Exploration of Transition-Metal-Catalyzed Direct C-H Arylation of Nitro-Substituted Heteroarenes and Further Transformations of Nitro Group

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Ashot Gevorgyan

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Dekan: Prof. Dr. Klaus Neymeyr

Gutachter der Dissertation:

1. Prof. Dr. Peter Langer

2. Prof. Dr. Wolfgang Maison

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Declaration

Hereby I declare that this thesis has been written without any assistance from third parties. Furthermore, I confirm that no sources have been used in the preparation of this thesis other than those indicated in the thesis itself.

Erklärung

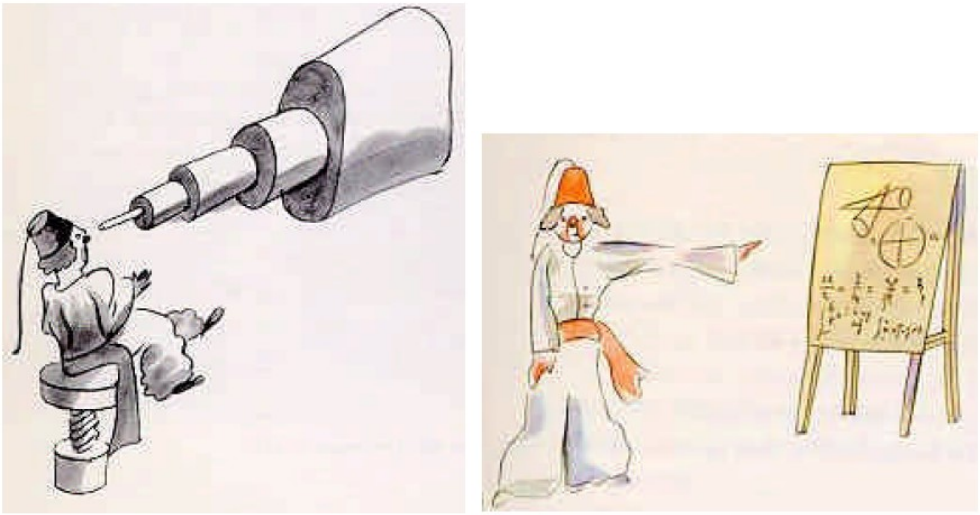
Hiermit erkläre ich, dass ich die vorliegende Arbeit selbstständig angefertigt und ohne fremde Hilfe verfasst habe, keine außer den von mir angegebenen Hilfsmitteln und Quellen dazu verwendet habe und die den benutzten Werken inhaltlich und wörtlich entnommenen Stellen als solche kenntlich gemacht habe.

Ashot Gevorgyan

Rostock, May 2015

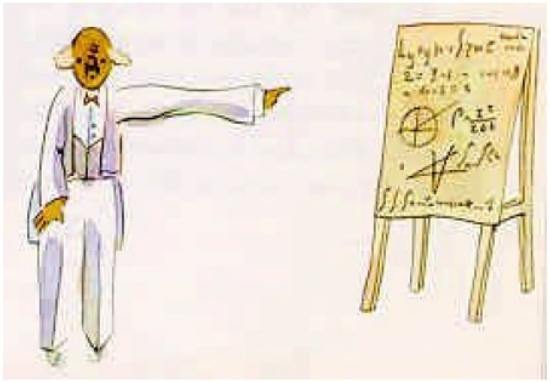
"I have serious reason to believe that the planet from which the little prince came is the asteroid known as B-612. This asteroid has only once been seen through the telescope. That was by a Turkish astronomer, in 1909. On making his discovery, the astronomer had presented it to the International Astronomical Congress, in a great demonstration. But he was in Turkish costume, and so nobody would believe what he said.

Grown-ups are like that...



Fortunately, however, for the reputation of Asteroid B-612, a Turkish dictator made a law that his subjects, under pain of death, should change to European costume. So in 1920 the astronomer gave his demonstration all over again, dressed with impressive style and elegance. And this time everybody accepted his report.

If I have told you these details about the asteroid, and made a note of its number for you, *it is on account of the grown-ups and their ways*. "



The Little Prince

Antoine de Saint-Exupéry

Acknowledgments

"Worthy are You, our Lord and our God, to receive glory and honor and power; for You created all things, and because of Your will they existed, and were created" (Rev 4:11).

The present work was accomplished at the Universität Rostock under the guidance of Prof. Dr. Peter Langer and Dr. Viktor Iaroshenko. I would like to thank them for the opportunity to study at the Uni-Rostock. I am grateful for their overall support during my stay in Rostock and interesting scientific discussions.

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Words are not enough to express my gratitude and love to my parents, brother and wife for their love, constant care, countless prayers and everything they have done for me. In spite of big physical distance they are always spiritually with me.

Ashot Gevorgyan

May 2015, Rostock

Abstract

The present work aimed to study the transition-metal-catalyzed direct C-H arylation of various nitro-substituted heteroarenes, including 4-nitroimidazole derivatives, 4-nitropyrazole derivatives, fused 3-nitropyridines, nitro-substituted pyrrole and thiophene. Under optimized reaction conditions a wide range of coupling partners were perfectly tolerated. Additional empirical studies indicated that the nitro group has influence on the regioselectivity of the reactions. In addition, the multipurpose nature of nitro group as a versatile directing group was explored. Particularly, the nitro group can be easily transferred to amino, N,N-dimethylamino groups etc *via* reduction; on the other hand, the nitro group was transferred to bromo substituent in one step which makes the substrates readily available for further C-C bond forming cross-coupling reactions.

Kurzbeschreibung

Die vorliegende Arbeit beschäftigt sich mit Studien von Übergangsmetall-katalysierten, direkten C-H-Arylierungsreaktionen (Arylierungen unter direkter C-H-Bindungsaktivierung) von verschiedenen Nitro-substituierten Heteroarenen einschließlich von Derivaten des 4-Nitroimidazols, des 4-Nitropyrazols, kondensierter 3-Nitropyridine sowie Nitro-substituierter Pyrrole und Thiophene. Unter optimierten Reaktionsbedingungen konnte eine breite Palette an Kupplungspartnern erfolgreich eingesetzt werden. Weitere empirische Studien ergaben, dass die Nitrogruppe auch Einfluss auf die Regioselektivität bei derartigen Kupplungsreaktionen haben kann. Ferner wurden Umwandlungen sowie die vielseitigen dirigierenden Eigenschaften der Nitrogruppe im Detail untersucht. Speziell die Umwandlungen in Amino-, N,N-Dimethylamino- und andere Gruppen durch Reduktion aber auch die in einem Schritt durchführbare Substitution durch einen Brom-Substituenten, die das Substrat für weitere C-C-Knüpfungsreaktionen zugänglich macht, konnten durchgeführt werden.

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1. Introduction: Biaryls in Industry, Medicine and Life Sciences

The Ar-Ar C-C bond forming reactions are not only of academic interest, but also play an increasingly important role in a number of industrial processes, life sciences, synthesis of natural products, chemistry of chiral catalysts, chiral stationary phase chemistry, production of electronic devices etc.[1]

In particular, several approaches have been employed to identify privileged substructures from the database of known drugs using pharmacophore modeling techniques and a variety of fragmentation algorithms. Interestingly, Bemis and coworkers identified a set of 32 molecular substructures which described almost 50% of all known drugs.[2] Among others the biaryl framework was found in more than 5% of all known drugs, indicating that the biaryl substructure is without doubt a privileged substructure.[3] The Comprehensive Medicinal Chemistry Database indicates the following distinct therapeutic classes for known drugs which contain biaryl framework: antiamebic, antifungal, antiinfective, antihypercholesterolemic, antihyperlipoproteinemic, fasciolicide, antirheumatic, analgesic, antiinflammatory, antithrombotic, uricosuric, and antiarrhythmic.[2,3] Biaryls are also known to possess an antitumor,[4] antihypertensive,[5] and antiatherosclerotic[6] activity.

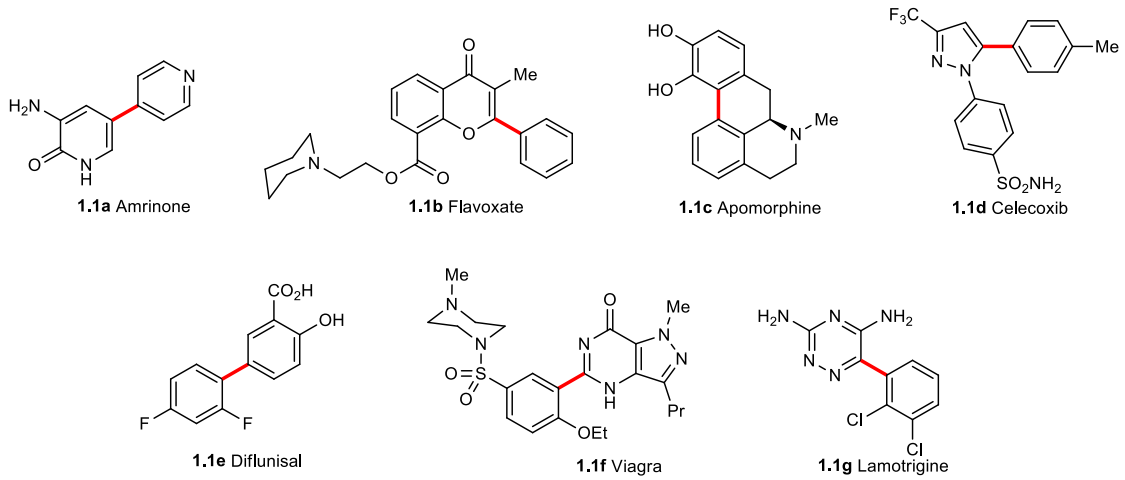


Figure 1.1. Some biaryl based pharmaceuticals.

Noteworthy, along with hydrophobic interactions with appropriate targets (receptors) aromatics have also been shown to form favorable interactions with polar substituents and even charged groups.[7] With this degree of versatility in binding interactions, it is not surprising that the biaryl framework is so common in pharmaceuticals. Some representatives of widely used drugs containing the biaryl fragment are presented in the Figure 1.1. The list

includes Amrinone **1.1a** - a vasodilator agent,[8a] Flavoxate **1.1b** - an anticholinergic agent,[8b] Apomorphine **1.1c** - a non-selective dopamine agonist,[8c] Celecoxib **1.1d** - a nonsteroidal anti-inflammatory drug,[8d] Diflunisal **1.1e** - an analgesic and anti-inflammatory drug,[8e] Viagra (Sildenafil citrate) **1.1f** - a drug used to treat erectile dysfunction,[8f] Lamotrigine (Lamictal) **1.1g** - an anticonvulsant drug[8g] etc (Figure 1.1). Many others can be found in classical textbooks on pharmacology.[8h]

Furthermore, biaryl based structures are widespread in many of naturally occurring products including alkaloids, lignans, terpenes, flavonoids, tannins, as well as polyketides, coumarins, peptides, glycopeptides etc (Figure 1.2). For instance, Vancomycin **1.2a** is a basic structure of several related glycopeptide antibiotics,[9a] the Dragmacidin D **1.2b** represents an emerging class of bioactive marine natural produc,[9b] Lamellarin D **1.2c** is a potent cytotoxic agent isolated from the marine prosobranch mollusc *Lamellaria*,[9c] Dictyodendrin A and B **1.2d**,**e** (isolated from the marine sponge *Dictyodendrilla verongiformis*) possess strong inhibitory activity against telomerase.[9d] Besides, a lot of natural pigments are based on biaryl framework; e.g. Gossypol **1.2f**, which is the major constituent of cottonseed pigment, possessing a male antifertility action.[9e] Among lignans, an illustrative example is Steganacin **1.2g** (a constituent of *Steganotaenia araliacea*), an important synthetic target of many scientific papers which possesses a significant antileukemic activity (Figure 1.2).[9f,g] Many others can be found in classical textbooks on biochemistry and phytochemistry.

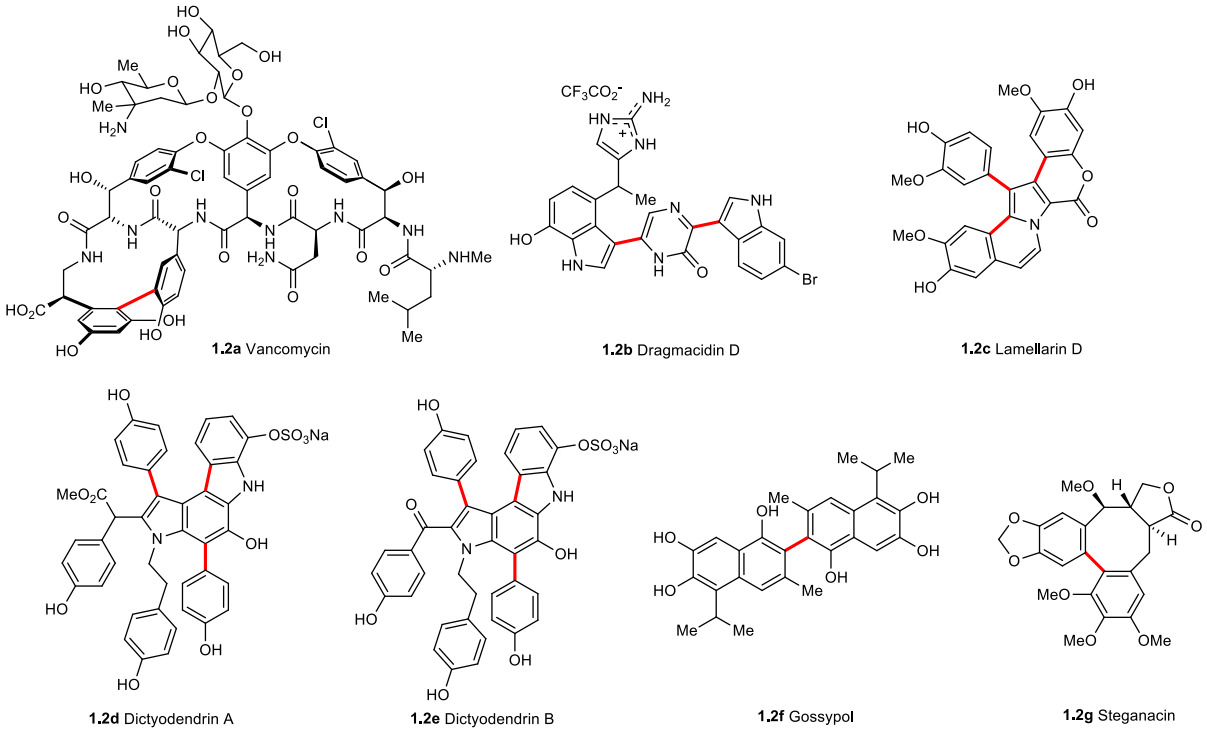


Figure 1.2. Some biaryl based naturally occurring products.

The biaryl structures are the basis of numerous chiral separations by crown ethers, inclusion complexes or preparative chromatography on the chiral stationary phases.[10] Biaryls play an increasingly important role in molecular recognition and development of artificial fluorescent chemosensors.[11] Chiral biaryls, binaphthols and related chiral auxiliaries are widely employed chemicals in some impressive industrial processes.[12] The simplest and historically the most important chiral biaryl molecule is 1,1'-bi-2-naphthol (BINOL) **1.3a** which is used as a chiral ligand or starting material in the production of several valuable catalysts for certain stereoselective reactions (Figure 1.3).[13]

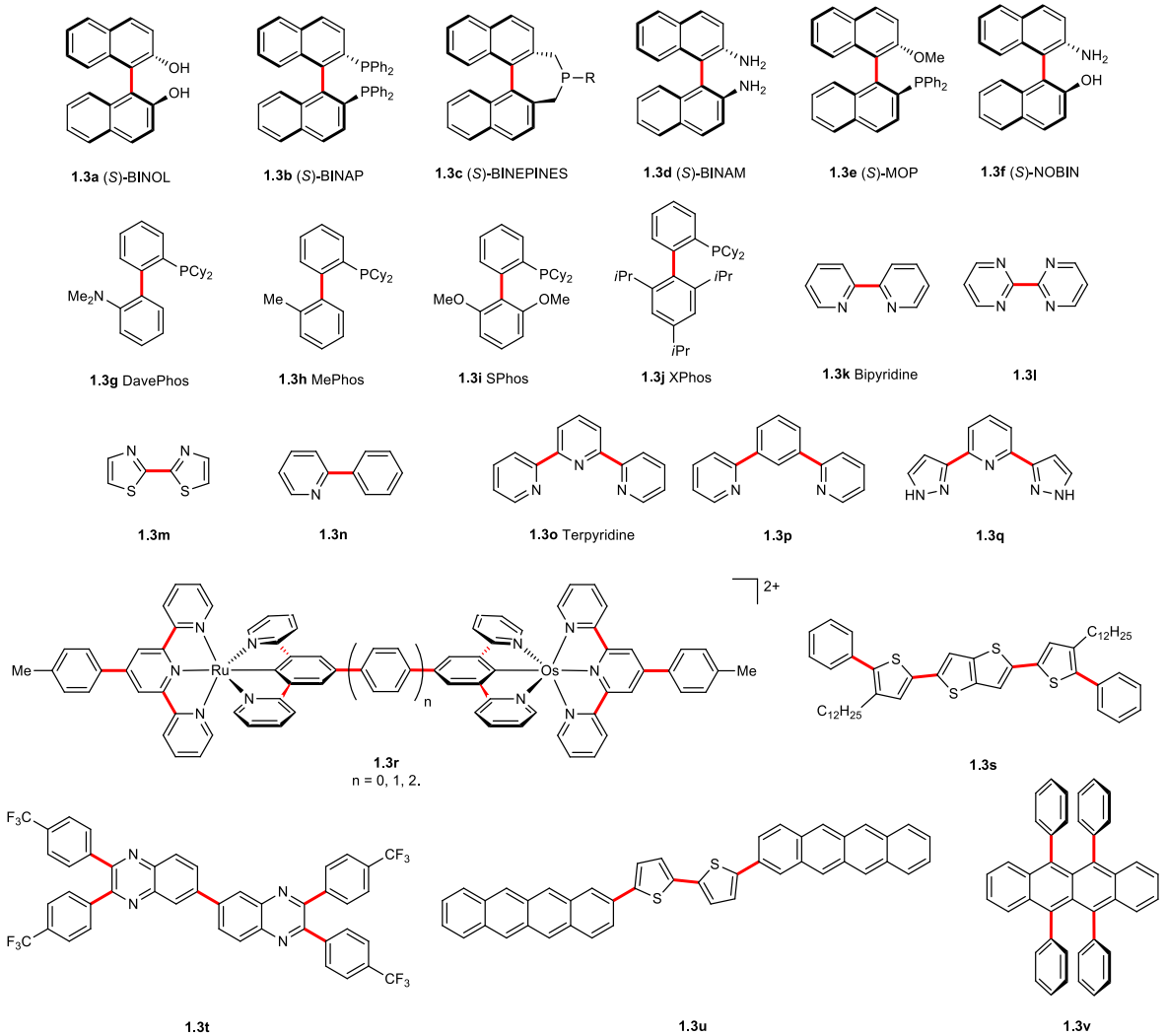


Figure 1.3. Selected examples of biaryl based substances used in industrial processes.

BINOL itself, however, does not always give satisfactory results in asymmetric catalysis, thus there is an ongoing interest in modified BINOL ligands.[13b,14] For this purpose a number of heterobidentate binaphthyls were prepared and successfully applied in asymmetric catalysis. The most frequently used binaphthyls are BINAP **1.3b**,[15a] BINEPINES **1.3c**,[15b] BINAM

1.3d,[14] MOP **1.3e**,[14] NOBIN **1.3f**,[14] and their substituted analogues.[15c-l] Besides, the rapid development of homogeneous catalysis, especially during the last decade, is largely driven by the implementation of new classes of ligands based on biaryl framework. The biaryl based phosphine ligands have proven to provide especially active catalysts in this context; representative examples are DavePhos **1.3g**, MePhos **1.3h**, SPhos **1.3i** and XPhos **1.3j** (Figure 1.3).[16] In addition, several heterobiaryls are among the important ligands in the coordination chemistry and in certain important catalysts. For instance, 2,2'-bipyridine **1.3k**,[17a,b] its derivatives and other heterobiaryls **1.3l**,**m** along with cyclometalated ligands **1.3n**[17c] are widely employed in homogeneous catalysis. Another example is terpyridine **1.3o** and its heteroanalogues **1.3p**,**q** which have been utilized as ligands in asymmetric catalysis; however, nowadays they have found another interesting application: namely they are able to form "mixed complexes" with transition metal ion forming novel supramolecular architectures **1.3r** (Figure 1.3).[18] That is to say, the current state of homogeneous and/or asymmetric catalysis would not have been possible without these valuable classes of ligands based on biaryls.

Moreover, many commercial dyes and fluorescent probes contain several aromatic rings bound together *via* Ar-Ar C-C bond.[19] Last but not least, π-conjugated systems of oligomers and/or polymers based on the Ar-Ar fragments are of considerable interest as futuristic materials for the development and production of the next generation of electronics.[20] Selected representatives of organic semiconductors **1.3s-v** are presented in Figure 1.3.

Owing this the synthesis of biaryls *via* Ar-Ar C-C bond construction was and remains an actual task.

2. Methods of Ar-Ar C-C Bond Construction: Past, Present and the Future

The construction of an Ar-Ar C-C bond remains one of the most important goals in the field of organic chemistry. The development of highly efficient methodologies for the synthesis of biaryls has been under considerable attention for over a century. Since Ullmann's initial reports more than a century ago, about the coupling reactions of aryl halides to biaryls initiated by copper bronze,[21] a number of highly efficient reactions and methods have been disclosed.[1]

Currently, the synthesis of biaryls continues to be the theme of numerous papers. This clearly shows the results of SciFinder search on keyword "arylation" (Figure 2.1). On the chart one can see that this field of research has been growing enormously especially during the last decade.

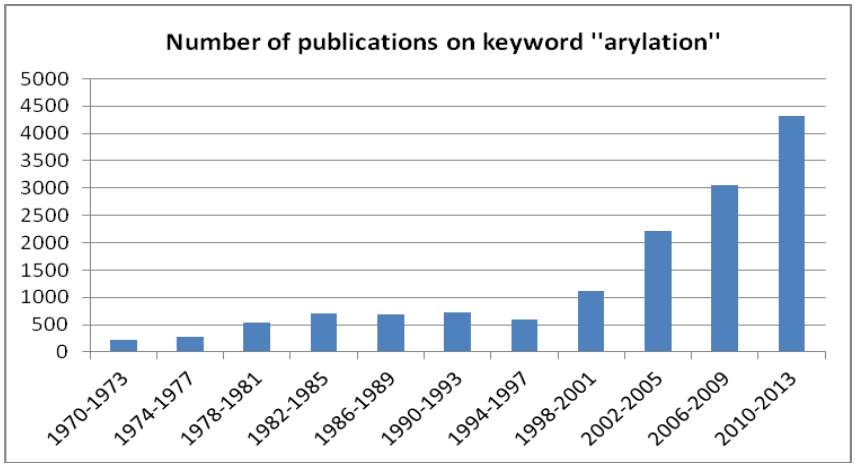
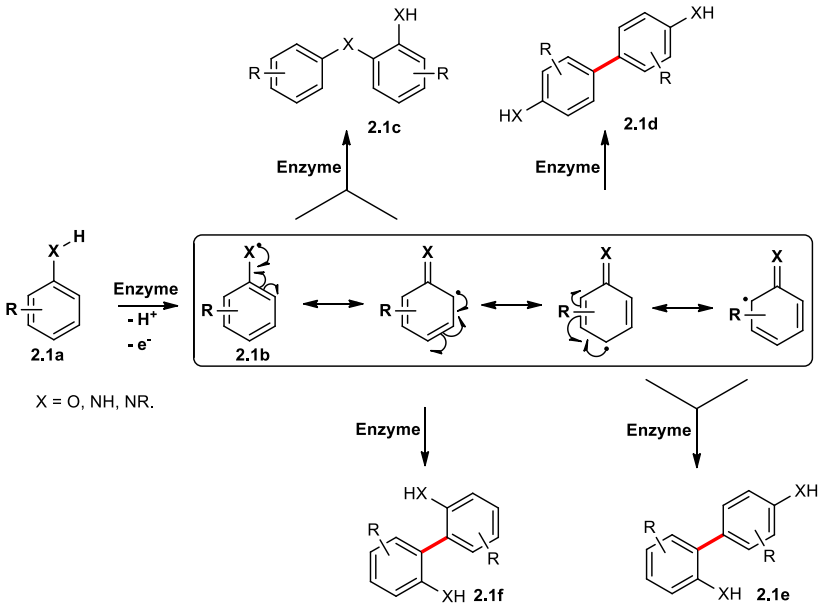


Figure 2.1. The number of publications in the period 1970-2013 on the topic of arylation. The data for the bar chart was obtained by a SciFinder search in November 2014 using keyword "arylation".

Apart from the several recent successful developments in the field of synthesis of biaryls, a number of basic problems are still waiting for efficient solutions. Most of the current methods for the construction of biaryls require prefunctionalization of substrates in order to activate the site of interest of the molecule that allows the construction of desired Ar-Ar bond with proper chemo- and regioselectivity. Alternatively, much more straightforward would be the direct and selective coupling of two unfunctionalized starting arenes to appropriate biaryls. A number of innovative methods of this type are emerging (see below), nevertheless they are still far from being applicable to a broad range of target complex natural product structures. In order to solve this problem once and for all, one should learn from the nature. In most of the cases the unifying principle for the construction of biaryls in natural product biosynthesis is based on oxidative couplings of phenols or aromatic amines (Scheme 2.1).[22] This oxidative process is commonly considered to involve an oxidative enzyme, such as a laccase, a peroxidase or a cytochrome P450 enzyme. In particular, the oxidative enzyme generates a radical at the phenol derivative **2.1a** either by deprotonation and single-electron transfer or by abstraction of a hydrogen atom from the phenol; accordingly creating the intermediate **2.1b** (similar considerations are equally actual for appropriate aromatic amines). Since the generated radical is delocalized in the phenol/aniline ring, the latter could either react with a second radical substrate generated by the enzyme or with another aromatic system *via* single-radical coupling with a subsequent abstraction of an atom of hydrogen (free-radical substitution at the aromatic ring) generating one of possible isomer products. That is to say, the both reaction pathways ultimately lead to the overall abstraction of two protons and two electrons (two hydrogen atoms) giving rise to corresponding biaryls **2.1d-f** or biaryl

ethers/arylamines **2.1c** (Scheme 2.1). This general process results in a large set of possible regiodivergent products with C-O-C (C-N-C in case of aromatic amines) or C-C linkages.[22]

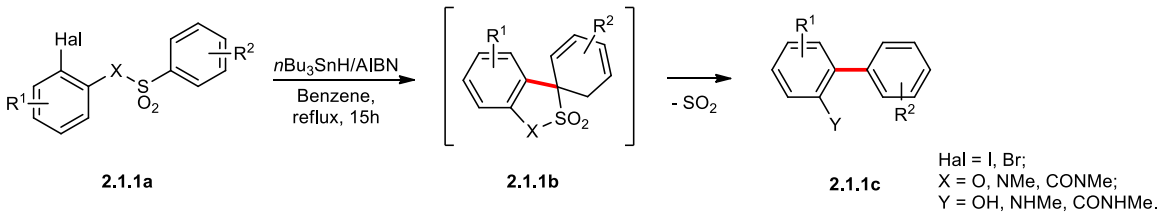


Scheme 2.1. Enzymatic Ar-Ar C-C bond construction in the nature.

In the present chapter an attempt will be made to present both older methods, which are still competitively efficient, and more recent concepts in the field of Ar-Ar C-C bond construction. The evolution of this field is also a good illustration of the development of modern organic synthesis; particularly, the increasingly important role of transition-metal-catalysis (TM-catalysis) in the chemistry. Every effort has been made to comprehensively review the literature within the framework outlined above, however due to the sheer size and scope of this work it is impractical to cover every detail. However, the vast amount of references provided in the work should fulfill the gap.

2.1. Classical Methods for Synthesis of Biaryls

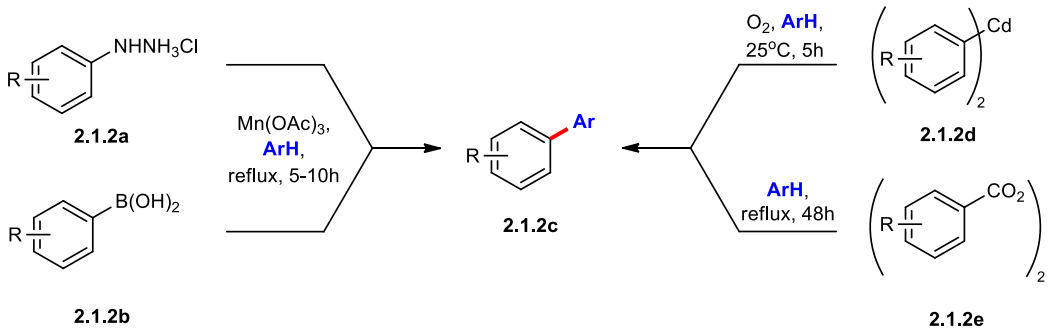
The Motherwell biaryl synthesis. Motherwell and coworkers developed an original approach for the synthesis of biaryls based on the intramolecular free-radical *ipso*-substitution reaction in respective sulfonates and sulfonamides **2.1.1a** (Scheme 2.1.1).[23] The method offers a useful strategy for the construction of biaryls and heterobiaryls. The reaction initiates the tri-*n*-butyltin hydride/azobisisobutyronitrile (AlBN) system (a typical radical initiator) in refluxing liquid arene producing spirocyclic intermediate **2.1.1b**, which, upon extrusion of sulfur dioxide, affords the substituted biphenyls **2.1.1c** from moderate to good yields.



