, heterocycles become highly valuable substrates for such transformations.

4-Aryl substituted 2,3,5,6-tetrachloropyridines (**4**) have been chosen as starting materials and synthesized following a known literature method[127] (Scheme 6). Aryl group was introduced to decrease the reactivity of the pyridine ring and, thereby improving site-selectivity of the Sonogashira cross-coupling reactions. Furthermore, the rate of the Sonogashira reaction at positions 3 and 5 of the pyridine is assumed to be decreased by steric effects with the site-selectivity being improved. It can be expected that alkynyl moieties with a different electronic character attached to heterocycle and the presence of a donor or acceptor substituent located at position 4 of the pyridine moiety may allow fine-tuning the photophysical properties of the molecules with regard to their emission wavelengths and quantum yields.[128]

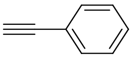
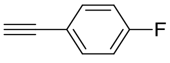
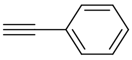
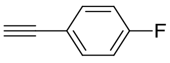
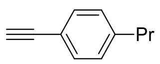


Scheme 6. Synthesis of initial tetrachloropyridines; *i:* DMAP*,* DCB, 60 ºC, 20 h; *ii:* NaOMe, MeOH, reflux, 6 h; *iii: n*-BuLi, 4-BrPhR, Et$_2$O, -78 ºC to 20 ºC.



Scheme 7. Synthesis of 3,5-dichloro-2,6-dialkynylpyridines **5a-e**; *i*: Pd(PPh$_3$)$_4$ (5 mol%), CuI (5 mol%), 1,4-dioxane, HN(*i*-Pr)$_2$, 100 ºC, 20h.

Table 1. Synthesis of **5a-e**.

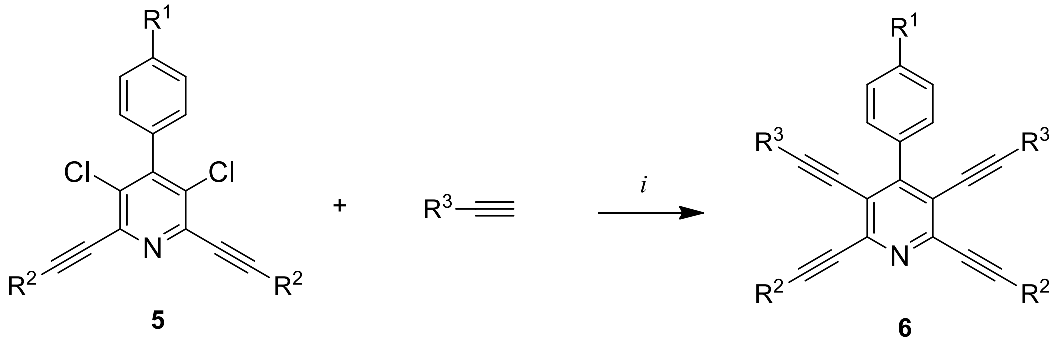
Product	R^1	Alkyne	[eq.]	Yield [%]^a
5a	OMe		2.1	59
5b	OMe		2.1	36
5c	CF$_3$		3.0	62
5d	CF$_3$		3.0	64
5e	CF$_3$		3.0	69

^{a} Yields of isolated products.

The Sonogashira reaction of pyridines **4** with various alkynes afforded the 2,6-dialkynyl-3,5-dichloropyridines **5a-e** (Scheme 7, Table 1). The products were obtained using $Pd(PPh_3)_4$ as the catalyst, CuI as co-catalyst and 1,4-dioxane as a solvent.

Reactions of 4-aryl-2,3,5,6-tetrachloropyridine **4b**, containing an electron-poor 4-CF_3-phenyl group, afforded 2,6-dialkynylpyridines **5c-e** with very good site-selectivity. The yields of products **5c-e** were higher than those of **5a, b** (Scheme 7, Table 1). A correlation between the amount of alkyne and the success of the reactions of 4-aryl-2,3,5,6-tetrachloropyridines **4a** and **4b** was observed. The reaction of pyridine **4a** gave relatively better results with 2.1 equiv. of phenylacetylene (59%) in comparison to the procedure with 2.4 equiv. (56%) for the desired product **5a**. In contrast, the starting pyridine **4b** required 3.0 equiv. of the corresponding alkyne to provide improved yields (42% yield of **5c** when 2.4 equiv. were used).

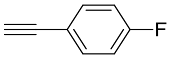
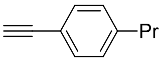
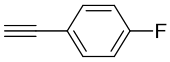
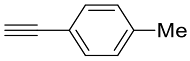
After the site-selective alkynylations of starting tetrachlorinated pyridines were successfully performed, follow up conversion of remaining C–Cl bonds of products **5** were carried out to obtain structures with mixed alkynyl moieties.



Scheme 8. Synthesis of unsymmetrical 2,3,5,6-tetraalkynylpyridines **6a-d**; *i*: $PdCl_2(CH_3CN)_2$ (4 mol%), XPhos (8 mol%), CuI (3 mol%) 1,4-dioxane, $HN(i\text{-}Pr)_2$, 100 ºC, 20h.

The Sonogashira reaction of 2,6-dialkynyl-3,5-dichloropyridines **5** with various alkynes afforded the 2,3,5,6-tetraalkynylpyridines **6** (Scheme 8, Table 2). The application of the same catalytic system did not prove to be efficient. However, reactions could be successfully accomplished with the use of bulky and highly basic XPhos ligand. Moreover, an excessive amount of alkynes were taken (3.5 equiv.) for the complete conversion of starting materials into corresponding products. All reactions proceeded in high yields ranging from 61 to 90%.

Table 2. Synthesis of **6a-d.**

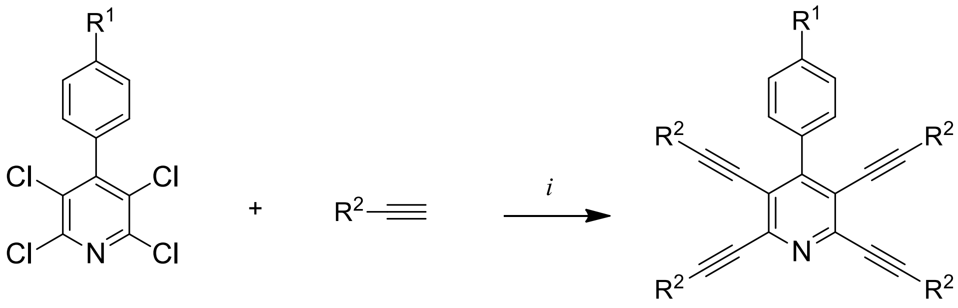
Product	Substrate	R^1	Alkyne	[eq.]	Yield [%]^a
6a	5a	OMe		3.5	62
6b	5c	CF$_3$		3.5	68
6c	5c	CF$_3$		3.5	61
6d	5e	CF$_3$		3.5	90

^{a} Yields of isolated products.

5.1.2 Full alkynylation of 2,3,5,6-tetrachloro-4-(aryl)pyridines

After title 2,3,5,6-tetraalkynylpyridines with mixed alkynyl moieties have been synthesized the focus was made on the one-pot synthesis of the corresponding symmetrical analogs. Direct four-fold Sonogashira reaction of starting pyridines **4a** and **4b** was not successful with the use of Pd(PPh$_3$)$_4$, whereas combination of more reactive PdCl$_2$(CH$_3$CN)$_2$ (4 mol%) and XPhos (8 mol%) afforded desired 2,3,5,6-tetraalkynylpyridines **7** and **8** in moderate to high yields reaching up to 80% (Scheme 9, Table 3). However, product **7g** derived from aliphatic 1-hexyne, was obtained in only 26% yield.

All tetrafold alkynylations with initial pyridines **4a** and **4b** were carried out with an excess of 6.5 equivalents of alkyne. When taken less than 6.5 equivalents the conversion of starting material into desired product remains incomplete according to the TLC analysis of the reaction mixture. Moreover, a reasonable amount of the three-fold alkynylated side product can be obtained when using 5.5 equivalents. So it has been found that the increase in the amount of alkyne leads to full conversion of starting material and reduces the amount of alkynylated by-products.

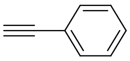
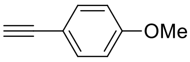
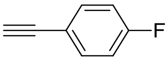
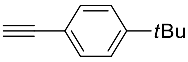
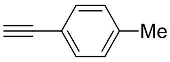
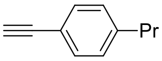
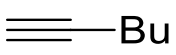
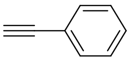
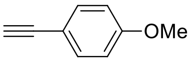
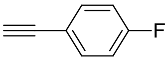
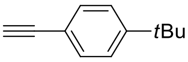
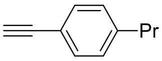


4

7 R=OMe
8 R=CF_3

Scheme 9. Synthesis of 2,3,5,6-tetraalkynylpyridines **7** and **8**; *i*: $PdCl_2(CH_3CN)_2$ (4 mol%), XPhos (8 mol%), CuI (3 mol%) 1,4-dioxane, $HN(i\text{-}Pr)_2$, 100 ºC, 20h.

Table 3. Synthesis of compounds **7-8**.

Product	R^1	Alkyne	[eq.]	Yield [%][a]
7a	OMe		6.5	80
7b	OMe	 OMe	6.5	58
7c	OMe	 F	6.5	73
7d	OMe	 *t*Bu	6.5	71
7e	OMe	 Me	6.5	63
7f	OMe	 Pr	6.5	71
7g	OMe	 Bu	6.5	26
8a	CF_3		6.5	50
8b	CF_3	 OMe	6.5	56
8c	CF_3	 F	6.5	63
8d	CF_3	 *t*Bu	6.5	75
8e	CF_3	 Pr	6.5	74

[a] Yields of isolated products.

5.1.3 Photophysical properties

UV/Vis and fluorescence properties of 2,3,5,6-tetraalkynylpyridines **7a-c** and **8a-c** were explored by steady-state absorption and fluorescence spectroscopy (Table 4). The photophysical data of 2,3,4,5,6-penta(alkynyl)pyridine **9a**[14] and 2,3,5,6-tetra(alkynyl)pyridines **10a-c**[15] are also shown for comparison with the gained results.

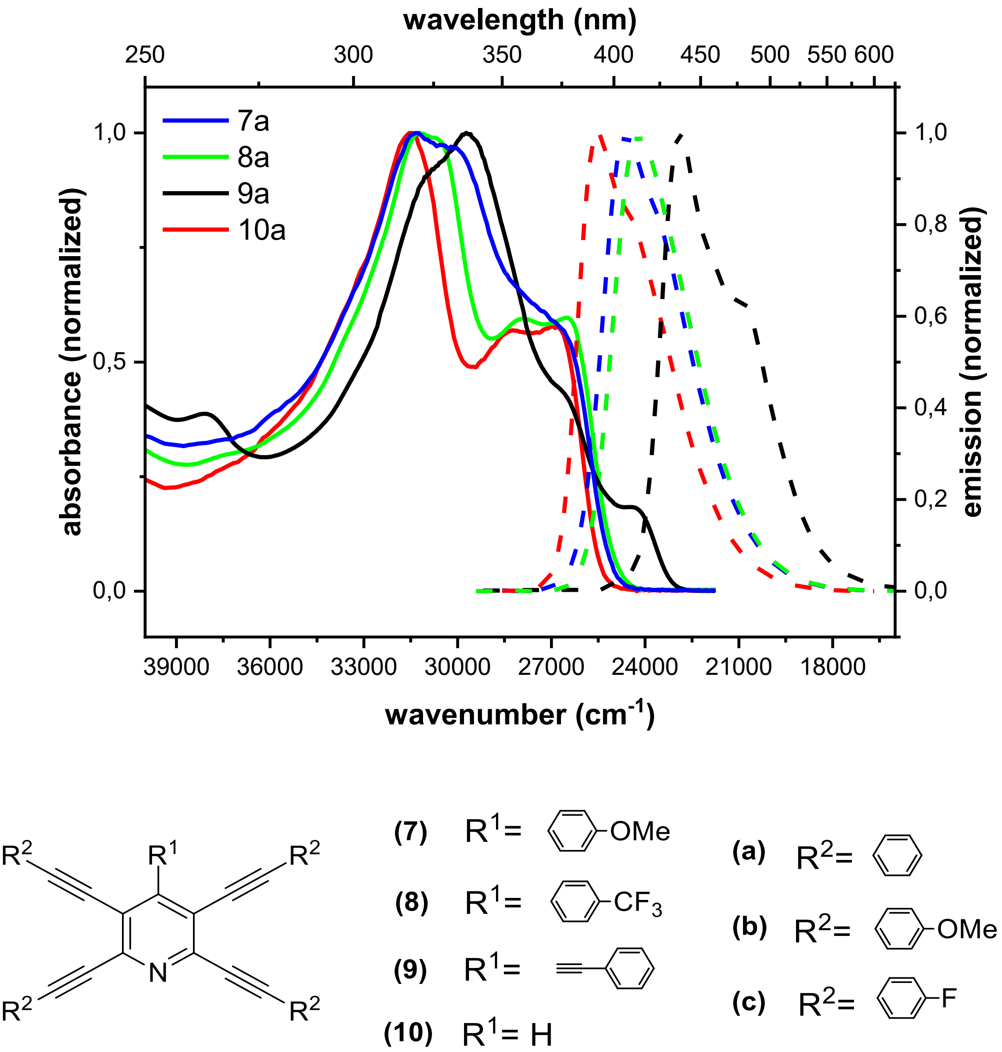


Figure 13. Normalized absorption and emission spectra of **7-10**.

As a matter of fact, absorption spectra of **7-10** show two transitions at 290-340 nm and 340-400 nm, respectively. The absorption and fluorescence spectra of the corresponding 2,3,5,6-tetraphenylethynyl and 2,3,5,6-tetra(4-fluorophenylethynyl)-substituted pyridines are almost the same, whereas the absorption peaks of the 2,3,5,6-tetra(4-methoxyphenylethynyl)pyridines (**7b**, **8b**) are bathochromically shifted. The absorption band of compounds **7a-c** and notably for compounds **8a-c** are rather narrow revealing a band structure. The conjugation between the pyridine moiety and the substituent located at the 4-position is rather poor. This assumption is supported by the comparative data of tetra(alkynyl)pyridine **10a** and the corresponding 4-aryl substituted derivatives **7a** and **8a**. Moreover, in case of 2,3,4,5,6-penta(alkynyl)pyridine **9a** – a derivative with a better conjugation over alkynyl moiety - the presence of an additional alkynyl group leads to a bathochromic shift of the absorption and emission spectra.

Table 4. UV/Vis absorption and fluorescence data of **7-10** in dichloromethane.

	$\lambda_{max}^{abs}[nm]$ ($\varepsilon_{abs}\ [10^{-4}M^{-1}cm^{-1}]$)	$\tilde{\nu}_{Stokes}$ $[cm^{-1}]$	λ_{max}^{fluo} $[nm]$	ϕ
7a	319 (6.9), 374sh	2100	406	0.25
7b	345 (14.2), 390 (8.4)	1900	421	0.31
7c	319 (7.9), 374sh	2100	406	0.25
8a	320 (6.1), 358 (3.6), 378 (3.6)	2250	413	0.44
8b	346 (11.8), 374 (7.3), 397 (7.6)	2300	437	0.60
8c	320 (10.2), 357 (6.2),375 (6.2)	2500	414	0.41
9a	338 (11.0), 376 (4.6), 421 (1.4)	750	438	0.55
10a	317 (10.0), 353 (5.7), 370 (5.8)	1500	392	0.42
10b	340 (10.9), 387 (6.8)	1600	412	0.45
10c	317 (11.4), 354 (6.6), 373 (6.6)	1300	392	0.43

The quantum yields of 4-methoxyphenylethynyl substituted pyridines are higher than ones from corresponding 4-fluorophenylethynyl and phenylethynyl products. The intramolecular charge transfer contributions of investigated compounds are apparently small. This can be explained by small Stokes shifts, the shape of the fluorescence bands and relatively high quantum yields. Considering these criteria, ICT might be relatively larger for 4-(4-methoxyphenyl)pyridine **7a** in comparison to literature known **9a**[14] and **10a**.[15] The highest fluorescence quantum yield of 60% was detected for derivative **8b**.

To conclude, relatively high fluorescence quantum yields were detected for 4-aryl-2,3,5,6-tetraalkynylpyridines bearing an electron-withdrawing substituent at position 4 of the pyridine core and alkynyl groups with electron-donating substituents. This correlation is likely associated with the push-pull substitution pattern of the molecules.

5.1.4 Liquid-crystalline properties

In addition, fluorinated alkynylpyridine **8c** was investigated with regard to its liquid-crystalline properties. Characterization and determination of the liquid-crystalline phase sequences with transition temperatures were carried out using polarized optical microscope equipped with a hot plate. The phase sequences of tested compounds were investigated only during the heating cycle due to the decomposition of the compound at higher temperatures.

Figure 14. Phase sequences and transition temperatures of compound **8c**; *compound starts to decompose at 250 °C.

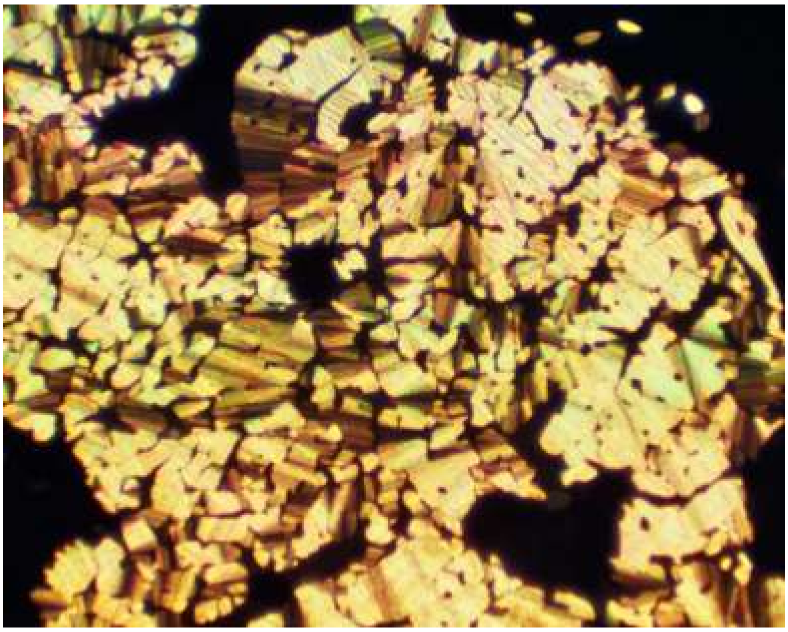


Figure 15. The liquid-crystal texture of compound **8c** observed by POM.

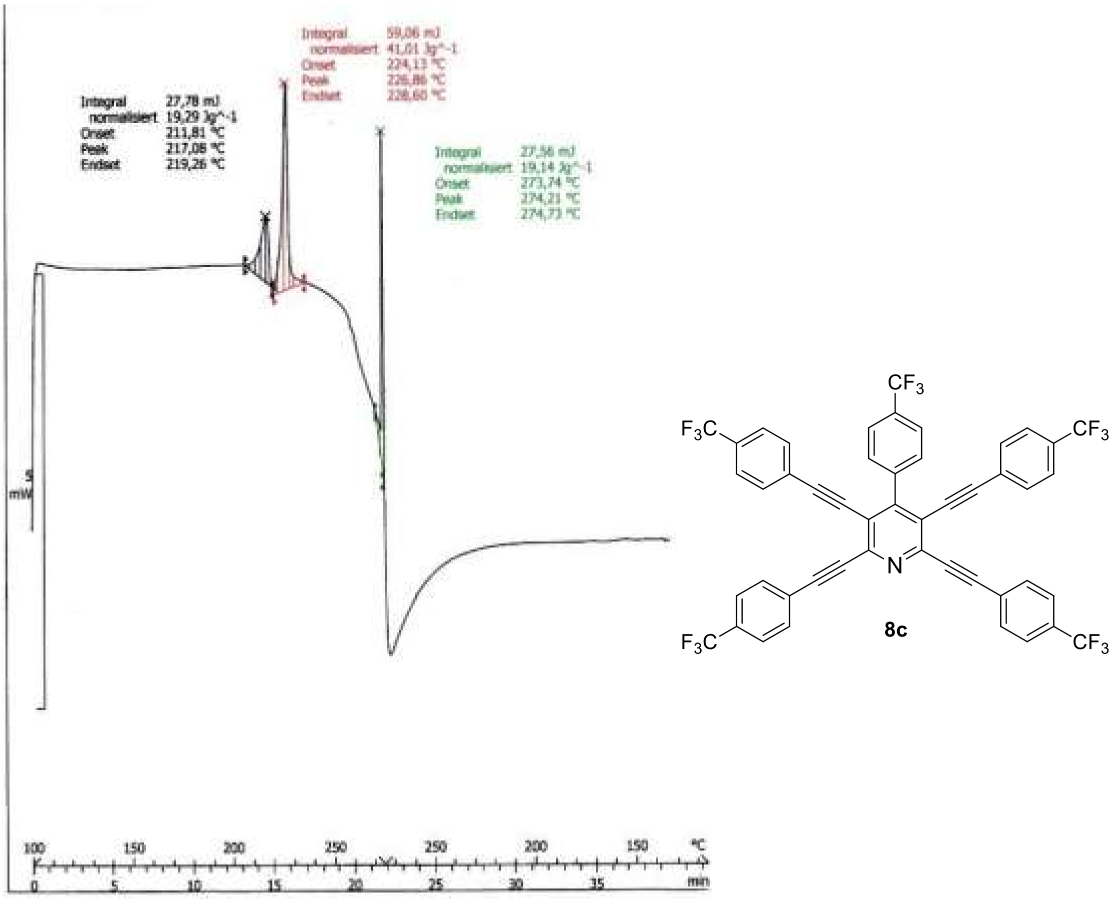


Figure 16. DSC plot with a phase diagram of **8c**.

5.1.5 Conclusion

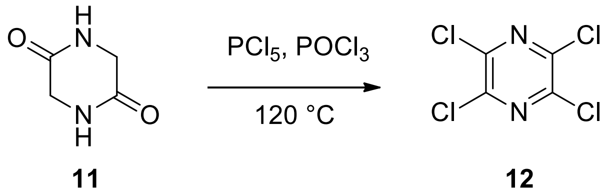
In conclusion, site-selective Sonogashira reactions of 4-aryl substituted tetrachloropyridines were developed. Synthesis of 2,6-dialkynyl pyridines was achieved in good yields with $Pd(PPh_3)_4$ as a catalyst of choice. Next, the synthesis of various symmetrical and non-symmetrical tetraalkynylated pyridines was carried out in good to excellent yields. In addition, UV/Vis and fluorescence spectra of several tetraalkynylated pyridines were measured together with quantum yields. Generally, synthesized tetraalkynylpyridines show high quantum yields which makes them ideal compounds for various optoelectronic applications. Variation of the functional groups of the alkynyl moieties and of the substituent located at position 4 of the pyridine moiety gives a possibility to switch prospective properties of those compounds and improve quantum yields. Moreover, the liquid-crystalline properties of selected fluorinated alkynyl pyridine by means of differential scanning calorimetry technique and polarized light microscopy was investigated.

5.2 Synthesis of 2,3,5,6-tetraalkynylpyrazines

5.2.1 Synthesis

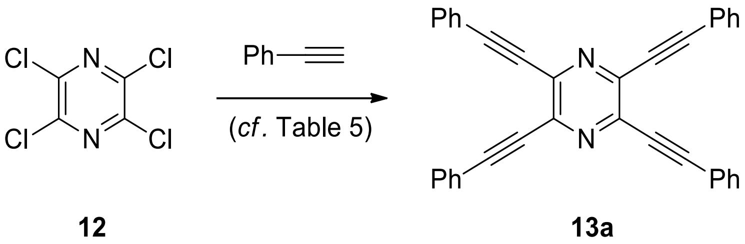
Herewith, results for the first synthesis of tetraalkynylpyrazines together with photophysical and electrochemical investigations of obtained products is disclosed. Additionally, the influence on photophysical properties of an additional nitrogen atom in the pyrazine core was investigated and the results were compared with the corresponding tetraalkynylated pyridine and benzene analogs.

Starting material tetrachloropyrazine was synthesized following a known literature method by the reaction of 2,5-dioxopiperazine (**11**) with phosphorus pentachloride and phosphoryl chloride (Scheme 10).[129]



Scheme 10. Synthesis of starting material tetrachloropyrazine.

After having the starting material, the reaction conditions of tetra-fold Sonogashira couplings were optimized. For the model reaction, phenylacetylene was chosen as the alkyne (Scheme 11, Table 5). Among all tested phosphine ligands, XPhos proved to be the most efficient one. The title product **13a** was isolated with the most optimal yield of 84% when the catalytic system was used in combination diisopropylamine base and 6 equivalents of alkyne. This result was achieved with amounts of catalyst and ligand being 3 mol% and 6 mol%, respectively.



Scheme 11. Optimization of the conditions for the synthesis of **13**a.

Table 5. Optimization of the synthesis of **13a**.

Entry	Catalyst and ligand	Co-catalyst	Alkyne [equiv.]	Base	Yield [%] [a]
1	$Pd(PPh_3)_4$ [5 mol%]	CuI [5 mol%]	8	HN(*i*-Pr)$_2$	14
2	$PdCl_2(CH_3CN)_2$ [5 mol%] XPhos [10 mol%]	CuI [5 mol%]	8	HN(*i*-Pr)$_2$	75
3	$PdCl_2(CH_3CN)_2$ [5 mol%] cata*CX*ium A [10 mol%]	CuI [5 mol%]	8	HN(*i*-Pr)$_2$	64
4	$PdCl_2(CH_3CN)_2$ [5 mol%] $[(t\text{-Bu})_3PH]BF_4$ [10 mol%]	CuI [5 mol%]	8	HN(*i*-Pr)$_2$	68
5	$PdCl_2(CH_3CN)_2$ [5 mol%] XPhos [10 mol%]	CuI [5 mol%]	8	HN(*i*-Pr)$_2$	88
6	$PdCl_2(CH_3CN)_2$ [5 mol%] XPhos [10 mol%]	CuI [5 mol%]	6	NEt_3	74
8	$PdCl_2(CH_3CN)_2$ [3 mol%] XPhos [6 mol%]	CuI [5 mol%]	6	HN(*i*-Pr)$_2$	84
9	$PdCl_2(CH_3CN)_2$ [1 mol%] XPhos [2 mol%]	CuI [5 mol%]	6	HN(*i*-Pr)$_2$	44
10	$PdCl_2(CH_3CN)_2$ [3 mol%] XPhos [6 mol%]	-	6	HN(*i*-Pr)$_2$	65

[a] Yields of isolated products.

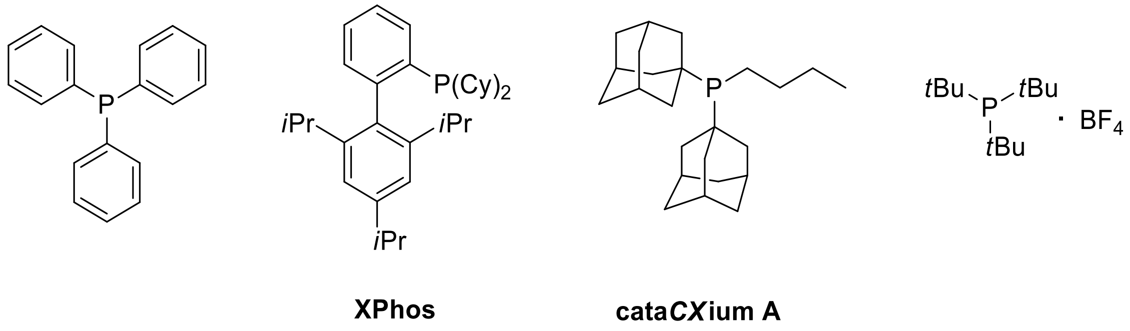
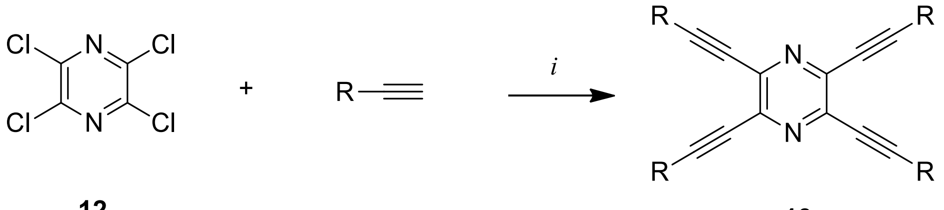


Figure 17. Phosphine ligands used during optimization reactions.

The yield of the reaction essentially decreases when the loading of the catalyst is reduced further. The presence of copper iodide as a co-catalyst proves high yields, although the product can be isolated in reasonable yield even in the absence of co-catalyst (Entry 10).

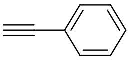
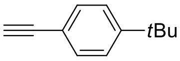
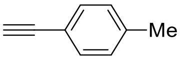
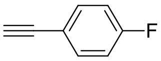
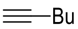
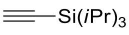
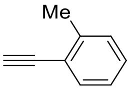
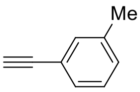
With the optimal reaction conditions in hands, the scope of the reaction was explored with the utilization of various alkynes. Tetraalkynylpyrazines **13a-m** were obtained in good to very good yields and all of them were strongly blue fluorescent under UV light (Scheme 12, Table 6). Several compounds like **13e**, **13j**, **13k**, were isolated in lower yield because of difficulties associated with the chromatographic purification.

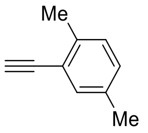
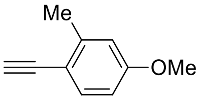
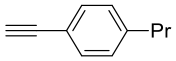
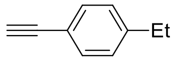
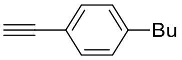


12 **13**

Scheme 12. Synthesis of **13a-m**; *i*: $PdCl_2(CH_3CN)_2$ (3 mol%), XPhos (6 mol%), CuI (5 mol%), HN(*i*-Pr)$_2$, 1,4-dioxane, alkyne (6.0 eq.), 100 °C, 20 h.

Table 6. Synthesis of **10a-m**.

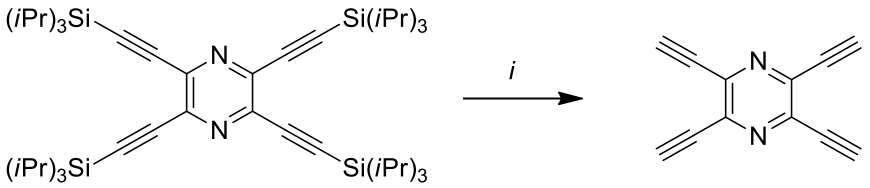
Product	Alkyne	Yield [%]^a
13a		84
13b		88
13c		83
13d		0^b
13e		44
13f		78
13g		82
13h		60

13i		79
13j		50
13k		49
13l		81
13m		60

[a] Yields of isolated products. [b] Product **13d** could not be isolated due to solubility problems.

After the reaction scope was investigated, it was also possible to gain the parent 2,3,5,6-tetraethynylpyrazine (**14**) in 86% yield by treating the silylated derivative **13f** with TBAF (Scheme 13). Later this procedure and compound were used by Sakamoto et al. for the synthesis of pyrazine-incorporated graphdiyne.[130]

Regrettably, attempts to perform site-selective double or mono alkynylations on tetrachloropyrazine failed. The reason is not only because of the symmetric structure of the molecule but also on the reactivity of the molecule which increases after every coupling step.



13f

14 (86%)

Scheme 13. Synthesis of **14**; *i*: TBAF, THF, 0 to 20 °C, 2 h.

5.2.2 Photophysical properties

UV/Vis and fluorescence properties of tetraalkynyl pyrazines were studied using dichloromethane as a solvent. Steady-state absorption and fluorescence spectra of **13a**, **13g** and **13j** were compared and shown in Figure 18. It has been observed that measured compounds show two absorption regions at 318 nm - 349 nm and 390 nm – 412 nm, respectively with fluorescence maxima between 429 nm and 461 nm.

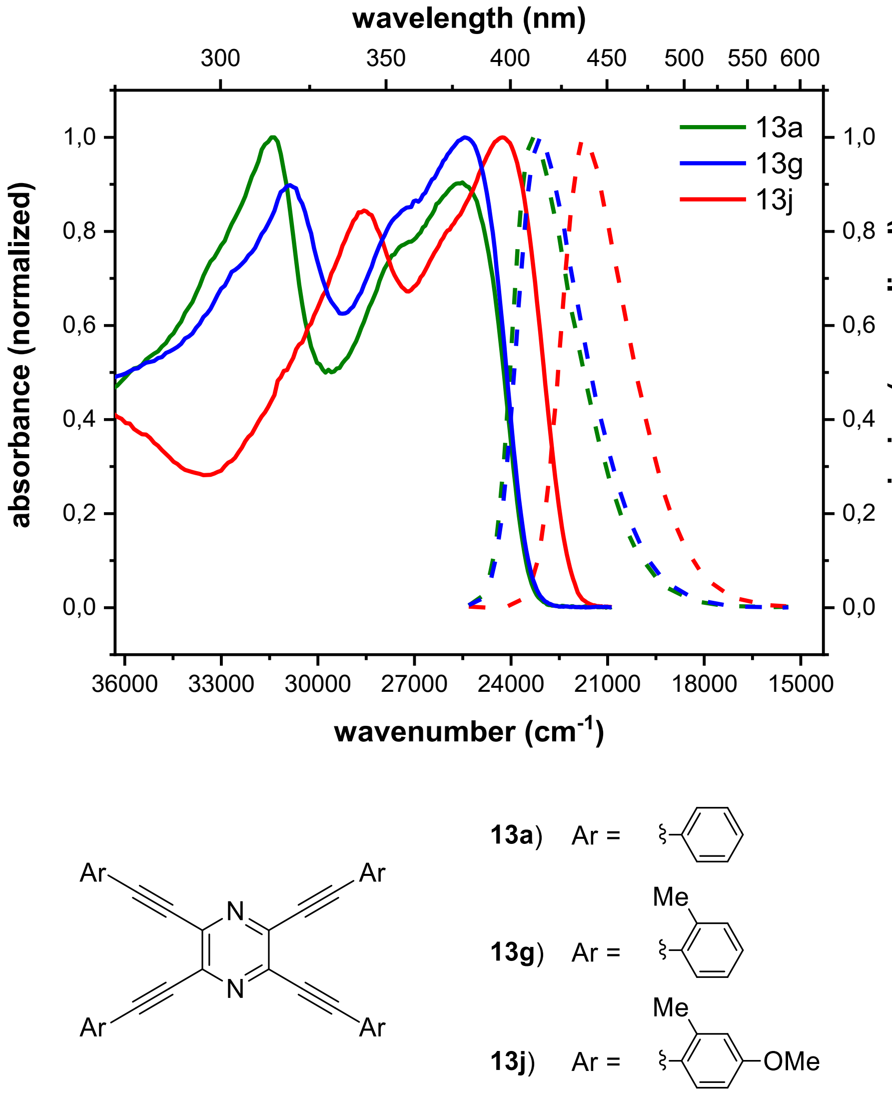


Figure 18. Normalized absorption and emission spectra of **13a**, **13g** and **13j**.

As can be seen, phenylethynyl moiety with σ-donating methyl group causes only slight bathochromic shift of the absorption- and fluorescence spectra. Whereas tertaalkynylpyrazine **13j** with extra π-donating methoxy group leads to significant redshift (Figure 18 and Table 7).

This redshift indicates a more pronounced π-electron delocalization relative to the other measured tertaalkynylpyrazines.

In order to understand how the introduction of an additional nitrogen atom into the central aromatic ring influences on the photophysical properties of molecules, the absorption and emission spectra of tetrakis(phenylethynyl)pyrazine (**13a**) was compared with its corresponding pyridine[131] (**10a**) and benzene (**15**) analogs (Figure 19, Table 7).

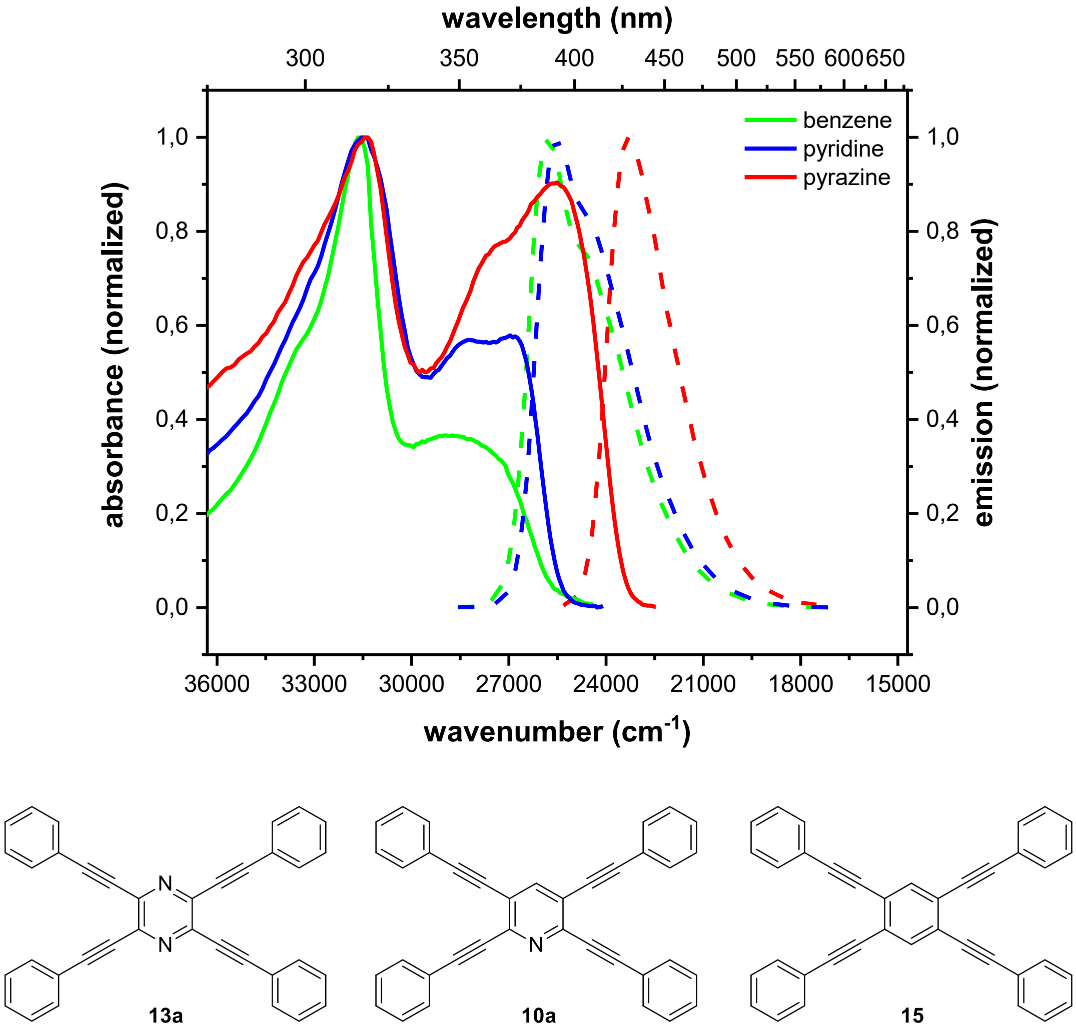


Figure 19. Comparison of absorption and fluorescence spectra of tetrakis(phenylethynyl)-pyrazine (**13a**) with its corresponding pyridine (**10a**) and benzene (**15**) derivatives.

While the first transitions in the UV/Vis spectra of **13a**, **10a** and **15** have almost the same wavelengths of maximum absorbance, the second transition shifts to higher wavelengths as the number of nitrogens in the aromatic ring grows. Nonetheless, comparison of absorption coefficients of transitions for pyrazine, pyridine and benzene derivatives shows that the second transition is almost the same for all compounds whereas the absorption coefficients of the first transition of **13a** are approximately twice smaller than those of **10a** and **15**.

The emission spectra of compounds shift bathochromically as the number of nitrogens grows in the aromatic ring. This can be explained by the push-pull pattern of the molecules causing the biggest intramolecular charge transfer contributions for the pyrazine derivative. It has been also observed that the substitution pattern of the peripheral substituents affect the quantum yields marginally, while the situation is different when the central aromatic ring is changed. To this extent, the quantum yields of tetraalkynyl pyrazine **13a** are approximately two times higher than those of corresponding pyridine **10a** and benzene **15** analogs. (Table 7).

Table 7. UV/Vis absorption and fluorescence data of **13**, **10a** and **15** in dichloromethane.

	$\lambda_{max}^{abs}[nm]$ (ε_{abs} $[10^{-4}M^{-1}cm^{-1}]$)	$\tilde{\nu}_{Stokes}$ $[cm^{-1}]$	λ_{max}^{fluo} $[nm]$	ϕ
13a	318 (5.4), 390 (4.8)	2330	429	0.81
13c	328 (5.8), 398 (5.5)	2350	439	0.83
13g	324 (4.2), 393 (4.7)	2350	433	0.77
13h	323 (5.4), 394 (5.1)	2290	433	0.85
13j	349 (4.9), 412 (5.8)	2580	461	0.79
10a	317 (10.0), 353 (5.7), 370 (5.8)	1520	392	0.42
15	317 (12.6), 347 (4.5)	3050	388	0.45

5.2.3 Electrochemical studies

Electrochemical experiments were performed to determine the potential values, electrochemical activity and the influence of the substitution pattern of selected compounds. The cyclic voltammograms of **13**, **10a** and **15** are shown in Figure 20. In all cases, two redox events were observed. The first redox event is represented by the oxidation of measured compounds at potentials of around 1.5 V [vs. Ag/AgCl/LiCl$_{sat.}$ in ethanol]. The oxidation event is electrochemically non-reversible and thus data from the corresponding reduction potentials are not depicted in Table 8. The second redox event was depicted at potentials below -0.5 V [vs. Ag/AgCl/LiCl$_{sat.}$ in ethanol] and is electrochemically reversible. Based on the measured potentials the HOMO and LUMO levels of the compound were calculated[132] (Table 8). HOMO and LUMO levels were calculated using the peak potentials of the oxidation event 1 and the reduction event 2 using equations $\mathrm{IP} = \mathrm{E}_{\mathrm{peak}}^{1-\mathrm{ox}} + 4.4\ \mathrm{eV}$ and $\mathrm{EA} = \mathrm{E}_{\mathrm{peak}}^{2-\mathrm{red}} + 4.4\ \mathrm{eV}$,[133] respectively. In order to compare the values of the band gaps obtained by optical spectroscopy, the electrochemical band gaps were calculated ($\mathrm{E}_{\mathrm{EC}} = \mathrm{IP} - \mathrm{EA}$).[132] As a matter of fact, these are a little larger than the numbers corresponding to band gaps from optical spectroscopy. However, a comparable correlation between the structure and the band gap can be observed.[134]

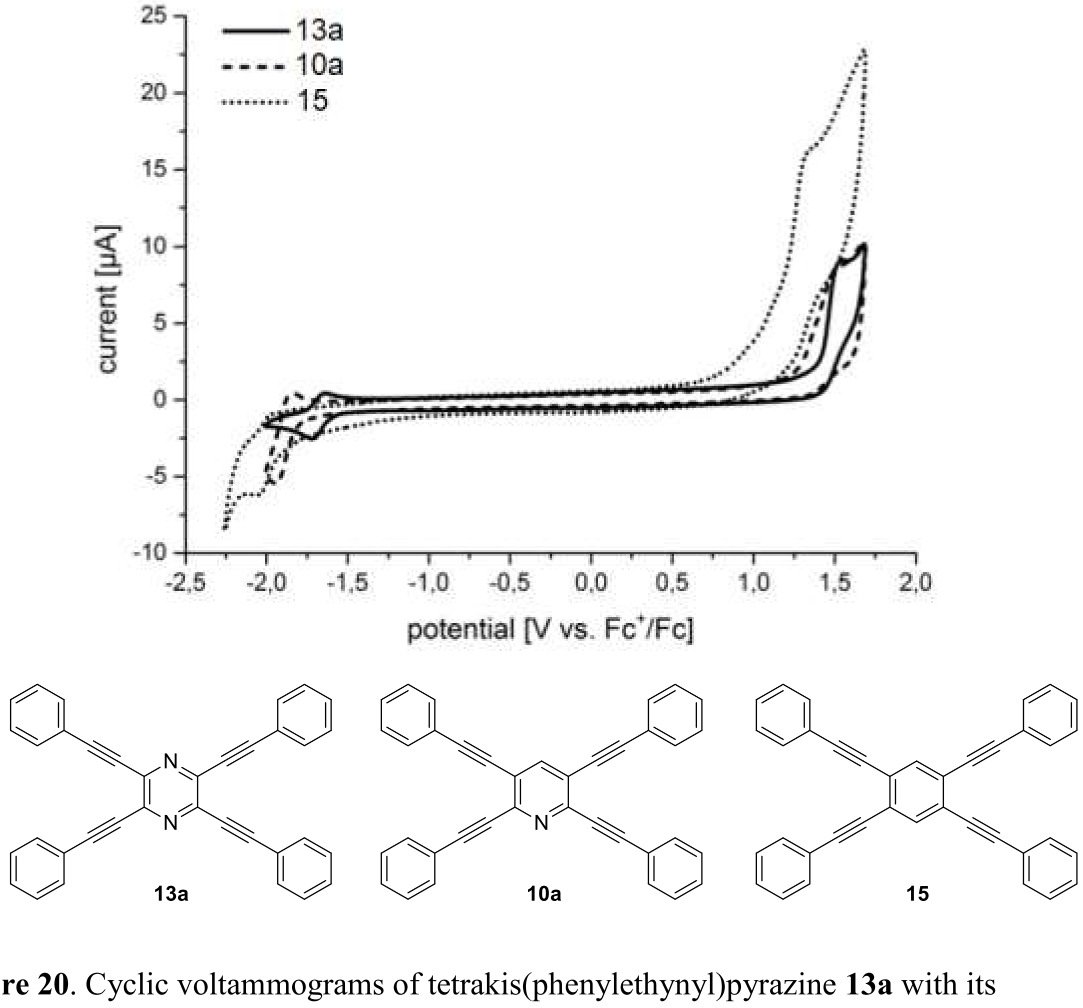


Figure 20. Cyclic voltammograms of tetrakis(phenylethynyl)pyrazine **13a** with its corresponding pyridine and benzene analogs **10a** and **15**, respectively.

Table 8. Redox properties of compounds **13a-e**, **10a** and **15** in acetonitrile.[1]

Compd	$E_{opt.}$ [eV]	E_{peak}^{1-ox} [V vs. Ag/AgCl]	E_{peak}^{1-ox} [V vs. NHE]	IP [eV]	E_{peak}^{2-red} [V vs. Ag/AgCl]	E_{peak}^{2-red} [V vs. NHE]	E_{peak}^{2-ox} [V vs. Ag/AgCl]	E_{peak}^{2-ox} [V vs. NHE]	EA [eV]	E_{EC} [eV]
13a	2.98	2.05	2.19	6.63	-1.21	-1.06	-1.13	-0,99	3.38	3.25
13c	2.92	2.04	2.18	6.62	-1.21	-1.06	-1.14	-1.00	3.38	3.24
13h	2.97	1.98	2.13	6.57	-1.25	-1.10	-1.17	-1.03	3.34	3.23
13g	2.96	1.97	2.12	6.56	-1.19	-1.05	-1.11	-0.97	3.39	3.17
13j	2.81	2.02	2.16	6.60	-0.82	-0.68	-0.72	-0.58	3.76	2.84
10	3.23	2.03	2.17	6.61	-1.43	-1.29	-1.33	-1.19	3.15	3.46
15	3.28	1.84	1.98	6.42	-1.53	-1.39	-1.47	-1.33	3.05	3.37

As can be seen in the table, ionization potentials for all compounds are rather comparable meaning that the energies for the oxidation of measured benzene, pyridine and pyrazine derivatives are in the same range. Contrary, pyrazine **13j** bearing a methoxy group has the highest LUMO energy level among other measured compounds making this derivative prone to an easier reduction. The lowest values of optical and electrochemical band gaps of **13j** correlate with its push-pull substitution pattern.

5.2.4 Conclusion

In conclusion, an efficient method for the one-pot synthesis of tetraalkynyl pyrazines was developed. Each coupling step of tetra-fold Sonogashira reaction requires only 0.75 mol% of a palladium catalyst. Further, photophysical and electrochemical investigations were carried out on tetraalkynyl pyrazines and the results were compared with their corresponding pyridine and benzene counterparts. The obtained alkynylated pyrazines proved to show very high quantum yields which makes them potential candidates to be used in optoelectronics. Given the good electronic communication of the molecules, the fluorescence can be fine-tuned by switching the peripheral substituents. While comparing the aromatic cores it has been demonstrated that the introduction of a nitrogen atom remarkably improves the fluorescence quantum yield. As a matter of fact, because of the push-pull character of the tetraalkynylated pyrazines, their

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[1] Electrochemical measurements were performed by Dr. Annette-Enrica Surkus from the Leibniz-Institue for Catalysis at the University of Rostock.

quantum yields are significantly higher than those of all corresponding pyridine and benzene analogs studied earlier. Electrochemical studies also showed a similar correlation between the structure and activity of the molecules. Cyclic voltammetry measurements were performed and HOMO and LUMO levels together with electrochemical band gaps were determined, which proved to be comparable with the data gained by optical spectroscopy. It has been also observed that the reduction event 2 is connected to the central aromatic ring. Moreover, reduction potentials and so the LUMO levels get higher by the number of nitrogen atoms increases in the central aromatic core.

6. Multiple Suzuki-Miyaura Reactions of Polychlorinated Pyridines and Pyrazine

Today, Suzuki-Miyaura reaction is by far the most widely used palladium-catalyzed cross-coupling reaction. As already mentioned in *Chapter 3.3*, it owes its success to the large variety of commercially available boronic acids, their low toxicity and high stability towards air, moisture and heat. Moreover, Suzuki coupling is beneficial because of the selectivity control features that it can provide.[135]

In the recent decade, interest in polyarylated compounds has largely increased given the promising properties of molecules which have a great potential to be used in optoelectronics. Therefore, a lot of research has been carried out towards the new synthetic methods to form polyaromatic heterocycles. The synthetic methods are represented by two general approaches: (i) either aryl functional groups are introduced in the starting materials and only after the ring closure takes place to form the heterocycle; (ii) or the functional groups are introduced directly to the heterocycle itself. Due to the great importance of pyridines and pyrazines in the pharmaceutical and agrochemical fields, as well as the increased attention in their electronic applications, the development of new synthetic methods towards the appropriate polyarylated heterocycles is of great importance.[136] In this regard, given the wide variety of commercially available boronic acids and polychlorinated heterocycles, the Suzuki-Miyaura reaction represents an interesting tool for the construction of multiply functionalized pyridines and pyrazines starting from corresponding polyhalogenated heterocycles.[73]

This chapter deals with the preparation of various pyridine and pyrazine derivatives by palladium-catalyzed Suzuki-Miyaura reactions starting from corresponding polychlorinated heterocycles. Both aryl and alkenyl boronic acids were applied as coupling partners and site-selectivity on pyridines was investigated.

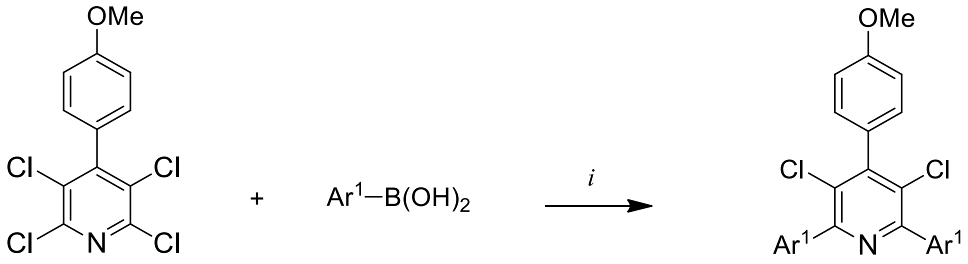
6.1 Synthesis of 2,3,5,6-tetraaryl-4-(4-methoxyphenyl)pyridines

6.1.1 Site-selective arylation of 2,3,5,6-tetrachloro-4-(4-methoxyphenyl)pyridine

The site-selective Suzuki reactions on polyhalogenated heterocycles have been a subject of intensive research in recent years.[73,137] The selectivity of the cross-coupling reactions can be tuned by the choice of the catalytic system, which is possible because of the contrasting distribution of electron density in the pyridine core.

Two-, three-, and tetra-fold Suzuki-reactions on corresponding chlorinated pyridine are presented below. The site-selective synthesis of various pentaarylated pyridines containing two or three different aryl moieties was easily achieved in two steps.[138]

First of all, starting tetrachloropyridine **4a** was synthesized in a three-step procedure as already described in *Chapter 5.1* (Scheme 6). The selective diarylation reactions were performed with the use of $Pd(PPh_3)_4$ as a catalyst and 3 equivalents of aryl boronic acid. The title pyridines **16** were obtained in moderate to good yields.

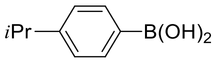
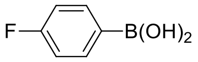
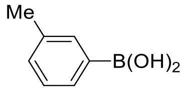
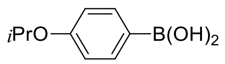


4a

16

Scheme 14. Synthesis of **16a-d**; *i*: $Pd(PPh_3)_4$ (5 mol%), Ar^1-$B(OH)_2$ (3.0 eq.), K_3PO_4 (3.0 eq.), toluene, 100 °C, 20 h.

Table 9. Synthesis of **16a-d**.

Product	Boronic acid	Yield [%][a]
16a		69
16b		63
16c		47
16d		71

[a] Yields of isolated products.

In order to get additional information and to prove expectations about the structure of synthesized regioisomers 2D NMR experiments, in particular, COSY and NOESY were performed. The characteristic NOESY correlations between neighboring aryl groups could not be determined because the aryl moieties are located far from each other, which indirectly proves the structure of **16d** excluding the option where aryl rings are attached to positions 3 and 5 (Figure 21).

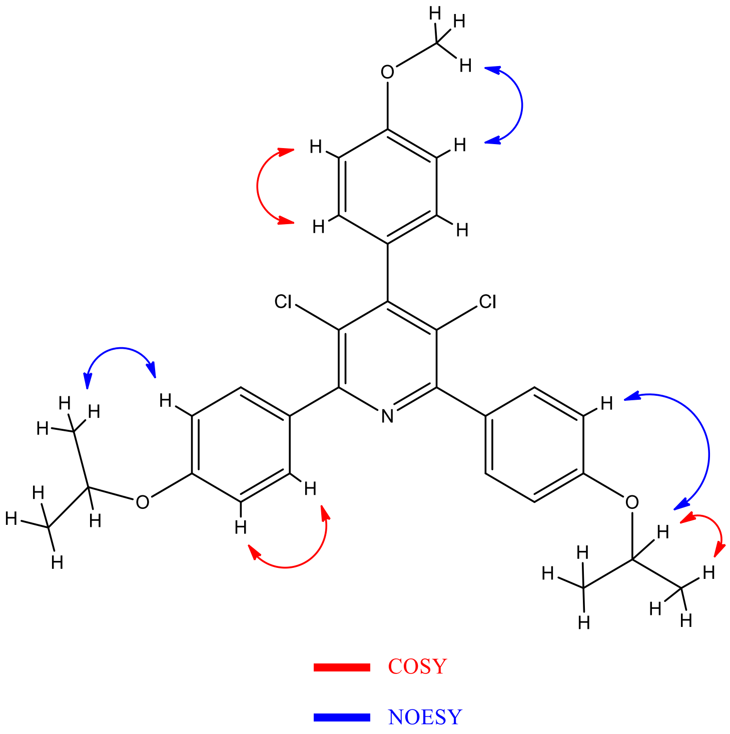
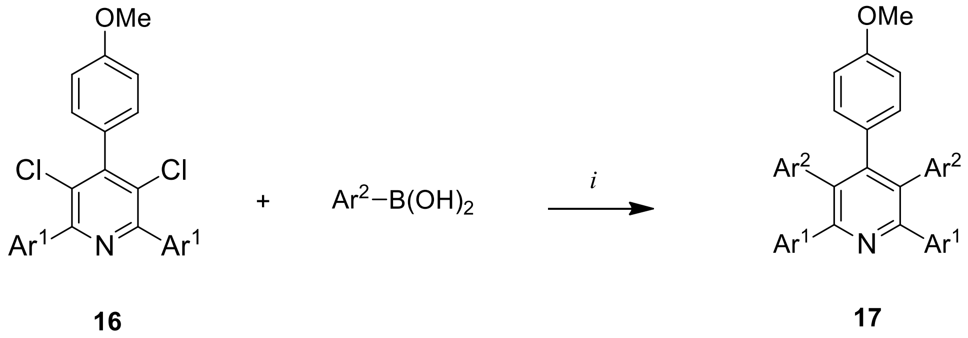


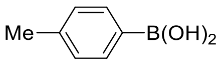
Figure 21. 2D NMR correlations for **16d**.

In the next step, the synthesized 3,5-dichloro-2,4,6-triarylpyridine **16b** was efficiently converted into the pentaarylpyridine **17** bearing different aryl moieties. The use of highly active catalytic system containing Buchwald’s biaryl phosphine ligand SPhos provided 99% yield of the reaction (Scheme 15).



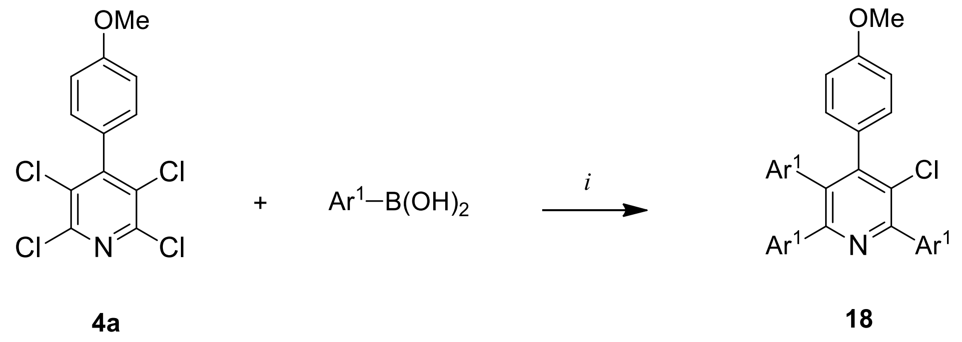
Scheme 15. Synthesis of **17**; *i*: $PdCl_2(CH_3CN)_2$ (5 mol%), SPhos (10 mol%), Ar^2-$B(OH)_2$ (4.0 eq.), K_3PO_4 (4.0 eq.), toluene, 100°C, 20h.

Table 10. Synthesis of **17**.

Product	Substrate	Boronic acid	Yield [%][a]
17	**16b**		99

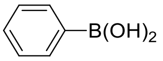
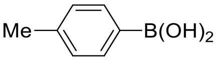
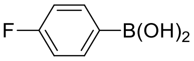
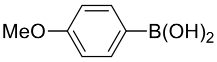
[a] Yield of isolated product.

After, selective three-fold Suzuki reaction of the initial **4a** was performed. It was found, that the reaction selectivity can be switched by using a stronger catalytic system like $PdCl_2(CH_3CN)_2$/ SPhos. The target pyridines **18** were successfully isolated in moderate to good yields. (Scheme 16)



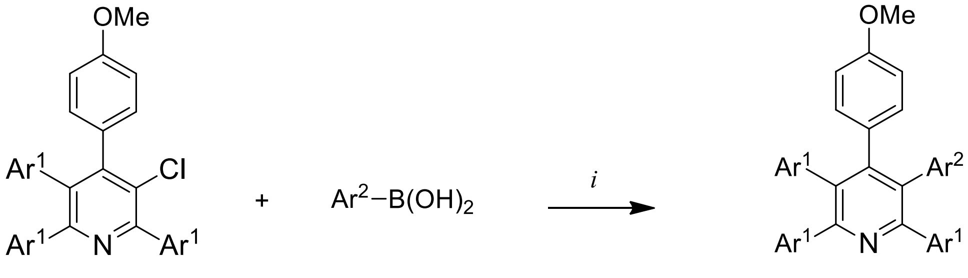
Scheme 16. Synthesis of **18**; *i*: $PdCl_2(CH_3CN)_2$ (5 mol%), SPhos (10 mol%), Ar^1-$B(OH)_2$ (3.0 eq.), K_3PO_4 (3.0 eq.), toluene, 100°C, 20h.

Table 11. Synthesis of **18a-d**.

Product	Boronic acid	Yield [%][a]
18a		54
18b		34
18c		62
18d		40

[a] Yields of isolated products.

Like in case of diarylated products, here also follow up Suzuki reaction towards the synthesis of pentaarylpyridines with mixed aryl moieties was performed. Reactions provided excellent yields (Scheme 17).

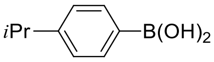
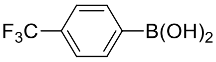


18

19

Scheme 17. Synthesis of **19**; *i*: $PdCl_2(CH_3CN)_2$ (5 mol%), SPhos (10 mol%), Ar^2-$B(OH)_2$ (2.5 eq.), K_3PO_4 (2.5 eq.), toluene, 100°C, 20h.

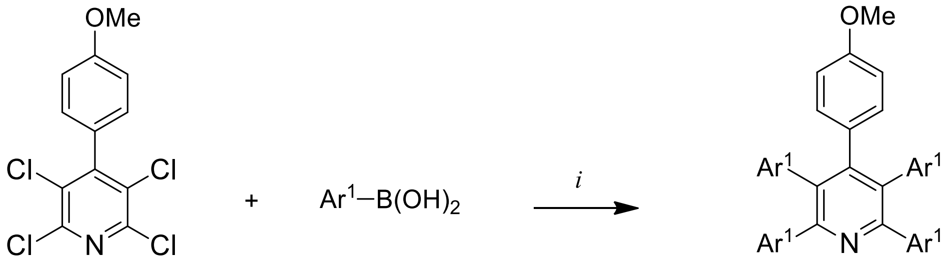
Table 12. Synthesis of **19**.

Product	Substrate	Boronic acid	Yield [%][a]
19a	**18a**		98
19b	**18b**		93

[a] Yields of isolated products.

6.1.2 Full arylation of 2,3,5,6-tetrachloro-4-(4-methoxyphenyl)pyridine

Along with the site-selective two- and three-fold Suzuki couplings, it was also possible to perform one-pot full arylations of initial tetrachloropyridine **4a**. The Suzuki reaction of starting material with various boronic acids containing electron-donating and withdrawing groups successfully afforded pentaarylpyridines **20** with symmetric structure. The application of SPhos proved to be very efficient and the products were isolated in 61 - 81% yields (Scheme 18, Table 13).

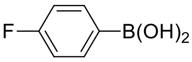
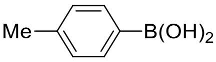
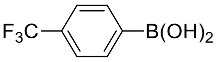
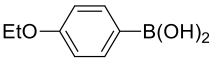


4a

20

Scheme 18. Synthesis of **20a-d**; *i*: $PdCl_2(CH_3CN)_2$ (5 mol%), SPhos (10 mol%), Ar^1-$B(OH)_2$ (8.0 eq.), K_3PO_4 (8.0 eq.), toluene, 100°C, 20h.

Table 13. Synthesis of **20a-d**.

Product	Boronic acid	Yield [%][a]
20a		78
20b		61
20c		81
20d		79

[a] Yields of isolated products.

Also in case of product **20b**, COSY and NOESY experiments were additionally performed in order to get insights into the structure. As a result, characteristic NOESY correlations between neighboring aryl groups were determined (Figure 22).

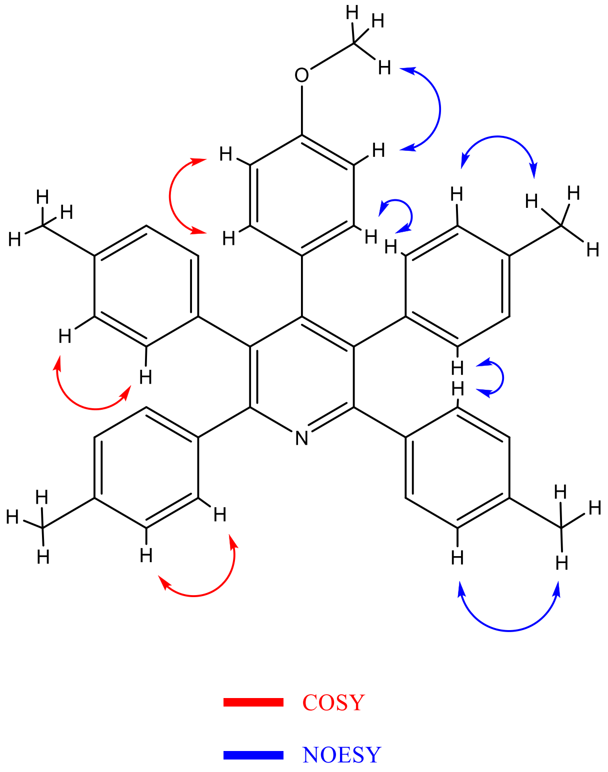


Figure 22. 2D NMR correlations for **20b**.

6.1.3 Conclusion

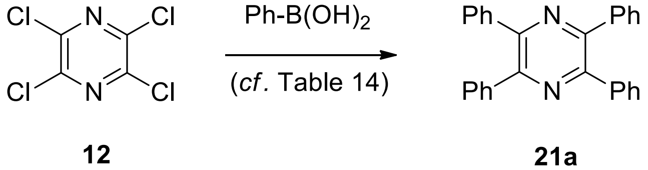
In conclusion, syntheses of various pentaaryl pyridines via palladium-catalyzed multiple Suzuki reactions were developed for the first time. Two- and three-fold site-selective arylation reactions were performed providing moderate to high yields of products with mixed aryl moieties. In addition, one-pot tetra-fold Suzuki couplings were carried out and the title symmetric pyridines were isolated in very high yields. Established protocols allow easy access to diverse polyarylated pyridines from easily available corresponding chlorinated starting materials.

6.2 Synthesis of 2,3,5,6-tetraarylpyrazines

Functionalized pyrazines can be found in different natural products and many of them possess pharmacological activities.[139] Particularly, several pyrazines with aryl functionalities were shown to act as cyclooxygenase-2 inhibitors,[140] anti-platelet aggregants,[141] regulators of estrogen receptors,[142] antihyperglycemics,[143] cannabinoid receptor 1 antagonists[144] etc. Moreover, given their photophysical characteristics, a number of arylpyrazines are considered as promising materials for medical imaging applications.[145]

There is a number of reports on the synthesis of aryl-substituted pyrazines and most of them include cyclization reactions of already prefunctionalized starting materials.[146,147] Those methods, like many others, have several drawbacks including the low outcome of the reactions, high-pressure condition or prefunctionalization of the starting compounds. In this regard, the development of new procedures for the straightforward and easy preparation of tetraarylpyrazines is of particular relevance. Over recent years, several palladium-catalyzed cross-coupling reactions have been used for the functionalization of dichloropyrazines.[148] A single example of a Sonogashira reaction on tetrahalogenated pyrazine has been reported so far using an excessive amount of catalyst.[149] Herewith, the first examples of multiple Suzuki-Miyaura cross-coupling reactions of tetrachloropyrazine are developed allowing a straightforward synthesis of symmetrical tetraarylpyrazines in very high yields.[145]

At first, starting tetrachloropyrazine (**12**) was synthesized following a procedure already described in *Chapter 5.2* (Scheme 10). To find out reaction conditions providing the best yields a thorough optimization was carried out. Different catalysts were screened in the model reaction of **12** with phenylboronic acid (Scheme 19).



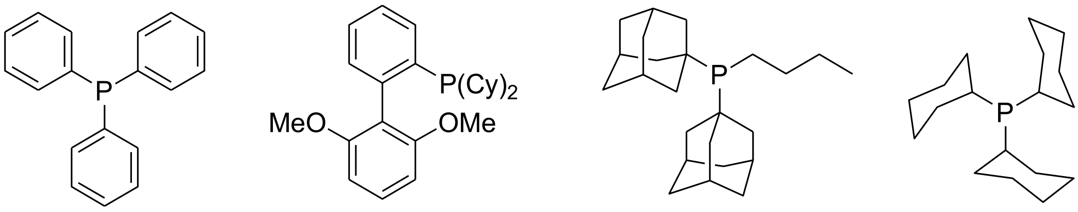
Scheme 19. Optimization of the synthesis of **21a**.

The employment of $Pd(PPh_3)_4$ with a common combination of the solvent and base resulted in title 2,3,5,6-tetraphenyl pyrazine in 83% yield (Table 14, Entry 1). It has been shown that the application of bulky ligands like cata*CX*ium A,[91] SPhos[150] or $P(Cy)_3$ provides yields higher than 90%. In particular, application of $Pd(OAc)_2$ (5 mol%) and $P(Cy)_3$ (10 mol%) afforded **21a** in 97% yield. Advantageously, the catalyst loading can be decreased twenty times without affecting the outcome of the reaction (Entries 7-10). However, further lowering of the catalyst amount slightly decreases yield to 88% (Entry 11). The optimization reactions were carried out at 100 °C and stirred for 18 h. It has been found that shortening the duration of the reaction to 10 h decreases the yield for around 15%. A decline of the yield is observed also when amounts of the base and boronic acid are decreased from 8.0 to 6.0 or 5.0 equivalents (Entries 5 and 6).

Table 14. Optimization of the synthesis of **21a**.