2.1.1a **2.1.1b** **2.1.1c**

Scheme 2.1.1. The Motherwell biaryl synthesis.

Intermolecular free-radical arylation of arenes. This includes the application of several typically substituted arenes which under some special circumstances are prone to generate corresponding aryl radicals. In particular Demir and coworkers showed that $Mn(OAc)_3$ can act as a selective oxidant for the generation of aryl radicals from arylhydrazines **2.1.2a**[24a,b] and arylboronic acids **2.1.2b**.[24c] When the oxidation is conducted in liquid arene (solvent), the free-radical arylation takes place to give corresponding biaryls **2.1.2c** in moderate yields (Scheme 2.1.2). Similarly, arylcadmium reagents in the presence of oxygen are prone to generate appropriate aryl radicals; in particular, diphenylcadmium **2.1.2d** in benzene in the presence of oxygen produces appropriate biphenyl **2.1.2c** along with some amounts of phenol (Scheme 2.1.2).[24d] Another typical example includes diaroyl peroxides **2.1.2e** which at elevated temperatures are prone to dissociate by homolytic pathway generating the arylcarboxy-radicals, $ArCO_2^{\bullet}$, which readily undergo a rapid decarboxylation forming the aryl radicals. The latter can react with the arene used as solvent, by the free-radical arylation mechanism.[24e-i] The main disadvantage of these methods is the formation of disastrous mixture of isomer biaryls (*ortho*, *meta*, *para*) in case of substituted starting arenes.

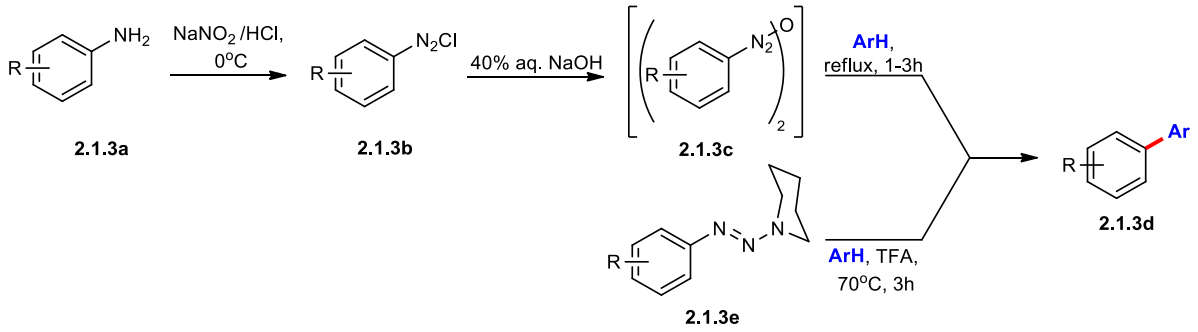


2.1.2a **2.1.2b** **2.1.2c** **2.1.2d** **2.1.2e**

Scheme 2.1.2. Intermolecular free-radical arylation of arenes.

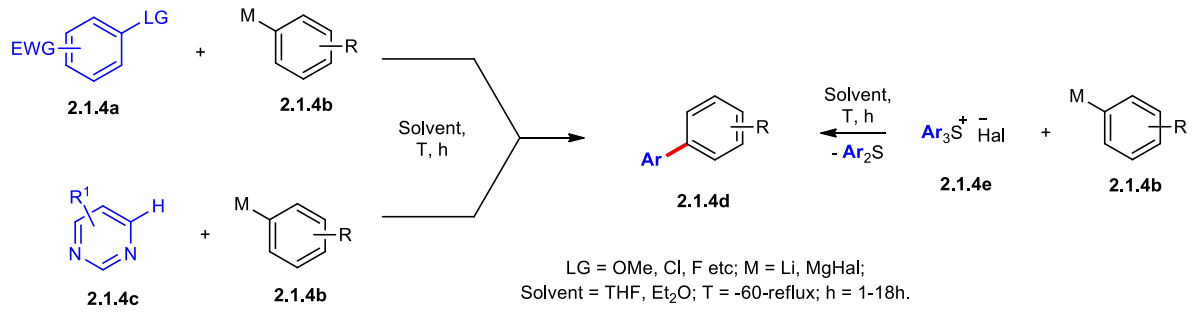
The Gomberg-Bachmann-Hey arylation and related reactions. The arylation of aromatic compounds with aryldiazonium salts initiated by a base is known as Gomberg-Bachmann-Hey reaction (for simplicity GBH reaction).[25] In this case the base reacts with the aryldiazonium salt **2.1.3b** producing the covalent dimer **2.1.3c** which is prone to undergo a homolytic

decomposition accompanied with generation of suitable aryl radical.[26] The latter can react with the arene used as solvent, to give corresponding biaryl **2.1.3d** in moderate yields (Scheme 2.1.3). Similar to the previous case here as well substituted starting arenes form a mixture of isomer biaryls. Additionally, there are some other common side processes, including the formation of polyaryls, parent arene, and arylazo compounds. However, the major limitation of the GBH reaction is that the parent arene has to be used as solvent; that is, it should be liquid and/or fusible. Since the original GBH reaction rarely gives satisfying results, further improvements have been introduced.[27] The more recent alterations of the GBH reaction are based on the thermal decomposition of appropriate aryltriazenes **2.1.3e** which generates corresponding aryl radicals (Scheme 2.1.3).[28]



Scheme 2.1.3. The Gomberg-Bachmann-Hey arylation and related reactions.

The Meyers synthesis of biaryls and related reactions. A number of good leaving groups for aromatic nucleophilic substitution can be effectively substituted by aryllithiums or aryl Grignard reagents **2.1.4b** giving rise to certain biaryls **2.1.4d** (Scheme 2.1.4). In this context, the substitution of methoxy group is well-known as Meyers synthesis of biaryls.[29]



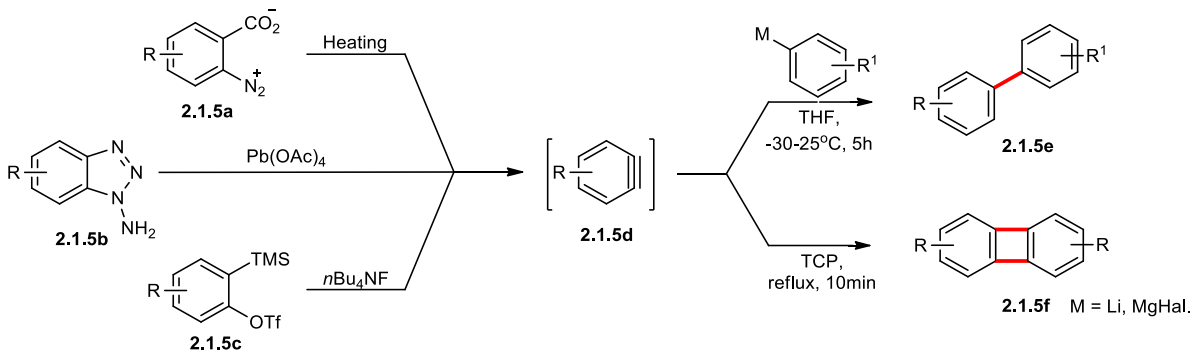
Scheme 2.1.4. The Meyers synthesis of biaryls and related reactions.

On the basis of the Meyers approach, others have introduced several related procedures based on arenes bearing various electron-withdrawing substituents which activate the leaving group

towards nucleophilic substitution.[30] On the other hand, electron deficient arenes, such as pyridines, pyrimidines **2.1.4c** etc, do not require electron-withdrawing substituents and are active enough to undergo an efficient nucleophilic substitution. Moreover, in these systems even hydrogen can serve as a good leaving group (Scheme 2.1.4).[31]

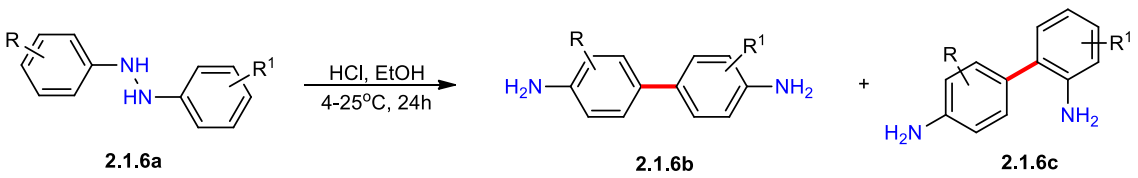
Alternatively, another interesting reaction was discovered by Wittig and Franzen. Thus, they have shown that triarylsulfonium salts **2.1.4e** are prone to react with phenyllithium **2.1.4b** giving rise to corresponding sulfide and biaryl (Scheme 2.1.4).[32]

Synthesis of biaryls from arynes. The arynes, generated *in situ*,[33] are prone to react with a number of aryl organometallics, including themselves, producing corresponding biaryls **2.1.5e**,**f** in various yields.[34] In this respect, as aryne **2.1.5d** precursors were applied benzenediazonium carboxylate **2.1.5a**, 1-aminobenzotriazole **2.1.5b**, 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **2.1.5c** etc (Scheme 2.1.5).[33]



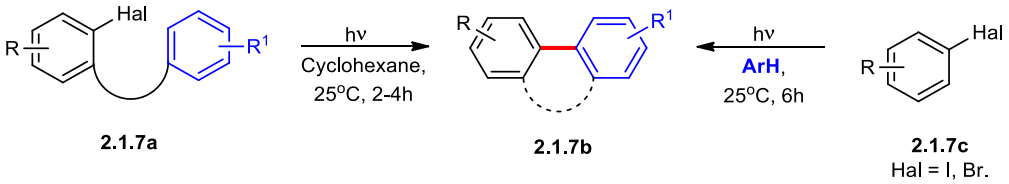
Scheme 2.1.5. Synthesis of biaryls from arynes.

Synthesis of biaryls *via* benzidine rearrangement. Another interesting approach to biaryls represents the acid-catalyzed rearrangement of N,N′-diarylhydrazines **2.1.6a** to *para*, *para*-diaminobiaryls **2.1.6b** (Scheme 2.1.6).[35] The benzidine rearrangement is an efficient approach for the synthesis of unsymmetrical biaryls and heterobiaryls, using suitable unsymmetrically substituted N,N′-diarylhydrazines.[35f,h,i] The main disadvantage of the reaction is that besides *para*, *para*-product, the rearrangement always produce some amounts of *ortho*, *para*-product **2.1.6c**.[35o]



Scheme 2.1.6. Synthesis of biaryls *via* benzidine rearrangement.

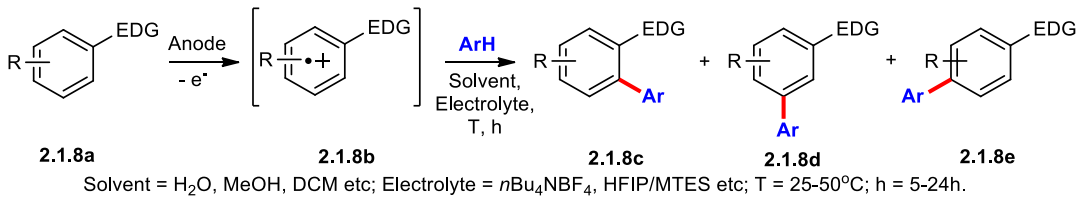
Photochemical synthesis of biaryls. The Ar-Ar C-C bond construction can be realized by photochemical irradiation of suitable aryl iodides or bromides, which upon photodehydrohalogenation form corresponding biaryls (Scheme 2.1.7).[36] This process has a free-radical nature. The photochemical syntheses of biaryls **2.1.7b** can be performed either intra- **2.1.7a** or intermolecularly **2.1.7c**.



Scheme 2.1.7. Photochemical synthesis of biaryls.

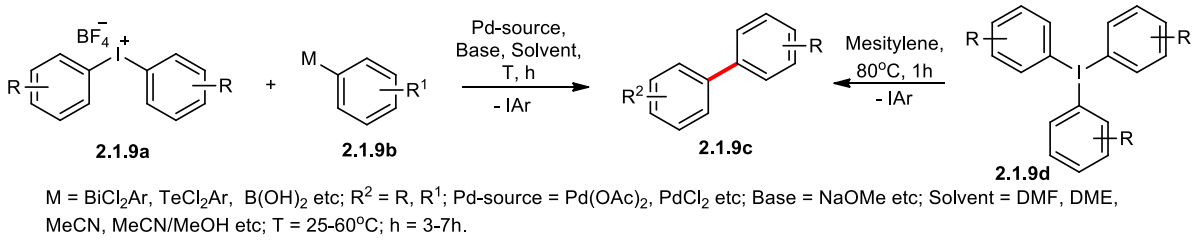
Electrochemical synthesis of biaryls. During the electrolysis corresponding substrate is subjected to the removal (anodic oxidation) or addition (cathodic reduction) of electrons. Particularly, at the anode, electron-rich arenes **2.1.8a**, anilines and phenols dimerize or react with appropriate arenes generating corresponding biaryls **2.1.8c-e** *via* intermediate radical cations **2.1.8b** (Scheme 2.1.8).[37] The basis of this process is the anodic transformation of the substrate to radical cation by removal of an electron.

This process is very much similar to the enzymatic Ar-Ar C-C bond construction in the nature (Scheme 2.1); however, usually the process is not selective, hence the formation of isomer products **2.1.8c-e** is commonly observed.



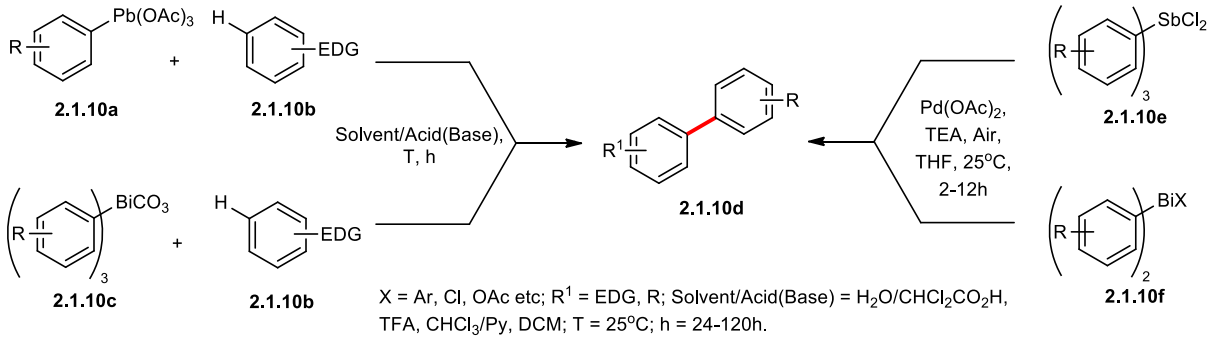
Scheme 2.1.8. Electrochemical synthesis of biaryls.

Synthesis of biaryls from hypervalent iodine compounds. Aryliodonium salts **2.1.9a** and some other hypervalent aryliodonium compounds[38] in the presence of Pd-catalysts smoothly react with arylboronic acids, diaryltellurium dichlorides and other organometallics **2.1.9b** forming certain biaryls **2.1.9c** in good yields (Scheme 2.1.9).[39] Empirical studies indicated that in unsymmetrical diaryliodonium salts, only the electron-rich aryl group participates in the formation of appropriate biaryl. Besides, triaryliodane and related compounds **2.1.9d**, being rather unstable, are prone to decompose to corresponding iodoarene and biaryl.[38b,39a]



Scheme 2.1.9. Synthesis of biaryls from hypervalent iodine compounds.

Synthesis of biaryls *via* aryllead(IV), arylbismuth and arylantimony reagents. The aryllead(IV) tricarboxylates **2.1.10a** are prone to arylate the electron-rich arenes **2.1.10b** under mild conditions within a few hours, generating appropriate biaryls **2.1.10d** in moderate yields (Scheme 2.1.10).[40]

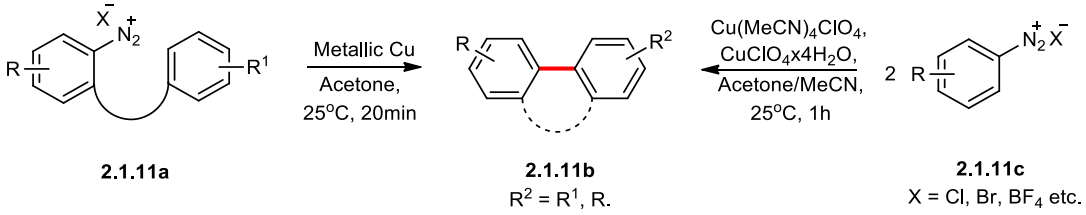


Scheme 2.1.10. Synthesis of biaryls *via* aryllead(IV), arylbismuth and arylantimony reagents.

In this case the aryllead(IV) tricarboxylates supposedly act as an aryl-cation donors, hence the transformation represents a kind of electrophilic aromatic substitution reaction. Expectedly, in case of monosubstituted arenes, all three isomeric biaryls were obtained. The main side process of the reaction is acid initiated protodeplumbylation of aryllead(IV) tricarboxylates which produces the parent arene. Related useful classes of organometallics for the synthesis of biaryls represents arylbismuth and arylantimony reagents.[41] Whereas the arylbismuth(III) **2.1.10f** and triarylantimony(III) **2.1.10e** reagents are convenient precursors for the Pd-catalyzed synthesis of symmetrical biaryls,[41c,d] the triarylbismuth(V) reagents **2.1.10c** are tend to act as aryllead(IV) tricarboxylates, thus, the direct arylation reaction of electron-rich arenes proceeds *via* electrophilic aromatic substitution generating biaryls in moderate yields.[41b]

Pschorr arylation and related reactions. The intramolecular coupling reaction of aryldiazonium salts **2.1.11a** with the arene subunit initiated by copper or an acid, is known as the Pschorr cyclization reaction (Scheme 2.1.11).[42a] The Cu-induced decomposition of aryldiazonium salts is a well-known process which is assumed to proceed through one

electron reduction with generation of an aryl radical, obviously not free, but held on the Cu surface.[42,43] The latter is prone to undergo further intramolecular arylation, a process which is somewhat similar to the Gomberg-Bachman-Hey reaction (Scheme 2.1.3). In spite of numerous attempts to increase the yields and versatility of the reaction, the Pschorr cyclization still remains an inconvenient and low yielding process. A closely related reaction to Pschorr arylation is the Gatterman synthesis of biaryls which includes the coupling reaction of two aryldiazonium salts **2.1.11c** initiated by metallic Cu or Cu(I) salts (Scheme 2.1.11).[44]

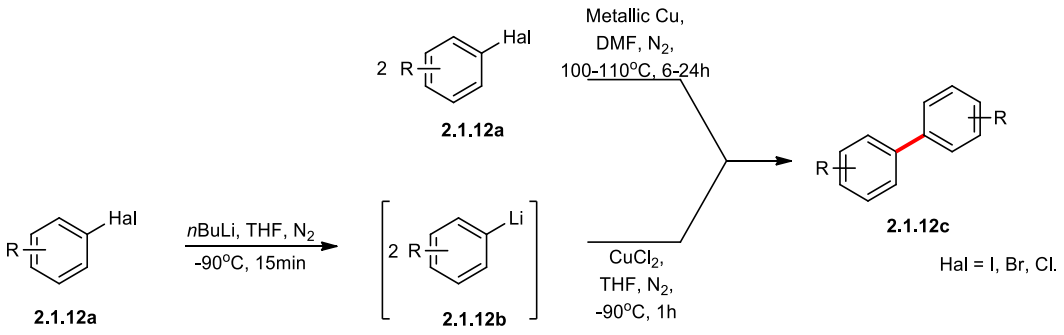


Scheme 2.1.11. Pschorr arylation and related reactions.

Ullmann arylation and related reactions. The synthesis of biaryls **2.1.12c** by the coupling of two molecules of an aryl halide **2.1.12a** in the presence of copper is one of the oldest methods in the field which is well-known as Ullmann arylation (Scheme 2.1.12).[21,45] Due to its simplicity, the Ullmann arylation was widely applied in the synthesis of numerous symmetrical and some classes of unsymmetrical biaryls.[45,46]

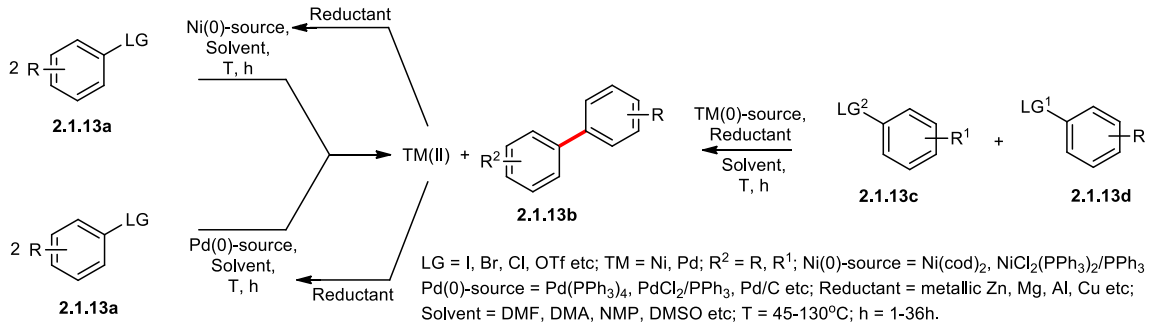
Usually the reaction requires from three to tenfold excess of Cu which limits the scalability of the reaction. In general, the order of reactivity of aryl halides is I > Br >> Cl; in the reaction fluorine usually remains intact.[45] Additionally, electronegative substituents exhibit an activating effect on the aryl halide. However, OH, NHR and free-carboxylic acid substituents as a rule prevent the formation of target biaryls due to some additional competing reaction pathways.[47]

The efficiency of Ullmann arylation towards unsymmetrical biaryls can be enhanced *via* using aryl halides with different reactivity; otherwise the result may be a complex mixture of products.[45] In this case another side reaction may arise, which is the halogen-exchange reaction induced by Cu.[48] Another modification of the Ullmann arylation is based on copper(II)-induced intra- and intermolecular homo-couplings of various arylmetallic reagents **2.1.12b** generated *in situ* from suitable aryl halides (Scheme 2.1.12). In this case the arylmetallic reagent undergoes transmetallation with the Cu(II) salt forming suitable diarylcopper(II) intermediate which is prone to undergo a rapid reductive elimination to form corresponding biaryl **2.1.12c**.[49]



Scheme 2.1.12. Ullmann arylation and related reactions.

Transition-metal-induced coupling reactions of aryl halides and sulfonates. Due to the numerous disadvantages and complications connected with classical Ullmann arylation and other methods described above, a number of attempts have been made to describe some more efficient alternatives for Ar-Ar C-C bond construction.[50] As a result, it was found that aryl halides and sulfonates **2.1.13a**,**c**,**d** can be coupled to biaryls **2.1.13b** using various salts and complexes of transition metals (Scheme 2.1.13). In the early phases, the transition metals were used as stoichiometric reagents.[50] In contrast, recent methods require only a catalytic amount of suitable transition metal complex in the presence of an inexpensive ultimate reductant. Among others, the Ni(0)[51] and Pd(0) complexes,[52] as well as Cu(I) salts in stoichiometric amounts,[53] proved to be the most promising initiators for coupling of aryl halides and sulfonates to corresponding symmetrical and unsymmetrical biaryls. In this regard, the most important methods for coupling of aryl halides to biaryls are based on the usage of catalytic amounts of Pd(0)-based catalysts. The basic principle of catalytic method is that the Pd(II) complex, formed during Pd(0)-catalyzed biaryl synthesis, is *in situ* reduced back to active Pd(0) catalyst with an ultimate reductant (the same refers to the Ni).[51,52]

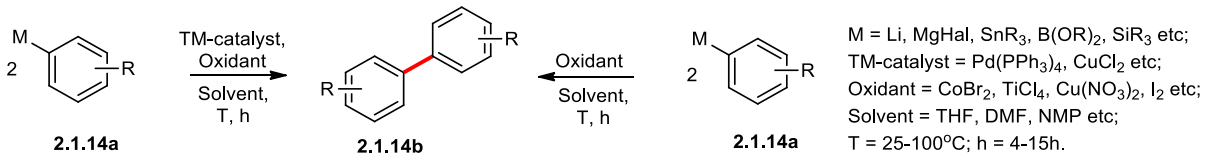


Scheme 2.1.13. Transition-metal-induced coupling reactions of aryl halides and sulfonates.

In addition to the coupling reactions catalyzed by Ni(0) and Pd(0) complexes, the active forms of metallic Ni,[54a-c] Co,[54c] and even In[54d] proved to be highly effective alternatives for the

homo-coupling of aryl halides. The efficient synthesis of unsymmetrical biaryls *via* Ni- or Pd-catalyzed coupling reactions of aryl halides still can be achieved under special circumstances;[55] although, the selectivity of the process is not that high. Accordingly, the most efficient approach to unsymmetrical biaryls is based on the use of an aryl halide with increased reactivity together with relatively inactive one (Scheme 2.1.13). Usually this approach causes preferential formation of the unsymmetrical cross-coupling product.[55]

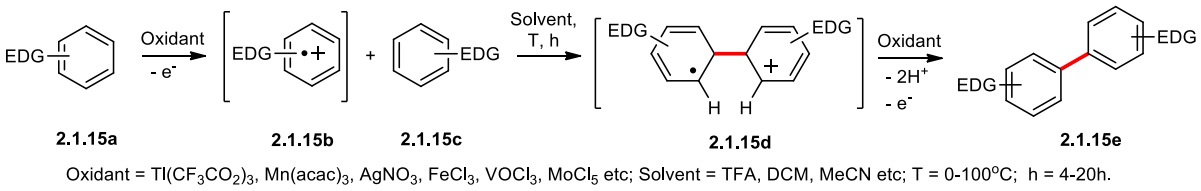
Homo-coupling reactions of arylmetallic reagents to biaryls. A number of arylmetallic reagents as formal aryl-carbanion donors are prone to be oxidatively coupled to symmetrical biaryls.[56] A representative example is the modified Ullmann arylation based on the homocoupling of aryllithiums induced by Cu(II) salts (Scheme 2.1.12, see also Scheme 2.1.10).[49] That is to say, transition metals which can be considered as one- or two-electron oxidants, as well as transition metals which tend to form suitable thermally unstable biarylmetals, can affect the homo-coupling reaction of appropriate organometallics **2.1.14a** (Scheme 2.1.14). For instance, aryllithiums, apart from the modified Ullmann arylation, have been coupled by $Fe(acac)_3$ which is an efficient one-electron oxidant.[57] Similarly, the aryl Grignard reagents,[58] arylzincs,[59] arylzirconiums,[60] arylboronic acids and tetraarylborates,[61] Stille reagents (aryltrimethyl- or tri-*n*-butylstannanes),[62] arylsilicon reagents,[63] arylmercuric halides[64] as well as diaryltellurium dichlorides[65] can be converted to symmetrical biaryls **2.1.14b** using different well established oxidant or TM-based coupling procedures.



Scheme 2.1.14. Homo-coupling reactions of arylmetallic reagents to biaryls.

Synthesis of biaryls by oxidative couplings of arenes. The direct construction of Ar-Ar C-C bond between two aromatic rings without pre-functionalization can be accomplished using various oxidative couplings (Scheme 2.1.15).[66] The methodology is especially suitable for electron-rich arenes such as thiophenes, pyrroles, phenols, anilines etc. However, benzene and electron-poor aromatics also can be subjected to the oxidative coupling reactions to form corresponding biaryls under certain circumstances.[66] The reaction supposedly proceeds through an aryl radical-cation **2.1.15b** which reacts with the second molecule of arene **2.1.15c** to give a bicyclohexadiene radical-cation **2.1.15d** which tends to lose two protons and an electron, initiated by an oxidant, providing corresponding biaryls **2.1.15e** (Scheme 2.1.15). In

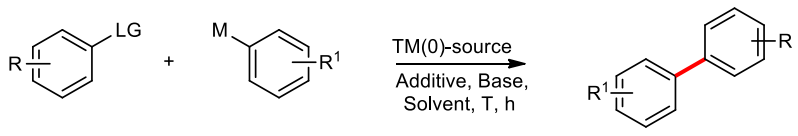
this respect a number of reagents are able to produce an aryl radical-cation from parent arenes. The representative classes of reagents include: Bronsted acids, e.g. H_2SO_4 etc; Lewis acids, e.g. $AlCl_3$, SnX_4 etc; some salts of transition metals, e.g. salts of Ag(II), Cu(II), Co(III), Ce(IV), Mo(V), V(IV) etc; halogens and many others.[66] Interestingly, some reagents can serve both as Lewis acid and oxidant, offering a highly efficient means for overall transformation. Thus, the oxidative coupling of simple arenes to biaryls have been performed using stoichiometric amounts of Tl(III) salts,[67] salts of Cr,[68] salts of Mn,[69] activated PbO_2,[70] V oxides,[71] salts of Ti,[72] salts of Mo,[73] salts of Ce,[74] salts of Pb,[75] salts of Ag,[76] salts of Cu,[77] salts of Pd,[78] salts of Fe,[79] salts of Ru,[80] salts of Co,[81] hypervalent iodine compounds,[82] and other reagents.[83] These processes are similar to the enzymatic Ar-Ar C-C bond construction (Scheme 2.1); nevertheless, the amount and toxicity of used oxidants together with reduced selectivity of the reaction dramatically limits the overall applicability of the process.



Scheme 2.1.15. Synthesis of biaryls by oxidative couplings of arenes.