Entry	Catalyst and ligand	K_3PO_4 : Ph-$B(OH)_2$	Time [h]	Yield [%] [a]
1	$Pd(PPh_3)_4$ [5 mol%]	8:8	18	83
2	$Pd(OAc)_2$ [5 mol%] SPhos [10 mol%]	8:8	18	96
3	$Pd(OAc)_2$ [5 mol%] cata*CX*ium A [10 mol%]	8:8	18	92
4	$Pd(OAc)_2$ [5 mol%] $P(Cy)_3$ [10 mol%]	8:8	18	97
5	$Pd(OAc)_2$ [5 mol%] $P(Cy)_3$ [10 mol%]	5:5	18	86
6	$Pd(OAc)_2$ [5 mol%] $P(Cy)_3$ [10 mol%]	6:6	18	90
7	$Pd(OAc)_2$ [3 mol%] $P(Cy)_3$ [6 mol%]	8:8	18	96
8	$Pd(OAc)_2$ [1 mol%] $P(Cy)_3$ [2 mol%]	8:8	18	97
9	$Pd(OAc)_2$ [0.5 mol%] $P(Cy)_3$ [1 mol%]	8:8	18	96
10	$Pd(OAc)_2$ [0.25 mol%] $P(Cy)_3$ [0.5 mol%]	8:8	18	97
11	$Pd(OAc)_2$ [0.1 mol%] $P(Cy)_3$ [0.2 mol%]	8:8	18	88
12	$Pd(OAc)_2$ [0.25 mol%] $P(Cy)_3$ [0.5 mol%]	8:8	10	82

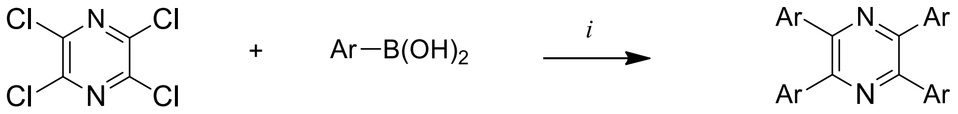
[a] Yields of isolated products; *conditions*: catalyst, tetrachloropyrazine, $PhB(OH)_2$, K_3PO_4, toluene, 100 °C, 18 h.



SPhos **cata*CX*ium A**

Figure 23. Structures of phosphine ligands used during optimization.

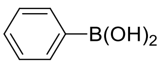
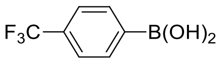
After identifying the best reaction conditions, different aryl boronic acids were applied to study the preparative scope of the reaction. Yields of isolated title compounds **21a-j** were in the range of very good to excellent. In some cases (**21k-p**), catalyst loading was increased to achieve better yields. In fact, aryl boronic acids with electron-donating and electron-withdrawing substituents were successfully applied to give similarly good yields. Moreover, the vinyl group was also tolerated giving the target compound in 76% isolated yield. Compounds **21a**,[151] **21c**[152] and **21e**[153] were previously prepared by other methods. However, there was no spectroscopic data described for **21c**.

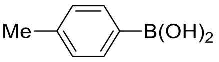
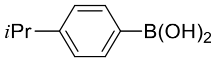
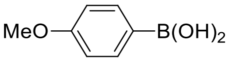
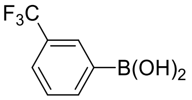
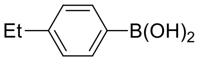
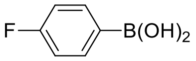
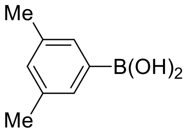
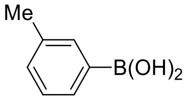
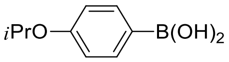
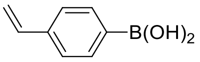
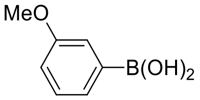
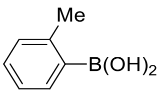
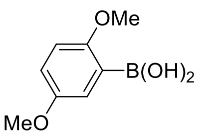
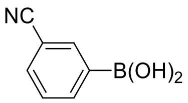


12 **21**

Scheme 20. Synthesis of **21a-p**; *i*: Ar-B(OH)$_2$ (8.0 equiv.), K$_3$PO$_4$ (8.0 equiv.), toluene, 100 °C, 18 h, for **21a-j**: Pd(OAc)$_2$ (0.25 mol%), P(Cy)$_3$ (0.5 mol%), for **21k-p**: Pd(OAc)$_2$ (2 mol%), P(Cy)$_3$ (4 mol%).

Table 15. Synthesis of **21a-p**.

Product	Boronic acid	Yield [%]^a
21a		97
21b		85

21c		93
21d		96
21e		90
21f		96
21g		87
21h		99
21i		81
21j		94
21k		92
21l		76
21m		99
21n		99
21o		74
21p		50

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[a] Yields of isolated products.

It was possible to obtain a single crystal of **21b** and to independently confirm its molecular structure by X-ray analysis. It was found that the aryl rings are twisted out of the pyrazine plane by 32-50 °forming a propeller-like arrangement (Figure 24). Given such conformation of terminal functionalities, tetraarylpyrazines possess aggregation-induced emission (AIE)[154] properties which makes them ideal candidates for being used as solid-state luminogens.[147]

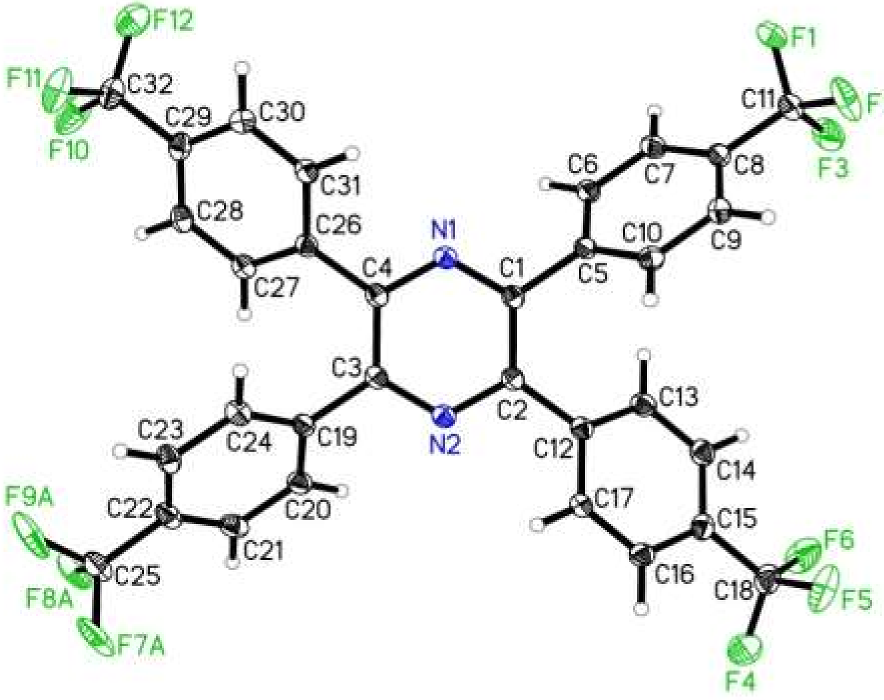


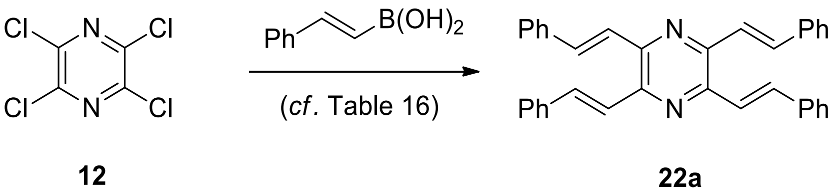
Figure 24. ORTEP of **21b** with displacement ellipsoids drawn at the probability level of 30%.

In conclusion, a facile procedure for the first synthesis of tetraaryl pyrazines via Suzuki-Miyaura reaction have been elaborated. An accurate optimization of the reaction conditions allowed the preparation of title products in good to excellent yields with the use of palladium catalyst as low as 0.25 mol% for tetra-fold coupling. The established method represents a new route towards symmetrical tetraarylated pyrazines and is more cost-efficient, provides better yields and has broader functional group tolerance in comparison to the methods reported earlier. The synthesized tetraaryl pyrazines are potential solid-state luminogens.

6.3 Synthesis of 2,3,5,6-tetraalkenylpyrazines

6.3.1 Synthesis

In continuation of the previous sub-chapter, results on multiple Suzuki-Miyaura reactions of tetrachloropyrazine with functionalized styryl boronic acids are presented herein. There are several reports on tetraalkenyl pyrazines and similar cross-shaped molecules with the focus on the electronic and optical properties of the compounds.[155] For example, owing to the two-photon absorption characteristics, several tetraalkenyl pyrazines serve as sensors and are used in the medical sphere.[156] Previously, several tetraalkenyl pyrazines were prepared by the condensation reaction of tetramethyl pyrazine with corresponding aldehydes.[156,157] Nonetheless, the application of the Suzuki-Miyaura reaction allows much milder and easier access to the target molecules providing very high yields.



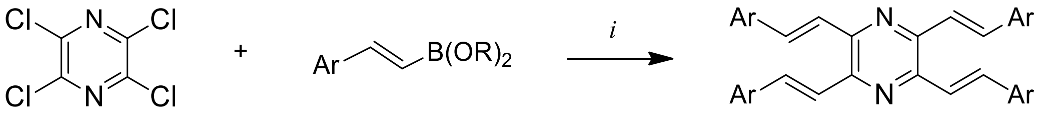
Scheme 21. Optimization of the synthesis of **22a**.

Table 16. Optimization of the synthesis of **22a.**

Entry	Catalyst and ligand	Solvent	Yield [%][a]
1	$Pd(OAc)_2$ [2 mol%] $P(Cy)_3$ [4 mol%]	toluene	12 [b]
2	$Pd(dba)_2$ [5 mol%] cata*CX*ium A [10 mol%]	dioxane	99
3	$Pd(dba)_2$ [4 mol%] cata*CX*ium A [8 mol%]	dioxane	98
4	$Pd(dba)_2$ [2 mol%] cata*CX*ium A [4 mol%]	dioxane	97
5	$Pd(dba)_2$ [1 mol%] cata*CX*ium A [2 mol%]	dioxane	95
6	$Pd(dba)_2$ [0.25 mol%] cata*CX*ium A [0.5 mol%]	dioxane	60

[a] Yields of isolated products; *conditions*: catalyst, tetrachloropyrazine, styrylboronic acid (8.0 equiv.), K_3PO_4 (8.0 equiv.), 1,4-dioxane, 100 °C, 20 h.
[b] *Conditions:* catalyst, tetrachloropyrazine, styrylboronic acid (8.0 equiv.), K_3PO_4 (8.0 equiv.), toluene, 100 °C, 20 h (identical to the conditions for the synthesis of tetraarylpyrazines, Scheme 20).

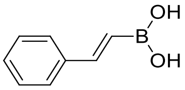
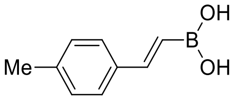
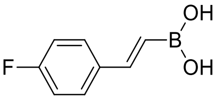
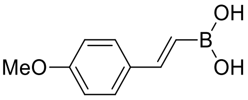
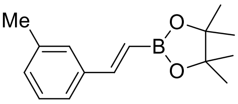
As a starting point, the reaction of starting material **12** with styryl boronic acid was tested under the conditions already developed for the synthesis of tetraarylpyrazines. Interestingly, the desired product was isolated only in 12% yield (Table 16, Entry 1). Nonetheless, the yield of the title compound **22a** was improved to quantitative by changing the phosphine ligand and the solvent.[131] As a matter of fact, the application of more sterically demanding cata*CX*ium A (10 mol%) with palladium precursor and 1,4-dioxane as the solvent proved to be extremely efficient for this reaction.



12 **22**

Scheme 22. Synthesis of **22**; *i*: Pd(dba)$_2$ (2 mol%), Cata*CX*ium A (4 mol%), alkenylboronic acid or -pinacol ester (8.0 equiv.), K$_3$PO$_4$ (8.0 equiv), 1,4-dioxane, 100 °C, 20 h.

Table 17. Synthesis of **22a-e**.

Product	Coupling partner	Yield [%][a]
22a		97
22b		95
22c		99
22d		93
22e		70

[a] Yields of isolated products.

Next, loading of the catalytic system was decreased to find out the most optimal amount for the efficient outcome of the reaction. It has been shown that the quantitative yield can be obtained even with 2 mol% of Pd-precursor and 4 mol% of phosphine ligand. Further, decrease to

0.25 mo% /0.5 mol% lowers the yield of desired tetrastyryl pyrazine to 60% (Table 16, Entry 6) Therefore, the reaction scope was investigated with the use of 2 mol% of Pd(dba)$_2$ and 4 mol% of the cata*CX*ium A (Table 17).

Various alkenyl boronic acids or their corresponding esters containing electron-withdrawing and electron-donating groups were employed to give tetraalkenyl pyrazines in good to excellent yields.

6.3.2 Photophysical Properties

As already mentioned, tetrastyryl pyrazines and similar cross-shaped structures possess various photophysical features. In this regard, it was interesting to study the UV/Vis and fluorescence properties of the synthesized 2,3,5,6-tetraalkenyl pyridines **22a**, **22c** and **22e**. It is known that similar molecules tend to undergo various photochemical reactions like isomerization or polymerizations under UV irradiation and even under daylight.[158] Therefore all the measurements were carried out with special care and only using freshly prepared probes.

The absorption wavelengths of all measured tetraalkenyl pyrazines are in the range of 323 nm – 459 nm and the spectra have three conspicuous transitions. The absorption of compound **22d** bearing electron-donating methoxy substituent is redshifted relative to the absorptions of **22a** and its fluorinated analog **22c** showing almost identical pictures. A similar tendency is observed in the emission spectra of the measured molecules. The emission spectrum of tetralkenyl pyrazine **22d** is redshifted with the fluorescence maximum of 522 nm. This shift suggests a more pronounced π-electron delocalization relative to the other measured analogs which is true in case of methoxy derivative given the push-pul pattern of the molecule. In contrast, emission maxima of products **22a** and **22c** correspond to 498 and 497 nm, respectively. The fluorescence spectra of the measured compounds have a small shoulder at lower wavenumbers. In comparison to absorbance and emission spectra, quantum yields of the measured compounds were only slightly affected by the nature of peripheral substituents of the tetraalkenyl pyrazines. The quantum yields of the products are rather high ranging from 0.55 to 061. Moreover, relatively small Stokes shifts and rather high quantum yields indicate weak intramolecular charge transfer (ICT) contributions of the measured tetraalkenyl pyrazines.

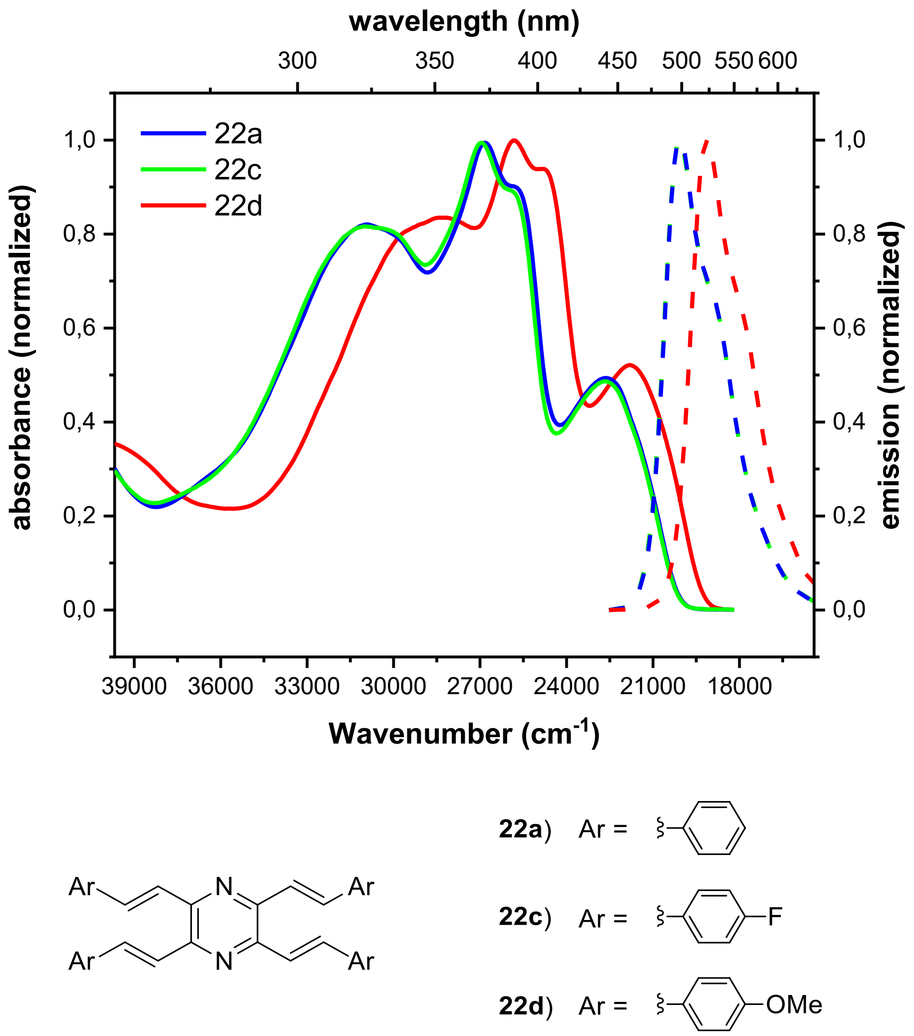


Figure 25. Normalized absorption and emission spectra of **22a**, **22c** and **22d**.

Table 18. UV/Vis absorption and fluorescence data of **22a**, **22c** and **22d** in dichloromethane.

	$\lambda_{max}^{abs}[nm]$ (ε_{abs} $[10^{-4}M^{-1}cm^{-1}]$)	$\tilde{\nu}_{Stokes}$ $[cm^{-1}]$	λ_{max}^{fluo} $[nm]$	ϕ
22a	323 (4.3), 373 (5.0), 441 (2.6)	2600	498	0.55
22c	324 (4.4), 371 (5.4), 441 (2.6)	2560	497	0.57
22d	353 (5.0), 388 (6.0), 459 (3.1)	2630	522	0.61

6.3.3 Conclusion

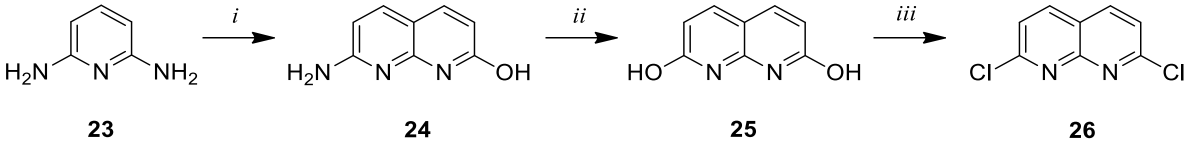
In conclusion, straightforward syntheses of several tetraalkenyl pyrazines by tetra-fold Suzuki-Miyaura reactions were performed. The desired products were isolated in high to quantitative yields consuming 0.5 mol% of palladium catalyst for each step. In addition, absorption and fluorescence spectra, as well as quantum yields of selected tetraalkenylated pyrazines, were measured. Prepared tetraalkenyl pyrazines show rather high quantum yields representing a potential candidacy for different optical and electronic applications.

6.4 Synthesis of 2,7-diaryl-1,8-naphthyridines

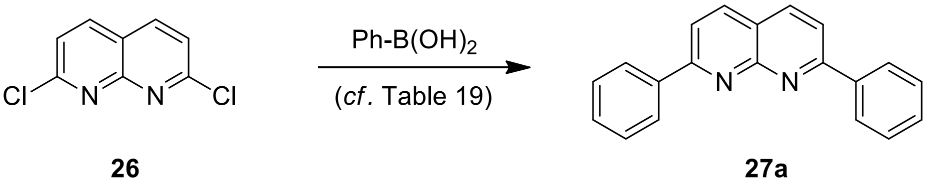
Functionalized naphthyridines have received attention due to their wide-ranging properties. For example, the feature to operate via non-covalent interactions allowed naphthyridines to be effectively used in supramolecular chemistry.[159,160] Several naphthyridines are used as sensitive probes towards biologically relevant molecules[161] and metal ions.[162] Moreover, the capacity to interact with human receptors by serving as multiple hydrogen bond acceptors makes naphthyridines interesting from the standpoint of pharmacology. It has been shown that several 2-aryl substituted 1,8-naphthyridines demonstrate high affinity towards A_1 adenosine receptor subtype. At the same time significant selectivity for the adenosine receptor A_1 as compared to the adenosine receptor subtypes A_{2a} and A_3 is determined. Consequently, those molecules can be considered as selective antagonists for A_1 subtype of adenosine receptor.[163] Another report showed that arylated naphthyridines may also serve as non-competitive antagonists of G protein-coupled metabotropic glutamate receptor 5 (mGluR 5). In this regard, non-competitive antagonists of mGluR 5 have considerable potential in the treatment of anxiety, pain, Parkinson’s disease and gastroesophageal reflux disease.[164] In addition to the above mentioned, 1,8-naphthyridines also possess a number of other pharmacological activities.[165]

Given the practical importance of the substituted 1,8-naphthyridines number of various reactions, including palladium-catalyzed cross-couplings were applied for the synthesis of new derivatives.[160,166] However, Suzuki-Miyaura reaction, which would provide a very elegant and convenient access towards the synthesis of 2,7-diaryl-1,8-naphthyridines, has not been reported before. In this sub-chapter results on the two-fold arylation of 2,7-dichloro-1,8-naphthyridines by palladium-catalyzed Suzuki coupling is presented.[167]

First of all, starting material 2,7-dichloro-1,8-naphthyridine (**26**) was synthesized in three steps following a known literature method.[168]



Scheme 23. Synthesis of 2,7-dichloro-1,8-naphthyridine; *i:* Malic acid, H_2SO_4, 110 ºC, 3 h; *ii:* $NaNO_2$, H_2SO_4, 20 °C, 5 min; *iii:* PCl_5, $POCl_3$, reflux, 2 h.



Scheme 24. Optimization of the synthesis of **27a**.

Table 19. Optimization of the synthesis of **27a**.[2]

Entry	Catalyst	Solvent	Base	T [ºC]	Yield [%][a]
1	$Pd(PPh_3)_4$	THF	Cs_2CO_3	60	27
2	$Pd_2(dba)_3$ / $HP(t\text{Bu})_3BF_4$	THF	Cs_2CO_3	60	51
3	$Pd_2(dba)_3$ / $P(Cy)_3$	THF	Cs_2CO_3	60	46
4	$Pd_2(dba)_3$ / X-Phos	THF	Cs_2CO_3	60	62
5	$Pd_2(dba)_3$ / S-Phos	THF	Cs_2CO_3	60	65
6	$Pd_2(dba)_3$ / S-Phos	dioxane	Cs_2CO_3	100	85
7	$Pd_2(dba)_3$ / S-Phos	toluene	Cs_2CO_3	100	75
8	$Pd_2(dba)_3$ / S-Phos	dioxane	K_3PO_4	100	90

[a] Yields of isolated product.

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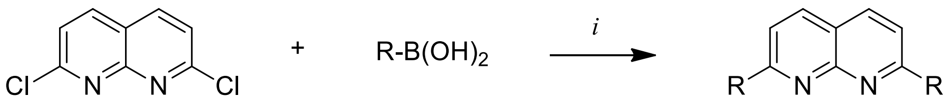
[2] Optimization reactions were performed by Dr. Peter Ehlers from the University of Rostock.

After having the starting material, conditions for the synthesis of **27a** were optimized to identify the best combination of catalyst, solvent and base. As a result, the highest yield was obtained when $Pd_2(dba)_3$ / S-Phos was used as the catalyst. At the same time, the use of potassium triphosphate and 1,4-dioxane proved to be important for reaching the most favorable result (Table 19, Entry 8).



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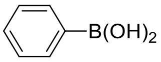
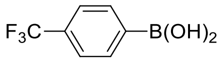
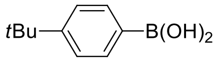
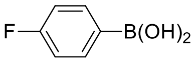
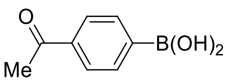
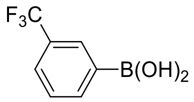
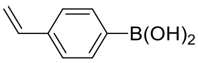
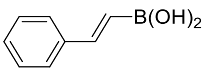
27

Scheme 25. Synthesis of **27**; *i*: $Pd_2(dba)_3$ (2.5 mol%), S-Phos (10 mol%), K_3PO_4, 1,4-dioxane, 100 ºC, 20h.

Table 20. Synthesis of **27a-h**.

Product	Boronic acid	Yield [%][a]
27a		90
27b		84
27c		92
27d		72
27e		82
27f		93
27g		64
27h		91

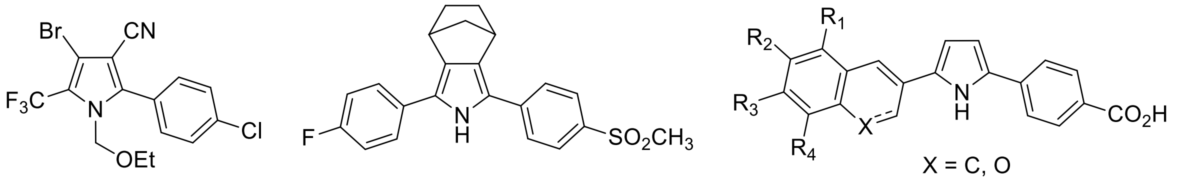
[a] Yields of isolated products.

Having the best conditions in hands, preparative scope was studied by utilization of various boronic acids (Table 20). Advantageously, the reaction has a good functional group tolerance and substituents like fluorine, acetyl- and vinyl groups were readily tolerated. Additionally, employment of *trans*-2-phenylvinylboronic acid successfully resulted in appropriate distyryl naphthyridine **27h**. The reaction with both electron-poor and electron-rich boronic acids proceeds with good to excellent yields. A slightly decreased yield (64%) of vinyl derivative **27g** may be the result of competing Heck reaction on the double bond.

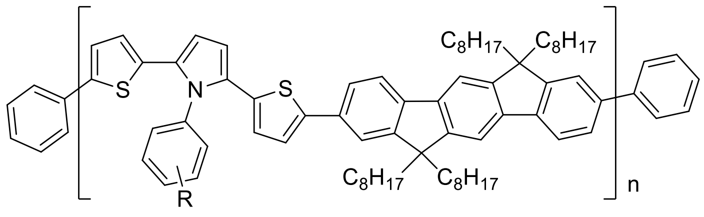
In conclusion, a convenient and easy approach for the synthesis of 2,7-diaryl-1,8-naphthyridines by Suzuki-Miyaura reactions was developed. A range of different substituents are tolerated and products are obtained in good to excellent yields. Moreover, by the application of appropriate boronic acids 2,7-dialkenyl-1,8-naphthyridines can also be prepared and isolated in very good yields.

7. Double Arylation of *N*-Phenylpyrrole by Palladium-Catalyzed C–H Activation

Pyrrole ring is represented in many important compounds in different fields of chemical research.[169] In particular, arylated pyrroles are widespread in nature and are widely used for the design and synthesis of pharmaceuticals as well as advanced materials.[170] Examples of natural products, containing pyrrole include pentabromopseudiline isolated from *Alteromonas luteo-violaceus* and the seabird hexahalogenated bipyrrole. Moreover, a number of different polymers with applications varying from biosensors to polymer light-emitting diodes have been synthesized based on pyrroles. Additionally, several arylated pyrroles have been reported to show inhibitory activity against lipoxygenase, myosin ATPase and β-secretase enzymes.[171]



Insecticide Potent COX-2 inhibitor Retinoic acid receptor agonist



Co-polymer for PLED and photovoltaic application

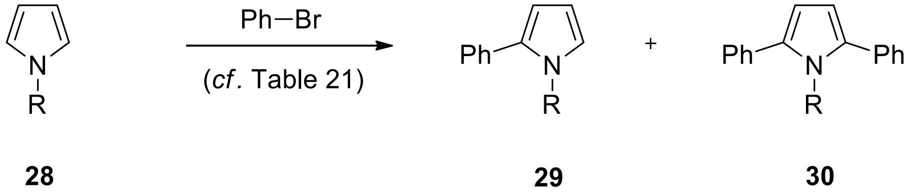
Figure 26. Several applications of aryl pyrroles.

Due to the practical importance of functionalized pyrroles, the elaboration of new and more convenient methods for the synthesis of aryl pyrroles is of great importance. In this regard, palladium-catalyzed cross-couplings are highly valuable.[58] Nonetheless, although transition metal-catalyzed traditional cross-coupling reactions are one of the most powerful and convenient tools, the development of new procedures providing better sustainability and environmental compatibility is in continuous demand. The importance of C–H activation[103] reactions in this regard has significantly increased over recent years given their advantages with respect to atom economy, cost-efficiency and environmental impact (*cf.* Chapter 4*).* However, the challenges of these reactions concerning regioselectivity still need to be addressed.[172] Additionally, C–H bond activation reactions often require solvents with relatively high toxicity and high temperatures which make them less attractive in terms of environmental friendliness.[173]

In recent years, functionalization of different five-membered heterocycles via palladium-catalyzed C–H activation reactions has been intensively investigated by several groups.[101,174] The high value of these conversions is based on the fact, that reaction selectivity can be better controlled owing to the polarization of the molecule induced by the heteroatom. Despite the big number of publications describing direct arylations of heterocycles, the majority of studies are related to monoarylations,[175] whereas multiple C–H activation is investigated much less.[176] One of the important aspects of this field is the development of environmentally friendly processes with regard to reaction media.[173] Furthermore, there is also a great interest in protocols providing ‘’ligand-free’’ conditions for C–H activation reactions.

In 2009, the group of Doucet reported monoarylation of different pyrroles through palladium-catalyzed C–H activation.[177] Later, the same research group published a paper describing the double arylation of *N*-substituted pyrroles using $PdCl(C_3H_5)(dppb)$ as the catalyst, KOAc as the base and DMAc as the solvent.[178] Independently, in our research group, a convenient method allowing the synthesis of diaryl pyrroles from another perspective has been investigated at the same time.[171] In particular, the emphasis was made to avoid the use of phosphine ligand and toxic solvents like DMA.

The reaction of *N*-methylpyrrole with bromobenzene was chosen as a model reaction for ligand-free arylations (Scheme 26). The first optimization tests with typical conditions using $Pd(OAc)_2$ and KOAc showed that the ratio of **29** and **30** is strongly affected by the solvent with monoarylated pyrrole being a major product. When tetrabutylammonium acetate (TBA-Ac) was used as the solvent the ratio changed dramatically towards the diarylation product with proportion 1:37 providing title compound in 75% yield (Table 21, Entry 5). The successful results of the application of TBA-Ac can be correlated with the reports stating that phase transfer catalysts can positively influence on the C–H activation reactions[179] and that the acetate ions can be actively involved in the catalytic cycle.[180] The importance of TBA-Ac was even more emphasized after poor results with other ionic liquids. Finally, while studying the influence of catalyst and base it was found that the combination of $Pd(OPiv)_2$ and CsOPiv allows the exclusive formation of the desired diarylated pyrrole derivative.



Scheme 26. Optimization of the synthesis of **30**; R=Me.

Table 21. Optimization of **30**[3]

Entry	PdX2	Base	Solvent	Additive	Ratio 29/30[a]	Yield of 30 [%][b]
1	$Pd(OAc)_2$	KOAc	NMP	-	2/1	21
2	$Pd(OAc)_2$	KOAc	DMA	-	3/1	7
3	$Pd(OAc)_2$	KOAc	PEG-400	-	1/2	41
4	$Pd(OAc)_2$	KOAc	PEG-400	TBA-Ac	1/1	34
5	$Pd(OAc)_2$	KOAc	TBA-Ac	-	1/37	75
6	$Pd(OAc)_2$	KOAc	TBA-Br	-	1/1	28
7	$Pd(OAc)_2$	KOAc	$[C_2MIM][BF_4]$	-	0	0
8	$Pd(OPiv)_2$	CsOPiv	TBA-Ac	-	0/1	79
9	$Pd(OPiv)_2$	CsOPiv	TBA-OPiv	-	0/1	63
10	$Pd(OPiv)_2$	-	TBA-Ac	-	0/1	43
11	-	KOAc	TBA-Ac	-	-	0
12	$Pd(OPiv)_2$	CsOPiv	$[C_2MIM][OAc]$	-	-	0

[a] Determined by ^{1}H NMR-spectroscopy of the crude product; [b] yield of isolated products; *conditions*: $Pd(X)_2$ (1 mol%), base (3.0 equiv.), Ph-Br (3.0 equiv.), solvent, additive, 140 °C, 20 h.

Having the optimal reaction conditions in hands, the two-fold arylation of *N*-phenylpyrrole with aryl halides was investigated to explore the scope and limitations of the developed method. In fact, reaction with *N*-phenylpyrrole worked smoothly to give corresponding diarylated pyrroles

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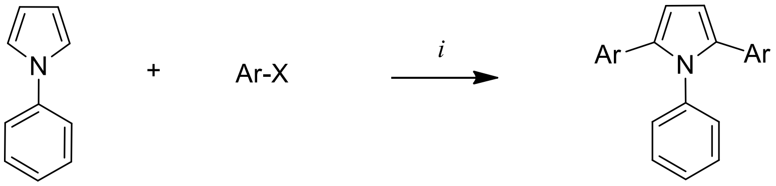
[3] Optimization reactions were performed by Dr. Peter Ehlers from the University of Rostock.

in moderate yields (Table 22). In comparison, the reaction with *N*-methyl pyrrole worked better[181] whereas *N*-Boc protected pyrrole did not provide reasonable yields.

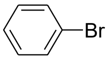
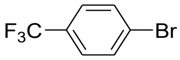
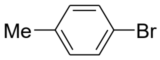
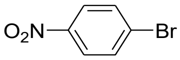
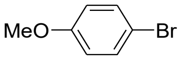
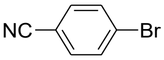
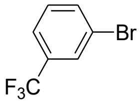
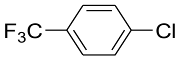
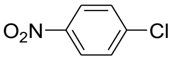
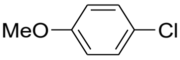


31

32

Scheme 27. Synthesis of **32a-j**; *i*: Pd(OPiv)$_2$ (1 mol%), CsOPiv, TBA-Ac, 140 ºC, 20h.

Table 22. Synthesis of **32a-j**.

Product	Aryl halide	Yield [%]^a
32a		52
32b		40
32c		37
32d		33
32e		15
32f		63
32g		31
32h		22
32i		35
32j		5^b

^{a} Yields of isolated products. ^{b} XPhos (2 mol%) is required.

Various aryl bromides were employed as coupling partners and as expected, electron-poor aryl bromides provided higher yields than electron-rich aryl bromides. Owing to the cheaper price of aryl chlorides, it was interesting to find out how efficiently they can be applied in this reaction. Therefore, several aryl chlorides have also been tested (Table 22, **32h-j**). As a result, activated aryl chlorides could also be converted into desired products although in moderate or poor yields. Contrary, no product was isolated under the same conditions when electron-rich 4-chloroanisole was used. Addition of XPhos allowed the formation of desired product **32j** only in 5% yield.

Tetrabutylammonium acetate plays a crucial role in this reaction. In various publications, it was shown, that in the presence of ammonium salts palladium acetate tends to form anionic palladates.[182] Moreover, there were reports on the reduction of those palladate complexes to zerovalent palladium at high temperatures in the presence of acetate anions.[183] Taking into account the literature data, a possible mechanism based on Pd(0)/Pd(II) catalytic cycle was proposed for this reaction (Figure 27).

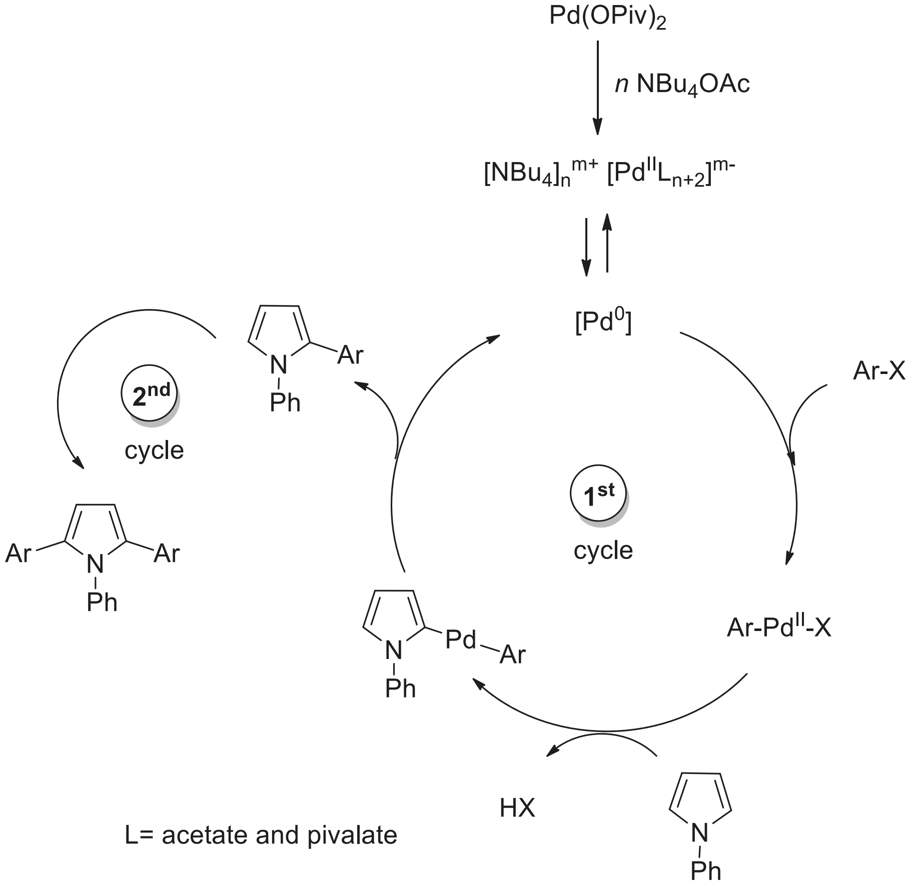


Figure 27. The proposed mechanism; species like Ar-Pd(II)-X are assumed to be negatively charged[184] due to their coordination with acetate anions.

According to the proposal, anionic palladate complexes are formed as a result of the reaction between ammonium salt and palladium(II) precursor. Meanwhile, at high temperatures, tetrabutylammonium acetate partly undergoes Hofmann elimination to from tributylamine. Subsequently, formed tributylamine molecules reduce positively charged palladium atoms into catalytically active palladium(0) species.[185] The application of ammonium acetate is substantial in terms of the multifunctional role that it plays. In such a manner, ammonium salt stabilizes catalytically active palladium(0) species, thus preventing its agglomeration to ‘’palladium black’’. Moreover, it functions as a ligand for palladium which runs a catalytic cycle. Also, ammonium salt increases the solubility of the organometallic complexes which are formed during the reaction.

In conclusion, a variety of aryl bromides and electron-poor aryl chlorides were used to synthesize different 2,5-diaryl-*N*-phenylpyrroles by twofold direct arylation of the corresponding pyrrole. The products were isolated in moderate yields and in contrast to the procedure suggested by Doucet *et al*., these reactions proceed under ‘‘ligand-free’’ conditions, which reduces the cost of the reactions. Moreover, the reactions were carried out in molten ammonium acetate and no toxic solvents were used. In fact, this approach is very advantageous in terms of both cost-effectiveness and environmental sustainability.

8. Summary and Outlook

The presented work describes the functionalization of various polychlorinated pyridines and pyrazine by Sonogashira and Suzuki cross-coupling reactions. The use of sterically demanding and highly basic monodentate phosphine ligands led to high yields of the corresponding products. With this synthetic approach, various tetraalkynylated pyridines and pyrazines were prepared. In addition, a number of different pentaarylpyridines, tetraarylpyrazines, diarylnaphthyridines as well as tetraalkenylpyrazines have been synthesized.

A number of polyalkynylated and polyalkenylated compounds were examined with regard to their optical properties by UV/ Vis and fluorescence spectroscopy and compared. When comparing the results it has been observed that the introduction of a nitrogen atom into the aromatic core remarkably improves the fluorescence quantum yield. So, given the push-pull character of the tetraalkynylated pyrazines, their quantum yields are almost twice higher than those of corresponding pyridine and benzene analogs. Electron donating substituents on the peripheral alkynyl residues resulted in an increase of the quantum yields. Compound **13d** was found to have the highest quantum efficiency of 85%. Electrochemical studies of tetraalkynylpyrazines were also performed showing similar structure-activity correlation. Synthesized tetraalkynyl heterocycles have great potential for optical and electronic applications.

Furthermore, the site-selective Suzuki and Sonogashira reactions of polychlorinated pyridines were investigated. In this context, pyridines bearing different functional groups have been isolated. This study is particularly interesting as the properties of molecules can be fine-tuned by varying the substitution pattern.

Next, the synthesis of 2,7-diaryl-1,8-naphthyridines by Suzuki-Miyaura reaction of the corresponding dichloronaphthyridine was developed. The products have been obtained in good to excellent yields and may potentially be biologically active.

Additionally, two-fold "ligand-free" C–H arylations of *N*-phenylpyrrole were performed. The reaction was carried out in molten tetrabutylammonium acetate as a solvent. The procedure is of interest in terms of environmental sustainability since an ionic liquid was used instead of toxic solvents. A possible mechanism of the reaction was proposed. The obtained products can be of particular interest from the perspective of pharmaceutical chemistry.

The gained results are expected to encourage further research interest towards the methodologies to access multiply functionalized heterocycles.

Appendix

Experimental Section

General Remarks

All reactions involving moisture- or air-sensitive reagents were carried out in oven-dried pressure tubes under argon atmosphere. Anhydrous solvents were purchased from commercial sources or dried by the usual methods. Solvents for column chromatography and extraction were always distilled before use. All chemicals, unless otherwise indicated, were obtained from commercial sources and were used without further purification steps. The synthesis of the starting materials, if not purchased, was carried out by literature methods.

Thin layer chromatography (TLC): Merck Silica 60 F254 on aluminum tin foil from Macherey-Nagel. Detection with UV light at 254 nm and/or 366 nm without dipping reagent

Column chromatography: Separation on Fluka silica gel 60 (0.063-0.200 mm, 70-320 mesh). Eluents were distilled before use.

^{1}H NMR-Spectroscopy: Bruker AV 300 (300 MHz), Bruker AV 400 (400 MHz), and Fourier 300 (300 MHz). Unless otherwise mentioned, all NMR spectra were collected in $CDCl_3$ solution. Chemical shifts are given as *δ*-values in ppm relative to the residual signal peak of the deuterated solvent. Coupling constants are indicated as *J* with residual peaks of $CHCl_3$ at $\delta = 7.24$ ppm and DMSO at $\delta = 2.49$ ppm. Peak characterization: s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, sept = septet, m = multiplet. In several cases, 2D NMR techniques (NOESY, COSY) were performed confirming the structures of the synthesized molecules. The spectra were measured with a standard number of scans.

^{13}C NMR-Spectroscopy: Bruker AV 300 (75 MHz), Bruker AV 400 (100 MHz), and Fourier 300 (75 MHz). Unless otherwise mentioned, all NMR spectra were collected in $CDCl_3$ solution. All chemical shifts are given in ppm. Coupling constants are indicated as *J* with residual peaks of $CHCl_3$ at $\delta = 77.0$ ppm and DMSO at $\delta = 39.52$ ppm. Peak characterization: d = doublet, q = quartet. DEPT method was used for determining the presence of primary, secondary, tertiary and quaternary carbon atoms. All spectra were measured with a standard number of scans.

^{19}F NMR-Spectroscopy: Bruker AV 300 (282 MHz). Spectra were measured with a standard number of scans.

Mass Spectrometry (MS): Finnigan MAT 95 XP (electron ionization EI, 70 eV) or LCQ (electrospray ionization, 70 eV). The ratio of mass to charge is indicated with intensities relative to the base peak (I = 100).

Gas Chromatography MS (GCMS): Agilent HP-5890 with an Agilent HP-5973 mass selective detector (EI) and HP-5 capillary column with helium carrier gas.

High resolution MS: Agilent 1969A TOF (ESI) or Finnigan MAT 95 XP (EI). Only the measurements with an average deviation from the theoretical mass of ± 2 mDa were accounted as correct.

Infrared spectroscopy (IR): Nicolet 550 FT-IR spectrometer with ATR sampling technique. Liquid probes were measured as film, solid probes were measured neat. Absorption is given in wavenumbers (cm-1). Signal characterization: w = weak, m = medium, s = strong.

UV/Vis spectroscopy: Lambda 5 (Perkin Elmer) or Specord 50 (Analytik Jena) or Perkin-Elmer Compounds were measured in dichloromethane and a concentration of 5×10^{-6} M was applied for the quantitative determination of molar extinction coefficients.

Fluorescence spectroscopy: Fluoromax-4 Spectrofluorometer (Horiba Scientific). Compounds were measured in dichloromethane in a concentration of 5×10^{-6} M. A solution of quinine sulfate in 0.05 M sulphuric acid was applied as a standard for the measurement of the fluorescence quantum yields ($\phi_f = 0.52$).[186] Air-equilibrated solutions of the sample and standard with an absorbance of ~0.1 at the excitation wavelength were used in the fluorescence measurements.

Electrochemistry: Autolab (PGSTAT 302N, Metrohm). All electrochemical studies were performed at room temperature in anhydrous acetonitrile under an argon atmosphere with 0.1 M tetrabutylammonium hexafluorophosphate as conducting salt. A glassy carbon disk electrode ($d = 2$ mm) was used as working electrode, a Pt-electrode as the counter electrode and an Ag/AgCl/LiCl$_{\text{sat.}}$ in EtOH-system as the reference electrode (all electrodes: Metrohm). All potentials mentioned in this work were measured with respect to this reference system and were checked by using the ferrocenium/ferrocene-internal reference system (potential of Fc$^+$/Fc: 0.51 V [*vs.* Ag/AgCl/LiCl$_{\text{sat.}}$ in EtOH]. The CV scans were done three times at a scan rate of 40 mV s^{-1}. The measurements were performed with 2 mM compound dissolved in the electrolyte.

X-Ray crystallography: STOE IPDS II diffractometer as well as Bruker Kappa APEX II Duo using graphite-monochromated MoKα radiation. The structures were solved by direct methods and refined by full-matrix least-squares procedures on *F2* with the SHELXTL software package.[187]

Differential Scanning Calorimetry (DSC): Mettler Toledo DSC 823e/2007. Phase transitions were determined in heating and cooling runs, respectively.

Polarization Microscopy (POM): LaborLux 12 Pol-5, Leica.

Elemental analysis: C/H/N/S – Microanalysator TruSpec CHNS (Leco). Abbreviated as EA.

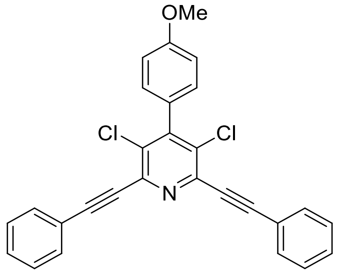
Melting point determination (mp): Micro-Hot-Stage GalenTM III Cambridge Instruments. The melting points are not corrected.

General Procedures and Product Characterization

Synthesis of 3,5-dichloro-2,6-dialkinylpyridines

0.025 mmol (5 mol%) $Pd(PPh_3)_4$, 0.025 mmol (5 mol%) CuI and 0,5 mmol of the 2,3,5,6-tetrachloropyridine **4a** or **4b** were added to an argon-flushed glass pressure tube. The solids were diluted with 5 ml of dry 1,4-dioxane and 2 ml of diisopropylamine. The solution was stirred at ambient temperature for ten minutes. Afterward, the appropriate alkyne was added. The pressure tube was closed with a teflon cap and the reaction mixture was stirred at 90 °C. After 20h the reaction was cooled down to room temperature and diluted with distilled water and dichloromethane. The water phase was extracted with dichloromethane (three times). The combined organic layers were dried with sodium sulfate, filtered and the solvent was evaporated under reduced pressure. Column chromatography (eluents: hexane/dichloromethane) was used to purify the desired dialkynylpyridines.

Dichloro-2,6-bis(phenylethynyl)-4-(4-methoxyphenyl)pyridine (5a)



According to the general procedure, compound **5a** was isolated as a dark yellow solid (107 mg, 59%); mp. = 160 – 162 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 3.87 (s, 3H, OCH$_3$), 7.00 - 7.05 (m, 2H, CH), 7.19 - 7.24 (m, 2H, CH), 7.32 - 7.39 (m, 6H, CH), 7.60 - 7.64 (s, 4H, CH).

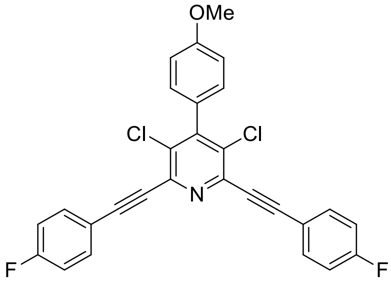
^{13}C NMR (75 MHz, CDCl$_3$): δ = 55.2 (OCH$_3$), 85.6, 95.2 (C≡C), 114.0 (CH), 121.7, 126.8 (C), 128.4, 129.5, 130.0, 132.2 (CH), 133.2, 140.7, 147.7, 160.0 (C).

MS (EI, 70 eV): m/z (%) = 453 (M$^+$, 100), 374 (5), 340 (9), 226 (10), 170 (5), 128 (5).

HRMS (EI, 70 eV): calcd. for $C_{28}H_{17}Cl_2NO$: 453.06817; found: 453.068246.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2930 (w), 2836 (w), 2214 (m), 1608 (m), 1504 (s), 1441 (m), 1369 (s), 1291 (m), 1248 (s), 1211 (m), 1175 (s), 1028 (m), 752 (s), 684 (s), 528 (s).

3,5-Dichloro-2,6-bis((4-fluorophenyl)ethynyl)-4-(4-methoxyphenyl)pyridine (5b)



According to the general procedure, compound **5b** was isolated as a yellow solid (70 mg, 36%); mp. = 121 – 123 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 3.81 (s, 3H, OCH$_3$), 6.94 - 7.03 (m, 6H, CH), 7.12 - 7.16 (m, 2H, CH), 7.51 - 7.57 (m, 4H, CH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 55.3 (OCH$_3$), 85.4, 94.2 (C≡C), 114.0 (CH), 115.8 (d, $^2J_{C–F}$ = 22.5 Hz, CH), 117.8 (d, $^4J_{C–F}$ = 3.2 Hz, C), 126.7 (C), 130.0 (CH), 133.2 (C), 134.3 (d, $^3J_{C–F}$ = 8.3 Hz, CH), 140.6, 160.0 (C), 163.2 (d, $^1J_{C-F}$ = 251.9 Hz, CF).

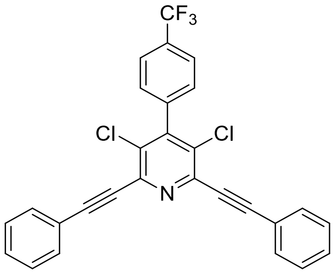
^{19}F NMR (282 MHz, $CDCl_3$): δ = -108.0 (s, 2F, CF). MS (EI, 70 eV): m/z (%) = 489 (M^+, 100), 376 (11), 246 (8), 231 (8), 174 (7), 137 (5).

HRMS (EI, 70 eV): calcd. for $C_{28}H_{15}Cl_2F_2NO$: 489.04933; found: 489.049254.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3048 (w), 2933 (w), 2840 (w), 2216 (m), 1599 (m), 1508 (s), 1371 (m), 1292 (m), 1227 (s), 1153 (s), 1025 (m), 830 (s), 768 (s), 528 (s), 399 (m).

EA: calcd. for $C_{28}H_{15}Cl_2F_2NO$ (490,33): C, 68.59; H, 3.08; N, 2.86; found: C, 68.76; H, 3.16; N, 2.81.

3,5-Dichloro-2,6-bis(phenylethynyl)-4-(4-(trifluoromethyl)phenyl)pyridine (5c)



According to the general procedure, compound **5c** was isolated as a yellow solid (86 mg, 62%); mp. = 208 – 210 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 - 7.42 (m, 8H, CH), 7.60 - 7.64 (m, 4H, CH), 7.78 (d, 2H, ^3J = 8.2 Hz, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 85.3, 95.9 (C≡C), 121.5 (C), 123.8 (q, $^1J_{C–F}$ = 272.3 Hz, CF_3), 125.7 (q, $^3J_{C–F}$ = 3.6 Hz, CH), 128.4, 129.1, 129.6 (CH), 131.2 (q, $^2J_{C–F}$ = 32.8 Hz, C), 132.2 (CH), 132.3, 138.1, 140.9, 146.6 (C).

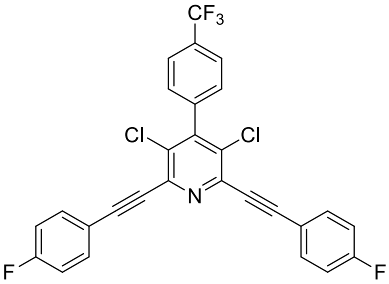
^{19}F NMR (282 MHz, $CDCl_3$):δ =-62.3 (s, 3F, CF_3).

MS (EI, 70 eV): m/z (%) = 491 (M^+, 100), 351 (7), 294 (20), 245 (7), 127 (6).

HRMS (EI, 70 eV): calcd. for $C_{28}H_{14}Cl_2F_3N$: 491.04499; found: 491.04493.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3055 (w), 2925 (w), 2211 (m), 1372 (m), 1321 (s), 1167 (m), 1120 (s), 1062 (s), 1018 (m), 846 (m), 754 (s), 685 (s), 527 (m).

3,5-Dichloro-2,6-bis((4-fluorophenyl)ethynyl)-4-(4-(trifluoromethyl)phenyl)pyridine (5d)



According to the general procedure, compound **5d** was isolated as a yellow solid (95 mg, 64%); mp. = 179 – 181 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.01 - 7.09 (m, 4H, CH), 7.39 - 7.41 (m, 2H, CH), 7.56 - 7.63 (m, 4H, CH), 7.76 - 7.79 (m, 2H, CH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 85.0 (d, $^5J = 1.3$ Hz, C≡C), 94.8 (C≡C), 115.9 (d, $^2J_{C\text{–}F} = 21.8$ Hz, CH), 117.5 (d, $^4J_{C\text{–}F} = 3.8$ Hz, C), 123.7 (q, $^1J_{C\text{–}F} = 272.5$ Hz, CF$_3$), 125.8 (q, $^3J_{C\text{–}F} = 3.8$ Hz, CH), 129.1 (CH), 131.2 (q, $^2J_{C\text{–}F} = 32.8$ Hz, C), 132.3 (C), 134.3 (d, $^3J_{C\text{-}F} = 8.3$ Hz, CH), 138.0, 140.8, 146.6 (C), 163.3 (d, $^1J_{C\text{–}F} = 252.3$ Hz, CF).

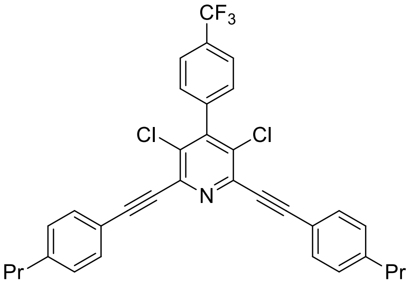
^{19}F NMR (282 MHz, CDCl$_3$): δ = -62.3 (s, 3F, CF$_3$), -107.6 (s, 2F, CF).

MS (EI, 70 eV): m/z (%) = 527 (M$^+$, 100), 387 (7), 312 (22), 264 (8), 145 (13).

HRMS (EI, 70 eV): calcd. for $C_{28}H_{13}Cl_2F_5N$ ([M+H]$^+$): 528.034; found: 528.034.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2216 (m), 1600 (m), 1508 (s), 1372 (m), 1321 (s), 1231 (s), 1155 (s), 1063 (s), 1018 (m), 833 (s), 770 (s), 529 (s), 445 (s).

3,5-Dichloro-2,6-bis((4-propylphenyl)ethynyl)-4-(4-(trifluoromethyl)phenyl)pyridine (5e)



According to the general procedure, compound **5e** was isolated as a brown oil (112 mg, 69%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, 6H, ^3J = 7.3 Hz, CH_3), 1.56 - 1.69 (m, 4H, CH_2), 2.58 (t, 4H, ^3J = 7.6 Hz, CH_2), 7.15 - 7.19 (m, 4H, CH), 7.39 - 7.41 (m, 2H, CH), 7.51 - 7.55 (m, 4H, CH), 7.76 - 7.78 (m, 2H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (CH_3), 24.2, 38.0 (CH_2), 85.0, 96.3 (C≡C), 118.6 (C), 123.8 (q, $^1J_{C–F}$ = 272.3 Hz, CF_3), 125.7 (q, $^3J_{C–F}$ = 3.8 Hz, CH), 128.6, 129.1 (CH), 131.1 (q, $^2J_{C–F}$ = 32.6 Hz, C), 131.9 (C), 132.2 (CH), 138.2, 141.0, 144.8, 146.4(C).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -62.2 (s, 3F, CF_3). MS (EI, 70 eV): m/z (%) = 575 (M^+, 100), 546 (57), 518 (12), 258 (48), 207 (16), 73 (13), 60 (14), 44 (37), 36 (17).

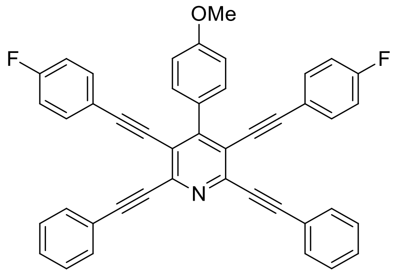
HRMS (ESI): calcd. for $C_{34}H_{27}Cl_2F_3N$ ($[M+H]^+$): 578.14469; found: 578.14466.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2959 (w), 2930 (w), 2871 (w), 2212 (m), 1513 (m), 1371 (m), 1321 (s), 1165 (m), 1062 (s), 1019 (m), 842 (m), 813 (m), 731 (m).

Synthesis of 2,3,5,6-tetraalkynylpyridines from 3,5-dichloro-2,6-dialkynylpyridines

0.006 mmol (2 mol%) $PdCl_2(CH_3CN)_2$, 0.012 mmol (4 mol%) XPhos, 0.006 mmol (2 mol%) CuI and 0,3 mmol of the corresponding 3,5-dichloro-2,6-dialkynylpyridine **5** were added to an argon-flushed glass pressure tube. The solids were diluted with 4.0 ml of dry 1,4-dioxane and 2 ml of diisopropylamine. The solution was stirred at ambient temperature for ten minutes. Afterward, the appropriate amount of acetylene was added. The pressure tube was closed with a teflon cap and the reaction mixture was stirred at 90 °C. After 18h the reaction was cooled down to room temperature and diluted with distilled water and dichloromethane. The water phase was extracted with dichloromethane (three times). The combined organic layers were dried with sodium sulfate, filtered and the solvent was evaporated under reduced pressure. Column chromatography (eluents: hexane/dichloromethane) was used to purify the corresponding tetraalkynylpyridines.

4-(4-Methoxyphenyl)-2,6-bis(phenylethynyl)-3,5-bis((4-fluorophenyl)ethynyl)pyridine (6a)



According to the general procedure, compound **6a** was isolated as a yellow solid (77 mg, 62%); mp. = 207 – 209 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 3.81 (s, 3H, OCH$_3$), 6.83 - 6.91 (m, 4H, CH), 6.94 - 6.99 (m, 2H, CH), 7.16 - 7.30 (m, 10H, CH), 7.51 - 7.54 (m, 4H, CH), 7.56 - 7.61 (m, 2H, CH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 55.3 (OCH$_3$), 85.7 (d, ^5J = 1.3 Hz, C≡C), 88.2, 94.6, 99.0 (C≡C), 112.9 (CH), 115.7 (d, $^2J_{C–F}$ = 21.8 Hz, CH), 118.7 (d, $^4J_{C–F}$ = 3.2 Hz, C), 120.7, 122.1, 128.3 (C), 128.4, 129.3, 131.3, 132.1 (CH), 133.4 (d, $^3J_{C–F}$ = 8.4 Hz, CH), 143.8, 152.2, 160.1 (C), 162.7 (d, $^1J_{C-F}$ = 251.0 Hz, CF).

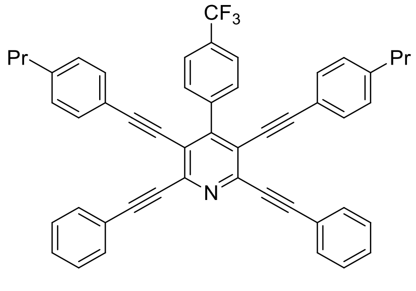
^{19}F NMR (282 MHz, CDCl$_3$): δ = -108.9 (s, 2F, CF).

MS (EI, 70 eV): m/z (%) = 621 (M$^+$, 100), 590 (14), 577 (19), 503 (62), 459 (13), 207 (7).

HRMS (ESI): calcd. for $C_{44}H_{26}F_2NO$ ([M+H]$^+$): 622.1977; found: 622.1975.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3051 (w), 2206 (m), 1597 (s), 1494 (s), 1387 (m), 1296 (m), 1222 (s), 1022 (s), 835 (s), 754 (s), 689 (s), 527 (s).

4-(4-(Trifluoromethyl)phenyl)-2,6-bis(phenylethynyl)-3,5-bis((4-propylphenyl)ethynyl)–pyridine (6b)



According to the general procedure, compound **6b** was isolated as a yellow solid (135 mg, 68%); mp. = 198 – 200 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.90 (t, 6H, ^3J = 7.3 Hz, CH$_3$), 1.54 - 1.66 (m, 4H, CH$_2$), 2.55 (t, 4H, ^3J = 7.6 Hz, CH$_2$), 7.06 - 7.14 (m, 8H, CH), 7.31 - 7.39 (m, 6H, CH), 7.62 - 7.65 (m, 4H, CH), 7.76 - 7.82 (m, 4H, CH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.7 (CH$_3$), 24.2, 37.9 (CH$_2$), 84.7, 88.0, 94.9, 101.4 (C≡C), 119.4, 120.8, 122.1 (C), 124.1 (q, $^1J_{C\text{–}F}$ = 272.3 Hz, CF$_3$), 124.7 (q, $^3J_{C\text{–}F}$ = 3.8 Hz, CH), 128.4, 128.6, 129.3, 130.2 (CH), 130.7 (q, $^2J_{C\text{–}F}$ = 32.6 Hz, C), 131.3, 132.2 (CH), 140.3, 143.5, 144.3, 151.0 (C).

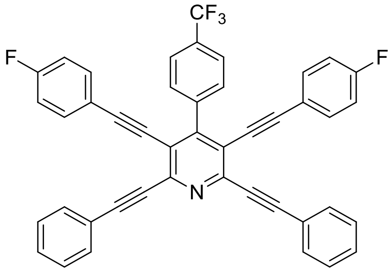
^{19}F NMR (282 MHz, CDCl$_3$): δ = -62.1 (s, 3F, CF$_3$).

MS (EI, 70 eV): m/z (%) = 707 (M$^+$, 100), 664 (7), 634 (4).

HRMS (EI, 70 eV): calcd. for $C_{50}H_{36}F_3N$: 707.27944; found: 707.27842.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2928 (w), 2864 (w), 2201 (m), 1499 (m), 1387 (m), 1320 (s), 1166 (s), 1110 (s), 1064 (s), 846 (m), 751 (s), 684 (s), 528 (m).

4-(4-(Trifluoromethyl)phenyl)-2,6-bis(phenylethynyl)-3,5-bis((4-fluorophenyl)ethynyl)–pyridine (6c)



According to the general procedure, compound **6c** was isolated as a yellow solid (101 mg, 61%); mp. = 199 – 201 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.91 - 6.99 (m, 4H, CH), 7.13 - 7.20 (m, 4H, CH), 7.31 - 7.40 (m, 6H, CH), 7.58 - 7.61 (m, 4H, CH), 7.75 - 7.82 (m, 4H, CH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 84.8 (d, ^5J = 1.2 Hz, C≡C), 87.8, 95.2, 99.9 (C≡C), 115.8 (d, $^2J_{C\text{–}F}$ = 21.8 Hz, CH), 118.3 (d, $^4J_{C\text{–}F}$ = 3.8 Hz, C), 120.5, 121.9 (C), 124.0 (q, $^1J_{C\text{–}F}$ = 272.1 Hz, CF$_3$), 124.8 (q, $^3J_{C\text{–}F}$ = 3.6 Hz, CH), 128.5, 129.5, 130.1 (CH), 130.9 (q, $^2J_{C\text{–}F}$ = 32.6 Hz, C), 132.1 (CH), 133.4 (d, ${}^{3}J_{C\text{-}F}$ = 8.3 Hz, CH), 140.2, 143.8, 151.2 (C), 163.0 (d, ${}^{1}J_{C\text{–}F}$ = 252.3 Hz, CF).

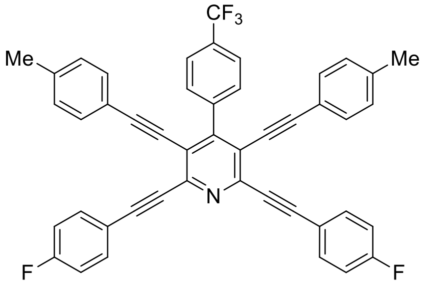
^{19}F NMR (282 MHz, $CDCl_3$): δ = -62.1 (s, 3F, CF_3), -108.4 (s, 2F, CF).

MS (EI, 70 eV): m/z (%) = 659 (M^+, 100), 590 (6).

HRMS (EI, 70 eV): calcd. for $C_{44}H_{22}F_5N$: 659.16669; found: 659.16518.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3048 (w), 2204 (m), 1598 (m), 1502 (s), 1330 (s), 1228 (m), 1104 (s), 1068 (s), 831 (s), 748 (s), 684 (m), 527 (s), 387 (m).

4-(4-(Trifluoromethyl)phenyl)-2,6-bis((4-fluorophenyl)ethynyl)-3,5-bis(*p*-tolylethynyl)pyridine (6d)



According to the general procedure, compound **6d** was isolated as a yellow solid (155 mg, 90%); mp. = 239 – 241 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32 (s, 6H, CH_3), 6.97 - 7.06 (m, 12H, CH), 7.52 - 7.59 (m, 4H, CH), 7.75 - 7.81 (m, 4H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (CH_3), 84.6, 87.8 (d, ${}^{5}J$ = 1.3 Hz, C≡C), 93.7, 101.3 (C≡C), 115.8 (d, ${}^{2}J_{C\text{–}F}$ = 22.5 Hz, CH), 118.2 (d, ${}^{4}J_{C\text{–}F}$ = 3.8 Hz, C), 119.1, 120.8 (C), 124.0 (q, ${}^{1}J_{C\text{–}F}$ = 272.1 Hz, CF_3), 124.6 (q, ${}^{3}J_{C\text{–}F}$ = 3.8 Hz, CH), 129.2, 130.2 (CH), 130.7 (q, ${}^{2}J_{C\text{–}F}$ = 32.4 Hz, C), 131.2 (CH), 134.1 (d, ${}^{3}J_{C\text{-}F}$ = 8.3 Hz, CH), 139.6, 140.1, 143.4, 150.9 (C), 163.1 (d, ${}^{1}J_{C\text{–}F}$ = 251.7 Hz, CF).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -62.1 (s, 3F, CF_3), -108.3 (s, 2F, CF).

MS (EI, 70 eV): m/z (%) = 687 (M^+, 100), 672 (12), 624 (27), 609 (13), 593 (21), 573 (25), 262 (15), 188 (19), 145 (17), 117 (12), 60 (16).

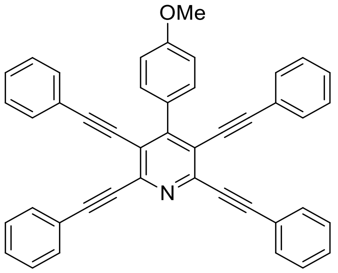
HRMS (EI, 70 eV): calcd. for $C_{46}H_{26}F_5N$: 687.19799; found: 687.19785.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3045 (w), 2202 (m), 1598 (m), 1507 (s), 1390 (m), 1321 (s), 1227 (s), 1154 (s), 1122 (s), 1064 (s), 1017 (m), 832 (s), 812 (s), 526 (s).

Synthesis of 2,3,5,6-tetraalkynylpyridines from 2,3,5,6-tetrachloropyridines

0.01 mmol (4 mol%) $PdCl_2(CH_3CN)_2$, 0.02 mmol (8 mol%) XPhos, 0.0075 mmol (3 mol%) CuI and 0,25 mmol of the corresponding 2,3,5,6-tetrachloropyridine **4a** or **4b** were added to an argon-flushed glass pressure tube. The solids were diluted with 3.5 ml of dry 1,4-dioxane and 2 ml of diisopropylamine. The solution was stirred at ambient temperature for ten minutes. Afterward, the appropriate amount of acetylene was added. The pressure tube was closed with a teflon cap and the reaction mixture was stirred at 90 °C. After 20h the reaction was cooled down to room temperature and diluted with distilled water and dichloromethane. The water phase was extracted with dichloromethane (three times). The combined organic layers were dried with sodium sulfate, filtered and the solvent was evaporated under reduced pressure. Column chromatography (eluents: hexane/dichloromethane) was used to purify the corresponding tetraalkynylpyridines.

4-(4-Methoxyphenyl)-2,3,5,6-tetrakis(phenylethynyl)pyridine (7a)



According to the general procedure, compound **7a** was isolated as a dark yellow solid (140 mg, 80%); mp. = 210 – 212 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.90 (s, 3H, OCH_3), 7.03 - 7.08 (m, 2H, CH), 7.25 - 7.38 (m, 16H, CH), 7.62 - 7.70 (m, 6H, CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.3 (OCH_3), 86.0, 88.3, 94.5, 100.1 (C≡C), 113.0 (CH), 120.9, 122.2, 122.7 (C), 128.3, 128.4 (CH), 128.5 (C), 128.8, 129.2, 131.3, 131.4, 132.1 (CH), 144.0, 152.3, 160.1 (C).

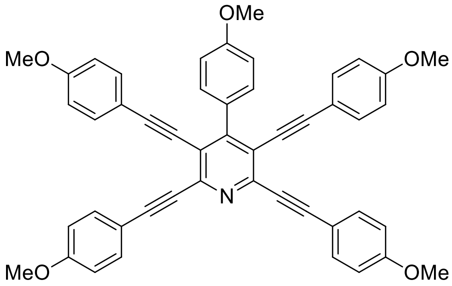
MS (EI, 70 eV): m/z (%) = 585 (M^+, 100), 554 (21), 541 (25), 485 (16), 465 (10), 105 (8).