Cross-coupling reactions of arylmetallic reagents with aryl halides and related reagents. In general, in the presence of TM-based catalysts arylmetallic reagents **2.1.16b** smoothly react with aryl halides, triflates and other related reagents **2.1.16a**, producing certain biaryls **2.1.16c** (Scheme 2.1.16).[84] In TM-catalyzed cross-coupling reactions, the organometallics of both electronegative (Sn, Hg etc) and electropositive (Li, Mg etc) metals as well as corresponding metalloids (B, Si etc) act as formal carbanion-donors, whereas the aryl halides, triflates and related reagents are formal carbocation-donors. Historically, the initial cross-coupling reactions of aryl halides were performed using Grignard and organolithium reagents. However, since these organometallics do not tolerate a number of common functional groups, accordingly, some less reactive organometallics were introduced. The reactivity of aryl halides in cross-coupling reactions follows the general order: I > Br >> Cl. Additionally, a number of other functionalized arenes such as diazonium salts, carboxylates, sulfonates, nitriles and even thioethers can be employed as alternative coupling partners (Scheme 2.1.16).[85] However, some of these functionalized arenes are less reactive than appropriate aryl halides; nevertheless, application of more active catalysts makes this approach to biaryls widely applicable.[85] The cross-coupling reactions can involve arylmetallic reagents of Zn, Sn,

B, Si, Hg, Cu, Mg as well as the slightly less studied Ti, In and Ge reagents and some others (Scheme 2.1.16).[86,56] Most of the cross-coupling reactions are well-known name reactions. For instance, the coupling of Grignard reagents with aryl halides is known as the Kharasch reaction, the arylzinc based analogue is called the Negishi reaction, the organostannanes are used in the Stille reaction, while the most important reaction in the field is based on organoboron reagents and is well-known as the Suzuki-Miyaura reaction. Noteworthy, these reactions can be widely used in the sp^2-sp^3, sp^2-sp, sp^2-sp^2, sp-sp, sp^3-sp, as well as sp^3-sp^3 C-C bond forming processes.[84,87] This chemistry was awarded by the Nobel prize in 2010, which indicates on the great importance of these transformations.[88]



2.1.16a **2.1.16b** **2.1.16c**

M = Li, MgHal, Cu, ZnHal, MnHal, TiR_3, InR_2, GeR_3, SnR_3, SiR_3, $B(OR)_2$, HgAr etc; LG = N_2X, I, Br, Cl, CO_2H, OTf etc;
TM(0)-source = $Pd(PPh_3)_4$, $Pd(PtBu_3)_2$, $NiCl_2$, Ni(dppp)Cl_2 etc; Additive = LiBr, $ZnCl_2$, TBAF, KF etc;
Base = K_2CO_3, $Ba(OH)_2$, K_3PO_4, Cs_2CO_3, KO*t*Bu etc; Solvent = THF, DMF, Benzene/H_2O etc; T = 25-140°C; h = 2-24h.

Scheme 2.1.16. Cross-couplings of arylmetallics with aryl halides and related reagents.

The Kharasch reaction. As it was mentioned above, aryllithium and Grignard reagents, derived from simple arenes, smoothly react with aryl halides and other related reagents, in the presence of various Ni- or Pd-based catalysts, giving rise to unsymmetrical biaryls in moderate yields (Scheme 2.1.16, M = Li, MgHal).[89-91] Since the aryllithiums and Grignard reagents are very strong bases and nucleophiles, several functional groups such as aldehydes, esters, amides etc, should be protected before the reaction. In this respect, the aryllithiums are more commonly subjected to transmetallation with $MgBr_2$, $ZnCl_2$, $ClSnR_3$, $B(OR)_3$ etc, to form corresponding ArMgBr, ArZnCl, $ArSnR_3$ and $ArB(OR)_2$ reagents which are far more convenient precursors for cross-coupling reactions.[92] In this regard, the Grignard reagents are relatively more convenient coupling partners for the Ni- and Pd-catalyzed[89] Kharasch cross-coupling reaction with aryl halides and other related reagents,[90] producing a wide variety of substituted biaryls in moderate yields.[91]

The Negishi reaction. Arylzinc reagents, being significantly less reactive organometallics than aryllithium and Grignard reagents, have become an extremely convenient class of compounds for TM-catalyzed cross-coupling reactions with aryl halides and other related reagents,[93] providing the formation of various valuable unsymmetrical biaryls in good yields (Scheme 2.1.16, M = ZnHal). In general, the Negishi reaction can be effectively catalyzed by

different combinations of salts of Ni and Pd with various ligands.[93,94] Thus, the Negishi cross-coupling reaction has been successfully employed by different groups in the synthesis of different types of unsymmetrical biaryls.[93-95]

The Stille reaction. Arylstannanes of general structure $ArSnAlk_3$, in the presence of various Pd(0)-catalysts, are prone to react with aryl halides and other related reagents[96] giving rise to the formation of suitable unsymmetrical biaryls in good yields (Scheme 2.1.16, M = SnR_3). The methodology represents another powerful tool for the construction of certain Ar-Ar C-C bond of interest. The most efficient catalysts for the Stille reaction appeared to be various salts of Pd combined with different ligands.[96] Besides, it was found that Cu(I) salts in stoichiometric quantities can dramatically accelerate the reaction.[97a] In addition, it has been shown that the salts of Cu(I) and Mn(II) can initiate the reaction in the absence of Pd-based catalysts.[97b,c] In general, the Stille cross-coupling reaction have been extensively used for the synthesis of numerous unsymmetrical biaryls.[96-98] However, the toxicity of arylstannanes dramatically limits the applicability of the reaction.

The Hiyama reaction. In the presence of Pd-based catalysts arylsilane reagents of general structure $ArSi(OR)_3$ (R = Alk, H), along with polysiloxanes bearing aryl groups, $(Si(Ar)(Me)O)_n$, are prone to react with different aryl halides generating appropriate biaryls in good yields (Scheme 2.1.16, M = SiR_3).[99] The most efficient catalysts of the reaction are based on various combinations of Pd-salts and ligands; additionally, sometimes some cocatalysts like TBAF, KF, Ag_2O etc may be required.[99] The synthesis of unsymmetrical biaryls on the basis of arylsilanes being more environmental friendly approach than other cross-coupling reactions currently is under the focus of extensive research.

The Suzuki-Miyaura reaction. The TM-catalyzed cross-coupling reactions of various organoboron compounds (boronic acids, esters etc) with aryl halides and other related reagents to produce unsymmetrical biaryls are well-known as Suzuki-Miyaura reaction (Scheme 2.1.16, M = $B(OR)_2$).[86-88,100] Noteworthy, the arylboronic acids and esters mostly are thermally stable and inert to water and oxygen; however, under special circumstances the organoboron compounds are prone to act as carbanion-donors similar to other arylmetallic reagents. The enhanced stability of organoboron compounds allows to perform the Suzuki-Miyaura reaction applying a wide range of reaction conditions (even in the water) using arenes bearing a wide variety of reactive functionalities, which is a difficult task for the most of arylmetallic reagents.[101] In most of the cases the Suzuki-Miyaura reaction was performed by using various Pd-based catalysts;[102] nevertheless, the reaction can be performed using Ni-based catalytic systems,[103] which are cheaper than Pd-based catalysts. Additionally, the Ni-

based catalysts usually are more reactive than Pd-based complexes; thereby they can be applied with less reactive substrates such as aryl chlorides, sulfonates etc.[103] Accordingly, the Suzuki-Miyaura reaction was widely applied in the synthesis of variously substituted biphenyls,[104] heterobiaryls[105] and some other classes of biaryls.[106] In case of arenes bearing several halogens or related substituents the cross-coupling reactions can be performed chemo- and/or regioselectively.[107] In this context the group of Langer has significantly contributed in the field.[108]

Cross-coupling reactions of miscellaneous arylmetallic reagents. Beletskaya and coworkers found that diarylmercurials of general structure Ar_2Hg, are prone to undergo the Pd-catalyzed cross-coupling with various aryl halides producing corresponding unsymmetrical biaryls in good yields (Scheme 2.1.16, M = HgAr).[109] Noteworthy, the both aryl groups can be effectively incorporated into the product; hence, the diarylmercurials can be used only in a half equivalent of aryl halide. It should be noted that despite the ecological problems connected with the use of diarylmercurials, the latter shows enhanced stability towards water, air and numerous functional groups.

Nilsson and coworkers found that in the presence of Pd-catalysts arylcopper(I) reagents of general structure ArCu readily react with aryl halides, producing suitable unsymmetrical biaryls in moderate yields (Scheme 2.1.16, M = Cu).[109a,110] Although, the reaction itself represents rather perspective approach to biaryls; the further developments are rare.

Another example includes the arylmanganese reagents of general structure ArMnX, which exhibit slightly less reactivity compared to corresponding arylzinc reagents (the Negishi reaction); hence, they are prone to react with suitable aryl halides selectively, tolerating a number of functionalities, giving rise to unsymmetrical biaryls in good yields (Scheme 2.1.16, M = MnHal).[111]

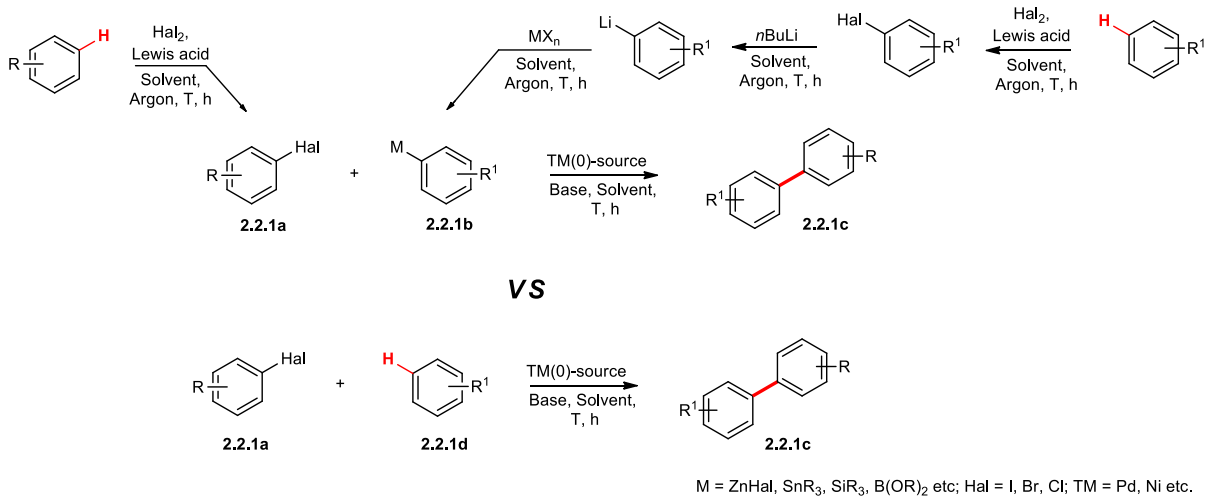
In addition, the aryltrialkoxytitanium ($ArTi(OR)_3$), diaryldialkoxytitanium reagents ($Ar_2Ti(OR)_2$),[112] as well as triarylindium reagents (Ar_3In)[113] have been successfully applied for the Ar-Ar C-C bond construction in Pd-catalyzed cross-coupling reactions with aryl halides (Scheme 2.1.16, M = TiR_3, InR_2). Similar to the diarylmercurials the diaryldialkoxytitanium reagents act as two Ar-group donors. In this respect, the triarylindium reagents act as extremely efficient organometallics which are able to transfer all three aryl groups. Interestingly, except triarylindium reagents, diarylindium halides (Ar_2InHal) and even arylindium dihalides ($ArInHal_2$), which tolerates water and numerous functional groups, are prone to react with aryl halides, under the standard Pd-catalyzed procedure, producing the biaryls in good yields.[113] Last but not least, corresponding arylgermanes reagents represent

another interesting class of organometallics capable for Pd-catalyzed cross-coupling reactions with appropriate aryl halides to produce various biaryls (Scheme 2.1.16, M = GeR_3).[114] Generally, the synthesis of biaryls using the organometallics listed here is under extensive investigations which would undoubtedly result in significant developments in the field.

Summarizing the chapter one should admit that the cross-coupling reactions are one of the most important methodologies for the selective synthesis of unsymmetrical biaryls of interest; however, several serious disadvantages dramatically limits the applicability of these methods. Among others, the most important drawback of the method represents the need for pre-functionalized starting materials. In particular, common methods to organometallics require the use of highly corrosive and unstable reagents (*n*BuLi etc); on the other hand, most of the starting materials themselves are not stable. Additionally, some of them are extremely toxic and far from being environmentally friendly. Besides, several side reactions are common for all cross-coupling reactions; the most important one is the homocoupling reaction of aryl organometallics to symmetrical biaryls. In other words, the diversity of the synthetic methods for synthesis of biaryls described in this chapter indicates that none of them is self-sufficient for practical organic synthesis.

2.2. The Present State of the Field: Direct C-H Arylation

The construction of new Ar-Ar C-C bond remains one of the most actual tasks of organic chemistry for the highly efficient synthesis of new target compounds and structures. In this context, as was demonstrated in the previous chapter, the cross-coupling reactions were the most useful tool to solve this problem over the past century (Scheme 2.1.16).



Scheme 2.2.1. Cross-coupling reactions and direct C-H arylation.

However, as it was described, in cross-coupling reactions the starting coupling partners should bear either a metal-containing functionality **2.2.1b** (nucleophilic component) or a halogen atom and related groups **2.2.1a** (electrophilic component) (Scheme 2.2.1). In this case in fact the preliminary preparation of two independent, expensive, starting materials is required. This process, except a number of disadvantages (generating stoichiometric amounts of waste materials, the use of unstable and corrosive chemicals etc), is time consuming. On the other hand, several alternative approaches to biaryls were well-established (Chapter 2.1); however, most of them have limited substrate scope and often are not selective. Alternatively, direct arylation of arenes **2.2.1d** *via* "C-H activation" constitutes a much more attractive approach, since in this case the preparation of aryl organometallics **2.2.1b** can be skipped (Scheme 2.2.1).

C-H bonds are ubiquitous in arenes, although most of them usually are inert and do not participate in the chemical reactions. Nevertheless, under special circumstances *via* "C-H activation" it is possible to overcome the inert nature for most of the C-H bonds, thus making them readily available for chemical transformations. The term "C-H activation" means treating a C-H bond in some way that would allow a reagent to smoothly react with the carbon atom of C-H bond.[115] Particularly, this process can be accomplished by using various complexes of transition metals.

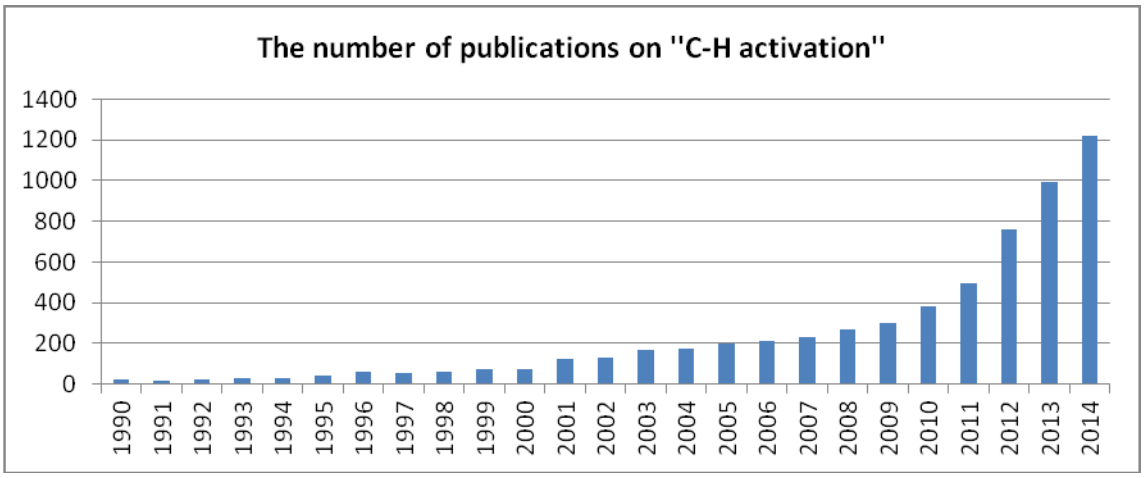


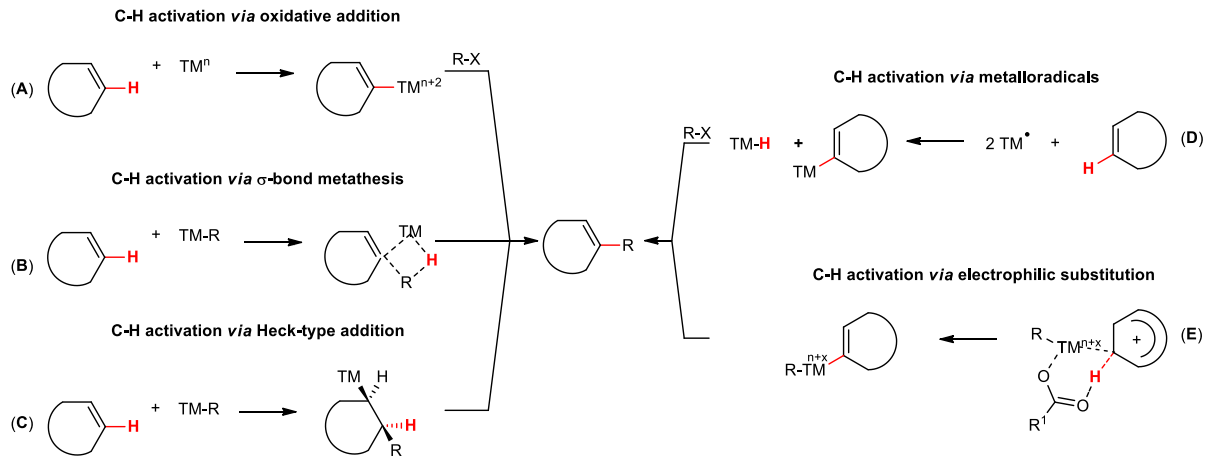
Figure 2.2.1. The number of publications on the topic "C-H activation". The data for the bar chart was obtained by a SciFinder search in January 2015 using keyword "C-H activation".

The recent unstoppable rush in TM-catalyzed direct C-H functionalizations, in particular C-H arylations, undoubtedly will have a significant impact on the further developments of synthetic organic chemistry (Figure 2.2.1).[116] Furthermore, these reactions certainly will revolutionize the chemical industry in the nearest future, since C-H activation allows

corresponding functional groups of interest be placed directly in the molecule preventing the preliminary functionalizations, a process that previously was not possible in a single step.[117] Besides, the C-H activation is of special value in shortening of multi-step synthesis which is commonly used in drug discovery and total synthesis of natural products.[117]

Noteworthy, the TM-catalyzed C-H activation is not that easy to attain as it might seem: first of all, the "activation" of single C-H bonds in the arene, so that they become active enough for chemical attack, is not always achievable. However, if, the "activation" of single C-H bonds in the arene is possible, another problem may arise; in particular, usually the distinction between reactivity of various C-H bonds in arene is negligible, hence targeting a specific C-H bond may be problematic. In this context, currently there are some approaches to overcome these problems, which will be discussed in detail.

Accordingly, various salts and complexes of Au,[118] Cu,[119] Fe,[120] Ni,[121] Os,[122] Rh,[123] Ru,[124] Pd,[125] Re,[126] rare earth metals[127] and others[128] proved to be capable to "activate" and "cleave" the C-H bond of interest by different mechanisms; thus, making them readily available for further transformations (Scheme 2.2.2). In particular, for TM-induced C-H activation of various aromatic substrates five distinct mechanisms were proposed: C-H activation *via* oxidative addition (**A**), σ-bond metathesis (**B**), Heck-type addition (**C**), metalloradicals (**D**), and electrophilic substitution (**E**).[129,118-128]

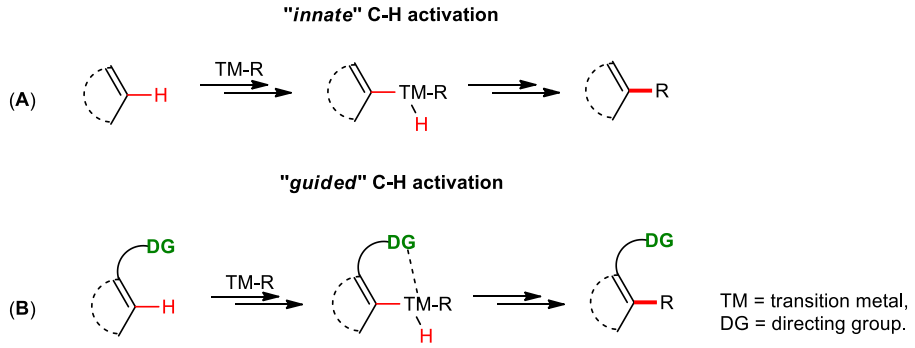


Scheme 2.2.2. Possible mechanisms of C-H activation.

The oxidative addition to the C-H bond is typical for electron-rich, low valent "late" transition metal complexes (Re, Fe, Ru, Os, Rh, Ir, and Pt). In contrast to this, the C-H activation *via* σ-bond metathesis is typical for alkyl or hydride complexes of "early" transition metals, such as transition metals of groups 3-5. The pathway of Heck-type addition was proposed for C-H activation of electron rich heterocycles with low valent "late" transition metal catalysts. The

C-H activation *via* metalloradicals is common for some porphyrin complexes of "late" transition metals. Eventually, the C-H activation *via* electrophilic substitution is typical for late- or post-transition metals in high oxidation states, such as Pd(II) and/or Pd(IV), Pt(II) and/or Pt(IV), Hg(II), Tl(III) etc. Noteworthy, this mechanism is the most probable mechanism for Pd-catalyzed C-H arylation of arenes.[130]

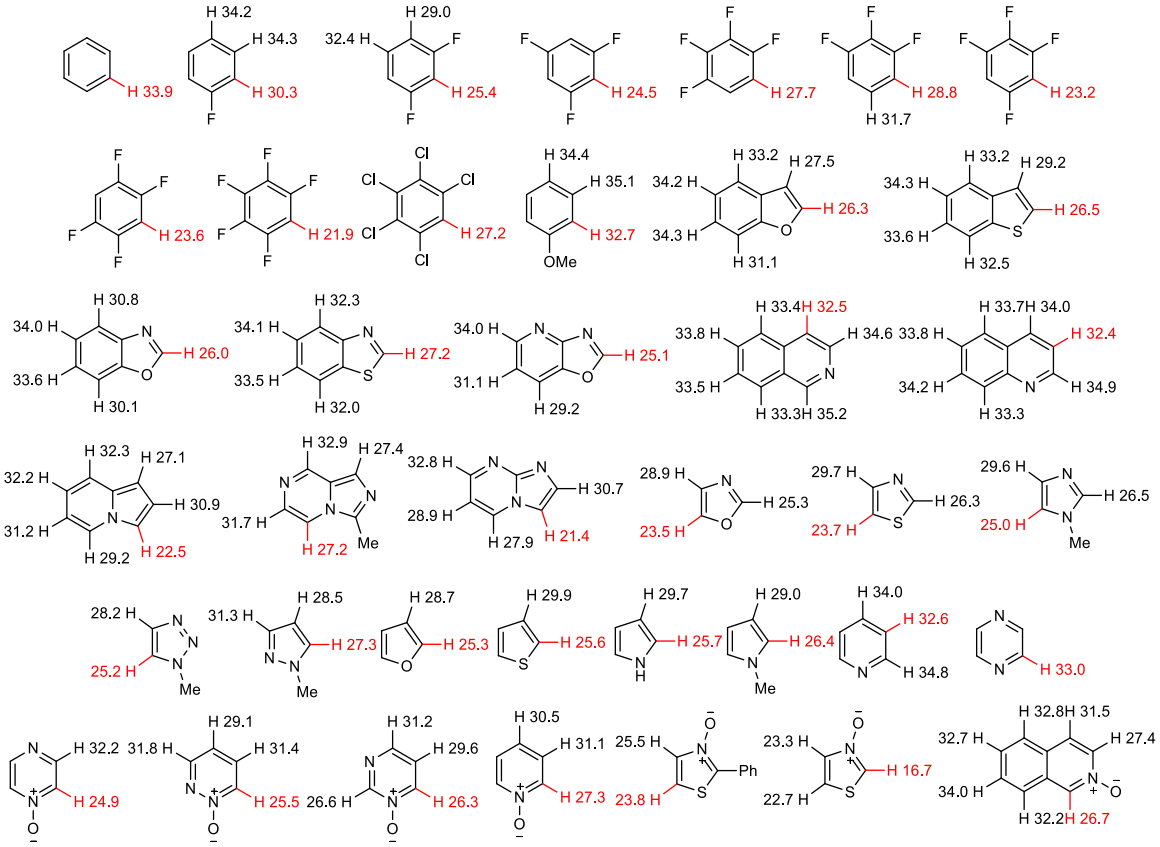
A more difficult task remains the chemo- and regioselectivity of C-H activation. This can become a real problem if several C-H bonds are capable to activation at the same time, resulting in the formation of various mixtures of isomers, or in some cases multi-functionalized final products. In this respect, there are two different strategies to solve the task of selectivity (Scheme 2.2.3).



Scheme 2.2.3. TM-catalyzed "*innate*" and "*guided*" C-H activation.

In most of the cases, there is, in principle, a natural distinction in reactivity between C-H bonds based on steric or electronic effects of corresponding arene, which in some cases may direct the C-H functionalization to specific positions without guidance. The TM-catalyzed direct and selective C-H functionalization of arenes, where the selectivity is caused by the different distribution of the electron density, is well-known as "*innate*" C-H activation (Scheme 2.2.3, **A**). In this context, Gorelsky[131] and others[132] have conducted several impressive mechanistic studies on the Pd-catalyzed direct arylation and related C-H activation reactions of various substrates including substituted benzenes,[133] tethered arenes,[134] heteroarenes like pyridine,[135] pyridine N-oxide[136] etc. Using density functional theory (DFT) calculations, activation barriers for Pd-catalyzed cleavage of various aromatic C-H bonds were assessed; the representative examples are presented in the Scheme 2.2.4.[131] Furthermore, the calculated barriers are in good correspondence with the experimental regioselectivity and relative reactivities of various arenes in the Pd-catalyzed direct C-H functionalizations; including, substituted benzenes,[137] benzene fused with heterocycles,[138] fused pyridines,[139] oxazoles,[140] thiazoles,[141] imidazoles,[142] triazoles and related heterocycles,[143] pyrazoles,[144]

pyrroles and related heterocycles,[145] pyridines,[146,135] pyridine N-oxides and related heterocycles[147] and many others.[148]



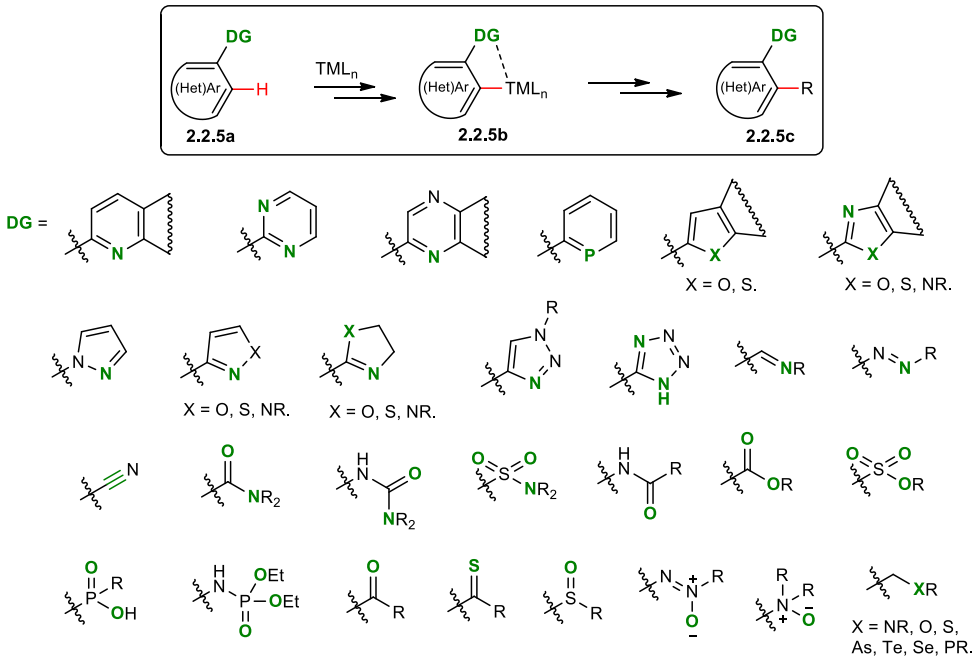
Scheme 2.2.4. Gibbs free energies of Pd-catalyzed C-H activation ($\Delta G^{\ddagger}_{298\ K}$, kcal mol^{-1}).

In contrast to "*innate*" C-H activation, it seems clear that TM-catalyzed C-H functionalization of the other positions of the same molecules have to be "*guided*" in order to get at least moderate levels of selectivity, because usually these positions are not accessible due to electronic and/or steric factors (Scheme 2.2.3, **B**). The "*guided*" C-H functionalization together with the "*innate*" C-H activation represents a straightforward approach for selective C-H activation of all targeted positions of a given substrate.

The most extended strategy to achieve a "*guided*" C-H functionalization lies on the use of functional groups bearing atoms with free lone pairs of electrons, such as N, O, P, S, or others; that is, atoms capable for the coordination, even weakly, to the catalyst (Scheme 2.2.5). As a result, the substrate **2.2.5a**, being a special type of ligand, forms an intermediate complex with the catalyst. In this way, once the catalyst is linked by the directing group, only certain C-H bonds fall in the vicinity of the catalyst; hence, only selected positions can be functionalized **2.2.5b**,**c**.[149] In principle, the number of directing groups suitable for the coordination of the catalyst to the position of interest is almost unlimited, since the only

requirement is to contain a heteroatom with free lone pairs of electrons capable for coordination. Accordingly, various functional groups such as pyridine,[150] pyrimidine[151] and related groups,[152] pyrazole,[153] oxazoline[154] and related groups,[155] imines,[156] amides,[157] anilides[158] and related groups,[159] carbonyl,[160] carboxyl,[161] ester[162] and related groups,[163] amines,[164] alcohols[165] and many others[166] are well-known to direct the C-H activation.