HRMS (EI, 70 eV): calcd. for $C_{44}H_{27}NO$: 585.20872; found: 585.208882.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3059 (w), 3035 (w), 3017 (w), 2206 (m), 1605 (m), 1491 (s), 1388 (m), 1293 (m), 1293 (m), 1254 (s), 1173 (m), 1024 (m), 910 (m), 831 (m), 748 (s), 684 (s), 526 (s).

EA: calcd. for $C_{44}H_{27}NO$ (585.69): C, 90.23; H, 4.65; N, 2.39; found: C, 90.03; H, 4.46; N, 2.57.

4-(4-Methoxyphenyl)-2,3,5,6-tetrakis((4-methoxyphenyl)ethynyl)pyridine (7b)



According to the general procedure, compound **7b** was isolated as an orange solid (123 mg, 58%); mp. = 191 – 193 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.83 (s, 6H, OCH_3), 3.86 (s, 6H, OCH_3), 3.94 (s, 3H, OCH_3), 6.81 - 6.86 (m, 4H, CH), 6.89 - 6.93 (m, 4H, CH), 7.05 - 7.10 (m, 2H, CH), 7.27 - 7.32 (m, 4H, CH), 7.59 - 7.63 (m, 4H, CH), 7.68 - 7.73 (m, 2H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.3 (3 x OCH_3), 85.1, 87.6, 94.6, 99.9 (C≡C), 112.9, 114.0, 114.1 (CH), 114.4, 115.0, 120.5, 128.8 (C), 131.3, 132.9, 133.7 (CH), 143.6, 151.6, 159.9, 160.0, 160.3 (C).

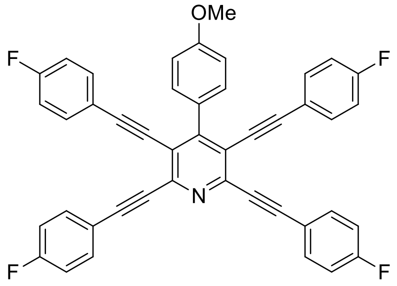
MS (EI, 70 eV): m/z (%) = 705 (M^+, 29), 147 (10), 131 (4), 114 (4), 85 (4), 73 (9), 69 (15), 60 (10), 55 (8), 44 (100).

HRMS (ESI): calcd. for $C_{48}H_{36}NO_5$ ($[M+H]^+$): 706.2588; found: 706.25855.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2931 (w), 2833 (w), 2196 (m), 1600 (s), 1508 (s), 1387 (m), 1244 (s), 1167 (s), 1022 (s), 825 (s), 531 (s).

EA: calcd. for $C_{48}H_{35}NO_5$ (705,80): C, 81.68; H, 5.00; N, 1.98; found: C, 81.64; H, 5.04; N, 1.94.

4-(4-Methoxyphenyl)-2,3,5,6-tetrakis((4-fluorophenyl)ethynyl)pyridine (7c)



According to the general procedure, compound **7c** was isolated as a yellow solid (144 mg, 73%); mp. = 238 – 240 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.90 (s, 3H, OCH_3), 6.93 - 7.08 (m, 10H, CH), 7.23 - 7.30 (m, 4H, CH), 7.55 - 7.66 (m, 6H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.4 (OCH_3), 85.6 (d, ^{5}J = 1.2 Hz, C≡C), 87.9 (d, ^{5}J = 1.2 Hz, C≡C), 93.5, 99.0 (C≡C), 113.0 (CH), 115.8 (d, $^{2}J_{C–F}$ = 22.5 Hz, CH), 115.9 (d, $^{2}J_{C–F}$ = 22.5 Hz, CH), 118.2 (d, $^{4}J_{C–F}$ = 3.2 Hz, C), 118.7 (d, $^{4}J_{C–F}$ = 3.0 Hz, C), 120.7, 128.3 (C), 131.2 (CH), 133.3 (d, $^{3}J_{C–F}$ = 8.3 Hz, CH), 134.1 (d, $^{3}J_{C–F}$ = 8.3 Hz, CH), 143.8, 152.3, 160.2 (C), 162.8 (d, $^{1}J_{C–F}$ = 251.7 Hz, CF), 163.1 (d, $^{1}J_{C–F}$ = 251.7 Hz, CF).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -108.2 (s, 2F, CF), -108.7 (s, 2F, CF).

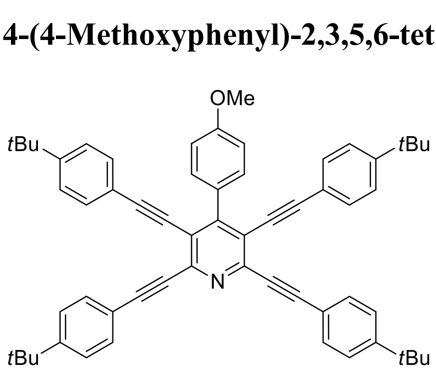
MS (EI, 70 eV): m/z (%) = 657 (M^+, 100), 626 (13), 613 (16), 585 (40), 541 (6).

HRMS (EI, 70 eV): calcd. for $C_{44}H_{23}F_4NO$: 657.17103; found: 657.171825.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3050 (w), 2930 (w), 2838 (w), 2212 (m), 1600 (m), 1505 (s), 1371 (w), 1295 (w), 1235 (s), 1177 (m), 1153 (m), 1021 (m), 830 (s), 595 (m), 527 (s), 391 (m).

EA: calcd. for $C_{44}H_{23}F_4NO$ (657.65): C, 80.36; H, 3.53; N, 2.13; found: C, 80.26; H, 3.36; N, 2.32.

4-(4-Methoxyphenyl)-2,3,5,6-tetrakis((4-*tert*-butylphenyl)ethynyl)pyridine (7d)



According to the general procedure, compound **7d** was isolated as a dark yellow solid (172 mg, 71%); mp. = 264 – 266 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.29 (s, 18H, CH$_3$), 1.32 (s, 18H, CH$_3$), 3.91 (s, 3H, OCH$_3$), 7.01 - 7.03 (m, 2H, CH), 7.25 - 7.33 (m, 8H, CH), 7.35 - 7.39 (m, 4H, CH), 7.56 - 7.61 (m, 4H, CH), 7.64 - 7.68 (m, 2H, CH).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 31.1 (2 x CH$_3$), 34.8, 34.9 (C), 55.3 (OCH$_3$), 85.6, 88.0, 94.7, 100.2 (C≡C), 113.0 (CH), 119.4, 119.9, 120.8 (C), 125.3, 125.4 (CH), 128.8 (C), 131.2, 131.3, 132.0 (CH), 143.8, 152.1, 152.2, 152.6, 160.0 (C).

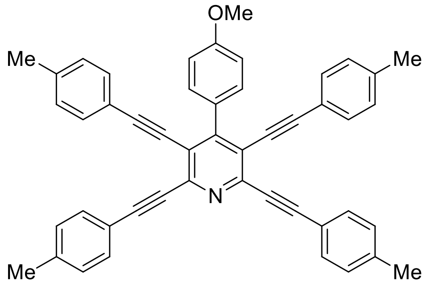
MS (EI, 70 eV): m/z (%) = 809 (M$^+$, 100), 752 (11), 696 (5), 57 (4).

HRMS (EI, 70 eV): calcd. for $C_{60}H_{59}NO$: 809.45912; found: 809.459528.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3036 (w), 2956 (m), 2902 (m), 2865 (m), 2206 (m), 1607 (m), 1502 (m), 1391 (m), 1247 (s), 1176 (m), 1104 (m), 829 (s), 558 (s).

EA: calcd. for $C_{60}H_{59}NO$ (810.12): C, 88.96; H, 7.34; N, 1.73; found: C, 88.78; H, 7.25; N, 1.66.

4-(4-Methoxyphenyl)-2,3,5,6-tetrakis(*p*-tolylethynyl)pyridine (7e)



According to the general procedure, compound **7e** was isolated as an orange solid (121 mg, 63%); mp. = 208 – 210 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.33 (s, 6H, CH$_3$), 2.37 (s, 6H, CH$_3$), 3.89 (s, 3H, OCH$_3$), 7.02 - 7.09 (m, 6H, CH), 7.14 - 7.17 (m, 4H, CH), 7.21 - 7.24 (m, 4H, CH), 7.52 - 7.55 (m, 4H, CH), 7.65 - 7.68 (m, 2H, CH).

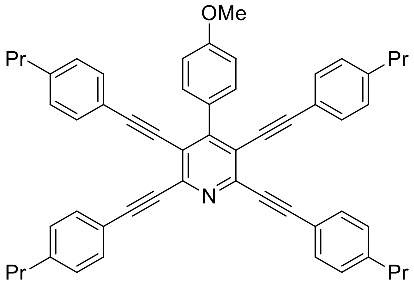
^{13}C NMR (75 MHz, CDCl$_3$): δ = 21.5, 21.6 (CH$_3$), 55.3 (OCH$_3$), 85.6, 87.9, 94.8, 100.2 (C≡C), 112.9 (CH), 119.3, 119.7, 120.7, 128.6 (C), 129.1, 129.2, 131.4 (2 x CH), 132.1 (CH), 139.1, 139.5, 143.8, 152.0, 160.0 (C). MS (EI, 70 eV): m/z (%) = 641 (M^+, 100), 626 (7), 610 (7), 576 (11), 220 (24).

HRMS (EI, 70 eV): calcd. for $C_{48}H_{35}NO$: 641.27132; found: 641.270953.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2951 (w), 2918 (w), 2203 (m), 1604 (m), 1509 (s), 1388 (m), 1292 (m), 1249 (s), 1176 (s), 1110 (m), 1025 (m), 808 (s), 526 (s).

EA: calcd. for $C_{48}H_{35}NO$ (641.80): C, 89.83; H, 5.50; N, 2.18; found: C, 89.74; H, 5.31; N, 2.11.

4-(4-Methoxyphenyl)-2,3,5,6-tetrakis((4-propylphenyl)ethynyl)pyridine (7f)



According to the general procedure, compound **7f** was isolated as an orange solid (160 mg, 71%); mp. = 91 – 93 °C.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 - 0.96 (m, 12H, CH_3), 1.54 - 1.70 (m, 8H, CH_2), 2.53 - 2.62 (m, 8H, CH_2), 3.90 (s, 3H, OCH_3), 7.01 - 7.10 (m, 6H, CH), 7.13 - 7.17 (m, 4H, CH), 7.22 - 7.26 (m, 4H, CH), 7.53 - 7.57 (m, 4H, CH), 7.64 - 7.68 (m, 2H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 13.7 (CH_3), 24.2, 24.2, 37.9, 38.0 (CH_2), 55.3 (OCH_3), 85.6, 87.9, 94.8, 100.2 (C≡C), 112.9 (CH), 119.5, 120.0, 120.7 (C), 128.5, 128.5 (CH), 128.7 (C), 131.3, 131.4, 131.5 (CH), 132.1, 143.8, 144.2, 152.0, 160.0 (C).

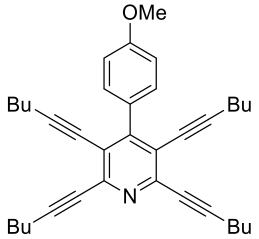
MS (EI, 70 eV): m/z (%) = 753 (M^+, 100), 724 (3), 710 (13), 667 (3), 220 (2), 91 (3), 73 (2).

HRMS (EI, 70 eV): calcd. for $C_{56}H_{51}NO$: 753.39652; found: 753.397094.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3028 (w), 2956 (m), 2927 (m), 2868 (m), 2204 (m), 1606 (m), 1508 (s), 1389 (s), 1292 (m), 1248 (s), 1176 (s), 1111 (m), 1030 (m), 811 (s), 532 (s).

EA: calcd. for $C_{56}H_{51}NO$ (754.01): C, 89.20; H, 6.82; N, 1.86; found: C, 89.36; H, 6.76; N, 1.86.

4-(4-Methoxyphenyl)-2,3,5,6-tetra(hex-1-ynyl)pyridine (7g)



According to the general procedure, compound **7g** was isolated as a brown oil (40 mg, 26%).

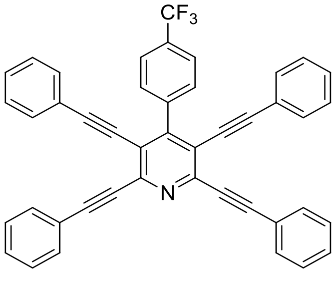
^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 0.80$ (t, 6H, $^3J = 7.2$ Hz, CH$_3$), 0.89 (t, 6H, $^3J = 7.2$ Hz, CH$_3$), 1.16 - 1.28 (m, 4H, CH$_2$), 1.32 - 1.62 (m, 12H, CH$_2$), 2.26 (t, 4H, $^3J = 6.8$ Hz, CH$_2$), 2.44 (t, 4H, $^3J = 6.8$ Hz, CH$_2$), 3.82 (s, 3H, OCH$_3$), 6.86 - 6.91 (m, 2H, CH), 7.32 - 7.37 (m, 2H, CH).

^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 13.5$, 13.6 (CH$_3$), 19.3, 19.4, 21.6, 21.9, 30.2, 30.3 (CH$_2$), 55.1 (OCH$_3$), 76.9, 79.8, 95.2, 100.7 (C≡C), 112.7 (CH), 120.6, 129.3 (C), 130.7 (CH), 143.7, 152.7, 159.4 (C).

MS (EI, 70 eV):m/z (%) = 505 (M$^+$, 100), 490 (10), 476 (15), 463 (24), 448 (16), 73 (10), 66 (16), 43 (10). HRMS (EI, 70 eV): calcd. for $C_{36}H_{43}NO$: 505.33392; found: 505.333727.

IR (ATR, cm^{-1}): $\tilde{\nu} = 2955$ (m), 2929 (m), 2226 (m), 1608 (m), 1495 (s), 1462 (m), 1388 (s), 1291 (m), 1246 (s), 1176 (m), 1032 (m), 832 (m).

4-(4-(Trifluoromethyl)phenyl)-2,3,5,6-tetrakis(phenylethynyl)pyridine (8a)



According to the general procedure, compound **8a** was isolated as a yellow solid (88 mg, 50%); mp. = 256 – 258 °C.

^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 7.10$ - 7.29 (m, 16H, CH), 7.52 - 7.55 (m, 4H, CH), 7.70 - 7.74 (s, 4H, CH).

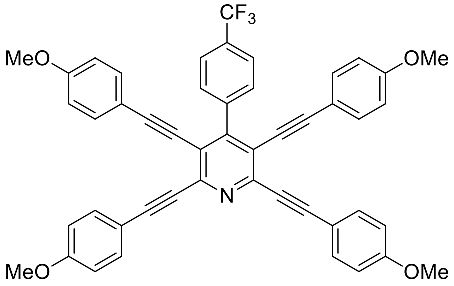
^{13}C NMR (75 MHz, $CDCl_3$): δ = 85.2, 87.9, 95.1, 100.9 (C≡C), 120.6, 122.0, 122.2 (C), 124.0 (q, $^1J_{C-F}$ = 272.2 Hz, CF_3), 124.7 (q, $^3J_{C-F}$ = 3.6 Hz, CH), 128.4 (2 x CH), 129.1, 129.4, 130.2 (CH), 130.8 (q, $^2J_{C-F}$ = 32.5 Hz, C), 131.4, 132.2 (CH), 140.2, 143.8, 151.2 (C).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -62.1 (s, 3F, CF_3). MS (EI, 70 eV): m/z (%) = 623 (M^+, 100), 554 (6), 546 (7), 275 (6).

HRMS (ESI): calcd. for $C_{44}H_{25}F_3N$ ($[M+H]^+$): 624.19336; found: 624.19312.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3053 (w), 2203 (m), 1490 (m), 1389 (m), 1321 (s), 1157 (m), 1116 (s), 1063 (s), 1018 (m), 847 (m), 748 (s), 684 (s), 525 (s), 396 (m).

4-(4-(Trifluoromethyl)phenyl)-2,3,5,6-tetrakis((4-methoxyphenyl)ethynyl)pyridine (8b)



According to the general procedure, compound **8b** was isolated as a yellow solid (105 mg, 56%); mp. = 223 – 225 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.78 (s, 6H, OCH_3), 3.82 (s, 6H, OCH_3), 6.76 - 6.81 (m, 4H, CH), 6.84 - 6.89 (m, 4H, CH), 7.11 - 7.16 (m, 4H, CH), 7.54 - 7.58 (m, 4H, CH), 7.74 - 7.80 (m, 4H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.3 (2 x OCH_3), 84.4, 87.3, 95.1, 100.8 (C≡C), 114.1 (2 x CH), 114.2, 114.5, 120.2 (C), 124.1 (q, $^1J_{C-F}$ = 272.3 Hz, CF_3), 124.6 (q, $^3J_{C-F}$ = 3.6 Hz, CH), 130.2 (CH), 130.6 (q, $^2J_{C-F}$ = 32.6 Hz, C), 132.9, 133.8 (CH), 140.6, 143.5, 150.5, 160.2, 160.4 (C).

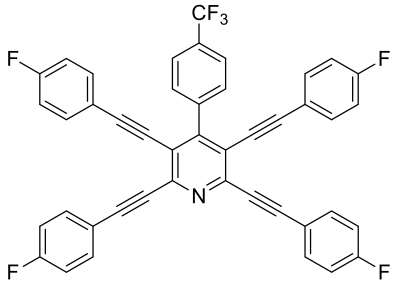
^{19}F NMR (282 MHz, $CDCl_3$): δ = -62.0 (s, 3F, CF_3).

MS (EI, 70 eV): m/z (%) = 743 (M^+, 100), 688 (13), 613 (6), 330 (40), 69 (14), 44(34).

HRMS (EI, 70 eV): calcd. for $C_{48}H_{32}F_3NO_4$: 743.22779; found: 743.22886.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3009 (w), 2934 (w), 2839 (w), 2202 (m), 1603 (s), 1509 (s), 1440 (m), 1326 (s), 1291 (s), 1248 (s), 1167 (s), 1114 (s), 1019 (s), 827 (s), 532 (s).

4-(4-(Trifluoromethyl)phenyl)-2,3,5,6-tetrakis((4-fluorophenyl)ethynyl)pyridine (8c)



According to the general procedure, compound **8c** was isolated as a yellow solid (122 mg, 63%); mp. = 252 – 254 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.93 - 7.08 (m, 8H, CH), 7.12 - 7.18 (m, 4H, CH), 7.54 - 7.61 (m, 4H, CH), 7.73 - 7.82 (m, 4H, CH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 84.7 (d, ^5J = 1.2 Hz, C≡C), 87.5 (d, ^5J = 1.2 Hz, C≡C), 94.0, 99.9 (C≡C), 115.9 (d, $^2J_{C–F}$ = 21.8 Hz, CH), 116.0 (d, $^2J_{C–F}$ = 21.8 Hz, CH), 118.0 (d, $^4J_{C–F}$ = 3.8 Hz, C), 118.2 (d, $^4J_{C–F}$ = 3.8 Hz, C), 120.5 (C), 124.0 (q, $^1J_{C–F}$ = 272.5 Hz, CF$_3$), 124.8 (q, $^3J_{C–F}$ = 3.8 Hz, CH), 130.1 (CH), 131.0 (q, $^2J_{C–F}$ = 32.6 Hz, C), 133.3 (d, $^3J_{C–F}$ = 8.3 Hz, CH), 134.1 (d, $^3J_{C–F}$ = 8.3 Hz, CH), 140.1, 143.7, 151.2 (C), 163.0 (d, $^1J_{C–F}$ = 251.7 Hz, CF), 163.2 (d, $^1J_{C–F}$ = 251.73 Hz, CF).

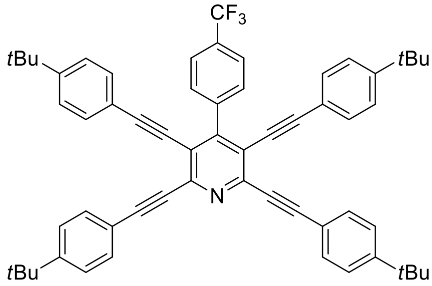
^{19}F NMR (282 MHz, CDCl$_3$): δ = -62.1 (s, 3F, CF$_3$), -107.8 (s, 2F, CF), -108.1 (s, 2F, CF).

MS (EI, 70 eV): m/z (%) = 695 (M$^+$, 100), 626 (10), 600 (9), 73 (6), 43 (10).

HRMS (EI, 70 eV): calcd. for $C_{44}H_{20}F_7N$: 695.14785; found: 695.14823.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3069 (w), 2208 (m), 1600 (m), 1505 (s), 1329 (s), 1229 (s), 1153 (s), 1101 (s), 1067 (s), 1019 (m), 828 (s), 525 (s), 387 (s).

4-(4-(Trifluoromethyl)phenyl)-2,3,5,6-tetrakis((4-(*tert*-butyl)phenyl)ethynyl)pyridine (8d)



According to the general procedure, compound **8d** was isolated as a yellow solid (160 mg, 75%); mp. = 214 – 216 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.29 (s, 18H, CH$_3$), 1.33 (s, 18H, CH$_3$), 7.14 - 7.18 (m, 4H, CH), 7.28 - 7.32 (m, 4H, CH), 7.36 - 7.40 (m, 4H, CH), 7.56 - 7.60 (m, 4H, CH), 7.76 - 7.82 (m, 4H, CH).

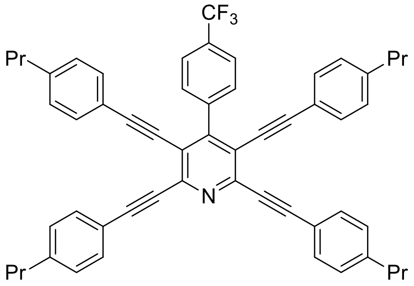
^{13}C NMR (75 MHz, CDCl$_3$): δ = 31.0, 31.1 (CH$_3$), 34.8, 34.9 (C), 84.8, 87.6, 95.4, 101.1 (C≡C), 119.1, 119.3, 120.5 (C), 124.1 (q, $^1J_{C\text{–}F}$ = 272.3 Hz, CF$_3$), 124.7 (q, $^3J_{C\text{–}F}$ = 3.8 Hz, CH), 125.4 (2 x CH), 130.2 (CH), 130.6 (q, $^2J_{C\text{–}F}$ = 32.4 Hz, C), 131.2, 132.0 (CH), 140.4, 143.7, 151.1, 152.5, 152.7 (C).

^{19}F NMR (282 MHz, CDCl$_3$): δ = -62.0 (s, 3F, CF$_3$).

MS (EI, 70 eV): m/z (%) = 847 (M$^+$, 100), 832 (7), 409 (7), 57 (7). HRMS (ESI): calcd. for C$_{60}$H$_{57}$F$_3$N ([M+H]$^+$): 848.44376; found: 848.44333.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2960 (m), 2904 (w), 2868 (w), 2207 (m), 1502 (m), 1392 (m), 1325 (s), 1266 (m), 1166 (s), 1121 (s), 1064 (s), 1017 (m), 831 (s), 559 (s).

4-(4-(Trifluoromethyl)phenyl)-2,3,5,6-tetrakis((4-propylphenyl)ethynyl)pyridine (8e)



According to the general procedure, compound **8e** was isolated as a yellow solid (165 mg, 74%); mp. = 152 – 154 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.88 - 0.97 (m, 12H, CH$_3$), 1.54 - 1.71 (m, 8H, CH$_2$), 2.53 - 2.62 (m, 8H, CH$_2$), 7.06 - 7.17 (m, 12H, CH), 7.54 - 7.56 (m, 4H, CH), 7.75 - 7.81 (m, 4H, CH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.7 (2 x CH$_3$), 24.2 (2 x CH$_2$), 37.9, 38.0 (CH$_2$), 84.8, 87.7, 95.3, 101.1 (C≡C), 119.3, 119.5, 120.5 (C), 124.1 (q, $^1J_{C\text{–}F}$ = 272.1 Hz, CF$_3$), 124.6 (q,

${}^3J_{C-F}$ = 3.8 Hz, CH), 128.6 (2 x CH), 130.2 (CH), 130.6 (q, ${}^2J_{C-F}$ = 32.6 Hz, C), 131.3, 132.1 (CH), 140.4, 143.7, 144.1, 144.4, 150.9 (C).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -62.0 (s, 3F, CF_3). MS (EI, 70 eV): m/z (%) = 791 (M^+, 100), 762 (2), 748 (6).

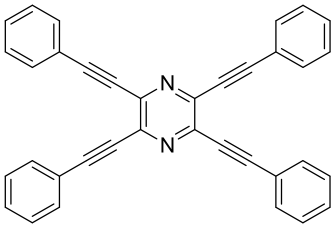
HRMS (ESI): calcd. for $C_{56}H_{49}F_3N$ ($[M+H]^+$): 792.38116; found: 792.38098.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956 (w), 2927 (w), 2867 (w), 2200 (m), 1507 (m), 1385 (m), 1323 (s), 1162 (s), 1123 (s), 1064 (s), 1018 (m), 843 (s), 812 (s), 710 (w), 529 (m), 397 (w).

Synthesis of 2,3,5,6-tetraethynylpyrazines

An argon-flushed glass pressure tube was charged with 2.3 mg of $[PdCl_2(CH_3CN)_2]$ (0.009 mmol, 3 mol%), 8.6 mg of XPhos (0.018 mmol, 6 mol%), 2.8 mg of CuI (0.015 mmol, 5mol%) and tetrachloropyrazine (65.4 mg, 0.3mmol), followed by the addition of anhydrous 1,4-dioxane (4 mL), 0.5 mL of HN(*i*-Pr)$_2$ and appropriate alkyne (1.8 mmol, 6 equiv.). The tube was sealed with a teflon cap and the reaction mixture was stirred at 100 °C for 20 hours. The resulting mixture was cooled down to room temperature, diluted with water and extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated. The crude residue was purified by column chromatography on silica gel using a mixture of hexane and dichloromethane as eluent.

2,3,5,6-Tetrakis(phenylethynyl)pyrazine (13a)



According to the general procedure, compound **13a** was isolated as a dark yellow solid (121 mg, 84%); mp. = 221 – 223 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 - 7.45 (m, 12H), 7.62 - 7.67 (m, 8H).

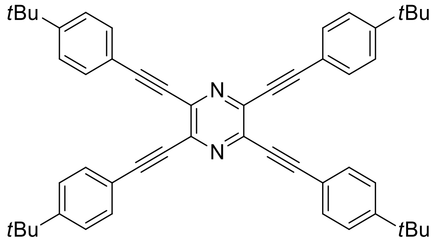
^{13}C NMR (75 MHz, $CDCl_3$): δ = 86.0 (C≡C), 97.7, 121.6 (C), 128.5, 129.8, 132.2 (CH), 139.0 (C).

MS (EI, 70 eV): m/z (%) = 480 (M^+, 100), 226 (47), 127 (3).

HRMS (EI, 70 eV): calcd. for $C_{36}H_{20}N_2$: 480.16210; found: 480.16222.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3052 (w), 2208 (m), 1489 (m), 1385 (m), 1164 (m), 1138 (m), 746 (s), 680 (s), 529 (s), 486 (m).

2,3,5,6-Tetrakis((4-(*tert*-butyl)phenyl)ethynyl)pyrazine (13b)



According to the general procedure, compound **13b** was isolated as a dark yellow solid (186 mg, 88%); mp. = 282 – 284 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.33 (s, 36H, CH$_3$), 7.38 - 7.42 (m, 8H), 7.57 - 7.61 (m, 8H).

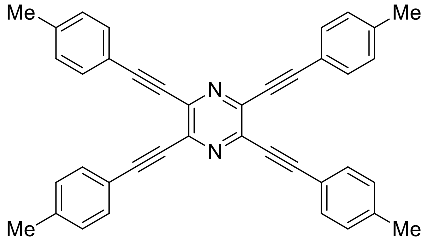
^{13}C NMR (75 MHz, CDCl$_3$): δ = 31.0 (CH$_3$), 34.9 ($C_{t\text{-Bu}}$), 85.8, 97.9 (C≡C), 118.6 (C), 125.5, 132.0 (CH), 138.9, 153.2 (C).

MS (EI, 70 eV): m/z (%) = 704 (M$^+$, 100), 690 (4), 456 (6), 337 (8).

HRMS (ESI): calcd. for $C_{52}H_{53}N_2$ ([M+H]$^+$): 705.42033; found: 705.4202.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956 (m), 2863 (w), 2206 (m), 1503 (m), 1386 (m), 1162 (m), 1104 (m), 828 (s), 557 (s).

2,3,5,6-Tetrakis(*p*-tolylethynyl)pyrazine (13c)



According to the general procedure, compound **10c** was isolated as a dark yellow solid (134 mg, 83%); mp. = 296 – 298 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.38 (s, 12H, CH$_3$), 7.16 - 7.19 (m, 8H), 7.51 - 7.55 (m, 8H).

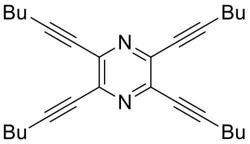
^{13}C NMR (75 MHz, CDCl$_3$): δ = 21.6 (CH$_3$), 5.8, 97.9 (C≡C), 118.6 (C), 129.3, 132.1 (CH), 138.9, 140.2 (C).

MS (EI, 70 eV): m/z (%) = 536 (M$^+$, 100), 268 (3), 254 (26), 239 (3), 44 (6).

HRMS (EI, 70 eV): calcd. for $C_{40}H_{28}N_2$: 536.22470; found: 536.22606.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2910 (w), 2195 (m), 1508 (m), 1374 (m), 1157 (m), 807 (s), 527 (s), 417 (m).

2,3,5,6-Tetra(hex-1-yn-1-yl)pyrazine (13e)



According to the general procedure, compound **13e** was isolated as a brown oil (53 mg, 44%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.90 (t, ^3J = 7.1 Hz, 12H, CH$_3$), 1.40 - 1.63 (m, 16H, CH$_2$), 2.46 (t, ^3J = 6.9 Hz, 8H, CH$_2$).

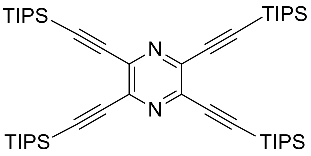
^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.5 (CH$_3$), 19.3, 21.9, 30.1 (CH$_2$), 77.8, 98.8 (C≡C), 138.6 (C).

MS (EI, 70 eV): m/z (%) = 400 (M$^+$, 100), 371 (10), 357 (18), 125 (12), 111 (22), 83 (26), 71 (28), 57 (44).

HRMS (EI, 70 eV): calcd. for $C_{28}H_{36}N_2$: 400.28730; found: 400.28703.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956 (m), 2927 (m), 2961 (w), 2228 (m), 1380 (s), 1160 (m), 496 (m).

2,3,5,6-Tetrakis((triisopropylsilyl)ethynyl)pyrazine (13f)



According to the general procedure, compound **13f** was isolated as a light yellow solid (188 mg, 78%); mp. = 234 – 236 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.08 - 1.17 (m, 84H).

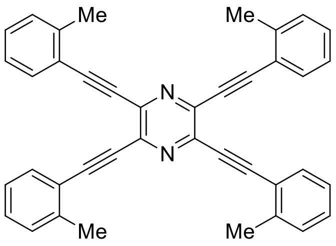
^{13}C NMR (75 MHz, CDCl$_3$): δ = 11.3 (CH), 18.6 (CH$_3$), 101.1, 102.5 (C≡C), 138.0 (C).

MS (EI, 70 eV): m/z (%) = 800 (M^+, 11), 757 (33), 715 (100), 611 (8), 569 (16).

HRMS (EI, 70 eV): calcd. for $C_{48}H_{84}N_2Si_4$: 800.57061; found: 800.57168.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2941 (m), 2864 (m), 1460 (m), 1350 (s), 1157 (m), 997 (m), 881 (s), 767 (m), 678 (s), 655 (s), 580 (m).

2,3,5,6-Tetrakis(*o*-tolylethynyl)pyrazine (13g)



According to the general procedure, compound **13g** was isolated as a yellow solid (132 mg, 82%); mp. = 214 – 216 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.49 (s, 12H, CH_3), 7.13 - 7.31 (m, 12H), 7.57 (dd, 4H, ^3J = 7.7 Hz, ^4J = 1.3 Hz).

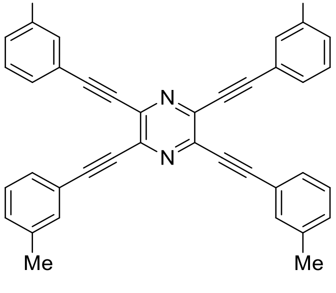
^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8 (CH_3), 89.7, 96.4 (C≡C), 121.4 (C), 125.6, 129.6, 129.7, 132.7 (CH), 138.9, 141.2 (C).

MS (EI, 70 eV): m/z (%) = 536 (M^+, 100), 521 (7), 268 (8), 252 (93), 239 (11), 140 (8), 115 (11).

HRMS (EI, 70 eV): calcd. for $C_{40}H_{28}N_2$: 536.22470; found: 536.22429.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2943 (w), 2200 (m), 1485 (m), 1454 (m), 1375 (m), 1147 (m), 755 (s), 713 (m), 491 (m).

2,3,5,6-Tetrakis(*m*-tolylethynyl)pyrazine (13h)



According to the general procedure, compound **13h** was isolated as a dark yellow solid (96 mg, 60%); mp. = 201 – 203 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.32 (s, 12H, CH$_3$), 7.20 - 7.29 (m, 8H), 7.44 - 7.48 (m, 8H).

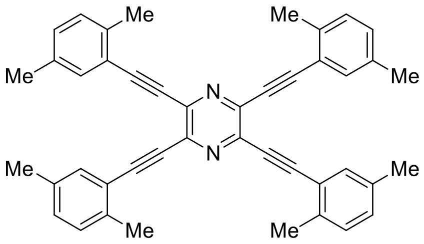
^{13}C NMR (75 MHz, CDCl$_3$): δ = 21.1 (CH$_3$), 85.9, 98.0 (C≡C), 121.4 (C), 128.4, 129.3, 130.7, 132.8 (CH), 138.2, 139.1 (C).

MS (EI, 70 eV): m/z (%) = 536 (M$^+$, 100), 254 (28), 69 (5), 44 (13).

HRMS (ESI): calcd. for $C_{48}H_{28}N_2$ ([M+H]$^+$): 537.23253; found: 537.23248.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2917 (w), 2197 (m), 1483 (m), 1380 (m), 1153 (m), 773 (s), 682 (s), 496 (s).

2,3,5,6-Tetrakis((2,5-dimethylphenyl)ethynyl)pyrazine (13i)



According to the general procedure, compound **13i** was isolated as a yellow solid (140 mg, 79%); mp. = 237 – 239 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.25 (s, 12H, CH$_3$), 2.45 (s, 12H, CH$_3$), 7.06 - 7.12 (m, 8H), 7.39 (bs, 4H).

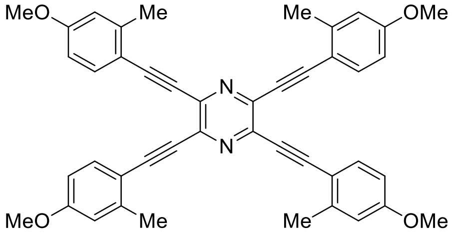
^{13}C NMR (75 MHz, CDCl$_3$): δ = 20.3, 20.6 (CH$_3$), 89.5, 96.8 (C≡C), 121.2 (C), 129.4, 130.6, 133.2 (CH), 135.0, 138.1, 139.0 (C).

MS (EI, 70 eV): m/z (%) = 592 (M$^+$, 100), 281 (6), 266 (9), 252 (6).

HRMS (EI, 70 eV): calcd. for $C_{44}H_{36}N_2$: 592.28730; found: 592.28697.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2916 (w), 2201 (m), 1496 (m), 1367 (m), 1154 (m), 828 (m), 809 (s), 496 (s), 460 (m).

2,3,5,6-Tetrakis((4-methoxy-2-methylphenyl)ethynyl)pyrazine (13j)



According to the general procedure, compound **13j** was isolated as a dark yellow solid (116 mg, 59%); mp. = 220 – 221 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.46 (s, 12H, CH$_3$), 3.80 (s, 12H, OCH$_3$), 6.68 - 6.74 (m, 8H), 7.49 (d, 4H, ^3J = 8.4 Hz).

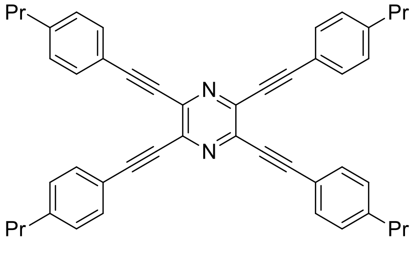
^{13}C NMR (75 MHz, CDCl$_3$): δ = 21.1 (CH$_3$), 55.2 (OCH$_3$), 89.1, 96.5 (C≡C), 111.4 (CH), 113.8 (C), 115.1, 134.2 (CH), 138.7, 143.2, 160.5 (C).

MS (EI, 70 eV): m/z (%) = 656 (M$^+$, 100), 641 (4), 569 (3), 328 (3), 226 (3), 84 (3), 66 (3), 44 (6).

HRMS (EI, 70 eV): calcd. for $C_{44}H_{36}N_2O_4$: 656.26696; found: 656.26471.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2931 (w), 2837 (w), 2195 (m), 1602 (m), 1565 (m), 1494 (m), 1280 (m), 1242 (m), 1115 (m), 1040 (m), 865 (s), 807 (s), 500 (s).

2,3,5,6-Tetrakis((4-propylphenyl)ethynyl)pyrazine (13k)



According to the general procedure, compound **13k** was isolated as a yellow solid (95 mg, 49%); mp. = 189 – 191 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.93 (t, 12H, ^3J = 7.3 Hz, CH$_3$), 1.58 - 1.71 (m, 8H, CH$_2$), 2.58 - 2.63 (m, 8H, CH$_2$), 7.16 - 7.20 (m, 8H), 7.53 - 7.57 (m, 8H).

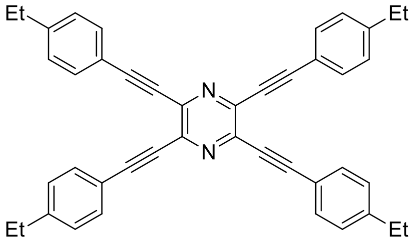
^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.7 (CH$_3$), 24.2, 38.0 (CH$_2$), 85.8, 97.9 (C≡C), 118.9 (C), 128.7, 132.2 (CH), 138.9, 144.9 (C).

MS (EI, 70 eV): m/z (%) = 648 (M$^+$, 100), 281 (11), 252 (6), 66 (6), 44 (17).

HRMS (EI, 70 eV): calcd. for $C_{48}H_{44}N_2$: 648.34990; found: 648.34993.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956 (w), 2930 (w), 2860 (w), 2201 (m), 1506 (m), 1378 (m), 1157 (m), 839 (m), 797 (m), 541 (s), 492 (m).

2,3,5,6-Tetrakis((4-ethylphenyl)ethynyl)pyrazine (13l)



According to the general procedure, compound **13l** was isolated as a dark yellow solid (108 mg, 61%); mp. = 206 – 208 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (t, 12H, ^3J = 7.6 Hz, CH_3), 2.67 (q, 8H, ^3J = 7.6 Hz, CH_2), 7.18 - 7.22 (m, 8H), 7.54 - 7.58 (m, 8H).

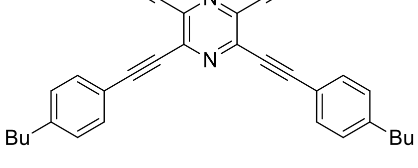
^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.2 (CH_3), 28.9 (CH_2), 85.8, 97.9 (C≡C), 118.8 (C), 128.1, 132.2 (CH), 138.9, 146.4 (C).

MS (EI, 70 eV): m/z (%) = 592 (M$^+$, 100), 267 (12), 133 (9), 71 (9), 57 (15), 44 (45).

HRMS (EI, 70 eV): calcd. for $C_{44}H_{36}N_2$: 592.28730; found: 592.28613.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2963 (w), 2929 (w), 2870 (w), 2199 (m), 1508 (m), 1379 (m), 1157 (m), 828 (s), 530 (m).

2,3,5,6-Tetrakis((4-butylphenyl)ethynyl)pyrazine (13m)



According to the general procedure, compound **13m** was isolated as a yellow solid (128 mg, 60%); mp. = 140 – 142 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.92 (t, 12H, ^3J = 7.3 Hz, CH$_3$), 1.29 - 1.41 (m, 8H, CH$_2$), 1.55 - 1.65 (m, 8H, CH$_2$), 2.63 (t, 8H, ^3J = 7.6 Hz, CH$_2$), 7.16 - 7.20 (m, 8H), 7.53 - 7.57 (m, 8H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.8 (CH$_3$), 22.2, 33.2, 35.7 (CH$_2$), 85.8, 97.9 (C≡C), 118.8 (C), 128.6, 132.2 (CH), 138.9, 145.1 (C).

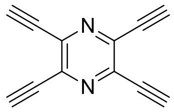
MS (EI, 70 eV): m/z (%) = 704 (M$^+$, 100), 619 (14), 352 (7), 295 (13), 267 (17), 252 (12).

HRMS (EI, 70 eV): calcd. for $C_{52}H_{52}N_2$: 704.41250; found: 704.41019.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2951 (w), 2926 (m), 2860 (w), 2201 (m), 1509 (m), 1377 (s), 1156 (s), 823 (s), 539 (s).

EA: calcd. for $C_{52}H_{52}N_2$ (704.98): C, 88.59; H, 7.43; N, 3.97; found: C, 88.56; H, 7.81; N, 3.90.

2,3,5,6-Tetrakis(phenylethynyl)pyrazine (14)



To a dissolved pyrazine **13f** (200 mg, 0.25 mmol in 6 mL of THF), 2.2 mL of TBAF (1 M in THF, 2.2 mmol) was added at 0°C and stirred for 2h. Afterward, water was added and the aqueous phase was three times extracted with Et$_2$O. Combined organic layers were dried over Na$_2$SO$_4$, filtered and the solvent was evaporated. The crude material was purified by column chromatography on silica gel using a mixture of hexane and dichloromethane as eluent. Compound **14** was isolated as a brown solid (38 mg, 86%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 3.60 (s, 4H, C≡CH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 78.6, 86.0 (C≡C), 139.0 (C).

MS (EI, 70 eV): m/z (%) = 176 (M$^+$, 62), 74 (100), 61 (5), 51 (10), 37 (9).

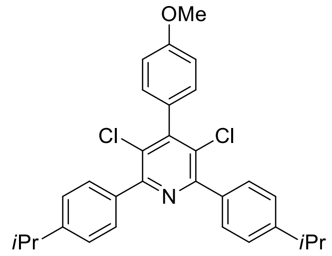
HRMS (ESI): calcd. for $C_{12}H_5N_2$ ([M+H]$^+$): 177.04472; found: 177.04475.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3284 (m), 3201 (m), 2105 (m), 1356 (s), 1162 (s), 680 (s), 660 (s), 503 (s).

Synthesis of 3,5-chloro-4-(4-methoxyphenyl)-2,6-diarylpyridines

An argon-flushed glass pressure tube was charged with $Pd(PPh_3)_4$ (0.025 mmol, 5 mol%), **4a** (0.5 mmol), the appropriate aryl boronic acid (1.5 mmol, 3.0 eq.), K_3PO_4 (1.5 mmol, 3.0 eq.) and anhydrous toluene (3.5 mL). The tube was sealed with a teflon cap and the reaction mixture was stirred at 100 °C for 20 hours. The resulting mixture was cooled down to room temperature, diluted with water and extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated. After, the crude residue was purified by column chromatography on silica gel using a mixture of hexane and dichloromethane as eluent.

3,5-Dichloro-2,6-bis(4-isopropylphenyl)-4-(4-methoxyphenyl)pyridine (16a)



According to the general procedure, compound **16a** was isolated as a white solid (169 mg, 69%); mp. = 81 – 83 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (d, 12H, ^3J = 6.9 Hz, CH_3), 2.99 (sept, 2H, ^3J = 6.9 Hz, $CH_{i\text{-Pr}}$), 3.89 (s, 3H, OCH_3), 7.06 - 7.09 (m, 2H, CH), 7.29 - 7.35 (m, 6H, CH), 7.74 - 7.77 (m, 4H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.8 (CH_3), 33.9 ($CH_{i\text{-Pr}}$), 55.1 (OCH_3), 113.8, 126.0 (CH), 128.6, 128.7 (C), 129.5, 130.1 (CH), 135.8, 148.9, 149.5, 154.6, 159.5 (C).

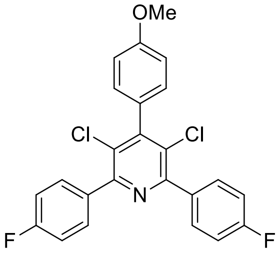
MS (EI, 70 eV): m/z (%) = 489 (M^+, 100), 474 (73), 458 (6), 432 (4), 230 (23), 215 (4), 158 (4).

HRMS (EI, 70 eV): calcd. for $C_{30}H_{29}Cl_2NO$: 489.16207; found: 489.16144.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2957 (m), 2868 (w), 2835 (w), 1609 (m), 1500 (s), 1460 (m), 1361 (s), 1290 (m), 1246 (s), 1018 (m), 828 (s), 731 (m), 657 (m), 557 (s).

EA: calcd. for $C_{30}H_{29}Cl_2NO$ (490.46): C, 73.47; H, 5.96; N, 2.86; found: C, 73.25; H, 5.90; N, 2.75.

3,5-Dichloro-2,6-bis(4-fluorophenyl)-4-(4-methoxyphenyl)pyridine (16b)



According to the general procedure, compound **16b** was isolated as a white solid (139 mg, 63%); mp. = 224 – 226 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 3.86 (s, 3H, OCH$_3$), 7.01 - 7.06 (m, 2H, CH), 7.08 - 7.16 (m, 4H, CH), 7.22 - 7.27 (m, 2H, CH), 7.71 - 7.78 (m, 4H, CH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 55.2 (OCH$_3$), 113.9 (CH), 115.0 (d, $^2J_{C–F}$ = 21.8 Hz, CH), 128.3, 129.1 (C), 130.0 (CH), 131.5 (d, $^3J_{C–F}$ = 8.3 Hz, CH), 134.1 (d, $^4J_{C–F}$ = 3.2 Hz, C), 149.4, 153.7, 159. 7 (C), 163.1 (d, $^1J_{C–F}$ = 249.0 Hz, CF).

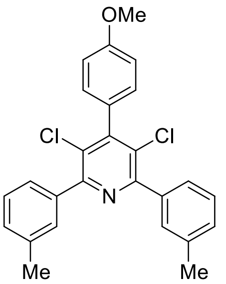
^{19}F NMR (282 MHz, CDCl$_3$): δ = -111.7 (s, 2F, CF). MS (EI, 70 eV): m/z (%) = 441 (M$^+$, 100), 406 (34), 363 (10), 327 (8), 207 (14).

HRMS (EI, 70 eV): calcd. for $C_{24}H_{15}Cl_2F_2NO$: 441.04933; found: 441.04912.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3004 (w), 2939 (w), 2838 (w), 1603 (m), 1504 (s), 1359 (m), 1292 (m), 1230 (s), 1156 (s), 834 (s), 529 (s).

EA: calcd. for $C_{24}H_{15}Cl_2F_2NO$ (442.28): C, 65.17; H, 3.42; N, 3.17; found: C, 65.20; H, 3.56; N, 3.19.

3,5-Dichloro-2,6-di-*m*-tolyl-4-(4-methoxyphenyl)pyridine (16c)



According to the general procedure, compound **16c** was isolated as a white solid (103 mg, 47%); mp. = 130 – 132 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.40 (s, 6H, CH$_3$), 3.87 (s, 3H, OCH$_3$), 7.01 - 7.06 (m, 2H, CH), 7.20 - 7.36 (m, 6H, CH), 7.52 - 7.54 (m, 4H, CH).

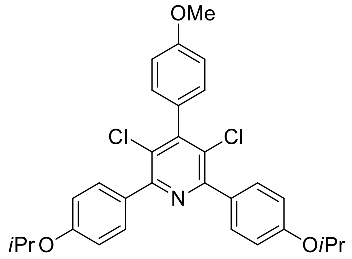
^{13}C NMR (75 MHz, CDCl$_3$): δ = 21.4 (CH$_3$), 55.2 (OCH$_3$), 113.8, 126.6, 127.8 (CH), 128.6, 129.0 (C), 129.6, 130.1 (CH), 137.7, 138.2, 148.9, 155.0, 159.6 (C).

MS (EI, 70 eV): m/z (%) = 433 (M$^+$, 100), 398 (66), 355 (8), 202 (10), 152 (9). HRMS (EI, 70 eV): calcd. for $C_{26}H_{21}Cl_2NO$: 433.09947; found: 433.09915.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3040 (w), 2921 (w), 2830 (w), 1605 (m), 1507 (s), 1356 (s), 1285 (m), 1243 (s), 1178 (m), 1022 (m), 790 (s), 774 (s), 698 (s), 586 (s).

EA: calcd. for $C_{26}H_{21}Cl_2NO$ (434.36): C, 71.89; H, 4.87; N, 3.22; found: C, 71.81; H, 5.13; N, 3.22.

3,5-Dichloro-2,6-bis(4-isopropoxyphenyl)-4-(4-methoxyphenyl)pyridine (16d)



According to the general procedure, compound **16d** was isolated as a white solid (186 mg, 71%); mp. = 173 – 175 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.37 (d, 12H, ^3J = 6.0 Hz, CH$_3$), 3.87 (s, 3H, OCH$_3$), 4.61 (sept, 2H, ^3J = 6.0 Hz, CH$_{i\text{-Pr}}$), 6.94 - 6.99 (m, 4H, CH), 7.02 - 7.07 (m, 2H, CH), 7.25 - 7.30 (m, 2H, CH), 7.74 - 7.79 (m, 4H, CH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 21.9 (CH$_3$), 55.1 (OCH$_3$), 69.7 (CH$_{i\text{-Pr}}$), 113.8, 114.9 (CH), 128.0, 128.9 (C), 130.0 (CH), 130.4 (C), 131.0 (CH), 149.0, 154.1, 158.4, 159.5 (C).

MS (EI, 70 eV): m/z (%) = 521 (M$^+$, 37), 437 (100), 402 (15), 219 (8), 43 (17).

HRMS (EI, 70 eV): calcd. for $C_{30}H_{29}Cl_2NO_3$: 521.15190; found: 521.15137.

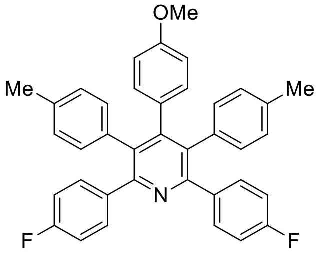
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2974 (w), 2934 (w), 2831 (w), 1607 (m), 1500 (s), 1363 (m), 1291 (m), 1247 (s), 1104 (s), 1040 (m), 950 (m), 830 (s), 785 (m), 638 (m).

EA: calcd. for $C_{30}H_{29}Cl_2NO_3$ (522.46): C, 68.97; H, 5.59; N, 2.68; found: C, 68.83; H, 5.76; N, 2.64.

Synthesis of 2,3,5,6-tetraaryl-4-(4-methoxyphenyl)pyridines from 3,5-dichloro-4-(4-methoxyphenyl)-2,6-diarylpyridines

An argon-flushed glass pressure tube was charged with $PdCl_2(CH_3CN)_2$ (0.0125 mmol, 5 mol%), SPhos (0.025 mmol, 10mol%), 3,5-dichloro-4-(4-methoxyphenyl)-2,6-diarylpyridine **16** (0.25 mmol), the appropriate aryl boronic acid (1.0 mmol, 4.0 eq.), K_3PO_4 (1.0 mmol, 4.0 eq.) and anhydrous toluene (3.5 mL). The tube was sealed with a teflon cap and the reaction mixture was stirred at 100 °C for 20 hours. The resulting mixture was cooled down to room temperature, diluted with water and extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated. After, the crude residue was purified by column chromatography on silica gel using a mixture of hexane and dichloromethane as eluent.

2,6-Bis(4-fluorophenyl)-4-(4-methoxyphenyl)-3,5-di-*p*-tolylpyridine (17)



According to the general procedure, compound **17** was isolated as a white solid (110 mg, 99%); mp. = 234 – 236 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.18 (s, 6H, CH_3), 3.63 (s, 3H, OCH_3), 6.44 - 6.48 (m, 2H, CH), 6.61 - 6.66 (m, 2H, CH), 6.70 - 6.74 (m, 4H, CH), 6.80 - 6.88 (m, 8H, CH), 7.30 - 7.37 (m, 4H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1 (CH_3), 54.9 (OCH_3), 112.4 (CH), 114.4 (d, $^2J_{C\text{–}F}$ = 21.2 Hz, CH), 128.3 (CH), 130.3 (C), 131.0, 131.4 (CH), 131.8 (d, $^3J_{C\text{–}F}$ = 7.8 Hz, CH), 134.0, 135.1, 135.8 (C), 136.9 (d, $^4J_{C\text{–}F}$ = 3.2 Hz, C), 150.4, 155.2, 157.6 (C), 162.1 (d, $^1J_{C\text{–}F}$ = 246.6 Hz, CF).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -114.4 (s, 2F, CF).

MS (EI, 70 eV): m/z (%) = 552 (M^+, 100), 167 (20), 149 (51), 107 (13), 97 (14), 84 (15), 71 (23), 66 (11), 57 (32), 43 (18).

HRMS (EI, 70 eV): calcd. for $C_{38}H_{28}F_2NO$: 552.21335; found: 552.21339.

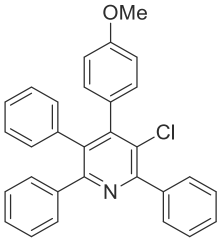
IR (ATR, cm^{-1}): $\tilde{\nu}$ =2923 (w), 1596 (m), 1498 (s), 1389 (m), 1287 (m), 1220 (s), 1155 (s), 1038 (m), 834 (m), 806 (s), 524 (s).

EA: calcd. for $C_{38}H_{29}F_2NO$ (553.64): C, 82.44; H, 5.28; N, 2.53; found: C, 82.54; H, 5.34; N, 2.43.

Synthesis of 3-chloro-4-(4-methoxyphenyl)-2,5,6-diarylpyridines

An oven-dried and argon-flushed pressure tube was charged with **4a** (0.3 mmol), $PdCl_2(CH_3CN)_2$ (0.015 mmol, 5 mol%), SPhos (0.03 mmol, 10.0 mol%), boronic acid (0.9 mmol, 3.0 eq.) and K_3PO_4 (0.9 mmol, 3.0 eq.), followed by anhydrous toluene (3 mL). The tube was sealed with a teflon valve and stirred at 100 °C for 20 h. The cooled reaction mixture was diluted with water and extracted with DCM. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography.

3-Chloro-4-(4-methoxyphenyl)-2,5,6-triphenylpyridine (18a)



According to the general procedure, compound **18a** was isolated as a white solid (73 mg, 54%); mp. = 206 – 208 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.74 (s, 3H, OCH_3), 6.73 - 6.78 (m, 2H, CH), 6.85 - 6.87 (m, 2H, CH), 6.98 - 7.03 (m, 5H, CH), 7.14 - 7.16 (m, 3H, CH), 7.28 - 7.31 (m, 2H, CH), 7.39 - 7.50 (m, 3H, CH), 7.85 - 7.88 (m, 2H, CH).

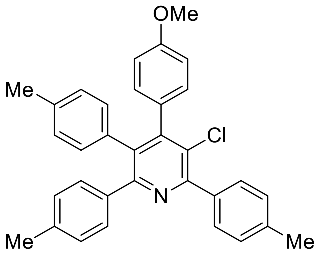
^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.0 (OCH_3), 113.1, 126.6, 127.5, 127.6 (2 x CH), 127.9, 128.5 (CH), 128.7, 129.3 (C), 129.7, 129.9, 130.9, 131.0 (CH), 135.5, 137.6, 139.2, 140.0, 149.6, 155.5, 155.6, 158.7 (C).

MS (EI, 70 eV): m/z (%) = 446 (M$^+$, 33), 400 (19), 369 (91), 317 (100), 287 (67), 220 (22), 205 (71).

HRMS (ESI): calcd. for $C_{30}H_{23}ClNO$ ([M+H]$^+$): 448.14627; found: 448.14655.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3029 (w), 2924 (w), 2851 (w), 1608 (m), 1507 (m), 1396 (m), 1357 (m), 1289 (m), 1244 (s), 1172 (m), 1149 (m), 1030 (m), 838 (m), 743 (m), 695 (s), 562 (m), 537 (m).

3-Chloro-4-(4-methoxyphenyl)-2,5,6-tri-*p*-tolylpyridine (18b)



According to the general procedure, compound **18b** was isolated as a white solid (50 mg, 34%); mp. = 142 – 144 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.19, (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 6.71 - 6.77 (m, 4H, CH), 6.81 - 6.83 (m, 2H, CH), 7.17 - 7.21 (m, 2H, CH), 7.25 - 7.28 (m, 2H, CH), 7.74 - 7.77 (m, 2H, CH).

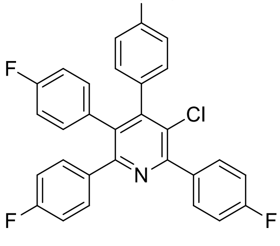
^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1 (2 x CH_3), 21.3 (CH_3), 55.0 (OCH_3), 113.1, 128.2, 128.3, 128.5, 129.6 (CH), 129.7 (C), 129.8, 130.8, 130.9 (CH), 134.7, 135.1, 136.0, 136.4, 137.1, 137.3, 138.3, 149.5, 155.2, 155.4, 158.5 (C).

MS (EI, 70 eV): m/z (%) = 488 (M$^+$, 61), 167 (26), 149 (75), 111 (24), 97 (36), 83 (38), 71 (64), 57 (100), 43 (85).

HRMS (EI, 70 eV): calcd. for $C_{33}H_{27}ClNO$: 488.17757; found: 488.17753.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3026 (w), 2918 (w), 2856 (w), 1610 (m), 1499 (m), 1391 (m), 1347 (m), 1293 (m), 1244 (s), 1183 (m), 1034 (m), 813 (s), 532 (s).

3-Chloro-2,5,6-tris(4-fluorophenyl)-4-(4-methoxyphenyl)pyridine (18c)



Starting with **4a** (97 mg, 0.3 mmol), $PdCl_2(CH_3CN)_2$ (3.9 mg, 5 mol%), SPhos (12.3 mg, 10 mol%), corresponding boronic acid (210 mg, 1.5 mmol), K_3PO_4 (318 mg, 1.5 mmol) and toluene (3 mL), compound **18c** was isolated as a white solid (93 mg, 62%); mp. = 181 – 183 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.75 (s, 3H, OCH_3), 6.73 - 6.79 (m, 6H, CH), 6.81 - 6.89 (m, 2H, CH), 6.92 - 6.97 (m, 2H, CH), 7.11 - 7.18 (m, 2H, CH), 7.21 - 7.21 (m, 2H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.1 (OCH_3), 113.3 (CH), 114.7 (d, $^2J_{C–F}$ = 21.6 Hz, CH), 114.9 (d, $^2J_{C–F}$ = 21.6 Hz, CH), 115.0 (d, $^2J_{C–F}$ = 21.6 Hz, CH), 128.8, 129.0 (C), 130.7 (CH), 131.6 (d, $^3J_{C–F}$ = 8.1 Hz, 2 x CH), 132.5 (d, $^3J_{C–F}$ = 8.1 Hz, CH), 133.3 (d, $^4J_{C–F}$ = 3.7 Hz, C), 134.5 (C), 134.9 (d, $^4J_{C–F}$ = 3.7 Hz, C), 135.7 (d, $^4J_{C–F}$ = 3.1 Hz, C), 150.0, 154.5, 154.8, 158.8 (C), 161.5 (d, $^1J_{C–F}$ = 247.3 Hz, CF), 162.3 (d, $^1J_{C–F}$ = 248.1 Hz, CF), 163.0 (d, $^1J_{C–F}$ = 248.1 Hz, CF).

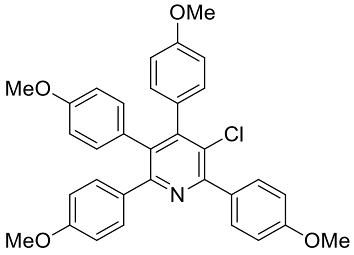
^{19}F NMR (282 MHz, $CDCl_3$): δ = -112.1 (s, 1F, CF), -113.3 (s, 1F, CF), -114.0 (s, 1F, CF).

MS (EI, 70 eV): m/z (%) = 500 (M^+, 90), 223 (19), 179 (18), 160 (18), 149 (23), 112 (61), 109 (19), 105 (80), 97 (48), 83 (63), 77 (28), 69 (60), 57 (100), 43 (84).

HRMS (ESI): calcd. for $C_{30}H_{20}ClF_3NO$ ($[M+H]^+$): 502.118; found: 502.1185.

IR (ATR, cm^{-1}): $\tilde{\nu}$ =2922 (w), 2841 (w), 1601 (m), 1498 (s), 1391 (m), 1290 (m), 1218 (s), 1157 (s), 1033 (m), 831 (s), 752 (m), 539 (s).

3-Chloro-2,4,5,6-tetrakis(4-methoxyphenyl)pyridine (18d)



According to the general procedure, compound **18d** was isolated as a yellowish solid (64 mg, 40%); mp. = 171 – 173 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.62, (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 6.48 - 6.53 (m, 2H, CH), 6.60 - 6.64 (m, 2H, CH), 6.66 - 6.72 (m, 4H, CH), 6.88 - 6.95 (m, 4H, CH), 7.16 - 7.21 (m, 2H, CH), 7.75 - 7.80 (m, 2H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 54.9, 55.0, 55.1, 55.2 (OCH_3), 113.0, 113.1 (CH), 113.2 (CH), 127.9, 129.8, 130.2 (C), 130.8, 131.1, 131.2 (CH), 131.8 (C), 132.1 (CH), 132.7, 134.4, 149.7, 154.7, 155.0, 158.0, 158.5, 159.0, 159.8 (C).

MS (EI, 70 eV): m/z (%) = 537 (M^+, 100), 539 (16), 313 (15), 149 (14), 99 (23), 85 (14), 71 (24), 57 (39).

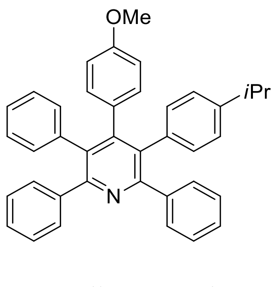
HRMS (EI, 70 eV): calcd. for $C_{33}H_{28}ClNO_4$: 537.17014; found: 537.16831.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2920 (m), 2849 (w), 1718 (w), 1607 (m), 1497 (m), 1461 (m), 1395 (m), 1289 (m), 1243 (s), 1173 (s), 1030 (s), 828 (s), 801 (s), 728 (m), 546 (s).

Synthesis of 2,3,5,6-tetraaryl-4-(4-methoxyphenyl)pyridines from 3-chloro-4-(4-methoxyphenyl)-2,5,6-diarylpyridines

An oven-dried and argon-flushed pressure tube was charged with 3-chloro-4-(4-methoxyphenyl)-2,5,6-diarylpyridine **18** (0.2 mmol), $PdCl_2(CH_3CN)_2$ (0.01 mmol, 5.0 mol%), SPhos (0,02 mmol, 10.0 mol%), boronic acid (0.5 mmol, 2.5 eq.) and K_3PO_4 (0.5 mmol, 2.5 eq.) followed by anhydrous toluene (3 mL). The tube was sealed with a teflon valve and stirred at 100 °C for 20h. The cooled reaction mixture was diluted with water and extracted with DCM. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography.

3-(4-Isopropylphenyl)-4-(4-methoxyphenyl)-2,5,6-triphenylpyridine (19a)



According to the general procedure, compound **19a** was isolated as a yellowish solid (104 mg, 98%); mp. = 189 – 191 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (d, 6H, ^3J = 6.9 Hz, CH_3), 2.74 (sept, 1H, ^3J = 6.9 Hz, $CH_{i\text{-}Pr}$), 3.61 (s, 3H, OCH_3), 6.42 - 6.47 (m, 2H, CH), 6.63 - 6.67 (m, 2H, CH), 6.76 - 6.79 (m, 2H, CH), 6.84 - 6.92 (m, 4H, CH), 6.98 - 7.02 (m, 3H, CH), 7.13 - 7.18 (m, 6H, CH), 7.35 - 7.42 (m, 4H, CH).

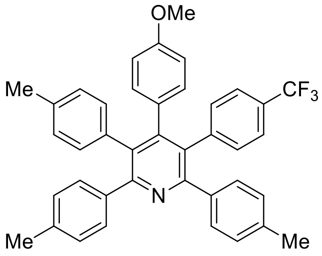
^{13}C NMR (75 MHz, CDCl$_3$): δ = 23.8 (CH$_3$), 33.5 (CH$_{i\text{-Pr}}$), 54.9 (OCH$_3$), 112.3, 125.4, 126.0 (CH), 127.1 (2 x CH), 127.3 (2 x CH), 127.4, 130.1, 130.2 (CH), 130.4 (C), 131.1, 131.3, 131.6, 133.8, 134.0, 135.7, 138.6, 141.0, 146.7, 149.8, 156.2, 156.4, 157.6 (C).

MS (EI, 70 eV): m/z (%) = 530 (M$^+$, 92), 281 (15), 155 (100), 127 (43), 111 (23), 97 (40), 85 (51), 71 (90), 57 (98), 43 (57).

HRMS (ESI): calcd. for $C_{39}H_{34}NO$ ([M+H]$^+$): 532.26349; found: 532.2641.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956 (w), 2923 (w), 2852 (w), 1731 (w), 1607 (w), 1510 (m), 1387 (m), 1244 (s), 1174 (m), 1028 (m), 835 (m), 753 (m), 693 (s), 671 (s), 564 (m).

4-(4-Methoxyphenyl)-5-(4-(trifluoromethyl)phenyl)-2,3,6-tri-*p*-tolylpyridine (19b)



According to the general procedure, compound **19b** was isolated as a white solid (112 mg, 93%); mp. = 188 – 190 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.19, (s, 3H, CH$_3$), 2.27 (s, 6H, CH$_3$), 3.63 (s, 3H, OCH$_3$), 6.44 - 6.48 (m, 2H, CH), 6.58 - 6.63 (m, 2H, CH), 6.74 - 6.83 (m, 4H, CH), 6.95 - 7.01 (m, 6H, CH), 7.21 - 7.30 (m, 6H, CH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 21.1 (2 x CH$_3$), 21.2 (CH$_3$), 54.9 (OCH$_3$), 112.6 (CH), 124.1 (q, $^1J_{C\text{–}F}$ = 271.9 Hz, CF$_3$), 124.3 (q, $^3J_{C\text{–}F}$ = 3.7 Hz, CH), 128.2 (2 x CH), 128.3 (CH), 130.1 (CH), 131.0, 131.4, 131.6 (CH), 132.1, 133.5, 135.3, 135.6, 137.0, 137.2, 137.5, 137.9, 143.0, 149.8, 155.8, 156.8, 157.8 (C).

^{19}F NMR (282 MHz, CDCl$_3$): δ = -61.9 (s, 3F, CF$_3$). MS (EI, 70 eV): m/z (%) = 598 (M$^+$, 100), 454 (12), 149 (16), 111 (19), 97 (28), 91 (18), 83 (25), 71 (38), 57 (54), 43 (26).

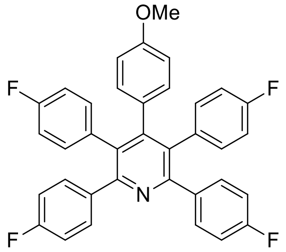
HRMS (EI, 70 eV): calcd. for $C_{40}H_{31}Cl_2F_3NO$: 598.23523; found: 598.23489.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2921 (w), 2853 (w), 1611 (m), 1501 (m), 1387 (m), 1320 (s), 1291 (m), 1246 (s), 1163 (s), 1123 (s), 1065 (s), 1015 (m), 817 (s), 666 (m).

Synthesis of 2,3,5,6-tetraaryl-4-(4-methoxyphenyl)pyridines from 2,3,5,6-tetrachloro-4-(4-methoxyphenyl)pyridines

An argon-flushed glass pressure tube was charged with $PdCl_2(CH_3CN)_2$ (0.015 mmol, 5 mol%), SPhos (0.03 mmol, 10mol%), 2,3,5,6-tetrachloro-4-(4-methoxyphenyl)pyridine (**4a)** (0.3 mmol), the appropriate aryl boronic acid (2.4 mmol, 8.0 eq.), K_3PO_4 (2.4 mmol, 8.0 eq.) and anhydrous toluene (6 mL). The tube was sealed with a teflon cap and the reaction mixture was stirred at 100 °C for 20 hours. The resulting mixture was cooled down to room temperature, diluted with water and extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated. After, the crude residue was purified by column chromatography on silica gel using a mixture of hexane and dichloromethane as eluent.

2,3,5,6-Tetrakis(4-fluorophenyl)-4-(4-methoxyphenyl)pyridine (20a)



According to the general procedure, compound **20a** was isolated as a white solid (131 mg, 78%); mp. = 252 – 254 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.65 (s, 3H, OCH_3), 6.47 - 6.51 (m, 2H, CH), 6.58 - 6.61 (m, 2H, CH), 6.70 - 6.75 (m, 4H, CH), 6.78 - 6.83 (m, 4H, CH), 6.84 - 6.90 (m, 4H, CH), 7.29 - 7.34 (m, 4H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.9 (OCH_3), 112.8 (CH), 114.6 (d, $^2J_{C\text{–}F}$ = 21.1 Hz, CH), 114.7 (d, $^2J_{C\text{–}F}$ = 21.9 Hz, CH), 129.6 (C), 131.3 (CH), 131.8 (d, $^3J_{C\text{–}F}$ = 8.2 Hz, CH), 132.7 (d, $^3J_{C\text{–}F}$ = 7.8 Hz, CH), 133.1 (C), 134.1 (d, $^4J_{C\text{–}F}$ = 3.6 Hz, C), 136.4 (d, $^4J_{C\text{–}F}$ = 2.8 Hz, C), 150.5, 155.6, 157.9 (C), 161.3 (d, $^1J_{C\text{–}F}$ = 246.7 Hz, CF), 162.2 (d, $^1J_{C\text{–}F}$ = 247.6 Hz, CF).