Traditional directing groups which usually contain heteroatoms like N, S or P, being a strong σ-donors and/or π-acceptors strongly chelate the catalyst, forming thermodynamically stable five- or six-membered metallacycles **2.2.5b**.[149] Accordingly, most of the known directed C-H activations fall into this category. The major disadvantage of this approach is that most of the directing groups mentioned above are synthetically restrictive, either because they are not the permanent part of the target molecule or because of inert nature they cannot be transformed to the other useful functional groups.

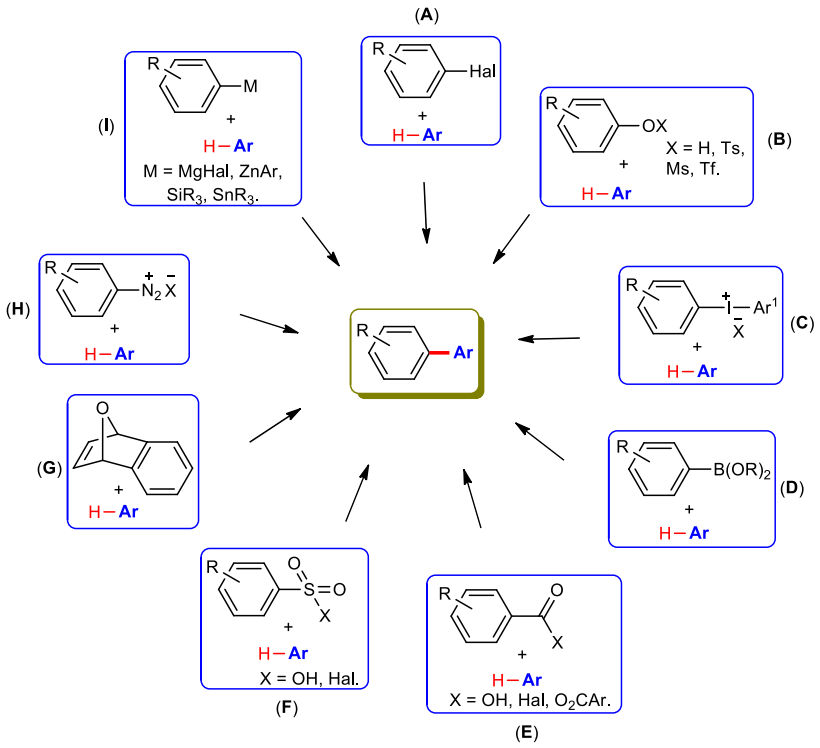


Scheme 2.2.5. Common directing groups (DG) in TM-catalyzed C-H activation.

Another problem is that strongly chelating directing groups commonly form thermodynamically stable cyclometalated intermediates **2.2.5b** which may be less reactive in the subsequent functionalization step. In some special circumstances the cyclometalated intermediates **2.2.5b** are stable enough to be used as catalyst for some typical cross-coupling reactions etc.[167] Furthermore, in some special cases the cyclometalated intermediates can be subjected to chemical transformations at aromatic ring without destruction.[168] This phenomenon may dramatically limit the range of useful nucleophiles and electrophiles for

directed C-H functionalizations. On the other hand, the C-H activation using weakly coordinating directing groups, such as nitro, carbonyl, carboxyl etc, have been far less actively studied; nevertheless, with weakly coordinating directing groups, the resulting metallacycles being thermodynamically less stable, and not necessarily isolable, may be coupled with a wide variety of coupling partners.[169]

The transition metals can catalyze a number of C-H functionalizations at aromatic ring including C-H alkylation,[170] alkynation,[171] olefination,[172] amination,[173] hydroxylation and related reactions,[174] halogenation[175] and fluorination,[176] carbonylation[177] and carboxylation,[178] borylation[179] etc.[180] Nevertheless, perhaps the most developed area in the field remains the Ar-Ar C-C bond formation *via* TM-catalyzed direct C-H arylation.[181] This involves the use of a preactivated aryl substrate as one coupling partner (in most of the cases as electrophilic component) and a simple unactivated aryl substrate as the other (nucleophilic component) (Scheme 2.2.6, see also Scheme 2.2.1). In this context, the extensive studies in the field showed that as coupling partners for direct arylation of aromatic C-H bonds can be used aryl halides (including fluoroarenes) (**A**),[181,182] phenols and their derivatives (**B**),[183] diaryliodonium salts (**C**),[184] organoboron compounds (**D**),[185] aryl carboxylic acids and their derivatives (**E**),[186] derivatives of aryl sulfonic acid (**F**),[187] 7-oxabenzonorbornadienes (**G**),[188] diazonium salts (**H**),[189] arylhydrazines,[190] Grignard reagents,[191] organozinc reagents,[192] aryl silanes[193] and arylstannanes (**I**)[194] (Scheme 2.2.6).



Scheme 2.2.6. TM-catalyzed direct C-H arylation.

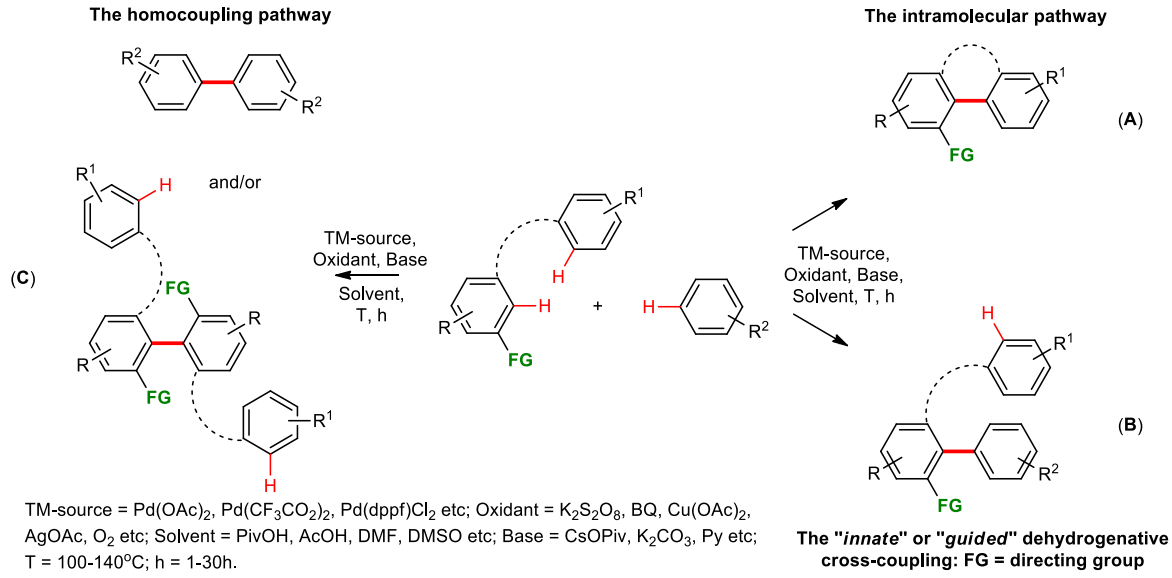
Regarding the reaction conditions of direct C-H arylation, the majority of transition metals of groups 8-11 can effectively catalyze the Ar-Ar C-C bond formation *via* C-H activation;[118-125,181] however, the second-row transition metals in low oxidation states (especially Ru, Rh and Pd) have proved to be the best catalysts for this transformation. Generally, depending on the nature of coupling partner, Ar-X, may arise a need for using a ligand (Scheme 2.2.6); for instance, in case of less reactive aryl chlorides and sulfonates bulky ligands or bidentate ligands with big bite angles are used in order to generate more active forms of the catalyst.[195] Although, sometimes the effect of the ligand on the catalyst may be rather complicated.[196] The direct arylation reactions usually require the use of base; in this respect, inorganic bases such as K_2CO_3, Cs_2CO_3, KOAc, KOPiv, and CsOPiv are frequently used. These carboxylates are prone to induce the C-H activation *via* a concerted base-assisted deprotonation of the arene.[197,130] Subsequently, for efficient decarboxylation of aryl carboxylic acid coupling partners, as base were applied appropriate salts of Ag and Cu (Scheme 2.2.6, **E**).[186] The TM-catalyzed C-H arylation was successfully performed using polar aprotic solvents such as MeCN, DMF, DMA, NMP, DMSO etc; though, nonpolar solvents like toluene, xylene etc also were effective. Furthermore, in some cases the C-H arylation can be effectively performed in the water.[198] Once the coupling partners are aryl organometallics, typically the use of oxidants is required in order to perform the reaction applying catalytic amounts of corresponding transition metal (Scheme 2.2.6, **D**, **I**).[185,191-194] In addition, usually the reactions require temperatures higher than 100°C; besides, heating from several hours to days may be required.

2.3. The Future Perspectives of Direct C-H Arylation

The TM-catalyzed C-H arylation has played a crucial role in development of organic synthesis over the past decade (Figure 2.2.1). The results are spectacular, yet the needs of "green chemistry" continually move chemists forward to substitute well established C-H arylation methods with more "greener" protocols, which may further improve already traditional TM-catalyzed C-H activation methodologies. In this context, as an illustrative example, one should notice the possibility to perform the C-H arylation in water, which was described above.[198] Nevertheless, the substrate scope for these reactions is rather limited; hence, further improvements are needed.

On the other hand, in theory, the most direct approach to suitable biaryls is based on oxidative construction of the Ar-Ar C-C bond from two C-H bonds with a net loss of two protons. The

synthesis of biaryls in the nature is based on this principle (Scheme 2.1). Besides, an attempt to prepare symmetrical biaryls by oxidative coupling of electron rich arenes was made previously (Scheme 2.1.15); however, the limited substrate scope, reduced selectivity and the need for using hazardous oxidants in stoichiometric amounts dramatically limits the applicability of the reaction. Nevertheless, compared to traditional methods for the synthesis of biaryls, the selective oxidative cross-coupling of two different unfunctionalized arenes may dramatically increase the synthetic efficiency of the process, since additional steps for pre-activation of starting arenes are not required. This approach has been feeding the minds of chemists for decades with the aim to develop modern, highly efficient synthetic protocols to biaryls. The huge catalytic potential of transition metals makes these approaches more real. Compared to classical oxidative coupling of electron rich arenes (Scheme 2.1.15) the TM-catalyzed dehydrogenative cross-coupling of unfunctionalized arenes can overcome the problems of selectivity and reduced substrate scope. Besides, this approach allows the synthesis of biaryls using mild and far less toxic oxidants.

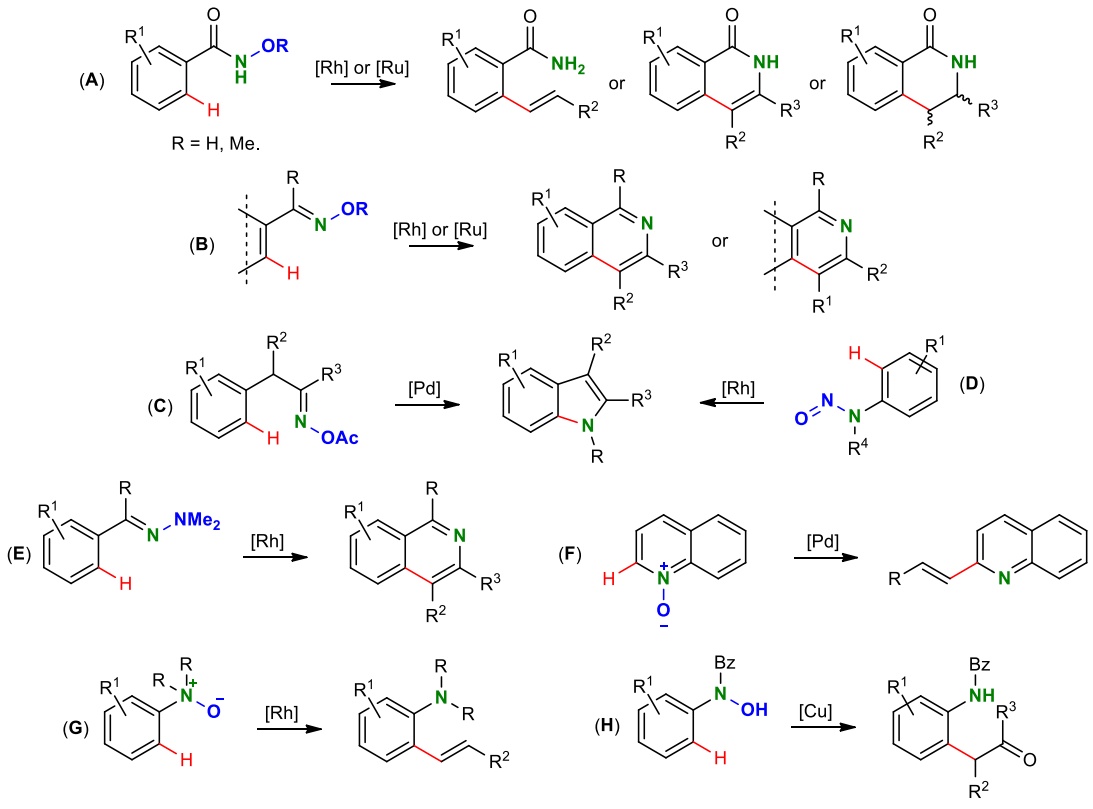


Scheme 2.3.1. Catalytic dehydrogenative cross-couplings of unfunctionalized arenes.

Historically, the first TM-catalyzed dehydrogenative cross-couplings of unfunctionalized arenes were intramolecular processes (Scheme 2.3.1, **A**).[199] In order to switch on the selective intermolecular cross-couplings, either the "*innate*" reactivity of arenes[200] or proper directing groups[201] must be used (**B**). Otherwise, one may face a problem connected with undesired homocoupling pathways of the reaction (**C**).[202] The last issue may become a serious problem forming disastrous mixtures of homocoupled and heterocoupled products; thereby, dramatically decreasing the applicability of the reaction. Even though the examples of

selective intermolecular TM-catalyzed dehydrogenative cross-couplings of unfunctionalized arenes are rare, however, the process being environmentally friendly and less time consuming undoubtedly will only continue to evolve.

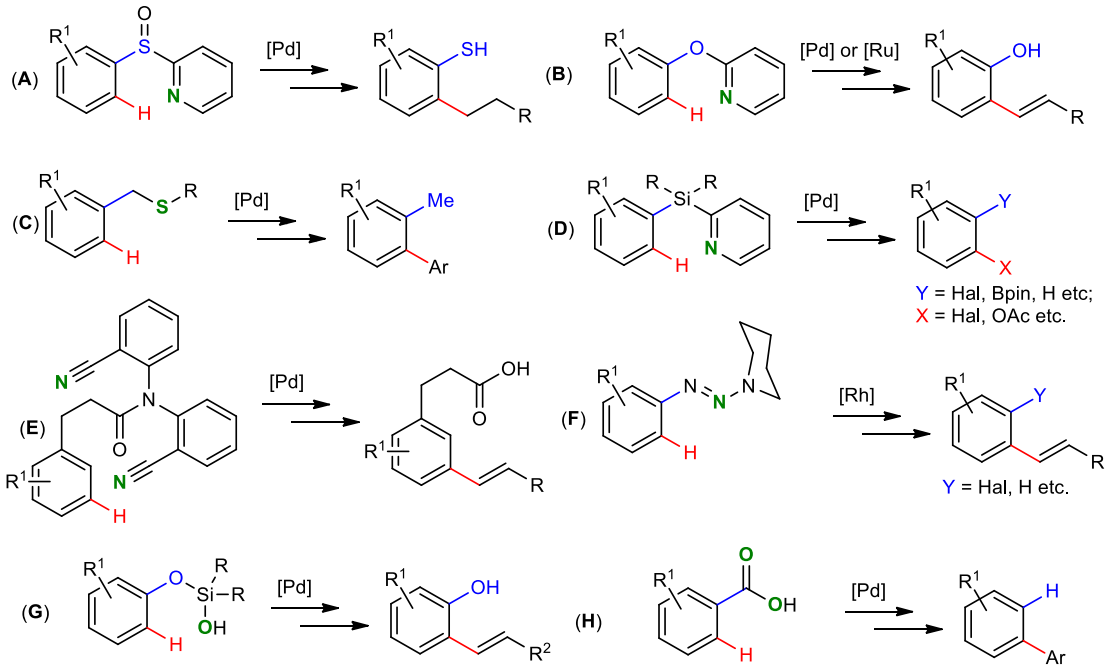
Another important direction for development of the field may become the design of new multipurpose directing groups. As it was mentioned above, in spite of a wide variety of directing groups suitable for TM-catalyzed C-H activation, most of them are not a permanent part of target molecules and/or are not prone to undergo some further transformations. A typical example is the pyridine, the most widely used directing group in the field, which is usually no longer needed after the direct C-H activation step. However, the pyridine, being rather inert towards chemical transformations, dramatically limits its practical application as directing group. Moreover, the needs of "green chemistry", which require high levels of atom economy and minimum wastes and subproducts, does not tolerate the presence of non-convertible functional groups. Accordingly, the development of multifunctional directing groups is of considerable practical interest.[203] A clear example of recent developments in the field is the use of oxidizing directing groups (Scheme 2.3.2).[203c] In this case, the directing group along with directing effect is responsible for oxidation of the catalyst; thus, avoiding the need for using external hazardous oxidants in stoichiometric amounts, which generate big quantities of waste.



Scheme 2.3.2. Directing groups with internal oxidant.

Accordingly, the recent examples include the use of benzoyl hydroxamate derivatives for the synthesis of alkenylated arenes, isoquinolones and related systems (**A**);[204] ketoximes for the synthesis of isoquinolines and pyridine derivatives (**B**);[205] oxime esters (**C**)[206] and N-nitrosoanilines (**D**)[207] for the synthesis of indoles; hydrazones for the synthesis of isoquinolines (**E**);[208] quinoline-N-oxides for the synthesis of 2-alkenylated quinolines (**F**);[209] N-oxides for the synthesis of alkenylated tertiary anilines (**G**)[210] and N-phenylbenzhydroxamic acid derivatives for the synthesis of alkylated anilides (**H**).[211] Noteworthy, the oxidizing directing groups were not used in the TM-catalyzed dehydrogenative cross-couplings of unfunctionalized arenes (Scheme 2.3.1), however, this is only a matter of time.

Another way to plan an efficient multi-step synthesis includes the use of multifunctional or removable directing groups (Scheme 2.3.3).[203a,b] In this case the basic idea of using multifunctional or removable directing groups is that after proper orientation of the reaction, the directing group (or part of it) can be easily transformed to another group of interest or removed during further steps of the synthesis.



Scheme 2.3.3. Multifunctional and removable directing groups.

In this respect, recently several directing groups, such as 2-pyridyl sulfoxide (**A**),[212] 2-pyridyl ether (**B**),[213] thioether (**C**),[214] pyridyldiisopropylsilyl (**D**),[215] nitrile (**E**),[216] triazene (**F**),[217] silanol (**G**),[218] carboxylates (**H**)[219] and some other groups[203a,b] have been developed and successfully applied in various TM-catalyzed C-H functionalizations (Scheme 2.3.3).

All these transformations can be considered as two-step processes. In the first step corresponding directing group orients the proper C-H bond activation. Further, the directing group is removed or transformed to another useful functional group *via* some additional operations. In fact, sometimes these two operations can be conducted in one-pot, otherwise, it is still possible to perform these transformations using semi-one-pot procedures. The development of new, highly efficient, multifunctional directing groups for TM-catalyzed direct C-H functionalizations undoubtedly will become one of the important topics of research over the next few decades.

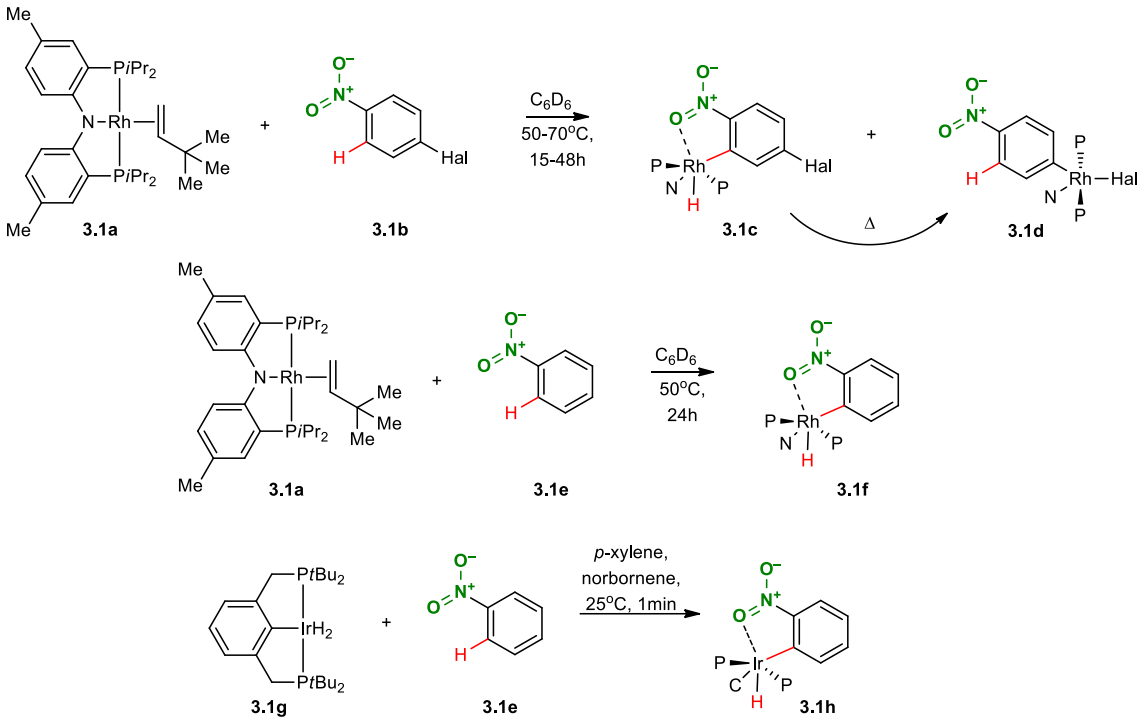
3. Why Nitro Group, and Why Nitroarenes? Our Strategy

Basing on the general movements in the field, one can state, that the nitro group due to its huge potential as multipurpose directing group may become an interesting alteration to classical directing groups for direct C-H arylation. It can behave as a classical directing group,[220] selecting the position where the metal has to be incorporated and, in addition, the tremendous chemical potential of nitro group makes it readily available for further functionalizations for the synthesis of multi-functionalized target products.

Particularly, Ozerov and coworkers during the course of investigations, regarding the oxidative addition of some aryl halides containing a *para*-NO_2 group **3.1b** to four-coordinate pincer complexes of Rh ((PNP)Rh(L)) **3.1a**, observed an interesting product of C-H activation directed by nitro group **3.1c** (Scheme 3.1).[220b] Analogous C-H activation product **3.1f** was observed for nitrobenzene **3.1e** as well. However, the C-H activation products **3.1c** were thermodynamically unstable with respect to the isomeric oxidative addition products of aryl halide **3.1d**, to which they convert upon thermolysis (Scheme 3.1). In this regard, earlier, Goldman and coworkers reported the C-H activation of nitrobenzene **3.1e** by closely related pincer complexes of Ir ((PCP)Ir) **3.1g** with apparently quantitative selectivity for the position *ortho* to the nitro group (Scheme 3.1).[220a] The product of cyclometalation **3.1h** was characterized by ^{1}H and ^{31}P NMR and X-ray analysis. These findings clearly demonstrate that the nitro group can effectively direct the TM-catalyzed C-H activation, in particular C-H arylation.

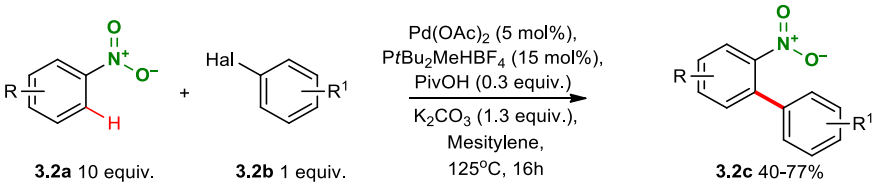
Nevertheless, the practical use of the nitro group as a regiodirecting substituent in C-H activations has scarcely been reported to date.[221] Accordingly, in 2008 Fagnou and coworkers showed that nitro-substituted benzenes **3.2a** exhibit useful reactivity in Pd-catalyzed direct arylation which allows to use them in the synthesis of a variety of functionalized biaryls **3.2c**

(Scheme 3.2).[221a]



Scheme 3.1. Nitro group directed cyclometalation of nitrobenzenes.

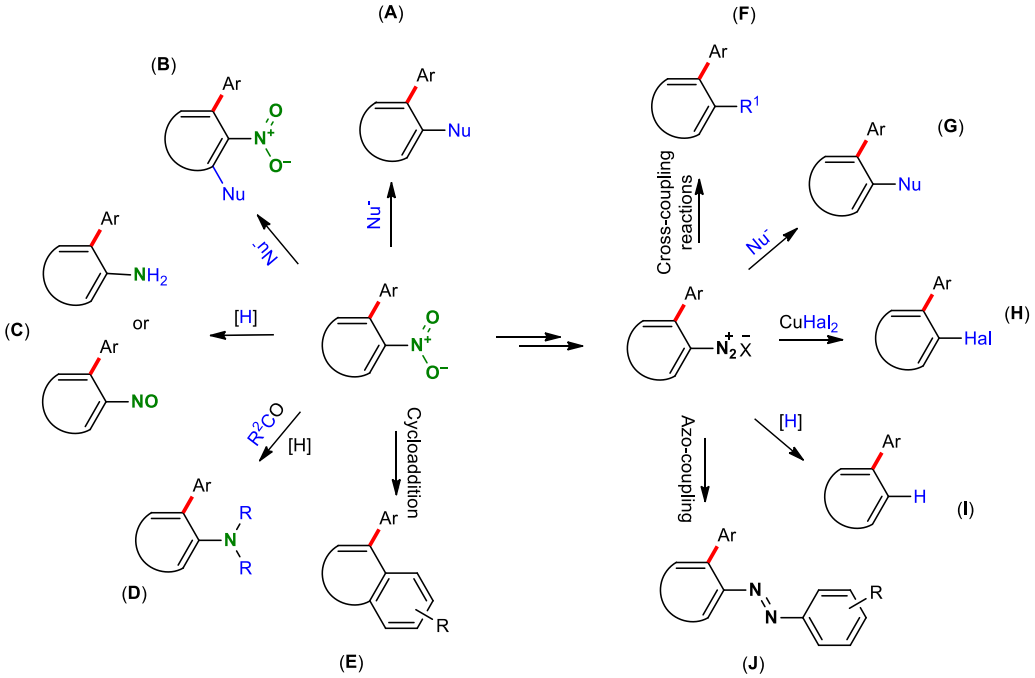
Noteworthy, in the study the authors used nitrobenzenes in large excess (as cosolvent). In most of the cases the conversion of aryl halides **3.2b** was complete leading to the *ortho*-arylation products in good yields and regioselectivity (Scheme 3.2). Besides, very recently, Sames and coworkers reported a new Pd-catalyzed protocol for selective C-H arylation of positions 4 and 5 of pyridines containing common and synthetically versatile electron withdrawing substituents such as nitro group, nitrile and halogens.[221b]



Scheme 3.2. C-H arylation of nitrobenzenes.