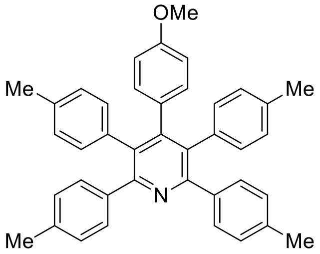
^{19}F NMR (282 MHz, $CDCl_3$): δ = -113.8 (s, 2F, CF), -114.8 (s, 2F, CF). MS (EI, 70 eV): m/z (%) = 560 (M^+, 100), 516 (12), 244 (4), 183 (4).

HRMS (EI, 70 eV): calcd. for $C_{36}H_{22}F_4NO$: 560.16320; found: 560.16315.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2932 (w), 2832 (w), 1603 (m), 1510 (s), 1389 (m), 1247 (s), 1220 (s), 1156 (s), 1040 (m), 815 (s), 533 (s).

EA: calcd. for $C_{36}H_{23}F_4NO$ (561.57): C, 77.00; H, 4.13; N, 2.49; found: C, 77.25; H, 4.48; N, 2.51.

4-(4-Methoxyphenyl)-2,3,5,6-tetra-*p*-tolylpyridine (20b)



According to the general procedure, compound **20b** was isolated as a white solid (100 mg, 61%); mp. = 234 – 236 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.18 (s, 6H, CH_3), 2.26 (s, 6H, CH_3), 3.63 (s, 3H, OCH_3), 6.42 - 6.47 (m, 2H, CH), 6.60 - 6.64 (m, 2H, CH), 6.71 - 6.75 (m, 4H, CH), 6.79 - 6.81 (m, 4H, CH), 6.94 - 6.97 (m, 4H, CH), 7.25 - 7.29 (m, 4H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1, 21.2 (CH_3), 54.9 (OCH_3), 112.3, 128.1, 130.1 (CH), 130.7 (C), 131.1, 131.5 (CH), 133.6, 135.4, 136.9, 155.8, 157.5 (C).

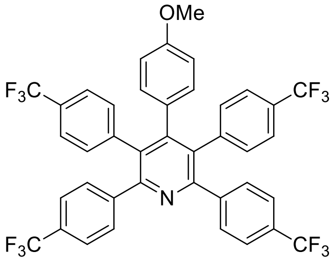
MS (EI, 70 eV): m/z (%) = 544 (M^+, 100), 529 (5), 500 (7), 234 (4), 227 (4), 220 (4), 69 (10), 44 (7).

HRMS (EI, 70 eV): calcd. for $C_{40}H_{34}NO$: 544.26349; found: 544.26318.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3025 (w), 2918 (w), 1611 (m), 1499 (m), 1242 (s), 1171 (m), 1049 (m), 808 (s), 748 (m), 521 (m).

EA: calcd. for $C_{40}H_{35}NO$ (545.71): C, 88.04; H, 6.46; N, 2.57; found: C, 88.26; H, 6.48; N, 2.45.

4-(4-Methoxyphenyl)-2,3,5,6-tetrakis(4-(trifluoromethyl)phenyl)pyridine (20c)



According to the general procedure, compound **20c** was isolated as a white solid (185 mg, 81%); mp. = 240 – 242 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 3.65 (s, 3H, OCH$_3$), 6.47 - 6.52 (m, 2H, CH), 6.56 - 6.61 (m, 2H, CH), 7.00 (d, 4H, ^3J = 8.1 Hz, CH), 7.32 (d, 4H, ^3J = 8.1 Hz, CH), 7.41 - 7.47 (m, 8H, CH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 55.0 (OCH$_3$), 113.1 (CH), 123.8 (q, $^1J_{C-F}$ = 272.3 Hz, CF$_3$), 123.9 (q, $^1J_{C-F}$ = 272.1 Hz, CF$_3$), 124.8 (q, $^3J_{C-F}$ = 3.8 Hz, CH), 128.3 (CH), 129.5 (q, $^2J_{C-F}$ = 32.9 Hz, C), 130.3, 131.2, 131.4 (CH), 133.5, 141.4, 143.4, 150.5, 155.7, 158.4 (C).

^{19}F NMR (282 MHz, CDCl$_3$): δ = -62.1 (s, 3F, CF$_3$), -62.2 (s, 3F, CF$_3$).

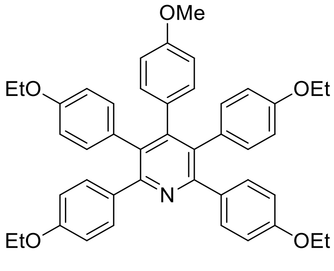
MS (EI, 70 eV): m/z (%) = 760 (M$^+$, 100), 742 (5), 716 (10), 381 (5).

HRMS (EI, 70 eV): calcd. for $C_{40}H_{22}F_{12}NO$: 760.15043; found: 760.14943.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2936 (w), 1616 (m), 1516 (m), 1321 (s), 1163 (s), 1106 (s), 1065 (s), 1015 (s), 853 (s), 833 (s), 669 (m).

EA: calcd. for $C_{40}H_{23}F_{12}NO$ (761.60): C, 63.08; H, 3.04; N, 1.84; found: C, 63.34; H, 3.36; N, 1.85.

2,3,5,6-Tetrakis(4-ethoxyphenyl)-4-(4-methoxyphenyl)pyridine (20d)



According to the general procedure, compound **20d** was isolated as a white solid (158 mg, 79%); mp. = 231 – 233 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.30 - 1.37 (m, 12H, CH$_3$), 3.63 (s, 3H, OCH$_3$), 3.88 (q, 4H, ^3J = 7.0 Hz, CH$_2$), 3.96 (q, 4H, ^3J = 7.0 Hz, CH$_2$), 6.44 - 6.48 (m, 2H, CH), 6.51 - 6.56 (m, 4H, CH), 6.59 - 6.64 (m, 2H, CH), 6.65 - 6.70 (m, 4H, CH), 6.72 - 6.76 (m, 4H, CH), 7.29 - 7.34 (m, 4H, CH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.7, 14.8 (CH$_3$), 54.9 (OCH$_3$), 63.0, 63.1 (CH$_2$), 112.4, 113.4, 113.5 (CH), 130.8, 131.0 (C), 131.4, 131.5, 132.3 (CH), 132.8, 155.6, 157.0, 157.4, 158.1 (C).

MS (EI, 70 eV): m/z (%) = 665 (M$^+$, 100), 636 (8), 575 (11), 99 (14), 44 (10).

HRMS (EI, 70 eV): calcd. for $C_{44}H_{43}NO_5$: 665.31357; found: 665.31230.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2979 (w), 2923 (w), 1605 (m), 1514 (m), 1388 (m), 1239 (s), 1172 (s), 1112 (s), 1040 (s), 824 (s), 655 (m), 553 (s).

EA: calcd. for $C_{44}H_{43}NO_5$ (665.82): C, 79.37; H, 6.51; N, 2.10; found: C, 78.89; H, 6.86; N, 2.09.

Synthesis of 2,3,5,6-tetraarylpyrazines

First of all, solutions of Pd(OAc)$_2$ and P(Cy)$_3$ were prepared in dried and filled with argon Schlenk tube*s* (both 0.0125 mmol, 5 mol%) using 1 mL of extra dry THF and toluene, respectively. Solutions were stirred at room temperature for 10 mins.

To an argon-flushed glass pressure tube, 50 µL of Pd(OAc)$_2$ solution (0.000625 mmol, 0.25 mol%) was added[4]. After the removal of THF via evacuation of pressure tube, 100µL of P(Cy)$_3$ (0.00125 mmol, 0.5 mol%), tetrachloropyrazine (54 mg, 0.25 mmol), the aryl boronic acid (2 mmol, 8.0 equiv.) and K$_3$PO$_4$ (2 mmol, 8.0 equiv.) were added, followed by the injection of dry toluene (3.5 mL). The tube was closed with a teflon screw cap and the reaction mixture was stirred at 100 °C for 18 hours. Subsequently, the mixture was cooled down to room temperature and diluted with water and dichloromethane. The aqueous layer was extracted three times with dichloromethane. Combined organic layers were dried over Na$_2$SO$_4$ and filtered. Unless otherwise noted, the solvent was evaporated and the residue was purified by column chromatography on silica gel using a mixture of hexane and dichloromethane as eluent.

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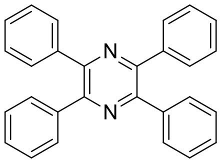
[4] In case of compounds **21k-p**, better yields have been obtained by increasing the amount of catalyst: Pd(OAc)$_2$ (1.1 mg, 2 mol%), P(Cy)$_3$ (2.8mg, 4 mol%).

2,3,5,6-Tetraphenylpyrazine (21a)



According to the general procedure, compound **21a** was isolated as a white solid (93 mg, 97%); mp. = 248 – 250 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29 - 7.34 (m, 12H), 7.60 - 7.66 (m, 8H).

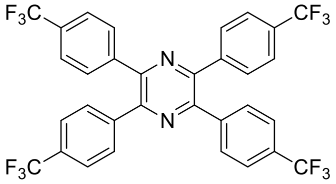
^{13}C NMR (75 MHz, $CDCl_3$): δ = 128.2 (CH), 128.5 (CH), 129.8 (CH), 138.4 (C), 148.4 (C).

MS (EI, 70 eV): m/z (%) = 384 (M^+, 100), 305 (7), 178 (44), 152 (8), 103 (10).

HRMS (ESI): calcd. for $C_{28}H_{21}N_2$ ($[M+H]^+$): 385.16993; found: 385.17036.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3038 (w), 1389 (m), 1170 (m), 1104 (m), 1011 (m), 762 (s), 692 (s), 536 (s).

2,3,5,6-Tetrakis(4-(trifluoromethyl)phenyl)pyrazine (21b)



According to the general procedure, compound **21b** was isolated as a white solid (139 mg, 85%); mp. = 265 – 266 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, 8H, ^3J = 8.2 Hz), 7.74 (d, 8H, ^3J = 8.2 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 123.8 (q, $^1J_{C-F}$ = 272.3 Hz, CF_3), 125.5 (q, $^3J_{C-F}$ = 3.8 Hz, CH), 130.1 (CH), 131.3 (q, $^2J_{C-F}$ = 32.6 Hz, C), 140.8 (C), 147.9 (C).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -62.3 (s, 12F, CF_3).

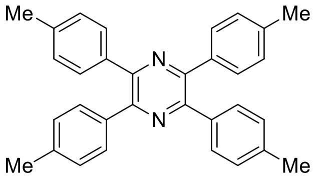
MS (EI, 70 eV): m/z (%) = 656 (M^+, 100), 637 (15), 587 (14), 314 (77), 295 (15), 264 (10), 225 (7), 171 (7).

HRMS (ESI): calcd. for $C_{32}H_{17}F_{12}N_2$($[M+H]^+$): 657.11946; found: 657.1192.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1322 (s), 1167 (m), 1105 (s), 1011 (m), 849 (s), 631 (m), 535 (m).

EA: calcd. for $C_{32}H_{16}F_{12}N_2$ (656.46): C, 58.55; H, 2.46; N, 4.27; found: C, 57.92; H, 2.32; N, 4.23.

2,3,5,6-Tetra-*p*-tolylpyrazine (21c)



According to the general procedure, compound **21c** was isolated as a white solid (103 mg, 93%); mp. = 284 – 286 °C.

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.35$ (s, 12H, CH_3), 7.09 - 7.13 (m, 8H), 7.52 - 7.56 (m, 8H).

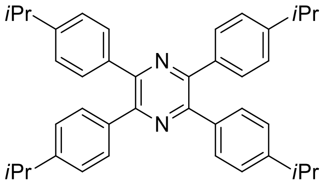
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.3$ (CH_3), 128.9 (CH), 129.6 (CH), 135.8 (C), 138.3 (C), 147.7 (C).

MS (EI, 70 eV): m/z (%) = 440 (M^+, 100), 425 (10), 206 (19), 189 (8).

HRMS (ESI): calcd. for $C_{32}H_{29}N_2$ ($[M+H]^+$): 441.23253; found: 441.23245.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2917 (w), 1385 (s), 1172 (m), 1096 (m), 1009 (m), 820 (s), 728 (s), 626 (m), 530 (s), 513 (s).

2,3,5,6-Tetrakis(4-isopropylphenyl)pyrazine (21d)



According to the general procedure, compound **21d** was isolated as off-white solid (133 mg, 96%); mp. = 279 – 281 °C.

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.24$ (d, 24H, $^3J = 6.9$ Hz, CH_3), 2.90 (sept, 4H, $^3J = 6.9$ Hz, $CH_{i\text{-Pr}}$), 7.13 - 7.17 (m, 8H), 7.56 - 7.60 (m, 8H).

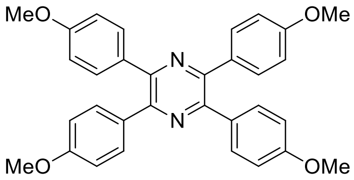
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 23.8$ (CH_3), 33.8 ($CH_{i\text{-Pr}}$), 126.2 (CH), 129.7 (CH), 136.1 (C), 147.5 (C), 149.2 (C).

MS (EI, 70 eV): m/z (%) = 552 (M^+, 100), 537 (11), 509 (7).

HRMS (ESI): calcd. for $C_{40}H_{45}N_2$ ($[M+H]^+$): 553.35773; found: 553.35861.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2959 (m), 2926 (w), 2866 (w), 1388 (s), 1181 (m), 1098 (m), 1006 (m), 839 (s), 632 (m), 552 (s).

2,3,5,6-Tetrakis(4-methoxyphenyl)pyrazine (21e)



According to the general procedure, compound **21e** was isolated as a light brown solid (113 mg, 90%); mp. = 278 – 280 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.81 (s, 12H, OCH_3), 6.81 - 6.86 (m, 8H), 7.56 - 7.61 (m, 8H).

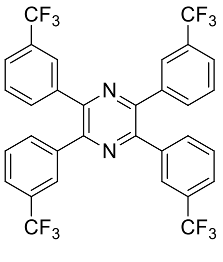
^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.2 (OCH_3), 113.6 (CH), 131.0 (CH), 131.2 (C), 146.8 (C), 159.8 (C).

MS (EI, 70 eV): m/z (%) = 504 (M^+, 100), 252 (12), 238 (15), 223 (34), 195 (10), 152 (12), 133 (11).

HRMS (EI, 70 eV): calcd. for $C_{32}H_{28}N_2O_4$: 504.20436; found: 504.20469.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2926 (w), 2834 (w), 1602 (s), 1573 (m), 1511 (s), 1418 (m), 1381 (s), 1295 (s), 1244 (s), 1164 (s), 1027 (s), 830 (s), 796 (s), 740 (m), 529 (s).

2,3,5,6-Tetrakis(3-(trifluoromethyl)phenyl)pyrazine (21f)



According to the general procedure, compound **21f** was isolated as a white solid (157 mg, 96%); mp. = 165 – 167 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (t, 4H, ^3J = 7.8 Hz), 7.65 (d, 4H, ^3J = 7.8 Hz), 7.75 (d, 4H, ^3J = 7.8 Hz), 7.86 (bs, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 123.6 (q, $^1J_{C–F}$ = 271.9 Hz, CF_3), 125.9 (q, $^3J_{C–F}$ = 3.6 Hz, CH), 126.7 (q, $^3J_{C–F}$ = 3.8 Hz, CH), 129.1 (CH), 131.1 (q, $^2J_{C–F}$ = 32.6 Hz, C), 133.0 (CH), 138.0 (C), 148.1 (C).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -62.5 (s, 12F, CF_3).

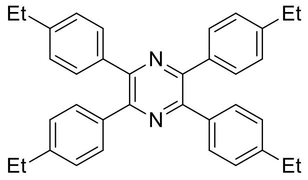
MS (EI, 70 eV): m/z (%) = 656 (M^+, 100), 637 (12), 314 (99), 295 (10), 264 (7), 225 (11), 171 (17).

HRMS (EI, 70 eV): calcd. for $C_{32}H_{16}F_{12}N_2$: 656.11164; found: 656.11102.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1323 (s), 1280 (m), 1164 (s), 1127 (s), 1069 (s), 908 (m), 801 (m), 700 (s).

EA: calcd. for $C_{32}H_{16}F_{12}N_2$ (656.46): C, 58.55; H, 2.46; N, 4.27; found: C, 58.85; H, 2.28; N, 4.35.

2,3,5,6-Tetrakis(4-ethylphenyl)pyrazine (21g)



According to the general procedure, compound **21g** was isolated as a white solid (108 mg, 87%); mp. = 235 – 236 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, 12H, ^3J = 7.5 Hz, CH_3), 2.65 (q, 8H, ^3J = 7.5 Hz, CH_2), 7.12 - 7.14 (m, 8H), 7.55 - 7.59 (m, 8H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3 (CH_3), 28.6 (CH_2), 127.7 (CH), 129.7 (CH), 136.0 (C), 144.6 (C), 147.6 (C).

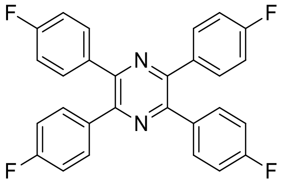
MS (EI, 70 eV): m/z (%) = 496 (M^+, 100), 467 (12), 219 (28), 204 (14), 116 (11).

HRMS (EI, 70 eV): calcd. for $C_{36}H_{36}N_2$: 496.28730; found: 496.28760.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2961 (m), 2929 (w), 2870 (w), 1387 (s), 1180 (s), 1097 (m), 1007 (m), 632 (m), 536 (m).

EA: calcd. for $C_{36}H_{36}N_2$ (496.68): C, 87.05; H, 7.31; N, 5.64; found: C, 86.96; H, 7.31; N, 5.63.

2,3,5,6-Tetrakis(4-fluorophenyl)pyrazine (21h)



According to the general procedure, compound **21h** was isolated as a white solid (113 mg, 99%); mp. = 233 – 234 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.97 - 7.05 (m, 8H), 7.54 - 7.61 (m, 8H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 115.4 (d, $^2J_{C–F}$ = 21.8 Hz, CH), 131.6 (d, $^3J_{C\text{-}F}$ = 8.3 Hz, CH), 134.0 (d, $^4J_{C\text{-}F}$ = 3.2 Hz, C), 147.3 (C), 163.1 (d, $^1J_{C–F}$ = 250.1 Hz, CF).

^{19}F NMR (282 MHz, CDCl$_3$): δ = -111.7 (s, 4F, CF).

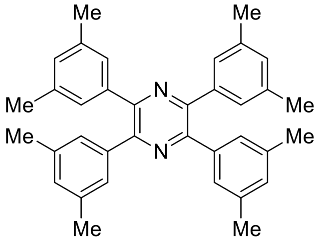
MS (EI, 70 eV): m/z (%) = 456 (M$^+$, 100), 359 (6), 214 (36).

HRMS (EI, 70 eV): calcd. for $C_{28}H_{16}F_4N_2$: 456.12441; found: 456.12366.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1602 (s), 1510 (s), 1415 (m), 1384 (s), 1226 (s), 1152 (s), 1108 (m), 1011 (m), 839 (s), 735 (m), 617 (m), 526 (s).

EA: calcd. for $C_{28}H_{16}F_4N_2$ (456.43): C, 73.68; H, 3.53; N, 6.14; found: C, 73.64; H, 3.33; N, 6.09.

2,3,5,6-Tetrakis(3,5-dimethylphenyl)pyrazine (21i)



According to the general procedure, compound **21i** was isolated as a white solid (101 mg, 81%); mp. = 275 – 277 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.24 (s, 24H, CH$_3$), 6.94 (bs, 4H), 7.19 (bs, 8H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 21.2 (CH$_3$), 127.6 (CH), 129.9 (CH), 137.3 (C), 138.5 (C), 148.8 (C).

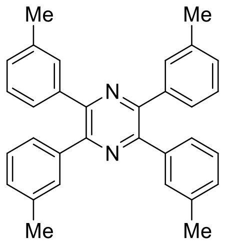
MS (EI, 70 eV): m/z (%) = 496 (M$^+$, 100), 248 (10), 133 (22).

HRMS (EI, 70 eV): calcd. for $C_{36}H_{36}N_2$: 496.28730; found: 496.28686.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3025 (w), 2912 (m), 2855 (w), 1600 (m), 1391 (s), 1374 (s), 1187 (m), 1154 (m), 855 (s), 843 (s), 691 (s), 424 (m).

EA: calcd. for $C_{36}H_{36}N_2$ (496.68): C, 87.05; H, 7.31; N, 5.64; found: C, 86.89; H, 7.44; N, 5.39.

2,3,5,6-Tetra-*m*-tolylpyrazine (21j)



According to the general procedure, compound **21j** was isolated as a white solid (104 mg, 94%); mp. = 153 – 154 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 12H, CH_3), 7.13 - 7.16 (m, 8H), 7.28 - 7.32 (m, 4H), 7.55 (bs, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4 (CH_3), 127.0 (CH), 127.8 (CH), 129.2 (CH), 130.4 (CH), 137.8 (C), 138.5 (C), 148.6 (C).

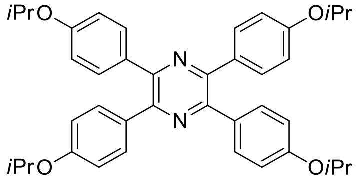
MS (EI, 70 eV): m/z (%) = 440 (M^+, 100), 425 (12), 384 (26), 258 (16), 206 (11), 102 (17), 69 (13), 57 (13).

HRMS (EI, 70 eV): calcd. for $C_{32}H_{28}N_2$: 440.22470; found: 440.22433.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3034 (w), 2915 (w), 1371 (m), 1167 (m), 847 (m), 778 (s), 704 (s), 471 (s), 447 (m).

EA: calcd. for $C_{32}H_{28}N_2$ (440.58): C, 87.24; H, 6.41; N, 6.36; found: C, 87.30; H, 6.36; N, 6.32.

2,3,5,6-Tetrakis(4-isopropoxyphenyl)pyrazine (21k)



According to the general procedure, but with increased amount of Pd(OAc)$_2$ (1.1 mg, 2 mol%) and P(Cy)$_3$ (2.8mg, 4 mol%), compound **21k** was isolated as a white solid (142 mg, 92%); mp. = 241 – 243 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.33 (d, 24H, ^3J = 6.1 Hz, CH$_3$), 4.55 (sept, 4H, ^3J = 6.1 Hz, C$H_{i\text{-Pr}}$), 6.79 - 6.82 (m, 8H), 7.55 - 7.59 (m, 8H).

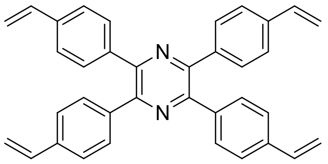
^{13}C NMR (75 MHz, CDCl$_3$): δ = 22.0 (CH$_3$), 69.7 (CH$_{i\text{-Pr}}$), 115.3 (CH), 131.0 (CH), 131.0 (C), 146.7 (C), 158.1 (C).

MS(EI, 70 eV): m/z (%) = 616 (M$^+$, 100), 574 (13), 447 (37), 224 (12), 210 (16), 57 (14), 43 (14).

HRMS (EI, 70 eV): calcd. for $C_{40}H_{44}N_2O_4$: 616.32956; found: 616.32852.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2974 (m), 2923 (w), 1603 (s), 1510 (s), 1382 (s), 1287 (m), 1240 (s), 1163 (s), 1116 (s), 948 (s), 834 (s), 742 (m), 742 (m), 623 (m), 536 (s).

2,3,5,6-Tetrakis(4-vinylphenyl)pyrazine (21l)



According to the general procedure, but with increased amount of Pd(OAc)$_2$ (1.1 mg, 2 mol%) and P(Cy)$_3$ (2.8mg, 4 mol%), compound **21l** was isolated as an off-white solid (93 mg, 76%); mp. > 375 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 5.27 (dd, 4H, $^3J_{\text{cis}}$ = 10.9 Hz, $^2J_{\text{gem}}$ = 0.7 Hz, CH=CH_{cis}-H), 5.77 (dd, 4H, $^3J_{\text{trans}}$ = 17.5 Hz, $^2J_{\text{gem}}$ = 0.7 Hz, CH=CH-H_{trans}), 6.71 (dd, 4H,J_{trans} = 17.5 Hz, $^3J_{\text{cis}}$ = 10.9 Hz, CH=CH$_2$), 7.34 - 7.38 (m, 8H), 7.60 - 7.64 (m, 8H).

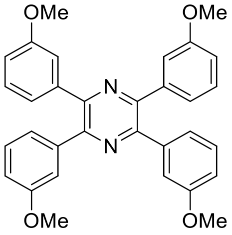
^{13}C NMR (75 MHz, CDCl$_3$): δ = 114.5 (CH), 126.1 (CH), 130.0 (CH), 136.3 (CH), 137.7 (C), 137.8 (C), 147.5 (C).

MS (EI, 70 eV): m/z (%) = 488 (M$^+$, 100), 461 (4), 230 (17), 202 (5), 71 (4).

HRMS (EI, 70 eV): calcd. for $C_{36}H_{28}N_2$: 488.22470; found: 488.22447.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2950 (w), 2917 (w), 2851 (w), 1627 (m), 1388 (s), 1174 (m), 1101 (m), 987 (s), 901 (s), 845 (s), 534 (s).

2,3,5,6-Tetrakis(3-methoxyphenyl)pyrazine (21m)



According to the general procedure, but with increased amount of Pd(OAc)$_2$ (1.1 mg, 2 mol%) and P(Cy)$_3$ (2.8mg, 4 mol%), compound **21m** was isolated as a light brown solid (125 mg, 99%); mp. = 170 – 172 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 3.69 (s, 12H, OCH$_3$), 6.85 - 6.89 (m, 4H), 7.15 - 7.22 (m, 12H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 55.2 (OCH$_3$), 114.8 (2 x CH), 122.4 (CH), 129.2 (CH), 139.6 (C), 148.2 (C), 159.2 (C).

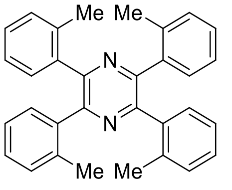
MS (EI, 70 eV): m/z (%) = 504 (M$^+$, 100), 262 (12), 207 (9), 188 (16), 145 (14), 117 (10), 73 (10). 60 (12), 43 (15).

HRMS (EI, 70 eV): calcd. for $C_{32}H_{28}N_2O_4$: 504.20436; found: 504.20339.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3006 (w), 2921 (m), 2853 (w), 1578 (s), 1424 (m), 1377 (s), 1290 (m), 1229 (s), 1028 (s), 775 (s), 719 (s).

EA: calcd. for $C_{32}H_{28}N_2O_4$ (504.58): C, 76.17; H, 5.59; N, 5.55; found: C, 76.49; H, 5.50; N, 5.42.

2,3,5,6-Tetra-*o*-tolylpyrazine (21n)



According to the general procedure, but with increased amount of Pd(OAc)$_2$ (1.1 mg, 2 mol%) and P(Cy)$_3$ (2.8mg, 4 mol%), compound **21n** was isolated as a white solid (109 mg, 99%); mp. = 252 – 254 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.27 (s, 12H, CH$_3$), 6.99 - 7.06 (m, 4H), 7.08 - 7.15 (m, 12H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 20.1 (CH$_3$), 125.2 (CH), 128.2 (CH), 130.2 (CH), 130.4 (CH), 136.2 (C), 137.7 (C), 151.6 (C).

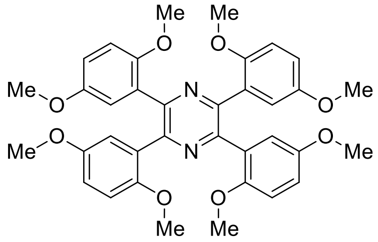
MS (EI, 70 eV): m/z (%) = 440 (M$^+$, 100), 425 (60), 349 (16), 205 (12), 73 (16), 60 (17), 43 (14).

HRMS (EI, 70 eV): calcd. for $C_{32}H_{28}N_2$: 440.22470; found: 440.22351.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3016 (w), 2921 (w), 2852 (w), 1382 (s), 1081 (m), 1016 (m), 757 (s), 723 (s), 460 (s).

EA: calcd. for $C_{32}H_{28}N_2$ (440.58): C, 87.24; H, 6.41; N, 6.36; found: C, 87.47; H, 6.69; N, 6.20.

2,3,5,6-Tetrakis(2,5-dimethoxyphenyl)pyrazine (21o)



Reaction was made according to the general procedure, but with increased amount of Pd(OAc)$_2$ (1.1 mg, 2 mol%) and P(Cy)$_3$ (2.8mg, 4 mol%). After combined organic layers were dried over sodium sulphate, filtered and solvent was removed, compound **21o** was isolated as a white solid by recrystallization of crude mixture from warm dichloromethane.(116 mg, 74%); mp. = 260 – 262 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 3.36 (s, 12H, OCH$_3$), 3.70 (s, 12H, OCH$_3$), 6.64 (d, 4H, ^3J = 8.9 Hz), 6.77 (dd, 4H, ^3J = 8.9 Hz, ^4J = 3.0 Hz), 7.05 (d, ^4J = 3.0 Hz, 4H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 55.4 (OCH$_3$), 55.8 (OCH$_3$), 111.9(CH), 115.3 (CH), 116.6 (CH), 129.4 (C), 149.4 (C), 150.8 (C), 153.3 (C).

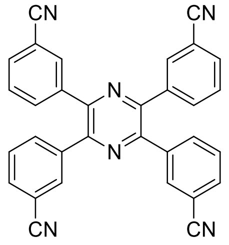
MS (EI, 70 eV): m/z (%) = 624 (M$^+$, 100), 609 (45), 593 (71), 579 (12), 487 (23), 312 (11), 60 (10).

HRMS (EI, 70 eV): calcd. for $C_{36}H_{36}N_2O_8$: 624.24662; found: 624.24559.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3002 (w), 2960 (w), 2833 (w), 1499 (s), 1447 (m), 1424 (s), 1275 (s), 1229 (s), 1079 (m), 1042 (s), 1016 (s), 873 (m), 802 (s).

EA: calcd. for $C_{36}H_{36}N_2O_8$ (624.68): C, 69.22; H, 5.81; N, 4.48; found: C, 69.58; H, 5.74; N, 4.66.

2,3,5,6-Tetrakis(3-cyanophenyl)pyrazine (21p)



According to the general procedure, but with increased amount of $Pd(OAc)_2$ (1.1 mg, 2 mol%) and $P(Cy)_3$ (2.8mg, 4 mol%), compound **21p** was isolated as a white solid (61 mg, 50%); mp. = 296 – 297 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (t, 4H, ^3J = 7.8 Hz), 7.70 - 7.76 (m, 8H), 7.96 (bs, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 113.4 (C), 117.9 (C), 129.6 (CH), 133.1 (CH), 133.2 (CH), 133.8 (CH), 138.0 (C), 147.2 (C).

MS (EI, 70 eV): m/z (%) = 484 (M^+, 100), 380 (7), 355 (5), 228 (38), 201 (8), 60 (5), 44 (5).

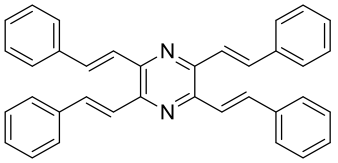
HRMS (EI, 70 eV): calcd. for $C_{32}H_{16}N_6$: 484.14310; found: 484.14195.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3062 (w), 2953 (w), 2227 (m), 1371 (m), 1164 (m), 917 (m), 799 (s), 697 (s), 515 (m).

Synthesis of 2,3,4,5-tetraalkenylpyrazines

An argon-flushed glass pressure tube was charged with $Pd(dba)_2$ (0.005 mmol, 2 mol%), Cata*CX*ium A (0.01 mmol, 4 mol%), tetrachloropyrazine (54.4 mg, 0.25 mmol), the appropriate alkenyl boronic acid or pinacol ester (2 mmol, 8.0 eq.), K_3PO_4 (2 mmol, 8.0 eq.) and anhydrous 1,4-dioxane (4 mL). The tube was sealed with a teflon cap and the reaction mixture was stirred at 100 °C for 20 hours. The resulting mixture was cooled down to room temperature, diluted with water and extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated. After, the crude residue was purified by column chromatography on silica gel using a mixture of hexane and dichloromethane as eluent. Gained solids, in the end, were washed with cold hexane to give pure orange-coloured products.

2,3,5,6-Tetra((*E*)-styryl)pyrazine (22a)



According to the general procedure, compound **22a** was isolated as an orange solid (119 mg, 97%); mp. = 258 – 259 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.31 - 7.35 (m, 4H, CH), 7.39 - 7.43 (m, 8H, CH), 7.54 (d, 4H, ^3J = 15.5 Hz, C*H*=CH), 7.66 - 7.68 (m, 8H, CH), 7.96 (d, 4H, ^3J = 15.5 Hz, CH=C*H*).

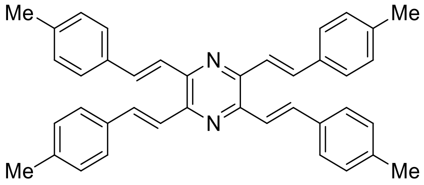
^{13}C NMR (100 MHz, CDCl$_3$): δ = 122.2 (*C*H=CH), 127.4, 128.6, 128.8 (CH), 135.9 (CH=*C*H), 136.8, 145.2 (C).

MS (EI, 70 eV): m/z (%) = 488 (M$^+$, 100), 411 (63), 397 (34), 320 (14), 167 (10), 115 (11), 91 (16). HRMS (EI, 70 eV): calcd. for $C_{36}H_{28}N_2$: 488.22470; found: 488.22372.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3019 (w), 1622 (m), 1493 (m), 1381 (m), 1165 (s), 955 (s), 740 (s), 685 (s), 588 (s), 457 (s).

EA: calcd. for $C_{36}H_{28}N_2$ (488.62): C, 88.49; H, 5.78; N, 5.73; found: C, 88.64; H, 5.54; N, 5.71.

2,3,5,6-Tetrakis((*E*)-4-methylstyryl)pyrazine (22b)



According to the general procedure, compound **22b** was isolated as an orange solid (129 mg, 95%); mp. = 292 – 294 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.39 (s, 12H, CH$_3$), 7.21 (d, 8H, ^3J = 7.9 Hz, CH), 7.48 (d, 4H, ^3J = 15.5 Hz, C*H*=CH), 7.55 (d, 8H, ^3J = 7.9 Hz, CH), 7.91 (d, 4H, ^3J = 15.5 Hz, CH=C*H*).