In spite of this, the authors did not demonstrate the huge chemical potential of nitro group for the synthesis of functionalized biaryls (Scheme 3.3). This two-step approach undoubtedly has an enormous synthetic capacity.[222] For instance, the nitro group can be easily replaced by aryl, alkyl, hydroxy, amino, thio groups etc, *via* aromatic nucleophilic substitution of nitro group

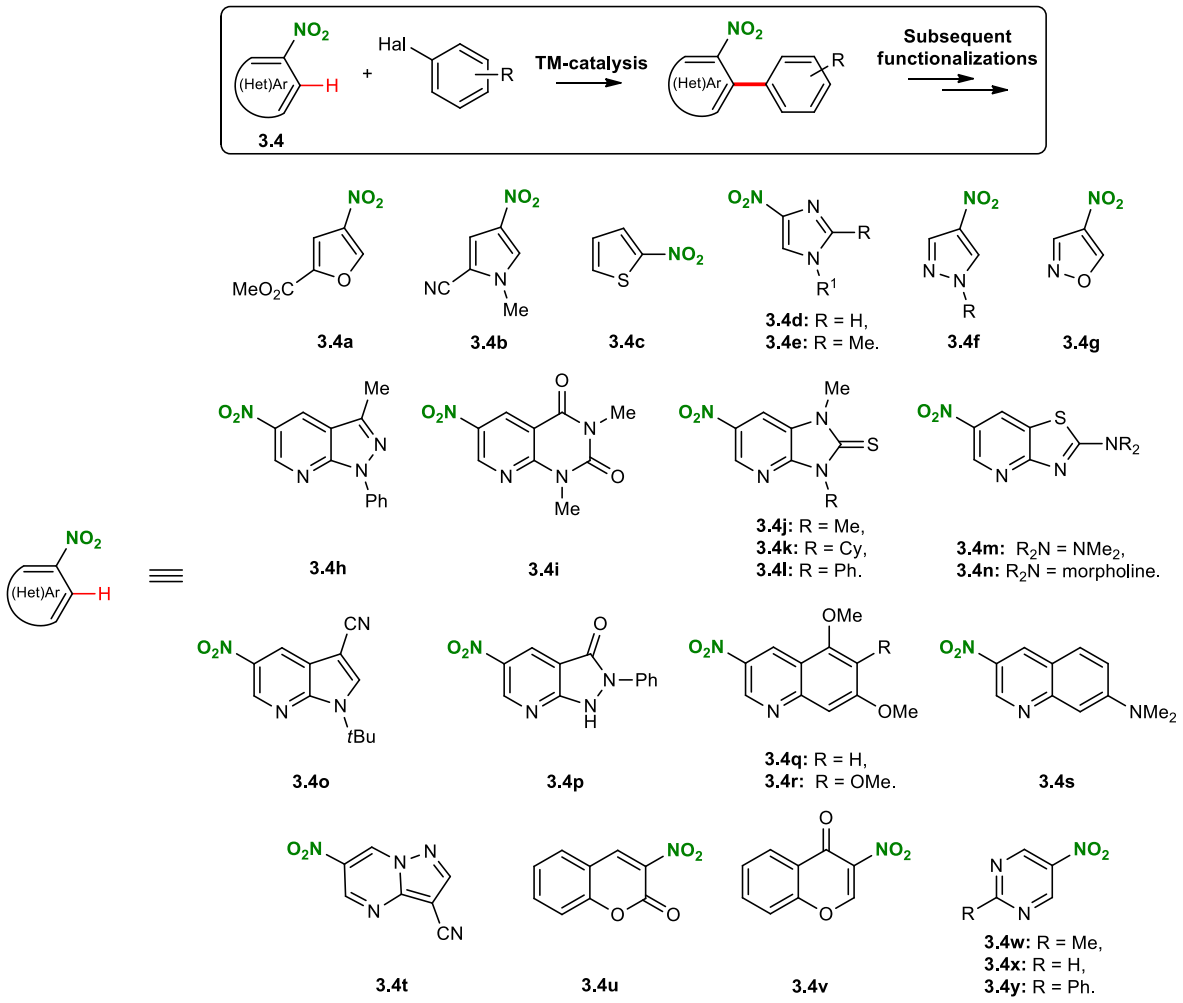
(**A**).[223] On the other hand, in similar reaction conditions nucleophilic aromatic substitution of hydrogen of nitroarenes may lead to the formation of various valuable polyfunctionalized biaryls (**B**).[224,31] Nevertheless, the main chemical transformation of nitro compounds is the reduction, enabling the synthesis of various nitrogen compounds, such as amines, imines, oximes etc (**C**, **D**).[225] Besides, it is known that some heteroarenes are prone to undergo a Diels-Alder reaction despite their aromaticity. In this context, the strong electron withdrawing nitro group dramatically increase the dienophilicity of heteroarenes, thus, making them readily available for cycloaddition reactions (**E**).[226] Moreover, transformation of nitro group to diazonium salts, using a semi-one-pot procedure, makes them readily available for well-defined cross-coupling reactions (**F**),[85c,k] azo-coupling (**J**)[227] etc (**G-I**).[228]



Scheme 3.3. The chemical potential of nitro group.

In the current work an attempt was made to investigate the directing ability of nitro group within the range of nitro-substituted heteroarenes for the synthesis of functionalized biaryls *via* C-H arylation. The list of heteroarenes, used in the work, is presented on the Scheme 3.4. Noteworthy, most of the heteroarenes presented here are of considerable interest, since their analogues possess numerous valuable properties which make them important targets for synthetic organic chemists. Accordingly, imidazole derivatives **3.4d**,**e** are versatile precursors for N-heterocyclic carbenes which represent one of the biggest classes of ligands used in homogeneous catalysis;[229] besides, they are widely applied in organocatalysis.[230] Moreover, imidazolium salts can be used as environmentally friendly ionic solvents[231] etc.[232] Pyrazole

derivatives **3.4f** are widespread in commercial drugs; in addition, a lot of ligands, used in homogeneous catalysis, are based on pyrazole framework.[233] Fused pyridines **3.4h-t** are an important class of purine-like compounds which are of great importance over the last six decades as anticancer agents etc (Scheme 3.4).[234]



Scheme 3.4. The scope of the work.

Following the general movements in the field, in order to achieve the desired arylation, a number of crucial challenges had to be overcome: 1) first, the reaction conditions should be optimized, so that only stoichiometric amounts of coupling partners could be used; 2) next, the regioselectivity of the reaction should be thoroughly investigated, since in most of the cases we have several directing groups and potentially activatable C-H bonds; 3) in this regard interrelation between "*guided*" and "*innate*" C-H arylation reactions should be investigated. Subsequently, the following criteria for an ideal directing group for C-H arylation should be fulfilled: 1) the group should be capable for directing the catalyst to corresponding C-H bonds; 2) the directing group should be sufficiently stable under typical

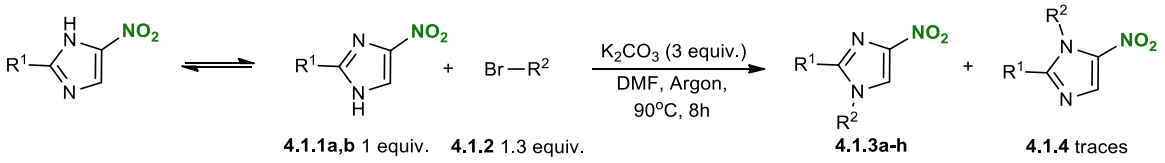
reaction conditions for TM-catalyzed C-H arylation; 3) and finally, it is extremely important to demonstrate the utility of nitro group in follow-up chemistry within the range of chosen heteroarenes.

4. Direct C-H Arylation of Nitroimidazoles

4.1. Preparation of Starting Nitroimidazoles

Inspired by the tremendous chemical potential of nitro group[222-228] in conjunction with the ability of nitro group to direct the C-H activation[220] and based on recent successful results on C-H arylation of different heteroarenes performed in our group,[235] we started the present study on C-H arylation of nitroimidazoles.[236]

In order to prevent the TM-catalyzed arylation of unprotected 1*H*-imidazoles,[237] it was decided to alkylate the starting nitroimidazoles by various alkyl groups. Accordingly, the starting N-substituted 4-nitroimidazoles **4.1.3a-h** were prepared applying simple alkylation of commercially available 4(5)-nitroimidazoles **4.1.1a**,**b** with suitable alkyl bromides **4.1.2** as illustrated in Table 4.1.1.[238]



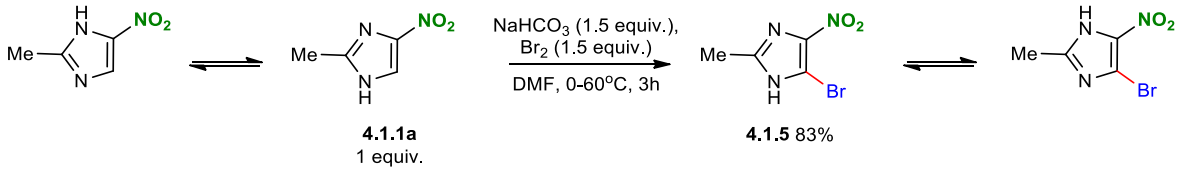
4.1.3	R^1	R^2	Yield (%)
a	Me	Ethyl	82
b	Me	*n*-Butyl	88
c	Me	$(CH_2)_2Ph$	93
d	H	$(CH_2)_2Ph$	80
e	Me	$(CH_2)_3Ph$	78
f	Me	$(CH_2)_2OPh$	89
g	Me	CH_2-4-Tol	83
h	Me	CH_2-C_6H_4-2-Br	83

Table 4.1.1. Synthesis of starting N-substituted 4-nitroimidazoles.

The alkylation reaction was performed under inert atmosphere in DMF at 90°C using K_2CO_3 as base. Noteworthy, the starting nitroimidazoles constitute a mixture of two tautomeric structures; however, upon alkylation only 1-alkyl-4-nitroimidazoles **4.1.3** were observed as a sole isomer. This observation may be the result of steric and/or electronic effects of nitro

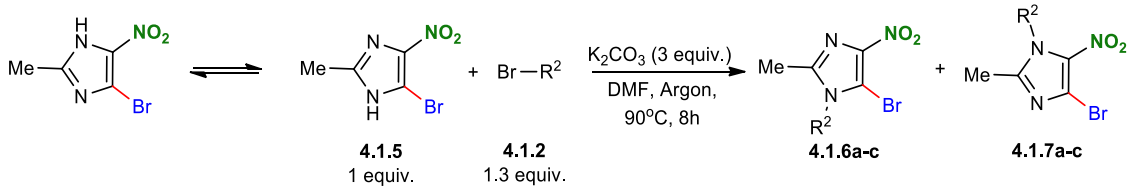
group. Applying the simple general procedure, eight distinct examples of N-substituted 4-nitroimidazoles **4.1.3** were prepared from good to excellent yields (Table 4.1.1). The reaction was well reproducible; all products were purified by simple recrystallization.

Additionally, we were interested in comparison of traditional cross-coupling reactions with TM-catalyzed direct C-H arylation of nitroimidazoles. To this end the bromination of commercially available nitroimidazole **4.1.1a** was performed utilizing a previously developed procedure (Scheme 4.1.1).[239] The bromination was accomplished in DMF with molecular bromine, using $NaHCO_3$ as base. After a standard work-up (dilution with solution of NH_4OH, filtration) desired 4(5)-bromo-5(4)-nitro-1*H*-imidazole **4.1.5** was isolated in 83% yield (Scheme 4.1.1).



Scheme 4.1.1. The synthesis of 5(4)-bromo-4(5)-nitro-1*H*-imidazole.

Further the 4(5)-bromo-5(4)-nitro-1*H*-imidazole **4.1.5** was alkylated in order to prepare desired starting N-substituted imidazoles. It should be mentioned that unlike alkylation of simple 4-nitroimidazoles (Table 4.1.1), the alkylation reaction of 4(5)-bromo-5(4)-nitro-1*H*-imidazole **4.1.5** afforded to a mixture of 5-bromo-4-nitroimidazole **4.1.6** and 4-bromo-5-nitroimidazole **4.1.7**, approximately in 2:1 ratio. This phenomenon can be explained by two distinct tautomeric forms of starting imidazole. As a result, applying the general procedure for alkylation, three pairs of N-substituted nitroimidazoles were prepared in moderate yields (31-58%) (Table 4.1.2).



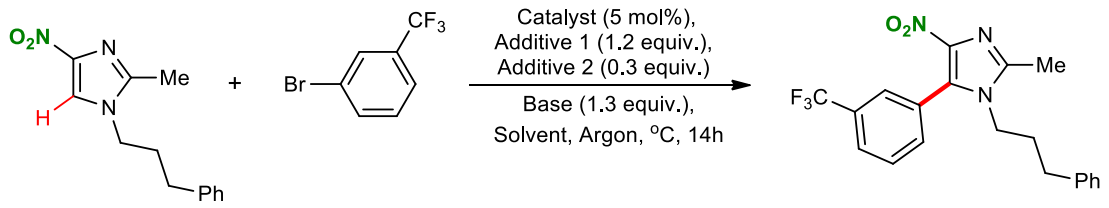
4.1.6, **4.1.7**	R^2	Yield of **4.1.6** (%)	Yield of **4.1.7** (%)
a	$(CH_2)_2Ph$	57	31
b	$(CH_2)_2OPh$	58	38
c	$(CH_2)_3Ph$	55	40

Table 4.1.2. Synthesis of N-substituted 5(4)-bromo-4(5)-nitroimidazoles.

4.2. C-H Arylation of Nitroimidazoles: Scope and Limitations

With the set of N-substituted 4-nitroimidazoles **4.1.3a-h** in hand, on the next stage of the work the optimization of reaction conditions for direct C-H arylation of nitroimidazoles was explored. For this purpose, in order to avoid further complications, regarding regioselectivity of the reaction etc, it was decided to use as a model compound 4-nitroimidazole **4.1.3e**. Basing on the previous results of our colleagues[235] and others,[240] the Pd-based catalysts with CuI as additive were considered to be the starting point in this study.

Gratifyingly, pilot experiments have indicated that indeed Pd/CuI catalytic system is rather efficient in order to activate C(5)-H bond of 4-nitroimidazole **4.1.3e** (Table 4.2.1, entry 1-5), in particular the best catalyst for the model compound **4.1.3e** turned up $PdCl_2(PPh_3)_2$, the desired product **4.2.1a** was isolated in 96% yield (entry 4).



4.1.3e 1 equiv. 2 equiv. **4.2.1a**

Entry	Catalyst	Ligand	Additive 1	Additive 2	Base	Solvent	°C	%[a]
1	$Pd(OAc)_2$	Cy_3PxHBF_4	CuI	PivOH	K_2CO_3	DMA	130	78
2	$Pd(OAc)_2$	-	CuI	PivOH	K_2CO_3	DMA	130	76
3	-	-	CuI	PivOH	K_2CO_3	DMA	130	-
4	**$PdCl_2(PPh_3)_2$**	-	**CuI**	**PivOH**	**K_2CO_3**	**DMA**	**130**	**96**
5	$PdCl_2(PPh_3)_2$	-	-	PivOH	K_2CO_3	DMA	130	71
6	$PdCl_2(PPh_3)_2$	-	CuCl	PivOH	K_2CO_3	DMA	130	83
7	$PdCl_2(PPh_3)_2$	-	Ag_2CO_3	PivOH	K_2CO_3	DMA	130	63
8	$PdCl_2(PPh_3)_2$	-	CuI	-	K_2CO_3	DMA	130	25
9	$PdCl_2(PPh_3)_2$	-	CuI	Ph_3CCO_2H	K_2CO_3	DMA	130	22
10	$PdCl_2(PPh_3)_2$	-	CuI	PivOH	K_3PO_4	DMA	130	46
11	$PdCl_2(PPh_3)_2$	-	CuI	-	KOAc	DMA	130	80
12	$PdCl_2(PPh_3)_2$	-	CuI	PivOH	K_2CO_3	DMF	130	94
13	$PdCl_2(PPh_3)_2$	-	CuI	PivOH	K_2CO_3	NMP	130	90
14	$PdCl_2(PPh_3)_2$	-	CuI	PivOH	K_2CO_3	dioxane	100	-
15	$PdCl_2(PPh_3)_2$	-	CuI	PivOH	K_2CO_3	toluene	100	15
16	**$NiCl_2(PPh_3)_2$**	-	**CuI**	**PivOH**	**K_2CO_3**	**DMA**	**130**	**64**

Table 4.2.1. Optimization of reaction conditions; [a] isolated yields.

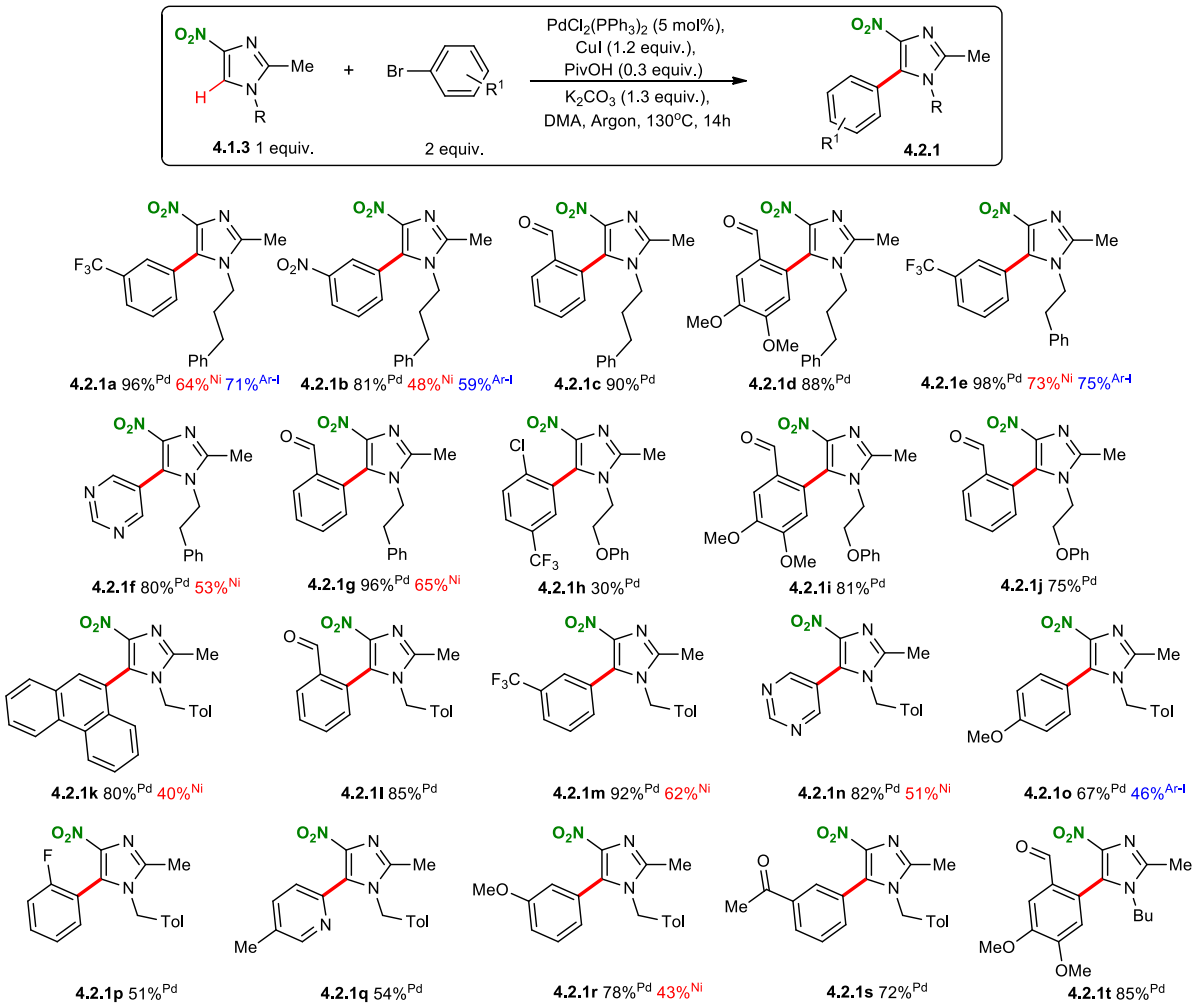
It was found that addition of phosphine ligands, such as Cy_3P, Ph_3P, as well as bidentate ligands like 1,10-phenanthroline, has no real impact on overall yields of the reaction (entry 1,

2, 4). Notably the use of copper(I) salt, such as CuI in stoichiometric amount provided desired arylation product in almost quantitative yield (entry 4). Though, absence or substoichiometric amounts of CuI did not prevent the C-H arylation, namely the desired product **4.2.1a** was isolated with reduced yield (entry 5).

Noteworthy, the use of Lewis acids like CuCl or Ag_2CO_3 still provided the desired C-H arylation product, however, with reduced yields (entry 6, 7). This may be the result of low solubility and/or side reactions. The best base for the reaction was found to be K_2CO_3/PivOH system; the replacement of pivalic acid (PivOH) by triphenylacetic acid as well as potassium carbonate by other salts of potassium decreased the yields of the reaction (entry 8-11). Additionally, employment of different solvents and temperatures has shown that the reaction runs effectively in DMF, DMA and NMP at 130°C without any notable differences in yields (entry 4, 12-15). The rebuff of the reaction in 1,4-dioxane and toluene may be the result of reduced solubility of reaction components, solvation effects etc (entry 14, 15). Finally, the screening of other transition metal based catalysts experienced a failure. However, perhaps, unsurprisingly the reaction catalyzed by $NiCl_2(PPh_3)_2$ occurred uneventfully leading to the formation of desired C-H arylation product; although, the conversion of reactants was not that high (Table 4.2.1, entry 16).

Having the optimized reaction conditions in hand, next, the generality of this protocol towards coupling partners was examined (Scheme 4.2.1). Gratifyingly, it was found that direct C-H arylation of imidazoles works well for both electron-rich and electron-deficient arenes. Notably, a broad number of functionalities, such as F (**4.2.1p**), Cl (**4.2.1h**), CF_3 (**4.2.1a**,**e**,**h**,**m**), OMe (**4.2.1d**,**i**,**o**,**r**,**t**), and variety of other functional groups, like acyl (**4.2.1s**), NO_2 (**4.2.1b**), and even aldehyde (**4.2.1c**,**d**,**g**,**i**,**j**,**l**,**t**) as well as heterocycles (**4.2.1f**,**n**,**q**) were perfectly tolerated under the optimal reaction conditions, providing target arylated nitroimidazoles from good to quantitative yields.

The broad functional group tolerance is significant, since most of these functionalities are unstable and/or reactive in the presence of TM-catalysts. For instance, fluorine can be replaced by other groups *via* nucleophilic substitution[241] or so called "C-F activation";[242,182] aryl chlorides can act as coupling partners for C-H arylation;[181] the TM-catalyzed functionalization of CF_3 group is an area of current interest, since the C-F bond represents one of the most inert functionalities in organic chemistry;[243] the methoxy and acyl groups can be arylated *via* so called TM-catalyzed "sp^3 C-H activation";[244] the nitro group can be easily reduced to amino group in the presence of transition metals and a reductant;[225] similarly, the aldehyde can be oxidized in the presence of transition metal and an oxidant[245] etc.

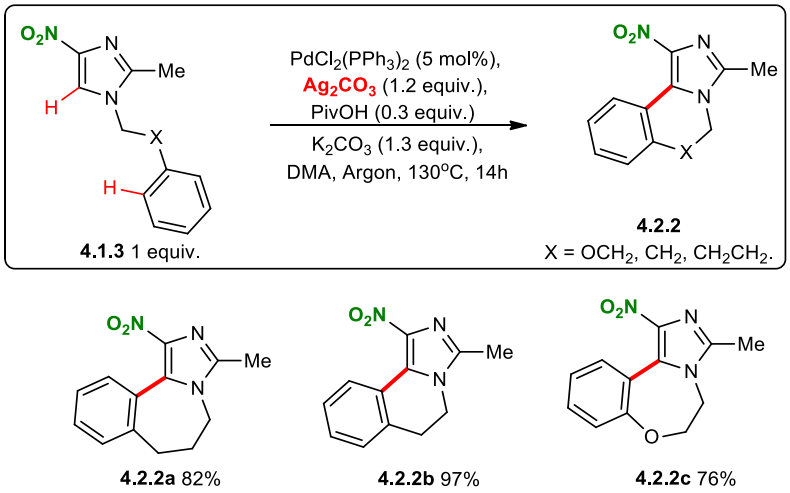


Scheme 4.2.1. Scope of the reaction with respect to aryl halides and N-substituted 4-nitroimidazoles.

Expectedly, the functional group tolerance was equally actual for a wide range of N-substituted 4-nitroimidazoles with no changes in the reaction conditions. Besides, the usage of aryl iodides (**4.2.1a**,**b**,**e**,**o**) resulted in formation of a great amount of corresponding symmetrical biaryls due to the homocoupling of aryl iodides induced by CuI:[53] this demanded the large excess of the aryl iodides, and the overall yields were visibly lower than with aryl bromides. Similarly, in case of reactive aryl bromides (electron-deficient aryl bromides) some amount of corresponding symmetrical biaryls was observed (see also Scheme 2.1.13).[50-53] Due to this side process, two equivalents of corresponding aryl bromides were required; otherwise, the overall yields of final C-H arylation products were reduced. Together with this, aryl chlorides, in general, were not active enough under optimized reaction conditions (**4.2.1h**). Subsequently, the scope and generality of the Ni-catalyzed C-H arylation reaction of appropriate 4-nitroimidazoles was examined. It was found that the reaction has general character and high functional group tolerance; thus, providing an efficient method for

introduction of an aryl group into the imidazole ring in moderate yields (Scheme 4.2.1, **4.2.1a**,**b**,**e**,**f**,**g**,**k**,**m**,**n**,**r**).

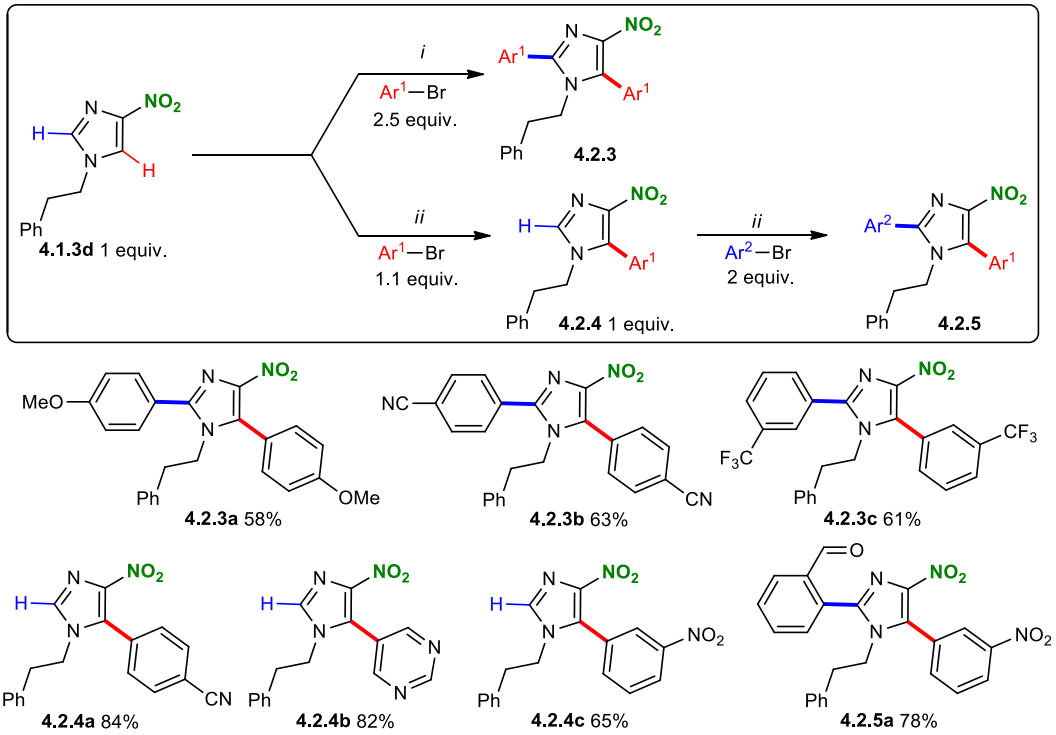
Surprisingly, during the course of optimization of the reaction conditions another interesting process was discovered. Namely, when CuI was replaced by Ag_2CO_3 along with C-H arylation by aryl bromide (Table 4.2.1, entry 7, 63%), a Pd-catalyzed intramolecular dehydrogenative cross-coupling occurred leading to the formation of an interesting fused system **4.2.2a** in 8% yield (Scheme 4.2.2).[66d,171b,199,246] Initially were observed traces of cyclisation product **4.2.2a** (8%) together with direct C-H arylation product **4.2.1a** (63%); nevertheless, further examinations have shown that reduction of the amount of aryl bromide dramatically increases the yield of intramolecular dehydrogenative cross-coupling reaction. In this context, it was shown that in the absence of aryl halide coupling partner presence of an oxidant (in this case Ag_2CO_3) can initiate an intramolecular dehydrogenative cross-coupling of 4-nitroimidazoles, leading to different fused systems **4.2.2a-c** from good to excellent yields (Scheme 4.2.2). These findings will be the basis for further investigations towards direct C-H arylation of nitroimidazoles *via* TM-catalyzed intermolecular dehydrogenative cross-coupling reaction.



Scheme 4.2.2. Synthesis of fused systems **4.2.2a-c**.

Naturally, after the development of an efficient Pd- and Ni-catalyzed method for arylation of 5-unsubstituted 4-nitroimidazoles, next we were interested in exploration of this procedure towards regioselective C-H arylation of 2,5-unsubstituted 4-nitroimidazole **4.1.3d**. Analysis of the literature shows that the regioselectivity of Pd-catalyzed C-H activation of simple imidazole depends on the used catalytic system.[142,240a,d,e] Accordingly, empirical studies indicate that in the presence of Pd-based catalyst, weak base and phosphine ligand the C-5

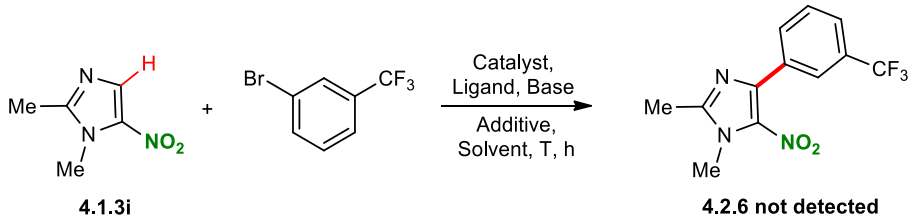
position of imidazole exhibits higher reactivity towards direct C-H arylation, than that at the C-2 position. The C-4 position remains relatively less reactive in this respect. Together with this, Miura and coworkers demonstrated that the addition of Cu(I) salts alters the bias toward the C-2 position.[142,240a] This reactivity pattern was consistent also with theoretically calculated CMD (concerted metalation-deprotonation) barriers for N-methylimidazole.[247] However, in case of current object of exploration the situation is different due to the nitro group that can direct the C-H arylation. Thus, when in the standard reaction conditions the Pd-catalyzed C-H arylation of 4-nitroimidazole **4.1.3d** was performed using 2.5 equivalents of aryl bromide, corresponding 2,5-diarylated imidazoles **4.2.3a-c** were observed in good yields (Scheme 4.2.3). Nevertheless, when the amount of aryl bromide was decreased to 1.1 equivalents, remarkably C-5 arylated 4-nitroimidazoles **4.2.4a-c** were the only observed regioisomer (Scheme 4.2.3). The changes of quantities of aryl bromide affected adversely on the outcome of the reaction; namely, in case of increased quantities of aryl bromide a mixture of products was observed, otherwise the yield of final product decreased significantly. Additionally, when the reaction was performed in the absence of CuI, the yield of the product decreased without any changes in regioselectivity (see also Table 4.2.1, entry 4, 5).