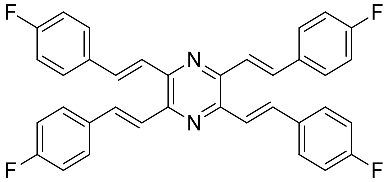
^{13}C NMR (75 MHz, CDCl$_3$): δ = 21.4 (CH$_3$), 121.3 (*C*H=CH), 127.3, 129.4 (CH), 134.2 (C), 135.5 (CH=*C*H), 138.6, 145.1 (C).

MS (EI, 70 eV): m/z (%) = 544 (M$^+$, 100), 453 (35), 439 (28), 287 (13), 195 (21), 119 (14), 105 (19), 44 (17), 36 (10). HRMS (EI, 70 eV): calcd. for $C_{40}H_{36}N_2$: 544.28730; found: 544.28748.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2913 (w), 1622 (m), 1508 (m), 1382 (m), 1165 (s), 956 (s), 797 (s), 474 (s).

EA: calcd. for $C_{40}H_{36}N_2$ (544.73): C, 88.20; H, 6.66; N, 5.14; found: C, 88.05; H, 6.61; N, 5.07.

2,3,5,6-Tetrakis((*E*)-4-fluorostyryl)pyrazine (22c)



According to the general procedure, compound **22d** was isolated as an orange solid (139 mg, 99%); mp. = 284 – 286 °C.

^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 7.25 - 7.33 (m, 8H, CH), 7.88 (d, 4H, ^3J = 15.5 Hz, C*H*=CH), 7.97 - 8.05 (m, 12H, CH, CH=C*H*).

^{13}C NMR (75 MHz, DMSO-d$_6$): δ = 115.8 (d, $^2J_{C–F}$ = 21.6 Hz, CH), 121.9 (*C*H=CH), 130.2 (d, $^3J_{C-F}$ = 8.3 Hz, CH), 133.3 (d, $^4J_{C-F}$ = 3.2 Hz, C), 134.5 (CH=*C*H), 144.8 (C), 162.5 (d, $^1J_{C–F}$ = 246.2 Hz, CF).

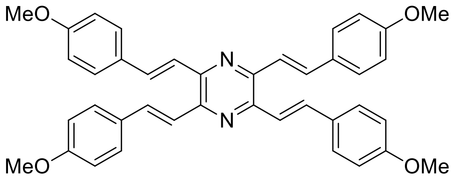
^{19}F NMR (282 MHz, CDCl$_3$): δ = -111.6 (s, 4F, CF). MS (EI, 70 eV): m/z (%) = 560 (M$^+$, 100), 465 (38), 451 (19), 356 (10), 109 (16), 69 (11), 44 (13).

HRMS (ESI): calcd. for $C_{36}H_{24}F_4N_2$ ([M+H]$^+$): 561.19484; found: 561.19421.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1590 (m), 1503 (s), 1415 (m), 1226 (s), 1153 (s), 1091 (m), 964 (s), 813 (s), 529 (s), 479 (s).

EA: calcd. for $C_{36}H_{24}F_4N_2$ (560.58): C, 77.13; H, 4.32; N, 5.00; found: C, 77.44; H, 4.42; N, 4.99.

2,3,5,6-Tetrakis((*E*)-4-methoxystyryl)pyrazine (22d)



According to the general procedure, compound **22d** was isolated as an orange solid (142 mg, 93%); mp. = 229 – 230 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 3.85 (s, 12H, OCH$_3$), 6.93 (d, 8H, ^3J = 8.5 Hz, CH), 7.35 (d, 4H, ^3J = 15.5 Hz, C*H*=CH), 7.58 (d, 8H, ^3J = 8.5 Hz, CH), 7.85 (d, 4H, ^3J = 15.5 Hz, CH=C*H*).

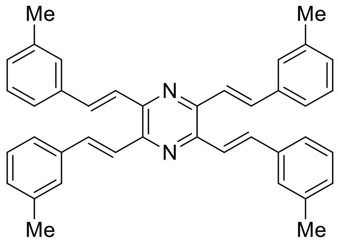
^{13}C NMR (75 MHz, CDCl$_3$): δ = 55.3 (OCH$_3$), 114.1(CH), 120.2 (*C*H=CH), 128.7 (CH), 129.8 (C), 134.7 (CH=*C*H), 144.9, 159.9 (C).

MS (EI, 70 eV): m/z (%) = 608 (M$^+$, 100), 501 (34), 487 (18), 227 (18), 121 (74).

HRMS (ESI): calcd. for $C_{40}H_{36}N_2O_4$ ([M+H]$^+$): 609.27478; found: 609.27537.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3007 (w), 2929 (w), 2834 (w), 1602 (s), 1573 (m), 1508 (s), 1420 (m), 1245 (s), 1162 (s), 1028 (s), 965 (s), 810 (s), 561 (s).

2,3,5,6-Tetrakis((*E*)-3-methylstyryl)pyrazine (22e)



According to the general procedure, compound **22e** was isolated as an orange solid (96 mg, 70%); mp. = 200 – 202 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.41 (s, 12H, CH$_3$), 7.16 (d, 4H, ^3J = 7.5 Hz, CH), 7.28 - 7.33 (m, 4H, CH), 7.44 - 7.50 (m, 12H, CH, C*H*=CH), 7.90 (d, 4H, ^3J = 15.5 Hz, CH=C*H*).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 21.4 (CH$_3$), 122.0 (*C*H=CH), 124.5, 128.2, 128.6, 129.4 (CH), 135.8 (CH=*C*H), 136.8, 138.3, 145.2 (C).

MS (EI, 70 eV): m/z (%) = 544 (M$^+$, 100), 453 (43), 439 (27), 195 (12), 119 (10), 105 (15), 44 (12).

HRMS (ESI): calcd. for $C_{40}H_{36}N_2$ ([M+H]$^+$): 545.29513; found: 545.29509.

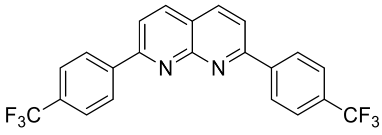
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2913 (w), 1623 (m), 1597 (m), 1371 (m), 1232 (m), 1156 (m), 962 (s), 766 (s), 685 (s), 431 (s).

EA: calcd. for $C_{40}H_{36}N_2$ (544.73): C, 88.20; H, 6.66; N, 5.14; found: C, 87.99; H, 6.64; N, 5.15.

Synthesis of 2,7-diaryl-1,8-naphthyridines

To an argon flushed glass pressure tube were added $Pd_2(dba)_3$ (0.01 mmol, 2.5 mol%), S-Phos (0.04 mmol, 10 mol%), **26** (80 mg, 0.4 mmol), the aryl boronic acid (1.2 mmol, 3.0 equiv.), K_3PO_4 (1.2 mmol, 3.0 equiv.), followed by dry 1,4-dioxane (3 mL). The tube was closed by a teflon screw cap and the reaction mixture was stirred at 100 °C for 20 hours. Subsequently, the mixture was cooled to room temperature and diluted with water and dichloromethane. The layers were separated and the aqueous layer was extracted two times with dichloromethane. The combined organic layers were dried with sodium sulfate, filtered and the solvent was evaporated. The residue was purified by column chromatography (silica gel, hexane/ dichloromethane).

2,7-Bis(4-(trifluoromethyl)phenyl)-1,8-naphthyridine (27b)



According to the general procedure compound **27b** was isolated as a white solid
(141 mg, 84%) with mp. = 216 – 218 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 – 7.78 (m, 4H, CH), 7.98 (d, ^3J = 8.4 Hz, 2H, CH), 8.29 (d, ^3J = 8.4 Hz, 2H, CH), 8.36 – 8.39 (m, 4H, CH).

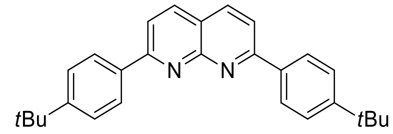
^{13}C NMR (75 MHz, $CDCl_3$): δ = 119.9 (CH), 121.2 (C), 124.0 (q, $^1J_{C-F}$ = 271.8 Hz, CF_3), 125.7 (q, $^3J_{C-F}$ = 3.86 Hz, CH), 128.3 (CH), 131.7 (q, $^2J_{C-F}$ = 32.6 Hz, C), 137.9 (CH), 141.7, 155.9, 159.6 (C).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1602 (w), 1525 (w), 1322 (m), 1128 (s), 1103 (s), 1063 (s), 1014 (m), 842 (s), 809 (s), 779 (m), 597 (m), 395 (w).

MS (EI, 70 eV): m/z (%) = 418 (M^+, 100), 399 (10), 349 (47), 209 (4), 199 (6), 189 (3), 177 (3), 165 (3).

HRMS (EI, 70 eV): calcd. for $C_{22}H_{12}N_2F_6$: 418.08992; found: 418.089463.

2,7-Bis(4-*tert*-butylphenyl)-1,8-naphthyridine (27c)



According to the general procedure compound **27c** was isolated as a white solid (145 mg, 92%) with mp. = 316 – 318 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.36 (s, 18H, CH$_3$), 7.51 – 7.55 (m, 4H, CH), 7.89 (d, ^3J = 8.5 Hz, 2H, CH), 8.15 (d, ^3J = 8.5 Hz, 2H, CH), 8.20 – 8.24 (m, 4H, CH).

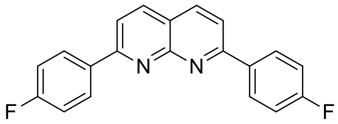
^{13}C NMR (75 MHz, CDCl$_3$): δ = 31.2 (CH$_3$), 34.7 (C), 119.1 (CH), 120.3 (C), 125.6, 127.7 (CH), 135.9 (C), 137.2 (CH), 153.2, 156.2, 160.6 (C).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2960 (m), 1597 (s), 1494 (s), 1362 (w), 1308 (w), 1268 (m), 1111 (m), 1014 (w), 780 (m), 748 (w), 562 (s), 541 (m).

MS (EI, 70 eV): m/z (%) = 394 (M$^+$, 41), 379 (100), 363 (22), 349 (7), 182 (13), 168 (11), 154 (8), 41 (4).

HRMS (EI, 70 eV): calcd. for $C_{28}H_{30}N_2$: 394.24035; found: 394.240085.

2,7-Bis(4-fluorophenyl)-1,8-naphthyridine (27d)



According to the general procedure compound **27d** was isolated as a white solid
(92 mg, 72%) with mp. = 199 – 200 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.14 – 7.22 (m, 4H, CH), 7.87 (d, ^3J = 8.5 Hz, 2H, CH), 8.19 (d, ^3J = 8.5 Hz, 2H, CH), 8.22 – 8.29 (m, 4H, CH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 115.7 (d, $^2J_{C\text{-}F}$ = 21.7 Hz, CH), 119.1 (CH), 120.3 (C), 129.9 (d, $^3J_{C\text{-}F}$ = 8.5 Hz, CH), 134.8 (d, $^4J_{C\text{-}F}$ = 2.9 Hz, C), 137.5 (CH), 155.9, 159.8 (C), 164.1 (d, $^1J_{C\text{-}F}$ = 250.0 Hz, CF).

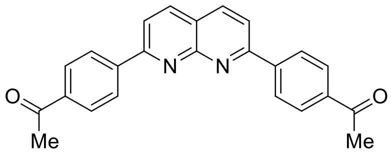
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1596 (s), 1510 (w), 1435 (w), 1308 (w), 1222 (s), 1160 (m), 839 (s), 808 (s), 779 (m), 677 (m), 554 (w), 535 (m), 518 (s), 500 (s), 485 (w).

MS (EI, 70 eV): m/z (%) = 318 (M^+, 100), 297 (3), 221 (3), 195 (4), 169 (3), 159 (4), 149 (7), 120 (4), 75 (4).

HRMS (EI, 70 eV): calcd. for $C_{20}H_{12}F_2N_2$: 318.09631; found: 318.095518.

EA: calcd. for $C_{20}H_{12}F_2N_2$ (318.10): C, 75.46; H, 3.80; N, 8.80; found: C, 75.45; H, 3.89; N, 8.58.

2,7-Bis(4-acetylphenyl)-1,8-naphthyridine (27e)



According to the general procedure compound **27e** was isolated as a white solid (120 mg, 82%) with mp. = 248 – 250 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.62 (s, 6H, CH_3), 7.97 (d, ^3J = 8.5 Hz, 2H, CH), 8.05 – 8.08 (m, 4H, CH), 8.26 (d, ^3J = 8.5 Hz, 2H, CH), 8.33 – 8.36 (m, 4H, CH).

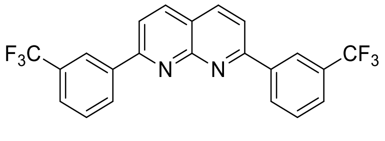
^{13}C NMR(100 MHz, $CDCl_3$): δ = 26.7 (CH_3), 120.0 (CH), 121.2 (C), 128.1, 128.6, 137.7 (CH), 137.8, 142.6, 155.9, 159.7 (C), 197.7 (C=O).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1676 (s), 1602 (s), 1518 (m), 1356 (m), 1262 (s), 1135 (w), 1076 (w), 1013 (w), 957 (m), 831 (m), 805 (s), 779 (m), 650 (w), 579 (m).

MS (EI, 70 eV): m/z (%) = 366 (M^+, 49), 351 (100), 323 (24), 280 (24), 168 (18), 140 (26), 126 (5), 43 (9).

HRMS (EI, 70 eV): calcd. for $C_{24}H_{18}N_2O_2$: 366.13628; found: 366.136075.

2,7-Bis(3-(trifluoromethyl)phenyl)-1,8-naphthyridine (27f)



According to the general procedure compound **27f** was isolated as a white solid (156 mg, 93%) with mp. = 144 – 146 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.61 – 7.66 (m, 2H, CH), 7.72 – 7.74 (m, 2H, CH), 7.98 (d, ^3J = 8.5 Hz, 2H, CH), 8.30 (d, ^3J = 8.5 Hz, 2H, CH), 8.44 – 8.47 (m, 2H, CH), 8.54 – 8.55 (m, 2H, CH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 119.7 (CH), 121.1 (C), 124.0 (q, $^1J_{C\text{-}F}$ = 272.3 Hz, CF$_3$), 124.8 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, CH), 126.6 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, CH), 129.3, 131.2 (CH), 131.3 (q, $^2J_{C\text{-}F}$ = 32.3 Hz, C), 138.0 (CH), 139.3, 155.9, 159.5 (C).

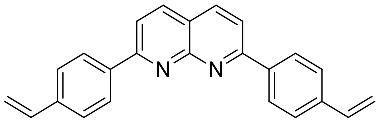
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1603 (w), 1333 (s), 1254 (m), 1173 (m), 1118 (s), 1095 (s), 1066 (s), 798 (s), 699 (s), 690 (s), 653 (m), 432 (w).

MS (EI, 70 eV): m/z (%) = 418 (M$^+$, 100), 399 (10), 349 (40), 209 (6), 199 (5), 189 (3), 164 (3).

HRMS (EI, 70 eV): calcd. for $C_{22}H_{12}N_2F_6$: 418.08992; found: 418.089450.

EA: calcd. for $C_{22}H_{12}N_2F_6$ (418.09): C, 63.16; H, 2.89; N, 6.70; found: C, 63.01; H, 2.78; N, 6.64.

2,7-Bis(4-vinylphenyl)-1,8-naphthyridine (27g)



According to the general procedure compound **27g** was isolated as a yellow solid (86 mg, 64%) with mp. = 217 – 218 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 5.32 (dd, $^3J_{cis}$= 10.9 Hz, $^2J_{gem}$ = 0.7 Hz, 2H, CH=CH_{cis}-H), 5.85 (dd, $^3J_{trans}$= 17.5 Hz, $^2J_{gem}$= 0.7 Hz, 2H, CH=CH-H_{trans}), 6.77 (dd, J_{trans} = 17.5 Hz, $^3J_{cis}$ = 10.9 Hz, 2H, CH=CH$_2$), 7.53 – 7.57 (m, 4H, CH), 7.92 (d, ^3J = 8.5 Hz, 2H, CH), 8.18 (d, ^3J = 8. 5 Hz, 2H, CH), 8.25 – 8.29 (m, 2H, CH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 115.0 (CH$_2$=CH), 119.3 (CH), 120.6 (C), 126.5, 128.2 (CH), 136.2 (CH=CH$_2$), 137.3 (CH), 137.9, 139.1, 156.1, 160.2 (C).

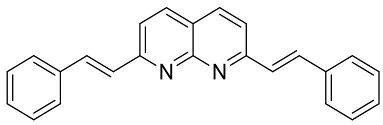
MS (EI, 70 eV): m/z (%) = 334 (M$^+$, 100), 307 (13), 207 (8), 193 (4), 159 (10), 44 (28), 32 (5).

HRMS (ESI, 70 eV): calcd. for $C_{24}H_{19}N_2$ ([M+H]$^+$): 335.15428; found: 335.15362.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3003 (w), 2981 (w), 1596 (m), 1401 (w), 1140 (w), 990 (m), 909 (m), 840 (s), 809 (s), 779 (m), 455 (m).

EA: calcd. for $C_{24}H_{18}N_2$ (334.41): C, 86.20; H, 5.43; N, 8.38; found: C, 85.90; H, 5.27; N, 8.13.

2,7-Distyryl-1,8-naphthyridine (27h)



According to the general procedure compound **27h** was isolated as a yellow solid (122 mg, 91%) with mp. = 250 – 252 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29 – 7.42 (m, 8H, CH)[5], 7.55 (d, ^3J = 8.2 Hz, 2H, CH), 7.60 – 7.64 (m, 4H, CH), 7.95 (d, ^3J = 16.2 Hz, 2H, C*H*=CH), 8.03 (d, ^3J = 8.2 Hz, 2H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 120.4 (CH), 120.9 (C), 127.4 (CH), 128.0 (*C* H=CH), 128.7, 128.8 (CH), 136.0 (CH=*C*H), 136.2 (C), 136.7 (CH), 156.1, 159.2 (C).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2995 (w), 1594 (w), 1507 (w), 1447 (w), 956 (s), 805 (s), 782 (m), 745 (s), 690 (s), 643 (m), 620 (m), 502 (m), 486 (m).

MS (EI, 70 eV): m/z (%) = 333 (M$^+$, 100), 257 (12), 229 (15), 166 (9), 159 (3), 77 (3).

HRMS (ESI, 70 eV): calcd. for $C_{24}H_{19}N_2$ ([M+H]$^+$): 335.15428; found: 335.15422.

Syntheses of *N*-phenyl-2,5-diarylpyrroles

In argon flushed glass pressure tube were placed 0.01 mmol (1.0 mol%) of $Pd(OPiv)_2$, 1.0 mmol of *N*-phenylpyrrole, 2.4 mmol of the appropriate aryl bromide or aryl chloride and 2.4 mmol of CsOPiv, followed by 1.5 g of tetrabutylammonium acetate. The pressure tube was closed with a teflon cap and the reaction mixture was stirred at 140 °C for 20 h. Afterward, the mixture was cooled to room temperature and diluted with distilled water and ethyl acetate. The water layer was extracted 2 times with ethyl acetate and the combined organic layers were washed with brine. The combined organic layers were dried with sodium sulfate and filtered. The solvent of the filtrate was evaporated and the product was purified by column chromatography.

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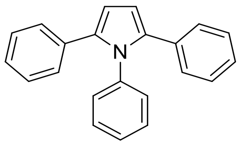
[5] Another peak of CH=C*H* can be detected under multiplet via 2D NMR: 7.39 (d, ^3J= 16.3 Hz, 2H, CH=C*H*).

1,2,5-Triphenyl-1*H*-pyrrole (32a)



According to the general procedure, **32a** was isolated as a light yellow solid (Ar-Br: 154 mg, 52%), mp. = 231 – 232 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.47 (s, 2H, CH), 7.00 - 7.06 (m, 6H, CH), 7.11 – 7.17 (m, 6H, CH), 7.20 – 7.23 (m, 3H, CH).

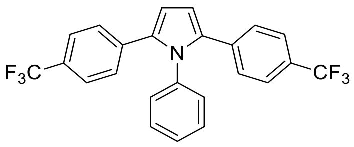
^{13}C NMR (75 MHz, $CDCl_3$): δ = 109.9 (CH), 126.2 (CH), 127.2 (CH), 127.8 (CH), 128.7 (2 x CH), 128.8 (CH), 133.2 (C), 135.8 (C), 138.9 (C).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3052 (w), 2916 (w), 1596 (m), 1494 (m), 1481 (m), 1395 (w), 1334 (w), 774 (s), 692 (s), 595 (m).

MS (EI, 70 eV): m/z (%) = 295 (M^+, 100), 217 (10), 191 (25), 165 (11), 139 (7), 115 (8), 77 (19), 51 (13).

HRMS (EI, 70 eV): calcd. for $C_{22}H_{17}N$: 295.13555; found: 295.13543.

N-Phenyl-2,5-bis(4-(trifluoromethyl)phenyl)-1*H*-pyrrole (32b or 32h)



According to the general procedure, title compound was isolated as a light yellow solid (**32b** with Ar-Br: 223 mg, 52%; **32h** with Ar-Cl: 95 mg, 22%). mp. = 187 – 189 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.56 (s, 2H, CH), 7.01 – 7.04 (m, 2H, CH), 7.11 – 7.14 (m, 4H, CH), 7.29 – 7.32 (m, 3H, CH), 7.39 – 7.42 (m, 4H, CH).

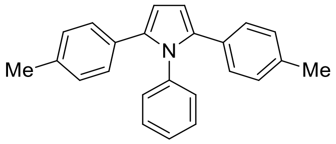
^{13}C NMR (75 MHz, $CDCl_3$): δ = 111.4 (CH), 124.1 (q, $^1J_{C-F}$ = 271.9 Hz, CF_3), 124.9 (q, $^3J_{C-F}$ = 3.9 Hz, CH), 128.0 (CH), 128.2 (q, $^2J_{C-F}$ = 32.2 Hz, C), 128.4 (CH), 128.7 (CH), 129.3 (CH), 135.1 (C), 136.3 (C), 138.2 (C).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1610 (w), 1497 (w), 1421 (m), 1347 (s), 1323 (s), 1162 (s), 1115 (s), 901 (m), 774 (s), 697 (s).

MS (EI, 70 eV): m/z (%) = 431 (M^+, 100), 412 (9), 259 (8), 191 (10), 146 (9), 77 (10).

HRMS (EI, 70 eV): calcd. for $C_{24}H_{15}F_6N$: 431.11032; found: 431.10984.

N-Phenyl-2,5-di(*p*-tolyl)-1*H*-pyrrole (32c)



According to the general procedure, **32c** was isolated as a light yellow solid (Ar-Br: 119 mg, 37%), mp. = 215 – 217 °C.

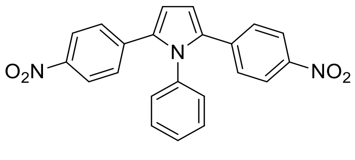
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.27 (s, 6H, CH_3), 6.43 (s, 2H, CH), 6.93 – 6.98 (m, 8H, CH), 7.02 – 7.04 (m, 2H, CH), 7.22 – 7.24 (m, 3H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 (CH_3), 109.4 (CH), 127.0 (CH), 128.5 (2 x CH), 128.6 (CH), 128.9 (CH), 130.4 (C), 135.6 (C), 135.7 (C), 139.1 (C).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2917 (w), 1494 (s), 1332 (m), 814 (s), 768 (s), 693 (s), 579 (s), 521 (s), 401 (s). MS (EI, 70 eV): m/z (%) = 323 (M^+, 100), 205 (8), 191 (9), 77 (13), 51 (6).

HRMS (EI, 70 eV): calcd. for $C_{24}H_{21}N$: 323.16685; found: 323.16660.

N-Phenyl-2,5-bis(4-nitrophenyl)-1*H*-pyrrole (**32d** or **32i**)



According to the general procedure, title compound was isolated as an orange solid using (**32d** with Ar-Br: 180 mg, 47%; **32i** with Ar-Cl: 135 mg, 35%), mp. = 253 – 255 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.67 (s, 2H, CH), 7.04 – 7.07 (m, 2H, CH), 7.12 – 7.17 (m, 4H, CH), 7.30 – 7.40 (m, 3H, CH), 7.99 – 8.04 (m, 4H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 112.9 (CH), 123.4 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 129.7 (CH), 135.2 (C), 137.7 (C), 138.8 (C), 145.9 (C).

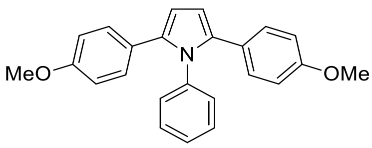
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1585 (s), 1501 (s), 1320 (s), 1105 (s), 850 (s), 772 (s), 747 (s), 697 (s), 521 (m).

MS (EI, 70 eV): m/z (%) = 385 (M^+, 100), 339 (7), 291 (24), 278 (8), 265 (6), 189 (7), 146 (10), 30 (6).

HRMS (EI, 70 eV): calcd. for $C_{22}H_{15}N_3O_4$: 385.10571; found: 385.10543.

EA: calcd. for $C_{22}H_{15}N_3O_4$ (385.37): C, 68.57; H, 3.92; N, 10.90; found: C, 68.37; H, 3.80; N, 11.03.

N-Phenyl-2,5-bis(4-methoxyphenyl)-1*H*-pyrrole (32e or 32j)



According to the general procedure, title compound was isolated as a yellow solid (**32e** with Ar-Br: 53 mg, 15%; **32j** with Ar-Cl: 18 mg, 5%), mp. = 149 – 151 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.73 (s, 6H, OCH_3), 6.37 (s, 2H, CH), 6.67 – 6.72 (m, 4H, CH), 6.94 – 7.02 (m, 6H, CH), 7.20 – 7.23 (m, 3H, CH).

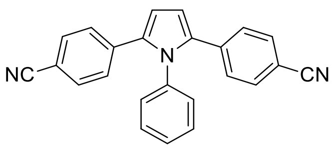
^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.1 (OCH_3), 108.9 (CH), 113.3 (CH), 125.9 (C), 127.0 (CH), 128.6 (CH), 128.9 (CH), 129.9 (CH), 135.1 (C), 139.0 (C), 158.0 (C).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2927 (w), 2831 (w), 1496 (s), 1382 (m), 1281 (m), 1239 (s), 1173 (s), 1025 (s), 824 (s), 751 (s), 695 (s), 583 (s), 523 (s).

MS (EI, 70 eV): m/z (%) = 355 (M$^+$, 100), 340 (56), 296 (6), 268 (10), 178 (9), 77 (10).

HRMS (EI, 70 eV): calcd. for $C_{24}H_{21}NO_2$: 355.15668; found: 355.15638.

N-Phenyl-2,5-bis(4-cyanophenyl)-1*H*-pyrrole (32f)



According to the general procedure, **32f** was isolated as a white solid (217 mg, 63%), mp. = 289 – 291 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.59 (s, 2H, CH), 7.00 – 7.03 (m, 2H, CH), 7.06 – 7.10 (m, 4H, CH), 7.28 – 7.37 (m, 3H, CH), 7.40 – 7.44 (m, 4H, CH).

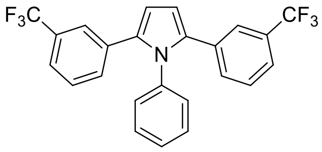
^{13}C NMR (75 MHz, $CDCl_3$): δ = 109.7 (C), 112.2 (CH), 118.8 (C), 128.4 (CH), 128.5 (2 x CH), 129.5, 131.8 (CH), 135.1, 136.9, 137.8 (C).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2221 (s), 1598 (s), 1532 (s), 1490 (s), 1428 (m), 1344 (s), 1178 (m), 840 (s), 778 (s), 697 (s), 560 (s).

MS (EI, 70 eV): m/z (%) = 345 (M$^+$, 100), 242 (6), 216 (13), 190 (8), 77 (16), 51 (12).

HRMS (EI, 70 eV): calcd. for $C_{24}H_{15}N_3$: 345.12605; found: 345.12565.

N-Phenyl-2,5-bis(3-(trifluoromethyl)phenyl)-1*H*-pyrrole (32g)



According to the general procedure, **32g** was isolated as a white solid (185 mg, 43%), mp. = 201 – 203 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.55 (s, 2H, CH), 7.00 – 7.03 (m, 2H, CH), 7.18 – 7.21 (m, 2H, CH), 7.26 – 7.30 (m, 7H, CH), 7.36 – 7.39 (m, 2H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 110.8 (CH), 122.9 (q, $^3J_{C-F}$ = 3.8 Hz, CH), 123.8 (q, $^1J_{C-F}$ = 272.3 Hz, CF_3), 125.2 (q, $^3J_{C-F}$ = 3.8 Hz, CH), 128.0 (CH), 128.3 (CH), 128.7 (CH), 129.2 (CH), 130.3 (q, $^2J_{C-F}$ = 32.2 Hz, C), 131.5 (CH), 133.5 (C), 134.8 (C), 138.0 (C).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1611 (m), 1498 (m), 1433 (m), 1318 (s), 1168 (s), 1104 (s), 1061 (s), 1013 (s), 837 (s), 778 (s), 703 (s), 597 (s), 493 (m).

MS (EI, 70 eV): m/z (%) = 431 (M$^+$, 100), 412 (7), 259 (10), 191 (9), 77 (12), 51 (6).

HRMS (EI, 70 eV): calcd. for $C_{24}H_{15}F_6N$: 431.11032; found: 431.10999.

EA: calcd. for $C_{24}H_{15}F_6N$ (431.37): C, 66.82; H, 3.50; N, 3.25; found: C, 67.01; H, 3.46; N, 3.28.

Crystallographic Data

Data of crystal structure analysis of 21b.

Crystal data for **21b**: $C_{32}H_{16}F_{12}N_2$, $M = 656.47$, monoclinic, $a = 11.6303(4)$, $b = 10.9593(2)$, $c = 22.1529(8)$ Å, $\beta = 102.842(3)°$, $V = 2752.98(15)$ Å^3, $T = 150(2)$ K, space group $P2_1/n$, $Z = 4$, 45142 reflections measured, 6328 independent reflections ($R_{int} = 0.0361$), final R values ($I > 2\sigma(I)$): $R_1 = 0.0420$, $wR_2 = 0.1122$, final R values (all data): $R_1 = 0.0666$, $wR_2 = 0.1184$, 443 refined parameters.

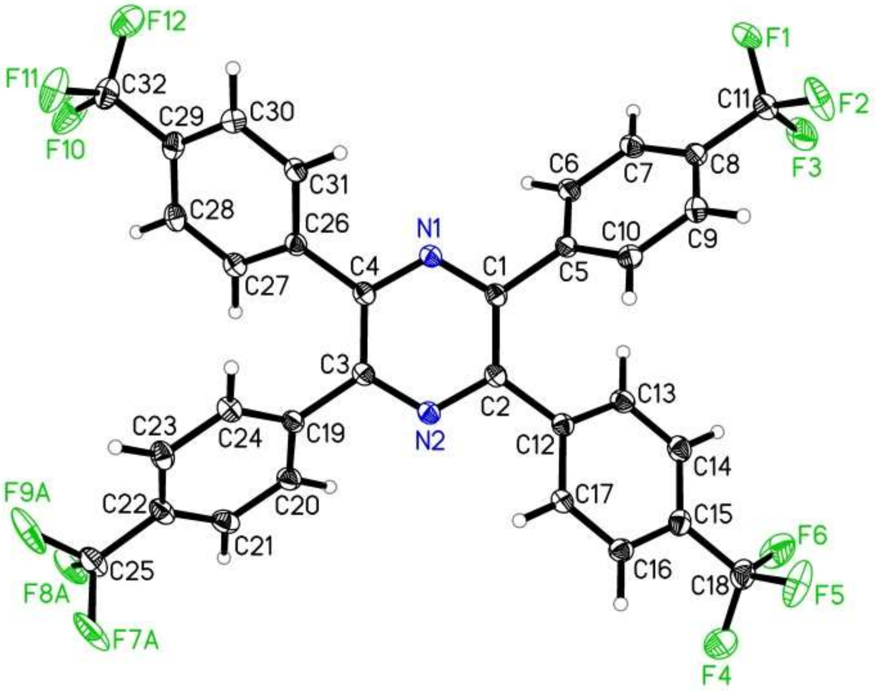


Figure 24. ORTEP of **21b**. Displacement ellipsoids are drawn at the 30% probability level.

Crystal data and structure refinement for compound **21b.**

Identification code	ks1361	
Empirical formula	$C_{32} H_{16} F_{12} N_2$	
Formula weight	656.47	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 11.6303(4) Å	α= 90°.
	b = 10.9593(2) Å	β= 102.842(3)°.
	c = 22.1529(8) Å	γ = 90°.
Volume	2752.98(15) Å^3	
Z	4	
Density (calculated)	1.584 Mg/m^3	
Absorption coefficient	0.150 mm^{-1}	
F(000)	1320	
Crystal size	0.50 x 0.20 x 0.12 mm^3	
Theta range for data collection	1.83 to 27.50°.	
Index ranges	-15<=h<=15, -14<=k<=14, -28<=l<=28	
Reflections collected	45142	
Independent reflections	6328 [R(int) = 0.0361]	
Completeness to theta = 27.50°	100.0%	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6328 / 39 / 443	
Goodness-of-fit on F^2	1.015	
Final R indices [I>2sigma(I)]	R1 = 0.0420, wR2 = 0.1122	
R indices (all data)	R1 = 0.0666, wR2 = 0.1184	
Largest diff. peak and hole	0.551 and -0.383 e.Å^{-3}	

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List of Publications

17. R. Hauptmann,[§] **A. Petrosyan**,[§] F. Fennel, M. A. Cordero, A.-E. Surkus, J. Pospech, *Chem. Eur. J.* **2019**, *25*, 4325–4329 ([§] equal contribution).
"Pyrimidopteridine N-Oxide Organic Photoredox Catalysts: Characterization, Application and Non-Covalent Interaction in Solid State"

16. **A. Petrosyan**, R. Hauptmann, J. Pospech, *Eur. J. Org. Chem.* **2018**, 5237–5252.
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15. S. Parpart, Z. Mardiyan, P. Ehlers, **A. Petrosyan**, A. F. Mkrtchyan, A. S. Saghyan, P. Langer, *Synlett* **2018**, *29*, 793–798.
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14. **A. Petrosyan**, T. V. Ghochikyan, S. A. Ejaz, Z. Z. Mardiyan, S. U. Khan, T. Grigoryan, A. Gevorgyan, M. A. Samvelyan, A. S. Galstyan, S. Parpart, Q. Rahman, J. Iqbal, P. Langer, *ChemistrySelect* **2017**, *2*, 5677–5683.
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13. S. Schmode, **A. Petrosyan**, F. Fennel, A. Villinger, S. Lochbrunner, R. Ludwig, *Angew. Chem. Int. Ed,* **2017**, *56*, 8564 –8567; *Angew.Chem.* **2017**, *129*, 8686–8690.
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9. **A. Petrosyan**, P. Ehlers, S. Reimann, T. V. Ghochikyan, A. S. Saghyan, A. Spannenberg, S. Lochbrunner, P. Langer, *Tetrahedron* **2015**, *71*, 6803–6812.
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8. P. Ehlers, **A. Petrosyan**, A. Neubauer, T. Brose, S. Lochbrunner, T. V. Ghochikyan, A. S. Saghyan, P. Langer, *Org. Biomol. Chem.* **2014**, *12*, 8627–8640.
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