Scheme 4.2.3. Regioselective C-H arylation of 4-nitroimidazole **4.1.3d**; *i*: $PdCl_2(PPh_3)_2$ (5 mol%), CuI (1.2 equiv.), PivOH (0.3 equiv.), K_2CO_3 (2.3 equiv.), DMA, under argon, 130°C, 14h; *ii*: $PdCl_2(PPh_3)_2$ (5 mol%), CuI (1.2 equiv.), PivOH (0.3 equiv.), K_2CO_3 (1.3 equiv.), DMA, under argon, 130°C, 14h.

These observations indicates the "*guiding*" effect of nitro group on C-H arylation of 4-nitroimidazole **4.1.3d**, which dramatically changes the regioselectivity of the reaction, even though in the reaction medium stoichiometric amount of CuI was presented. After these astonishing findings, further a stepwise synthesis of 2,5-diaryl-4-nitroimidazole with two different aryl groups was performed. Thus, starting from compound **4.2.4c** under standard reaction conditions corresponding 2,5-diarylated imidazole **4.2.5a** was successfully prepared in 78% yield (Scheme 4.2.3).

Inspired by the successful results on regioselective C-H arylation of positions 2 and 5 of 4-nitroimidazoles, next it was proposed that TM-catalyzed C(4)-H arylation of commercially available 5-nitroimidazole **4.1.3i** can be an excellent extension of scope of the work (Scheme 4.2.4). For this purpose, a number of conditions were designed and tested; nevertheless, the reaction failed. For all cases, in spite of partial conversion of starting 5-nitroimidazole, only an inseparable mixture of products was observed. At this point the problem was solved applying another suitable procedure towards 4-arylaed 5-nitroimidazoles.



4.1.3i **4.2.6 not detected**

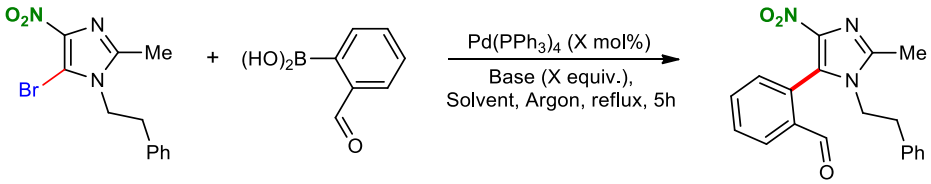
Catalyst = $PdCl_2(PPh_3)_2$, $NiCl_2(PPh_3)_2$; Ligand = tBu$_3$P, BINAP, XantPhos etc; Base = K_2CO_3, CsOPiv, KOtBu etc; Additive = CuI, AgOAc etc; Solvent = DMF, NMP, Toluene etc; T = 100-190^oC, h = 5-48h.

Scheme 4.2.4. Unsuccessful trials on C(4)-H arylation of 5-nitroimidazole **4.1.3i**.

4.3. Arylation of Nitroimidazoles *via* Suzuki-Miyaura Cross-Coupling Reaction

Since it was not possible to get any positive result from TM-catalyzed C-H arylation reaction of commercially available 5-nitroimidazole **4.1.3i**, further it was decided to overcome this problem applying well-defined TM-catalyzed cross-coupling reactions. For this purpose the Suzuki-Miyaura cross-coupling reaction of 5(4)-bromo-4(5)-nitroimidazoles **4.1.6**, **4.1.7** was studied. In order to identify a practical and versatile catalytic procedure for efficient arylation of nitroimidazoles, numerous reaction parameters were designed and thoroughly examined, including transition metal catalyst; base; loading of reactants; solvent and temperature; the selected results are listed in Table 4.3.1. According to the new pathway for the test reaction, the imidazole **4.1.6a** and 2-formylphenylboronic acid were used as model coupling partners (Table 4.3.1). As a catalyst for this transformation $Pd(PPh_3)_4$ was chosen, since analysis of the

literature indicates that the latter is the most successful Pd source for Suzuki-Miyaura cross-coupling reaction.[86-88,102] During the course of optimization of the reaction conditions initially the influence of solvent on the outcome of the reaction was examined. Thus, a number of solvents were tested such as dioxane, toluene etc. Unfortunately, all primary attempts to perform the desired coupling appeared unsuccessful, most probably due to the reduced solubility of the reaction components, solvation effects etc (Table 4.3.1, entry 1, 2). Hence, at this stage different combinations of solvents were used. Gratifyingly, it was found that when the reaction was performed in standard solvents mentioned above, using a drop of water, the desired arylation of nitroimidazole occurs in 20% and 27% yields in dioxane/H_2O and toluene/H_2O systems respectively (entry 3, 4).



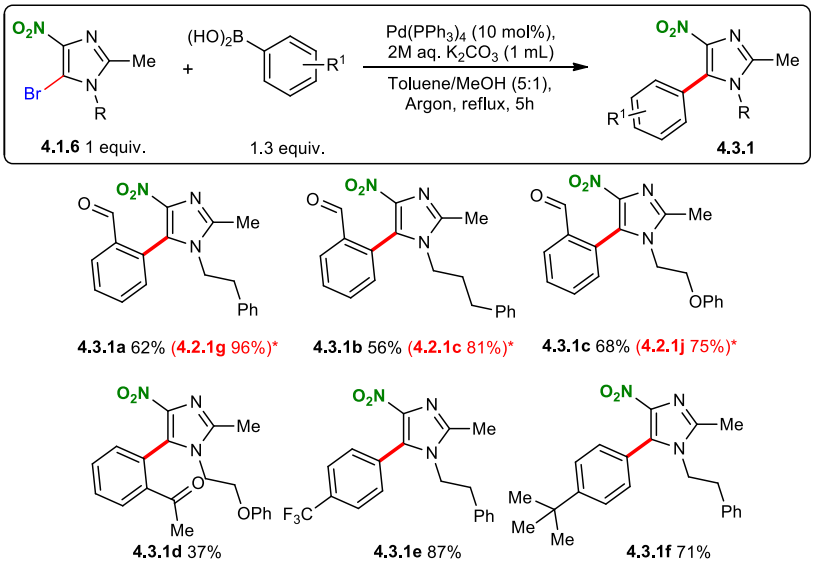
4.1.6a 1 equiv. X equiv. **4.3.1a**

Entry	Catalyst	$ArB(OH)_2$	Base	Solvent	%[a]
1	$Pd(PPh_3)_4$ 10 mol%	1.3 equiv.	K_2CO_3 (2 equiv.)	dioxane	-
2	$Pd(PPh_3)_4$ 10 mol%	1.3 equiv.	K_2CO_3 (2 equiv.)	toluene	-
3	$Pd(PPh_3)_4$ 10 mol%	1.3 equiv.	K_2CO_3 (2 equiv.)	dioxane/H_2O (4:1)	20
4	$Pd(PPh_3)_4$ 10 mol%	1.3 equiv.	K_2CO_3 (2 equiv.)	toluene/H_2O (4:1)	27
5	$Pd(PPh_3)_4$ 10 mol%	1.3 equiv.	K_3PO_4 (2 equiv.)	toluene/H_2O (4:1)	15
6	$Pd(PPh_3)_4$ 10 mol%	1.3 equiv.	K_2CO_3 (2 equiv.)	toluene/MeOH (5:1)	36
7	**$Pd(PPh_3)_4$ 10 mol%**	**1.3 equiv.**	**2M aq. K_2CO_3 (1 mL)[b]**	**toluene/MeOH (5:1)**	**62**
8	$Pd(PPh_3)_4$ 10 mol%	1.0 equiv.	2M aq. K_2CO_3 (1 mL)[b]	toluene/MeOH (5:1)	50
9	$Pd(PPh_3)_4$ 10 mol%	2.0 equiv.	2M aq. K_2CO_3 (1 mL)[b]	toluene/MeOH (5:1)	61
10	$Pd(PPh_3)_4$ 5 mol%	1.3 equiv.	2M aq. K_2CO_3 (1 mL)[b]	toluene/MeOH (5:1)	56

Table 4.3.1. Optimization of reaction conditions for the synthesis of compound **4.3.1a**; [a] isolated yields; [b] for 1 mmol of starting imidazole.

Meanwhile, the replacement of K_2CO_3 by K_3PO_4 decreased the yield of product (Table 4.3.1, entry 5), therefore, during further test reactions only K_2CO_3 was used as a base. In addition, once distilled technical MeOH was used instead of water, curiously the yield of the reaction increased up to 36% (Table 4.3.1, entry 6). Moreover, *via* using an aqueous solution of K_2CO_3 as a base, the yield of desired arylation product was increased up to 62% (Table 4.3.1, entry 7). During the next steps of optimization, attempts were made to increase the yields by changing the loading of 2-formylphenylboronic acid. Nevertheless, the results were quite unsuccessful, 1.3 equivalent of 2-formylphenylboronic acid showed the best efficiency (Table

4.3.1, entry 7-9). Similar observations were obtained on loading of catalyst (Table 4.3.1, entry 10). Finally, it should be mentioned that performing the reaction at slightly high temperatures (under reflux) in inert atmosphere was essential in order to get good yields of arylated nitroimidazole. Naturally, after development of an efficient Pd-catalyzed Suzuki-Miyaura cross-coupling reaction of 5-bromo-4-nitroimidazoles **4.1.6**, on the next stage of the work under the newly developed conditions an attempt was made to prepare similar arylated nitroimidazoles to those that were prepared by TM-catalyzed direct C-H arylation of nitroimidazoles (Scheme 4.3.1).

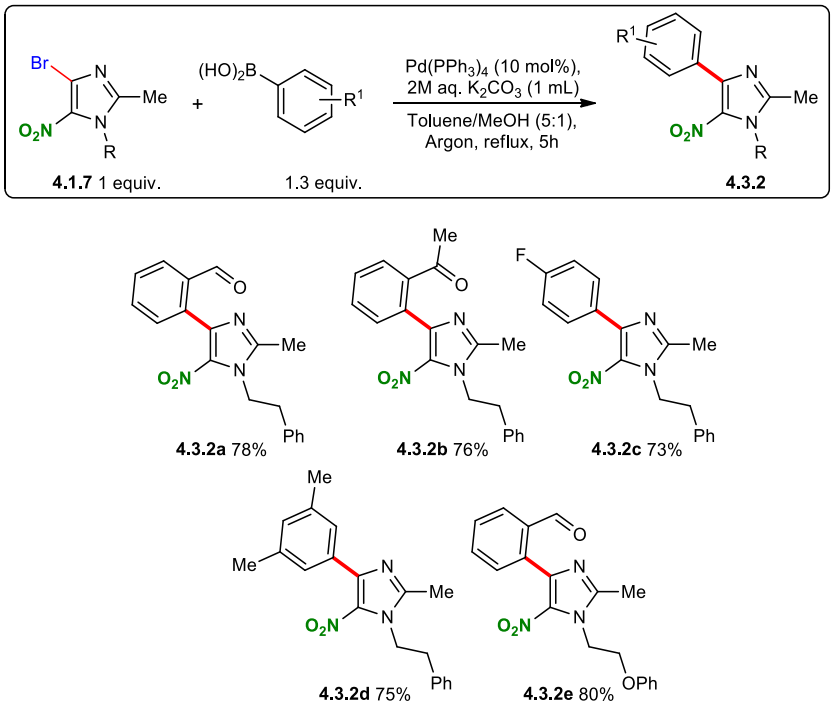


Scheme 4.3.1. Scope of the Suzuki-Miyaura reaction; * in the brackets on red are mentioned the yields of C-H arylation (see also Scheme 4.2.1).

The comparison of these two procedures as well as replacement of traditional cross-coupling reactions by corresponding direct C-H transformations remains an actual task, since cross-coupling reactions require more synthetic effort and expensive starting materials (Scheme 2.2.1). In this context, the exploration of substrate scope of the reaction showed that the yields of Suzuki-Miyaura cross-coupling reaction of 5-bromo-4-nitroimidazoles **4.1.6** are slightly lower in comparison to the yields obtained for similar compounds in direct C-H arylation of 4-nitroimidazoles. Altogether, using this procedure six examples of arylated nitroimidazoles **4.3.1a-f** were prepared from moderate to good yields (Scheme 4.3.1). The reduced yields may be the result of steric factors and/or poor solubility of the reaction components. On the other hand, while in TM-catalyzed couplings the comparative reactivity of aryl halides increases together with electron-withdrawing ability of substituents on aromatic ring the reactivity of aryl boronic acids is contrary to this rule (aryl halides with electron-withdrawing groups are

more reactive than aryl halides with electron-donating groups while aryl boronic acids with electron-withdrawing groups are less reactive than aryl boronic acids with electron-donating groups).[86-88] This may be another reason for relatively poor yields.

Although the C(4)-H bond of 5-nitroimidazoles exhibits very low reactivity in the Pd- and Ni-catalyzed C-H arylation (Scheme 4.2.4), precluding direct arylation of this position, nevertheless, it was possible to overcome this problem applying the Pd-catalyzed Suzuki-Miyaura cross-coupling reaction of 4-bromo-5-nitroimidazoles **4.1.7**. Accordingly, using the procedure developed for 5-bromo-4-nitroimidazoles, a number of 4-arylated-5-nitroimidazoles **4.3.2a-e** were prepared with good yields (73-80%) (Scheme 4.3.2).

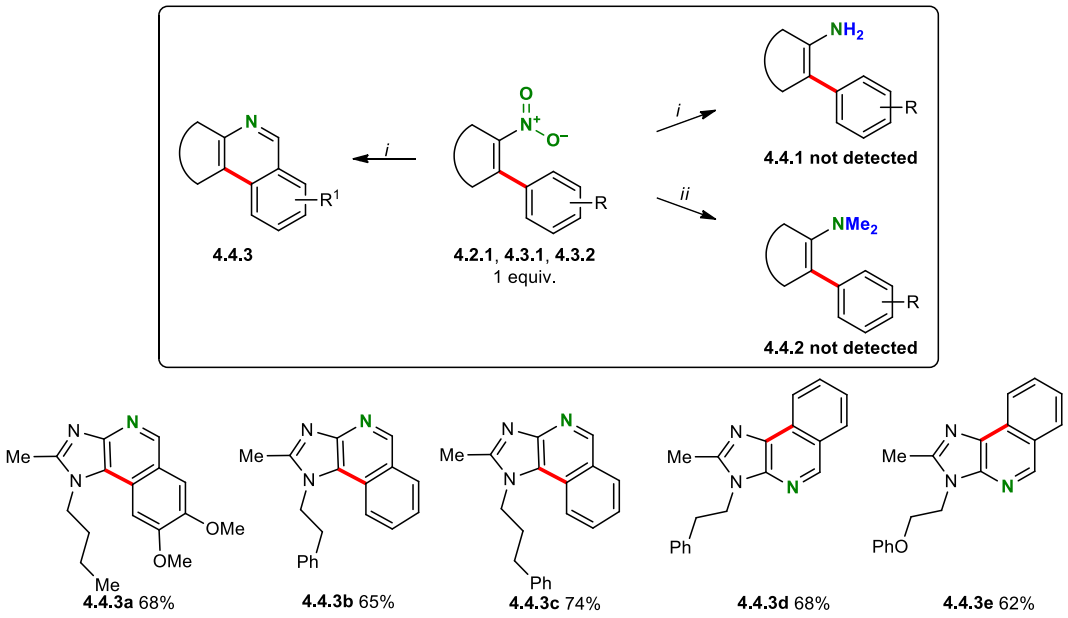


Scheme 4.3.2. Synthesis of 4-arylaed 5-nitroimidazoles *via* Suzuki-Miyaura reaction.

4.4. Exploration of Further Transformations of Nitro Group

In this part of the work in order to fully demonstrate the synthetic potential of this methodology, it was decided to briefly explore the chemical versatility of directing group. For this purpose the simple reduction of nitro group was tested first (Scheme 4.4.1). However, at this stage of the work an inseparable mixture of products was observed along with an intensive polymerization, because of instability of formed 4(5)-aminoimidazoles **4.4.1**. Noteworthy, 4(5)-aminoimidazoles are rather unstable compounds, although they can be prepared *in situ* for subsequent transformations.[448] Unfortunately, the reduction of arylated

nitroimidazoles in the presence of an excess of formalin also experienced a failure; in particular, instead of N,N-dimethylamines **4.4.2** an inseparable mixture of products was obtained. In this regard, the overall instability of 4(5)-aminoimidazoles significantly diminished the efficiency of further transformations of directing group. Fortunately, in the course of further examinations it was found that the reduction of arylated 4(5)-nitroimidazoles, which contain an *ortho* carbonyl group **4.2.1t 4.3.1a**,**b 4.3.2a**,**e**, leads to the formation of imidazo[4,5-*c*]isoquinoline system as a single product in good yields. In this case probably *in situ* generated reduction product amine undergoes a subsequent intramolecular cyclocondensation with carbonyl group which leads to the formation of aromatic isoquinoline system. The reaction has general character for arylated nitroimidazoles which contain an *ortho* carbonyl group. Namely, the Pd-catalyzed reduction of suitable nitroimidazoles in MeOH under hydrogen atmosphere at ambient temperature leads to the formation of corresponding products **4.4.3a**-**e** in 62-74% yields (Scheme 4.4.1).

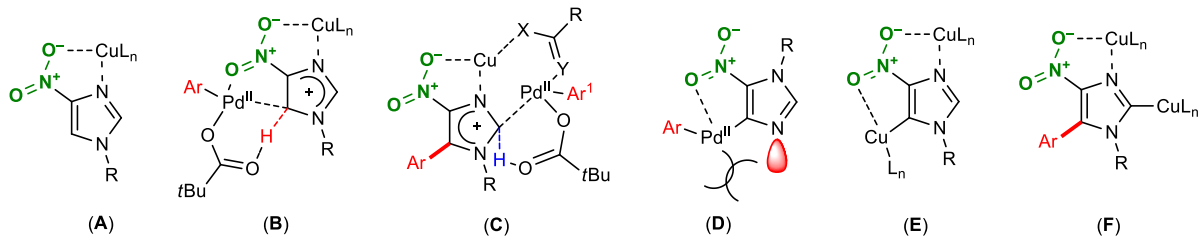


Scheme 4.4.1. Reduction of nitro group; *i*: MeOH, H_2 balloon, Pd/C (10 mol%), 20°C, 5h; *ii*: MeOH, H_2 balloon, Pd/C (10 mol%), CH_2O in H_2O (37%, 6 equiv.), 20°C, 5h.

4.5. Possible Mechanisms of Transformations and Further Experiments

The regioselectivity of direct C-H arylation of 4-nitroimidazoles might be explained by an assumption that the catalyst (Pd or Ni) coordinated by the nitro group initiates the C(5)-H arylation *via* concerted metalation-deprotonation (CMD) as illustrated in Scheme 4.5.1 (**B**). This hypothesis is strongly supported by numerous theoretical calculations and practical

observations.[130,131,133-136,197] In this context, it should be mentioned that the salt of copper *via* double chelation by nitro group and nitrogen of imidazole ring can immobilize the nitro group in the plane of imidazole, thus supporting the C-H bond cleavage by Pd or Ni (Scheme 4.5.1, **A**, **B**). This assumption supports the recent work of Huang and coworkers in which they found that the lone pair on the nitrogen atom in benzothiazole, 1-methylbenzimidazole and related systems can bind to the copper center thereby initiating Pd-catalyzed C-H bond cleavage.[249]

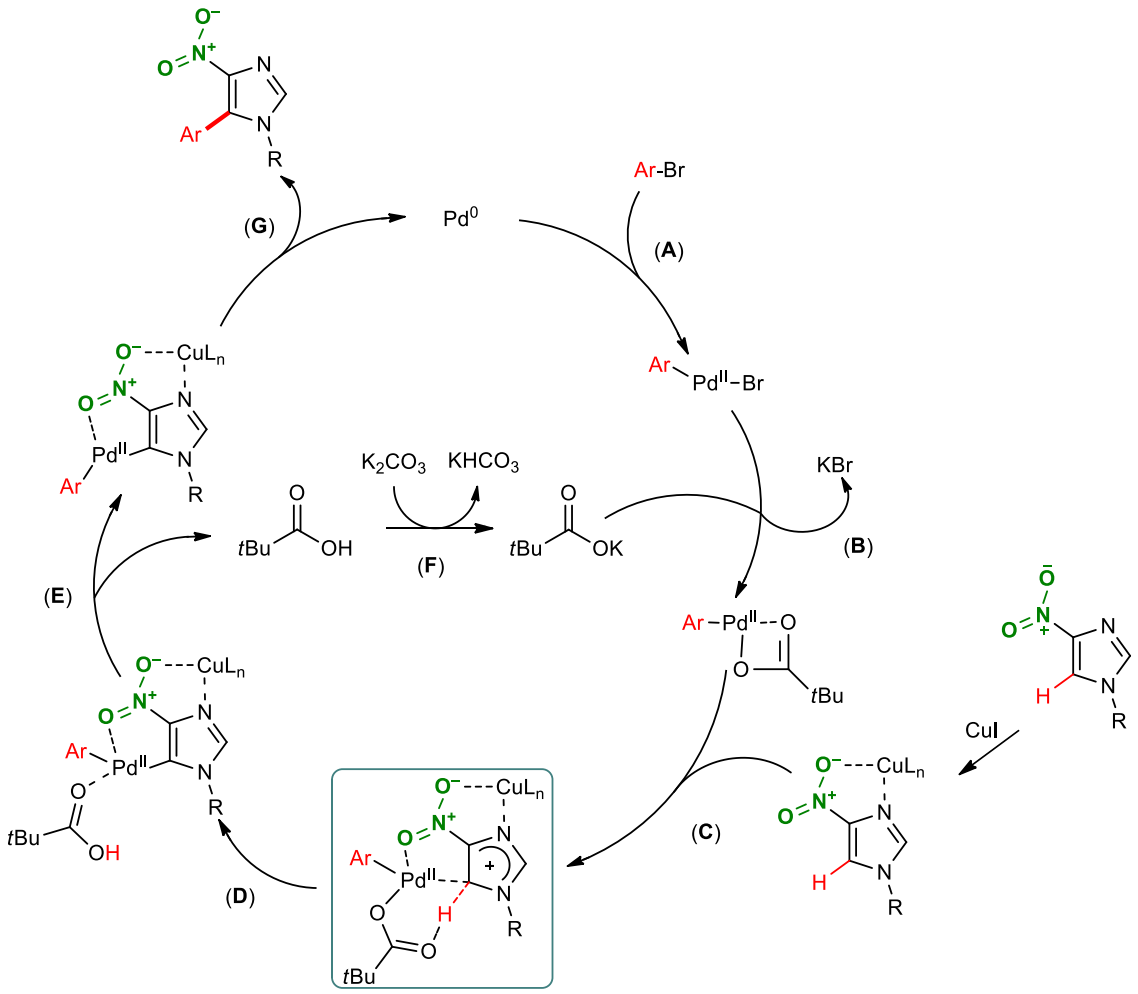


Scheme 4.5.1. Proposed mechanistic explanation of the regioselectivity.

Based on these considerations we assume that the catalytic cycle starts with oxidative addition of aryl bromide to the catalyst Pd(0) delivering Ar-Pd(II)-Br complex (Scheme 4.5.2, **A**, similar considerations are equally true for Ni). Noteworthy, the oxidative addition of aryl halide to the catalyst represents the rate determining step for many coupling reactions. In the next step the product of oxidative addition undergoes a ligand exchange reaction with potassium pivalate (**B**). It should be noted that the real base of the reaction is KOPiv which is formed by the reaction of K_2CO_3 and PivOH and is far more soluble in DMA (DMF, NMP). Subsequently, the Ar-Pd(II)-OPiv species first coordinates to the nitro group of imidazole which is followed by a carboxylate-assisted C-H bond cleavage *via* concerted metalation-deprotonation (**C**, **D**). This process is accompanied by regeneration of PivOH; therefore, the PivOH can be used in catalytic amounts (**E**, **F**). In the final step of the process the reductive elimination of catalyst Pd(0) leads to the formation of desired Ar-Ar C-C bond and regeneration of components of catalytic cycle (Scheme 4.5.2, **G**).

Accordingly, for Pd-catalyzed C(2)-H arylation of imidazoles we assume that a cooperative action of Pd and Cu, chelated by a bidentate ligand (solvent, carboxylate), may enable the direct C-H activation (Scheme 4.5.1, **C**).[250] Concerning the low reactivity of C(4)-H bond of imidazoles towards Pd-catalyzed C-H activation, several authors described this phenomenon by the electronic repulsion between the electron lone pair on the N-(3) of imidazole and the C-Pd bond (Scheme 4.5.1, **D**).[251] Eventually, we do not exclude the possibility of formation of appropriate cuprates of imidazole[200q,202f,252] which can be followed by transmetallation to Pd or Ni (Scheme 4.5.1, **E**, **F**). In this respect, recently DFT calculations made by Fu and

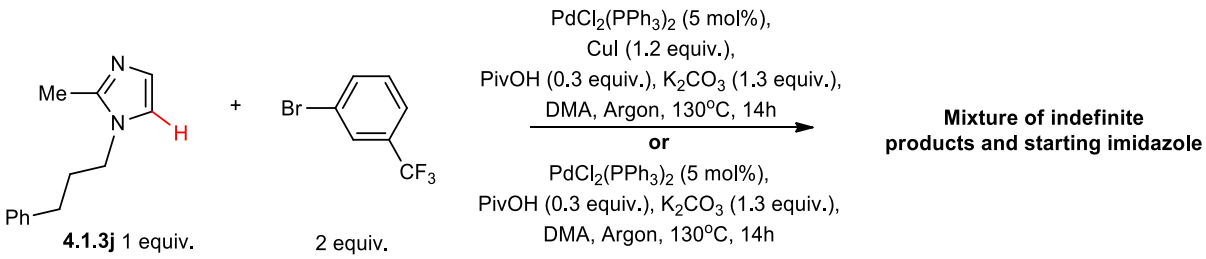
coworkers indicate that the C-H activity of different Ar-H species and both the dissociation of the Ar-H bond and the formation of the Ar-Cu bond make important contributions to the concerted C-H activation.[252g]



Scheme 4.5.2. Possible mechanism of Pd-catalyzed C(5)-H arylation of 4-nitroimidazoles.

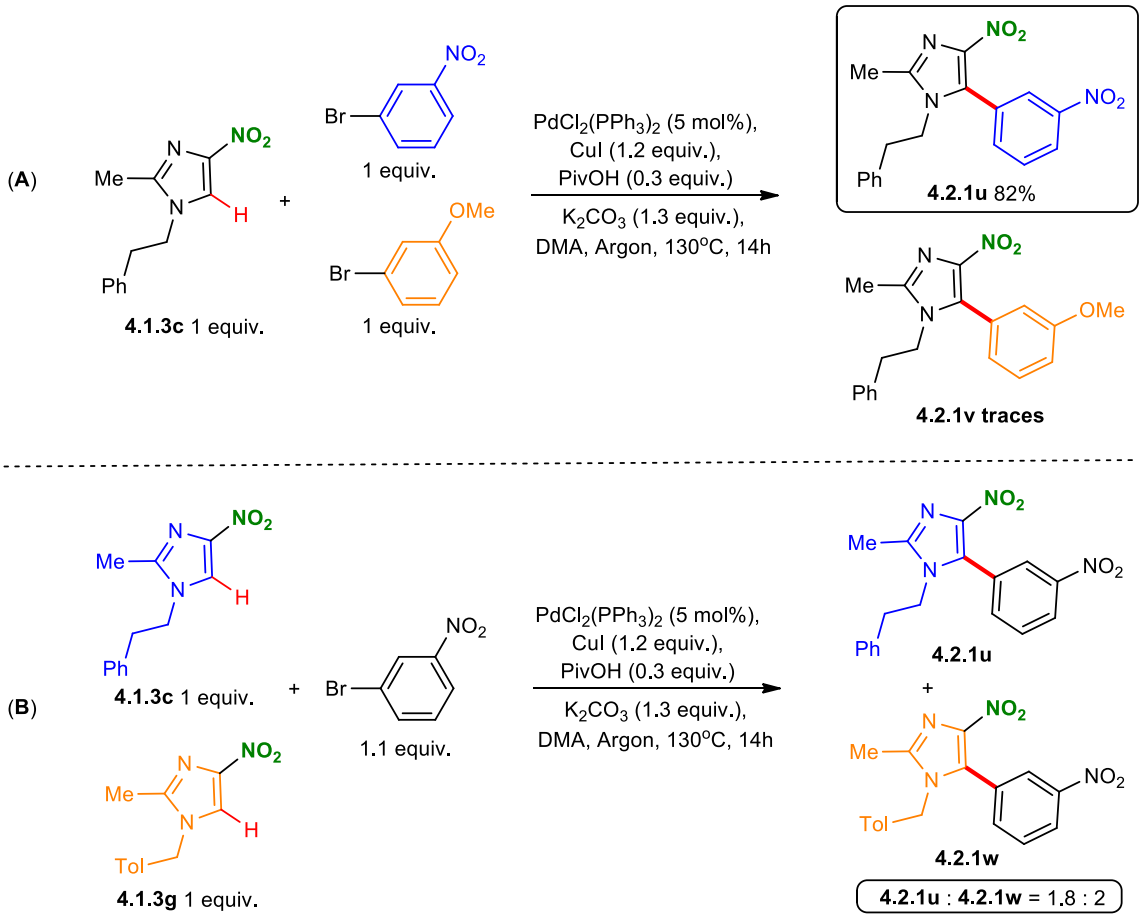
In order to obtain more insights into the reaction mechanism and the directing ability of nitro group, the imidazole **4.1.3j** was synthesized applying the procedure described in Table 4.1.1. Afterwards, the latter was subjected to our standard Pd-catalyzed reaction conditions (Scheme 4.5.3). Nevertheless, all attempts to perform the C-H arylation in standard conditions, developed for 4-nitroimidazoles were unsuccessful; an inseparable mixture of products was formed along with some quantities of starting imidazole **4.1.3j**. These findings clearly show the crucial effect of nitro group on the outcome of the reaction.

Subsequently, to gain more insight into the reaction pattern, a competitive experiment was conducted between imidazole **4.1.3c** and two electronically different aryl bromides, namely with 1-bromo-3-methoxybenzene and 1-bromo-3-nitrobenzene (Scheme 4.5.4).



Scheme 4.5.3. Exploration of directing ability of nitro group.

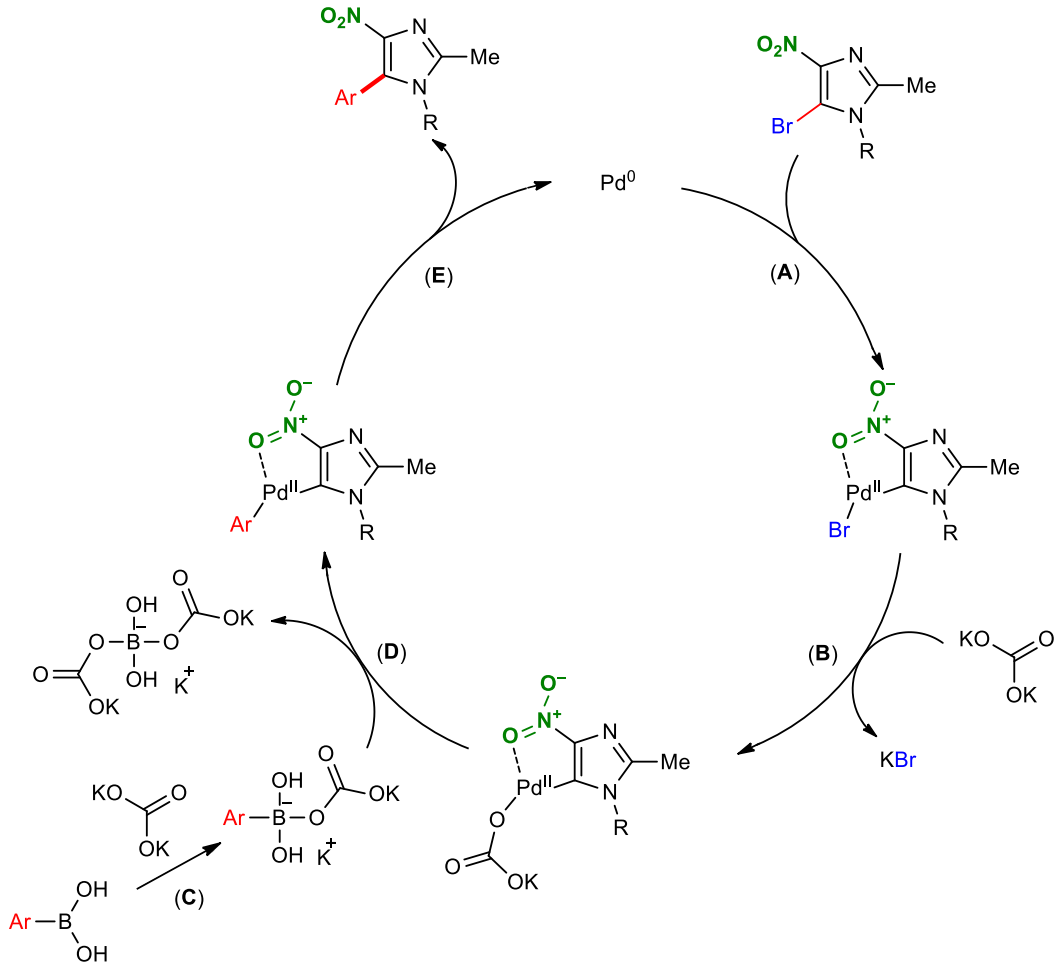
The aim of the study was the identification of comparable reactivities of electronically different aryl bromides in Pd-catalyzed direct C-H arylation of 4-nitroimidazoles. The results revealed that under applied conditions the reaction is favoured by electron-deficient aryl bromides. In particular, performing the competitive arylation with two different aryl bromides (Scheme 4.5.4, **A**), it was possible to isolate only one product **4.2.1u** corresponding to C-H arylation by 1-bromo-3-nitrobenzene in 82% yield. This experiment clearly shows that aryl bromides with electron-withdrawing groups are much more reactive in Pd-catalyzed C-H arylation reactions than the respective aryl bromides with electron-donating groups.



Scheme 4.5.4. The competitive experiments between imidazoles and aryl bromides.

On the next stage of the study the reaction between various imidazoles (**4.1.3c** and **4.1.3g**) and electron-deficient 1-bromo-3-nitrobenzene was explored (Scheme 4.5.4, **B**). In this case the aim of the study was the identification of comparable reactivities of two different N-substituted imidazoles. Understanding of the impact of steric influence of substituents in the position 1 of imidazole ring represents another actual task. Interestingly, during the course of the study it was found that there is almost no distinction between two imidazoles; in particular, a mixture of both arylated imidazoles with almost similar quantities was observed (Scheme 4.5.4, **B**).

The possible mechanism of Pd-catalyzed Suzuki-Miyaura cross-coupling reaction of 5-bromo-4-nitroimidazoles is depicted on the Scheme 4.5.5. The Pd-catalyzed cross-coupling reaction of arylboronic acids with aryl halides starts with oxidative addition of aryl halide to the catalytically active Pd(0) complex affording Ar-Pd(II)-Br intermediate (Scheme 4.5.5, **A**). In the next step the product of oxidative addition undergoes a ligand exchange reaction with potassium carbonate (**B**). Noteworthy, these two steps are very much similar to the initial steps of Pd-catalyzed C-H arylation (Scheme 4.5.2).



Scheme 4.5.5. Possible mechanism of Pd-catalyzed Suzuki-Miyaura cross-coupling reaction.

The next step of the process represents transmetallation of the Ar-group from the parent arylboronic acid to the Ar-Pd(II)-CO_3K species giving rise to the $Ar_2Pd(II)$ complex (**D**). As it was mentioned in the Chapter 2.1, the C-B bond possesses a strong covalent character; however, under special circumstances the arylboronic acids can act as aryl carbanion-donors similar to other typical aryl organometallics.

In particular, the coordination of potassium carbonate to the boron atom is an efficient method for increasing the carbanionic nature of aryl group which further can be readily transferred from boron to the electrophilic Pd(II) (**C**, **D**). The final step of catalytic cycle constitutes the reductive elimination of arylated nitroimidazole with regeneration of catalytically active Pd(0) complex (**E**) which is closely related to the final step of Pd-catalyzed C-H arylation of nitroimidazoles (Scheme 4.5.2).

4.6. Structure Identification

The structures of synthesized compounds were mainly established by NMR, IR spectroscopy and mass spectrometry. Noteworthy, in all arylated nitroimidazoles the aryl groups do not possess bulky functional groups near imidazole ring which indicates on free rotation around newly formed Ar-Ar C-C bond and absence of atropisomers (at room temperature).[1e,f,253]

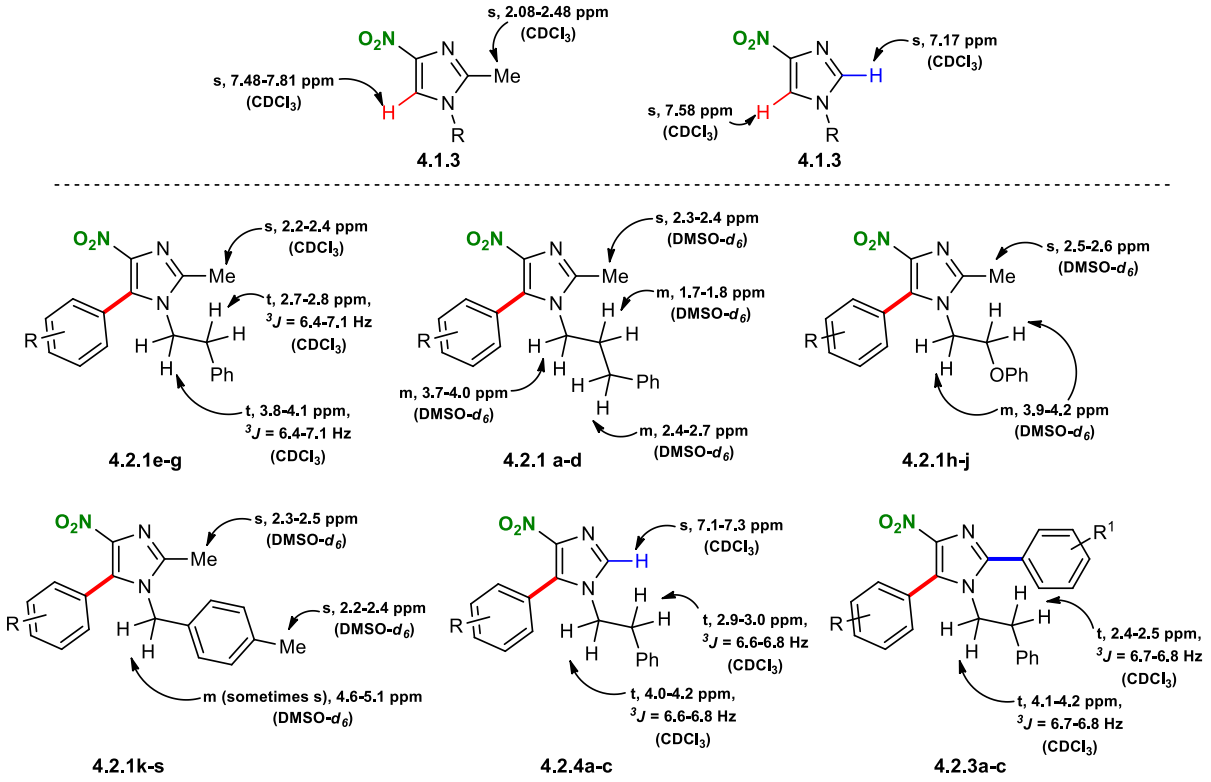


Figure 4.6.1. Observations from NMR experiments.

In the ^{1}H NMR spectra of starting imidazoles **4.1.3** the singlets of C*H* bonds of imidazole ring appears at 7.17-7.81 ppm ($CDCl_3$) (Figure 4.6.1). In the products of C-H arylation **4.2.1**-**4.2.4** the singlet disappears; instead of this the number of aromatic signals increases (Figure 4.6.2). The singlet of *Me* group of imidazole ring appears at 2.08-2.48 ppm ($CDCl_3$) and 2.06-2.45 ppm (DMSO-d_6). Additionally, the typical signals of CH_2 groups of N-alkyl substituents appear at range 1.7-4.9 ppm. In particular, the triplets of CH_2 groups of phenethyl functionality were detected at 2.7-2.8 ppm (CH_2Ph) and 3.8-4.1 ppm (NCH_2) ($CDCl_3$) with a coupling constant ^{3}J = 6.4-7.1 Hz (Figure 4.6.1, **4.2.1e-g**). The multiplets of CH_2 groups of phenyl propyl functionality appears at 1.7-1.8 ppm ($CH_2CH_2CH_2Ph$), 2.4-2.7 ppm ($CH_2CH_2CH_2Ph$) and 3.7-4.0 ppm ($CH_2CH_2CH_2Ph$) (DMSO-d_6) (Figure 4.6.1, **4.2.1a-d**). The multiplets of phenoxyethyl CH_2 groups were seen at 3.9-4.2 ppm (DMSO-d_6) (Figure 4.6.1, **4.2.1h-j**). The singlet of *Me* group of *p*-methylbenzyl functionality along with the signal of benzyl CH_2 group appears at 2.2-2.4 ppm and 4.6-5.1 ppm respectively (DMSO-d_6) (Figure 4.6.1, **4.2.1k-s**). Finally, the triplets of CH_2 groups of phenethyl functionality of C-H arylation products **4.2.4** and **4.2.3** were detected at 2.9-3.0 ppm (CH_2Ph), 4.0-4.2 ppm (NCH_2) and 2.4-2.5 ppm (CH_2Ph), 4.1-4.2 ppm (NCH_2) respectively with a coupling constant ^{3}J = 6.6-6.8 Hz ($CDCl_3$) (Figure 4.6.1).

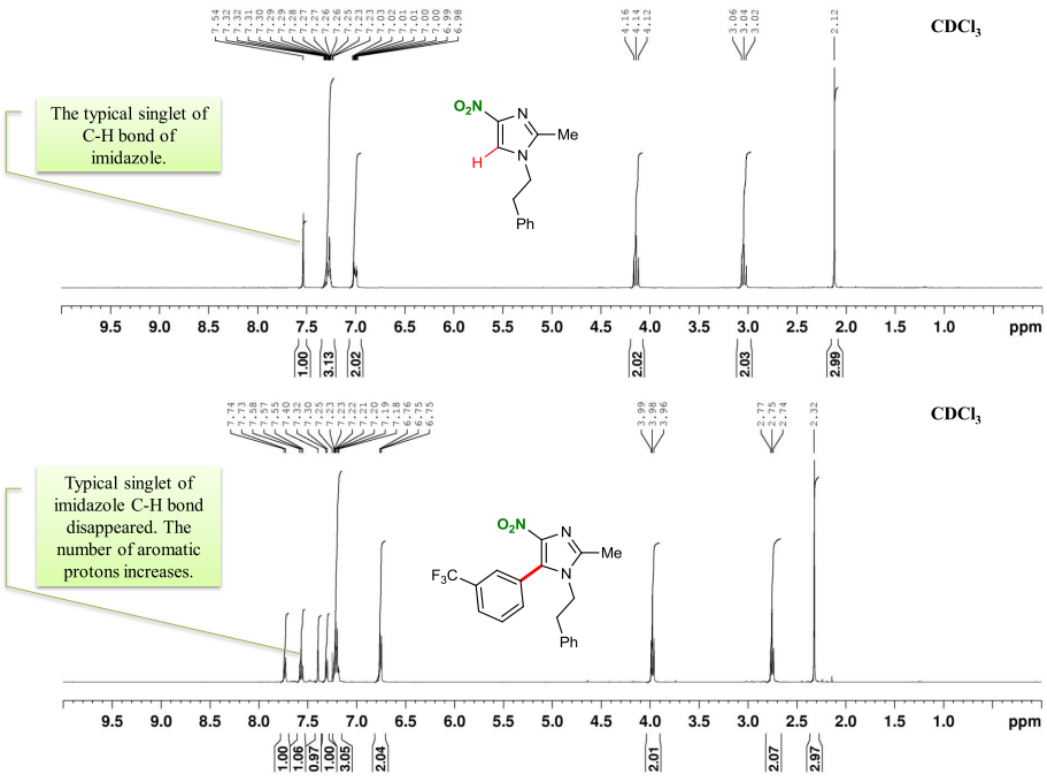
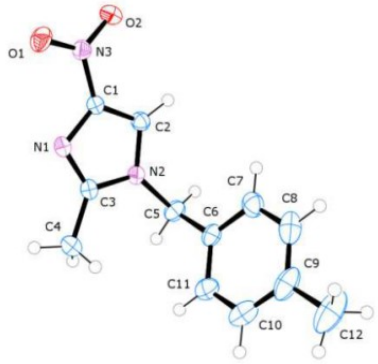
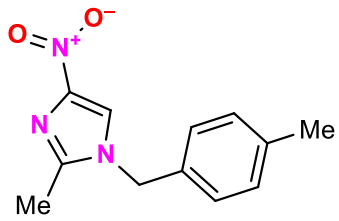
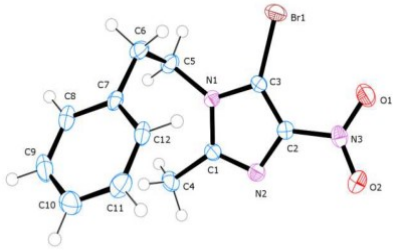
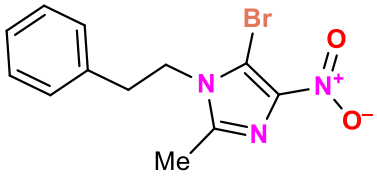
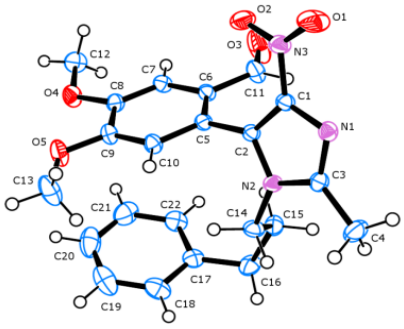
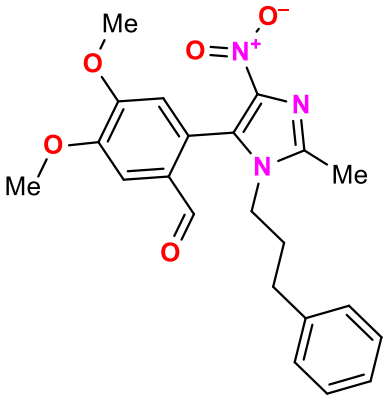
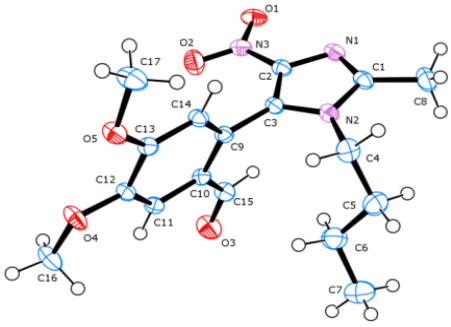
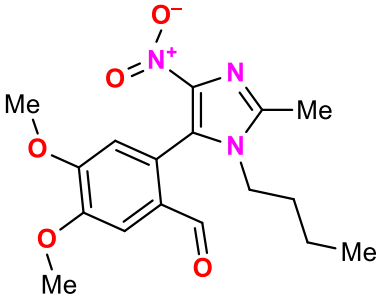
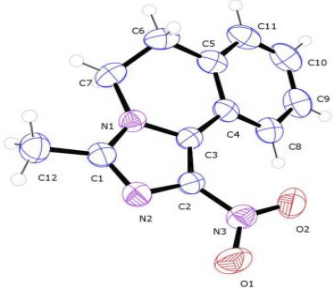
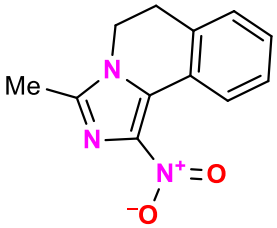


Figure 4.6.2. Comparison of ^{1}H NMR spectra of starting imidazole **4.1.3c** and corresponding C-H arylation product **4.2.1e**.

Compound	Crystal structure	Structure
4.1.3g		
4.1.6a		
4.2.1d		
4.2.1t		
4.2.2b		

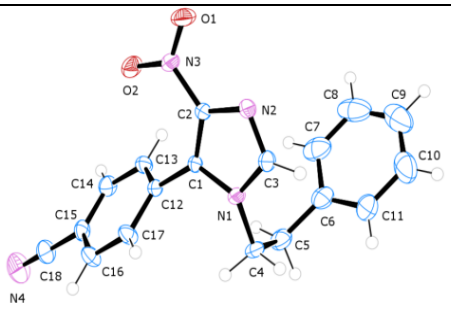
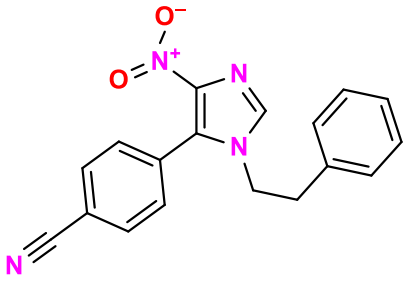
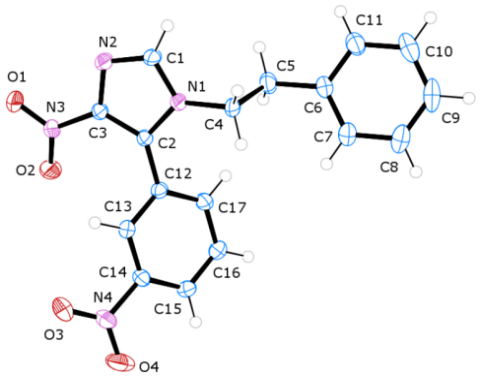
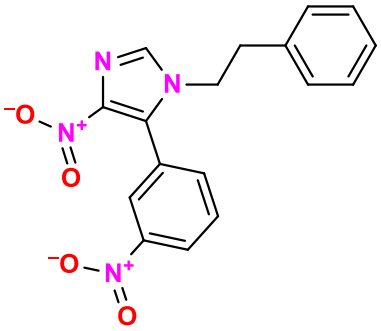
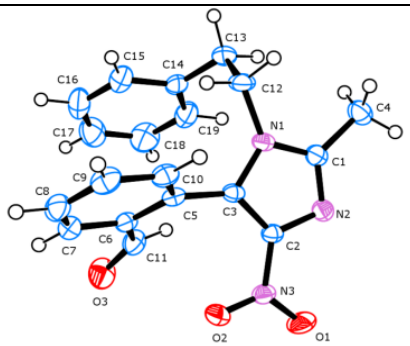
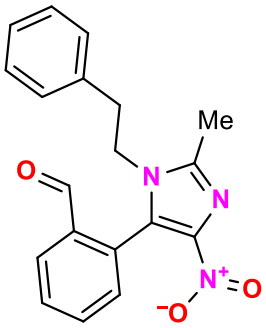
Compound	Crystal structure	Structure
4.2.4a		
4.2.4c		
4.3.1a **(4.2.1g)**		

Table 4.6.1. Crystal structures of compounds **4.1.3g**, **4.1.6a**, **4.2.1d**,**t**, **4.2.2b**, **4.2.4a**,**c**, **4.3.1a**.

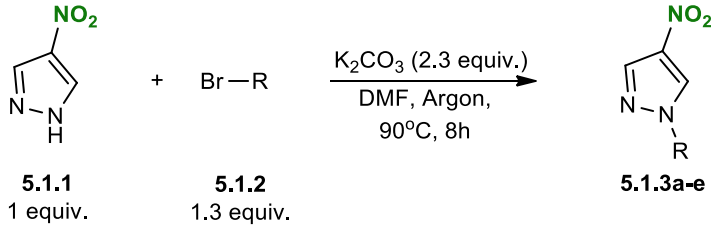
The singlet of C(5)-H bond of pyridine ring in reduction product imidazo[4,5-*c*]isoquinolines **4.4.3** was detected at 8.5-8.9 ppm ($CDCl_3$). Besides, in the ^{13}C NMR spectra of synthesized compounds the *Me* and CH_2 groups as well as typical quartets of CF_3 group (^1J = 270-274 Hz, DMSO-d_6) were observed. In the ^{19}F NMR spectra the CF_3 group appears from -61.0 to -62.9 ppm (DMSO-d_6). Furthermore, in the IR spectra of nitroimidazoles the N-O stretching vibrations of NO_2 group (medium intensity) were observed at 1506-1574 cm^{-1} (asymmetrical) and 1328-1358 cm^{-1} (symmetrical).

The structures of compounds **4.1.3g**, **4.1.6a**, **4.2.1d**,**t**, **4.2.2b**, **4.2.4a**,**c** and **4.3.1a** (**4.2.1g**) were confirmed by X-ray single crystal analyses (Table 4.6.1). Thus, the regioselectivity of alkylation of unprotected nitroimidazoles as well as TM-catalyzed direct C-H arylation was independently proved by X-ray analysis.

5. Direct C-H Arylation of 4-Nitropyrazoles

5.1. Preparation of Starting 4-Nitropyrazoles

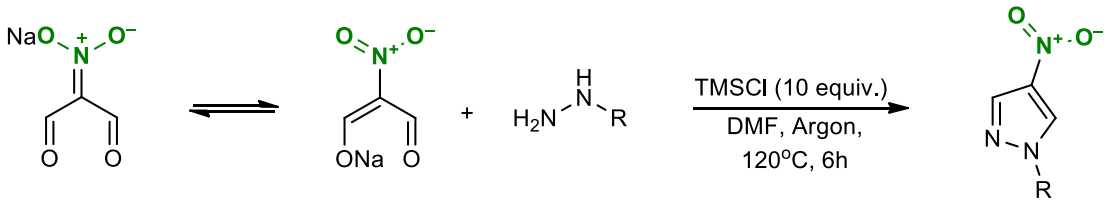
Inspired by successful results on TM-catalyzed direct C-H arylation of 4-nitroimidazoles (Chapter 4)[236] we started the current study on C-H arylation of 4-nitropyrazoles.[254] In this case as well in order to prevent the TM-catalyzed arylation of unprotected 1*H*-pyrazoles[237] it was decided to alkylate the starting commercially available 4-nitro-1*H*-pyrazole **5.1.1** beforehand (Table 5.1.1). Accordingly, the N-substituted 4-nitropyrazoles **5.1.3a-e** were prepared utilizing the alkylation procedure which was applied for alkylation of nitroimidazoles (Table 4.1.1, 4.1.2).[238] In particular, the alkylation of commercially available 4-nitro-1*H*-pyrazole **5.1.1** with suitable alkyl bromides **5.1.2** was performed in DMF using K_2CO_3 as base; thus, five distinct examples of 4-nitropyrazoles were prepared from good to excellent yields.



5.1.1 1 equiv. **5.1.2** 1.3 equiv. **5.1.3a-e**

5.1.3	R	Yield (%)
a	*n*-Butyl	84
b	$(CH_2)_2Ph$	89
c	$(CH_2)_3Ph$	87
d	$(CH_2)_2OPh$	93
e	CH_2-4-Tol	83

Table 5.1.1. Synthesis of starting N-substituted 4-nitropyrazoles *via* alkylation.



5.1.4 1.5 equiv. **5.1.5** 1 equiv. **5.1.3f,g**

5.1.3	R	Yield (%)
f	Me	81
g	4-Tol	87

Table 5.1.2. Synthesis of starting N-substituted 4-nitropyrazoles *via* cyclocondensation.

Alternatively, the target N-substituted 4-nitropyrazoles **5.1.3f,g** were synthesized utilizing the cyclocondensation reaction of corresponding hydrazines **5.1.5** and enolate of nitromalonaldehyde **5.1.4** (Table 5.1.2).[255] The reaction was conducted in a pressure tube using TMSCl as a water scavenger.[256] Thus, two examples of 4-nitropyrazole were prepared in good yields (81-87%).

5.2. C-H Arylation of 4-Nitropyrazoles: Scope and Limitations

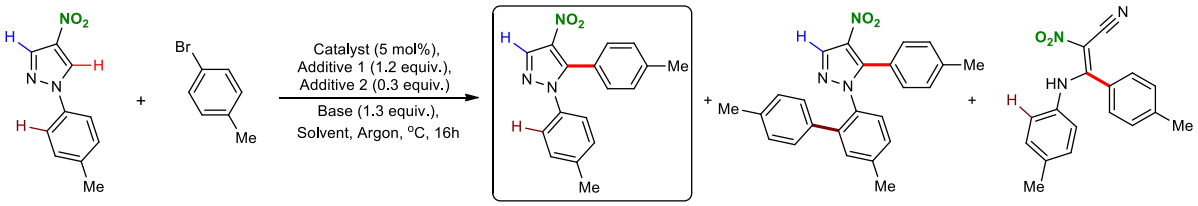
With the desired starting N-substituted 4-nitropyrazoles **5.1.3a-g** in hand, the optimization of reaction conditions for direct C-H arylation of 4-nitropyrazoles was studied. To this end, as a starting point the reaction of model compound 4-nitro-1-(*p*-tolyl)-1*H*-pyrazole **5.1.3g** and 4-bromotoluene was explored. The 4-nitropyrazole **5.1.3g** is an interesting substrate, since it has several directing groups and potentially activatable C-H bonds. During the optimization of reaction conditions a number of parameters were thoroughly examined. Some of representative trials are presented in Table 5.2.1.

Basing on previous results on Ni- and Pd-catalyzed direct C-H arylation of nitroimidazoles[236] and other systems,[235] the Pd/Cu catalytic system was considered to be the starting point in this study. Accordingly, a number of parameters were changed to optimize the Pd/Cu system catalyzed C-H arylation (Table 5.2.1, entries 2-10). Gratifyingly, it was found that the C(5)-H arylation product **5.2.1a** of model 4-nitropyrazole **5.1.3g** represents the only regioisomer which forms in the presence of Pd/Cu catalytic system. The best yield of C(5)-H arylation product **5.2.1a** (83%) was obtained in the presence of 4 equivalents of 4-bromotoluene using $PdCl_2(PPh_3)_2$ (5 mol%) as catalyst with stoichiometric amounts of CuI (1.2 equivalents) (Table 5.2.1, entry 5).

Exploration of other parameters showed that the reaction runs effectively in the presence of K_2CO_3/PivOH system using DMF as solvent at 120°C (Table 5.2.1, entry 5). The change of base (K_2CO_3) and/or replacement of PivOH by other carboxylic acids decreased the yields of C-H arylation. On the other hand, it was found that the reaction can be effectively performed in DMA (entry 9, 81%); however, the use of other solvents, such as toluene and dioxane, turned to be ineffective (entries 7, 8). In addition, the use of various ligands had no effect on overall outcome of the reaction. Perhaps unsurprisingly, these findings are quite similar to the observations on 4-nitroimidazoles (Chapter 4.2, Table 4.2.1).

Noteworthy, the use of salts of copper(I) or silver(I) in stoichiometric amounts was crucial. In these cases only one regioisomer was observed, namely the C(5)-H arylation product,

otherwise the conversion of pyrazole was reduced together with formation of some undesired side products. In particular, in the absence of CuI a product of C-H arylation at both pyrazole and phenyl rings **5.2.1'** (12%) was observed. Besides, it was possible to isolate another unusual product corresponding to the structure **5.2.1''** (30%), as a result of sequential C(5)-H arylation of the pyrazole and subsequent cleavage of the N-N bond (Table 5.2.1, entry 1). It is worth mentioning that this type of TM-induced N-N bond cleavage was previously observed by other authors on related systems.[257] This observation will be explored in our ongoing research program.



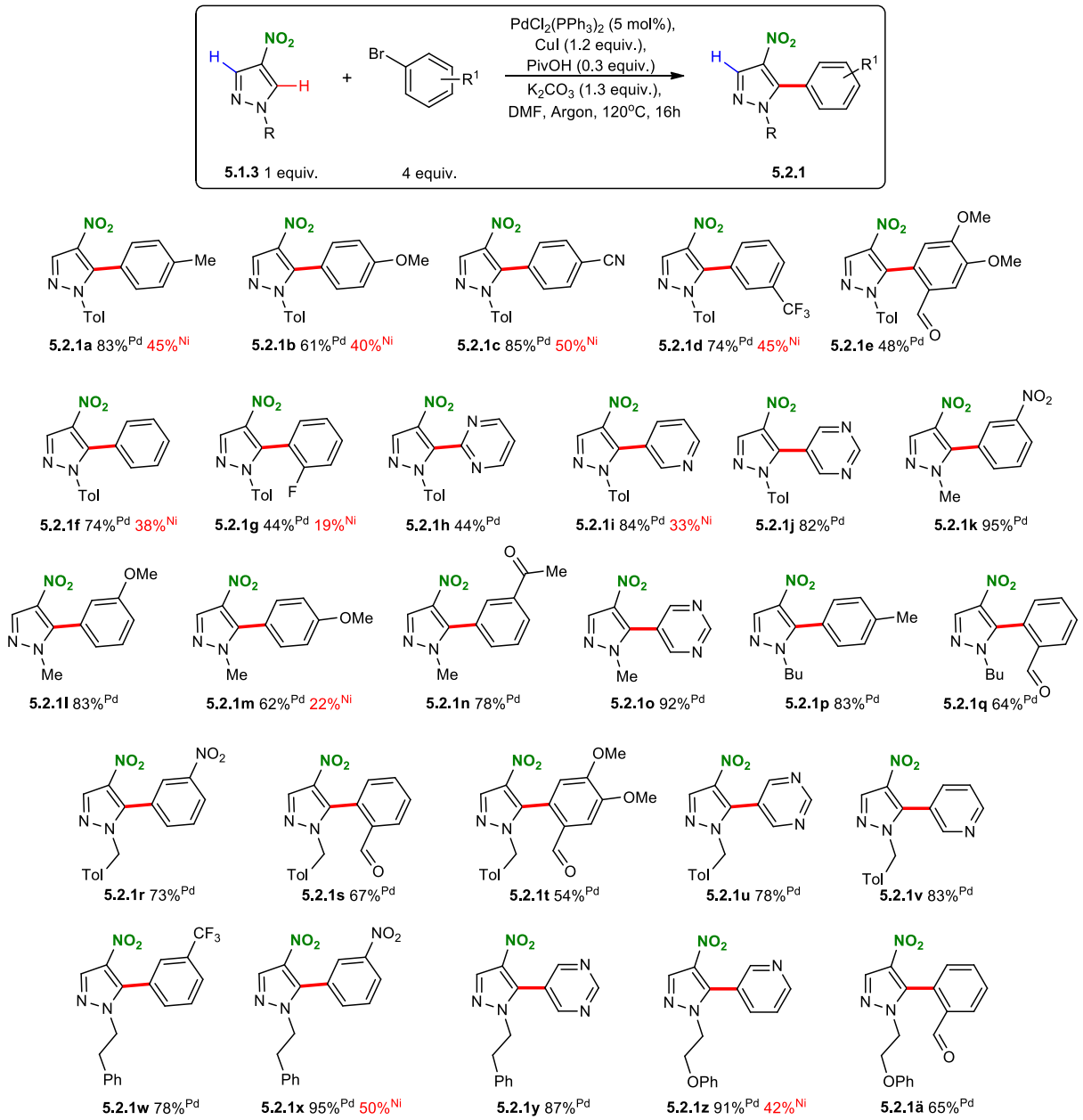
5.1.3g 1 equiv. 4 equiv. **5.2.1a** **5.2.1'** **5.2.1''**

Entry	Catalyst	Ligand	Additive 1	Additive 2	Base	Solvent	°C	% of **5.2.1a**[a]
1	$Pd(OAc)_2$	Cy_3PxHBF_3	-	PivOH	K_2CO_3	DMF	120	mixture
2	$Pd(OAc)_2$	-	Ag_2CO_3	PivOH	K_2CO_3	DMF	120	30
3	$Pd(OAc)_2$	-	CuI	PivOH	K_2CO_3	DMF	120	63
4	$Pd(OAc)_2$	-	CuI	PivOH	Cs_2CO_3	DMF	120	60
5	**$PdCl_2(PPh_3)_2$**	-	**CuI**	**PivOH**	**K_2CO_3**	**DMF**	**120**	**83**
6	$PdCl_2(PPh_3)_2$	-	CuI	Ph_3CCO_2H	K_2CO_3	DMF	120	66
7	$PdCl_2(PPh_3)_2$	-	CuI	PivOH	K_2CO_3	toluene	100	-
8	$PdCl_2(PPh_3)_2$	-	CuI	PivOH	K_2CO_3	dioxane	90	-
9	$PdCl_2(PPh_3)_2$	-	CuI	PivOH	K_2CO_3	DMA	120	81
10	$PdCl_2(PPh_3)_2$	-	CuI	-	K_2CO_3	DMF	120	5
11	$NiCl_2$[dppe]	-	CuI	PivOH	K_2CO_3	DMF	120	30
12	$NiCl_2$[dppp]	-	CuI	PivOH	K_2CO_3	DMF	120	34
13	**$NiCl_2(PPh_3)_2$**	-	**CuI**	**PivOH**	**K_2CO_3**	**DMF**	**120**	**45**
14	[Ru(*p*-cymene)Cl_2]$_2$	-	CuI	PivOH	K_2CO_3	DMF	120	-
15	[Rh(cod)Cl]$_2$	-	CuI	PivOH	K_2CO_3	DMF	120	-

Table 5.2.1. Optimization of reaction conditions; [a] isolated yields.

Next, the Ni/Cu system catalyzed C-H arylation of 4-nitropyrazole **5.1.3g** was explored (entries 11-13). In this regard numerous Ni-based catalysts, including Ni with different bidentate ligands, were thoroughly examined. Gratifyingly, the reaction catalyzed by $NiCl_2(PPh_3)_2$ (5 mol%) under otherwise identical conditions, provided the desired C(5)-H arylation product of 4-nitropyrazole **5.2.1a** in 45% yield (Table 5.2.1, entry 13). The other Ni-based catalysts were less effective; besides, the Ni-based catalysts proved to be inefficient in

the absence of CuI and, in general, were less effective than the Pd/Cu catalytic system (entry 5, 13). In this respect, a number of other transition metal based catalysts, including salts of Rh, Ru, Ir, Co, and Fe were studied; however, the results were quite unsatisfactory (entry 14, 15).



Scheme 5.2.1. Scope of C-H arylation of 4-nitropyrazoles.

With the optimal reaction conditions in hand, next, the scope and limitations of the methodology towards N-substituted 4-nitropyrazoles and aryl halide coupling partners were explored (Scheme 5.2.1). Gratifyingly, in this case as well it was possible to demonstrate that the TM-catalyzed direct C(5)-H arylation of various 4-nitropyrazoles works well for a broad

range of aryl bromides. Namely, the reaction of pyrazoles **5.1.3a-g** with diverse aryl bromides afforded corresponding arylated 4-nitropyrazoles **5.2.1a-ä** in good yields and excellent regioselectivity (Scheme 5.2.1). It is worth mentioning that under optimized conditions any other regioisomer and/or TM-induced N-N bond cleavage was not observed.

Notably, in this case as well a broad number of functional groups, such as F (**5.2.1g**), CF_3 (**5.2.1d**,**w**), CN (**5.2.1c**), OMe (**5.2.1b**,**e**,**l**,**m**,**t**), acyl (**5.2.1n**), NO_2 (**5.2.1k**,**r**,**x**) and aldehyde (**5.2.1e**,**q**,**s**,**t**,**ä**) as well as various heteroarenes (**5.2.1h**,**i**,**j**,**o**,**u**,**v**,**y**,**z**) were perfectly tolerated under the optimal reaction conditions. Expectedly, under optimized conditions the functional group tolerance turned out to be equally actual for a wide range of N-substituted 4-nitropyrazoles (Scheme 5.2.1).

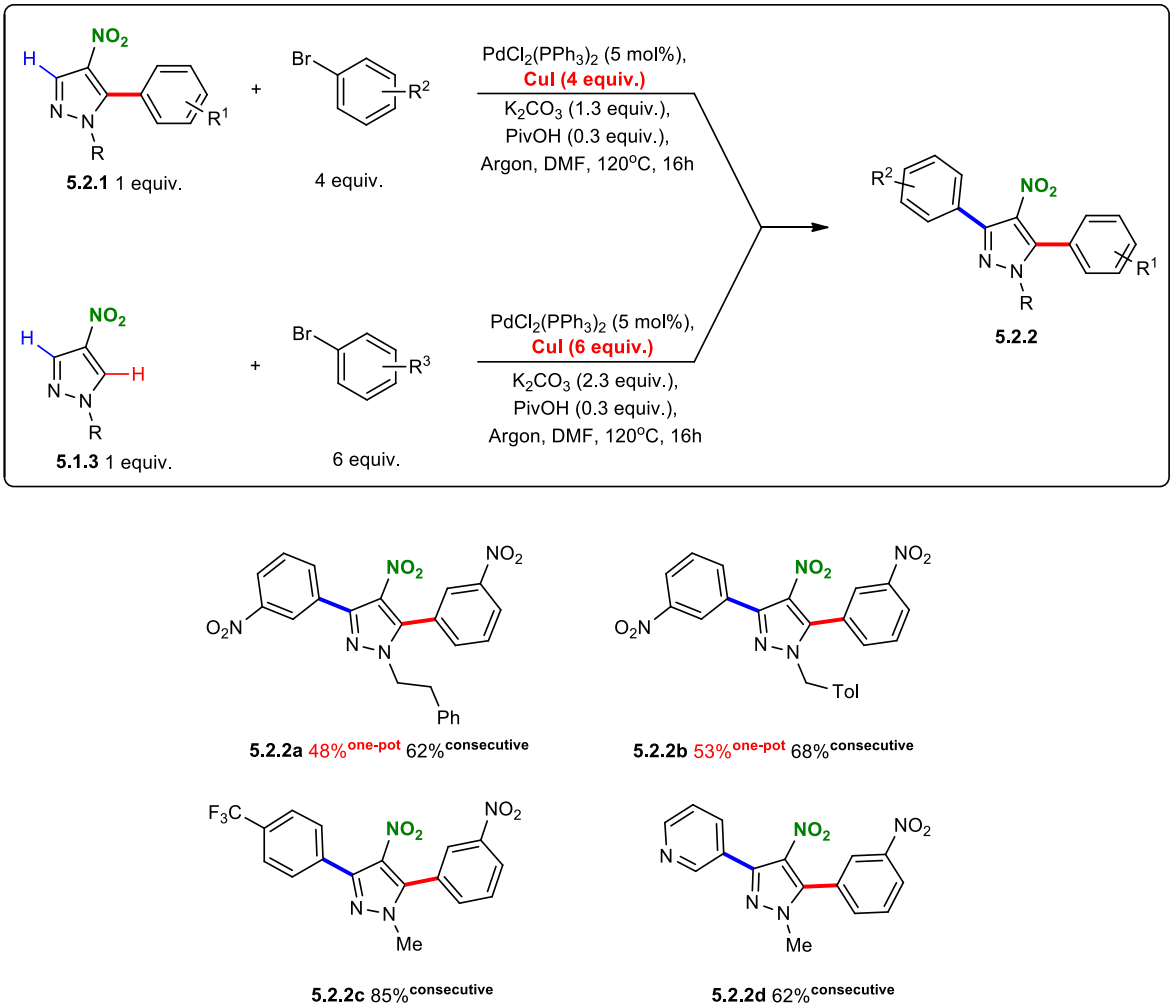
In general, under the applied reaction conditions aryl bromides proved to be the most successful coupling partners, while corresponding aryl chlorides were unreactive. In the case of aryl iodide coupling partners, an extensive formation of symmetrical biaryls was observed *via* homocoupling of aryl iodides induced by CuI:[53] this demanded the large excess of the aryl iodides, and the overall yields were visibly lower than with aryl bromides. Similarly, for electron-deficient aryl bromides as well, some amount of corresponding symmetrical biaryls was observed (see also Chapter 2.1, Scheme 2.1.13).[50-53]

Due to this side process, in order to get good yields of target arylated pyrazoles and full conversion of the reactant, 4 equivalents of corresponding aryl bromides were required. These observations were similar to those observed on nitroimidazoles (Chapter 4.2). In addition, it is worth to note that the Pd-catalyzed C-H arylation of 4-nitropyrazoles can be performed on a gram scale; for instance, compound **5.2.1n** was successfully prepared in 10 gram scale with 78% yield. It should be noted that unlike N-substituted nitroimidazoles for corresponding 4-nitropyrazoles the oxidant (Ag_2CO_3) induced intramolecular dehydrogenative cross-coupling reaction did not work (Chapter 4.2, Scheme 4.2.2), even though the reaction was performed in the absence of aryl halide coupling partner. In this respect 4-nitropyrazoles appeared to be less reactive than corresponding nitroimidazoles.

Subsequently, the scope and limitations of the Ni-catalyzed C-H arylation reaction of N-substituted 4-nitropyrazoles was explored. Gratifyingly, for 4-nitropyrazoles as well it was found that the reaction has general character and high functional group tolerance, allowing an efficient introduction of an aryl group into the pyrazole ring in moderate yields (Scheme 5.2.1, **5.2.1a**,**b**,**c**,**d**,**f**,**g**,**i**,**m**,**z**).

Inspired by the successful results on regioselective C(5)-H arylation of 4-nitropyrazoles, next the TM-catalyzed C(3)-H arylation of C(5)-H arylation product 4-nitropyrazoles **5.2.1** was

considered as an excellent extension of scope of the work (Scheme 5.2.2). For this purpose a number of reaction conditions were designed and thoroughly examined.



5.2.2a 48%$^{\text{one-pot}}$ 62%$^{\text{consecutive}}$

5.2.2b 53%$^{\text{one-pot}}$ 68%$^{\text{consecutive}}$

5.2.2c 85%$^{\text{consecutive}}$

5.2.2d 62%$^{\text{consecutive}}$

Scheme 5.2.2. TM-catalyzed direct C(3)-H arylation of 5-aryl-4-nitropyrazoles.

In particular, besides Ni- and Pd-based catalysts a number of other TM-based catalysts were examined, including salts of Ag, Fe, Ru, Rh, Ir, Co, and Pt. In addition, an attempt was made to switch the regioselectivity by variation of ligands. To this end, the influence of different phosphine-based ligands on TM-catalyzed C(3)-H arylation of 4-nitropyrazoles was examined. Trials included monodentate phosphine ligands like SPhos, XPhos, PCy_3, P(*t*Bu)$_3$, (2-biphenyl)di-1-adamantylphosphine, *rac*-2-(di-*tert*-butylphosphino)-1,1′-binaphthyl, $(C_6H_5O)_3P$, tris(diethylamino)phosphine, $(C_6F_5)_3P$, $(C_6F_5)_2PhP$; as well as bidentate ligands including dppm, dppe, dppp, dppf, BINAP, DIOP, XantPhos, DPEPhos, 1,2-bis(diphenylphosphino)benzene and 1,2-bis(dicyclohexylphosphino)ethane. Nevertheless, for all cases in spite of partial conversion of starting 5-aryl-4-nitropyrazoles **5.2.1**, only an inseparable mixture of products was observed.

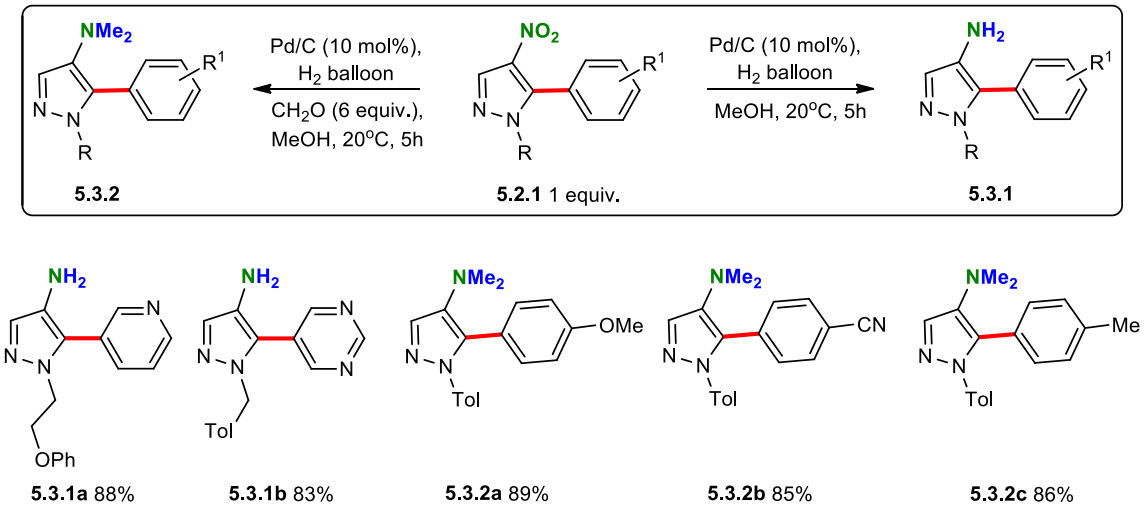
Being motivated by recent works of Baran and coworkers,[149f,258] on the next stage of the study numerous trials were made to overcome this problem applying well-defined Minisci reaction.[259] Therefore, under various conditions the starting 4-nitropyrazoles were treated with different aromatic carboxylic acids and boronic acids. However, in this case as well, all attempts to perform the desired arylation by Minisci reaction experienced a failure; in most of the cases were observed inseparable mixtures of undefined nature.

Fortunately, after some further examinations it was found that the excess of CuI can initiate the desired C(3)-H arylation. Thus, it was possible to demonstrate that the starting N-substituted 4-nitropyrazoles **5.1.3** can be successfully arylated at both possible positions in one step using 6 equivalents of CuI (instead of 1.2 equivalents), which leads to the formation of 3,5-diaryl-4-nitropyrazoles **5.2.2a**,**b** in good yields (Scheme 5.2.2).

Alternatively, the preparation of unsymmetrically arylated pyrazoles **5.2.2c**,**d** was possible utilising the reaction of C(5)-H arylation product 4-nitropyrazole **5.2.1k** with corresponding aryl bromides in the presence of 4 equivalents of CuI. Noteworthy, the synthesis of symmetrically arylated pyrazoles can be performed in one-pot; nonetheless, the consecutive procedure was more effective (Scheme 5.2.2).

5.3. Exploration of Further Transformations of Nitro Group

After the development of efficient and regioselective Ni- and Pd-catalyzed direct C-H arylation methodologies for both feasible positions of 4-nitropyrazoles, next the chemical versatility of nitro group was explored. Accordingly, in this part of the work the simple reduction of nitro group was tested first (Scheme 5.3.1).

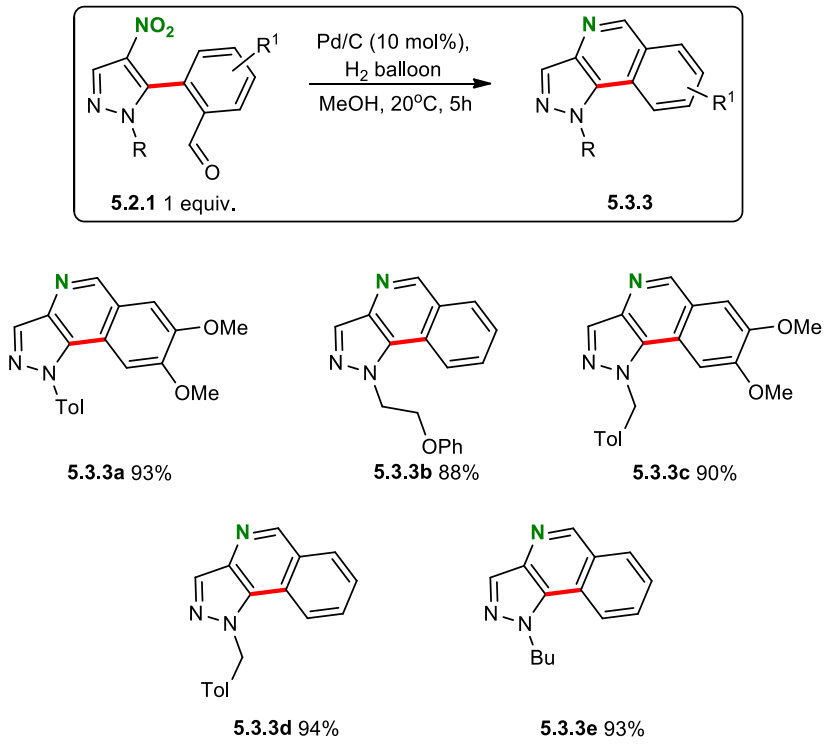


Scheme 5.3.1. Reduction of arylated 4-nitropyrazoles.

It was found that unlike corresponding arylated nitroimidazoles (Chapter 4.4, Scheme 4.4.1), the Pd-catalyzed reduction of arylated 4-nitropyrazoles **5.2.1u**,**z** represents a useful approach for the synthesis of arylated 4-aminopyrazoles **5.3.1a**,**b** which are difficult to access by other methods.

The reaction was carried out using Pd/C as catalyst, under hydrogen atmosphere, in distilled technical MeOH at ambient temperatures for 5 hours. In case of 4-nitropyrazoles the overall outcome of the reaction was well predictable; namely, two examples of arylated 4-aminopyrazole were isolated in 83% and 88% yields respectively (Scheme 5.3.1).

Subsequently, when the Pd-catalyzed reduction of arylated 4-nitropyrazoles **5.2.1a**,**b**,**c** was performed in the presence of an excess of formalin (37% solution in the water, stabilized by MeOH), the anticipated N,N-dimethylamines **5.3.2a-c** were obtained in good yields (Scheme 5.3.1).



Scheme 5.3.2. Preparation of pyrazolo[4,3-*c*]isoquinolines.

Additionally, in the course of further examinations it was possible to show that the Pd-catalyzed reduction of C-H arylation products, which bear an *ortho* carbonyl functional group **5.2.1e**,**q**,**s**,**t**,**ä**, leads to the formation of pyrazolo[4,3-*c*]isoquinoline system (Scheme 5.3.2). In this case probably *in situ* generated reduction product amine undergoes a subsequent intramolecular cyclocondensation with carbonyl group giving rise to the aromatic isoquinoline system. The reaction has general character for arylated 4-nitropyrazoles which

contain an *ortho* carbonyl group at phenyl ring. Namely, the Pd-catalyzed reduction of suitable 4-nitropyrazoles in MeOH, under hydrogen atmosphere at ambient temperature leads to the formation of corresponding pyrazolo[4,3-*c*]isoquinolines **5.3.3a-e** in 88-94% yields (Scheme 5.3.2).

Noteworthy, the reduction product pyrazolo[4,3-*c*]isoquinolines **5.3.3** demonstrated significant fluorescent properties. As depicted in the Figure 5.3.1, at first were considered the solutions of pyrazolo[4,3-*c*]isoquinolines in chloroform, then the solutions of most fluorescent pyrazolo[4,3-*c*]isoquinoline **5.3.3a** in different solvents (2 mg from each pyrazolo[4,3-*c*]isoquinoline was dissolved in 1 mL of corresponding solvent). Empirical considerations indicated that compound **5.3.3a** demonstrates the strongest fluorescent properties in acidic solutions which may become an object of further physicochemical investigations (Figure 5.3.1).

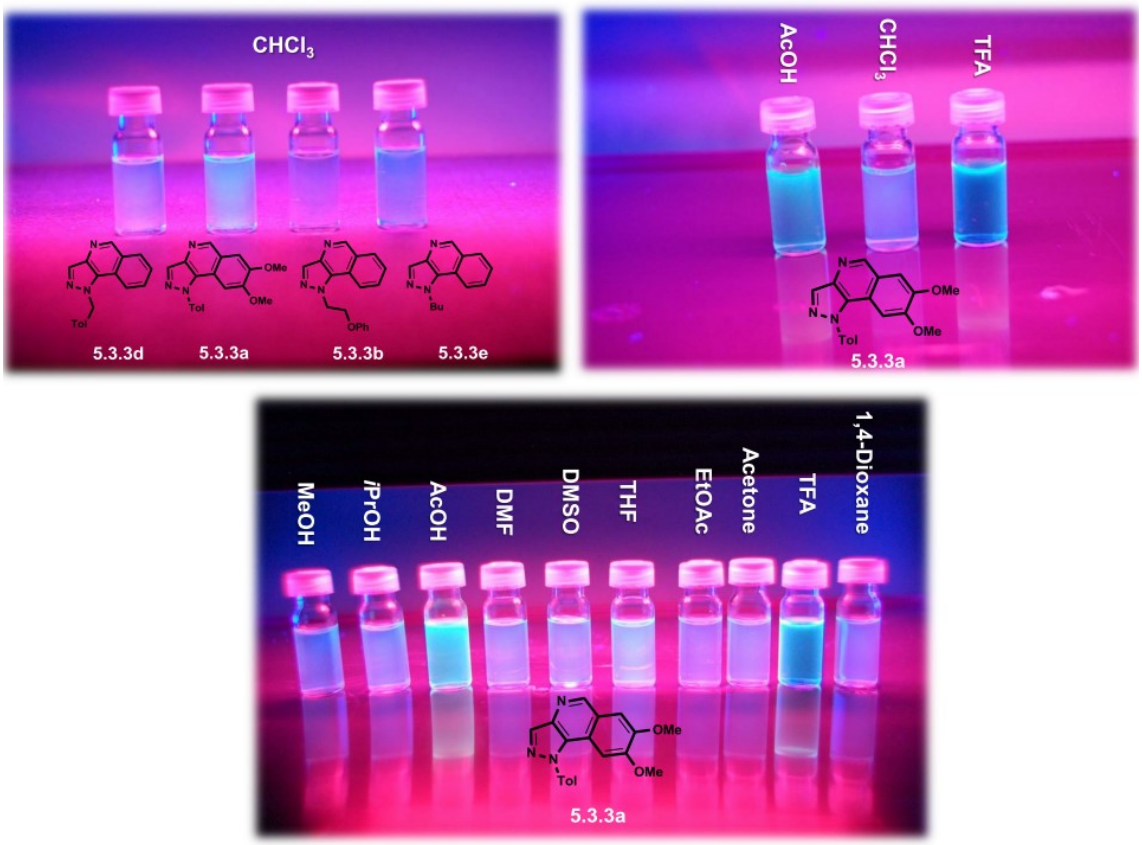
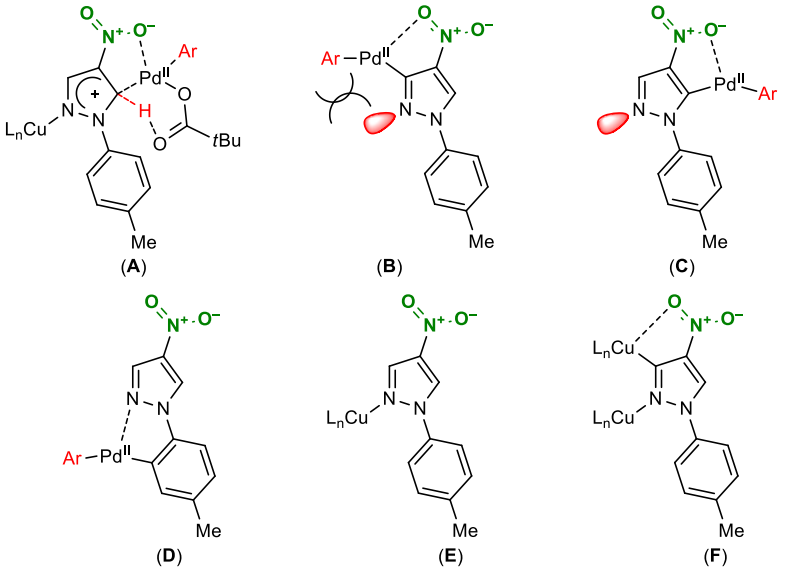


Figure 5.3.1. Fluorescent properties of pyrazolo[4,3-*c*]isoquinolines **5.3.3a**,**b**,**d**,**e**.

5.4. Possible Mechanisms of C-H Arylation and Further Experiments

The regioselectivity of Pd-catalyzed direct C(5)-H arylation of 4-nitropyrazoles can be explained by an assumption that the catalyst coordinated by the nitro group initiates the C(5)-

H bond cleavage *via* concerted metalation-deprotonation (CMD), as illustrated in Scheme 5.4.1 (**A**) (similar considerations are equally applicable for Ni). This hypothesis is strongly supported by numerous theoretical calculations and practical observations.[130,131,133-136,197] Based on the explanation of the reduced reactivity of C(4)-H bond of imidazoles towards Pd-catalyzed C-H arylation,[251] the low reactivity of C(3)-H bond of 4-nitropyrazoles can be the result of electronic repulsion between the electron lone pair on the N-(2) atom of pyrazole and the C-Pd bond (Scheme 5.4.1, **B**). In this regard, intermediate (**C**) should be more favourable.

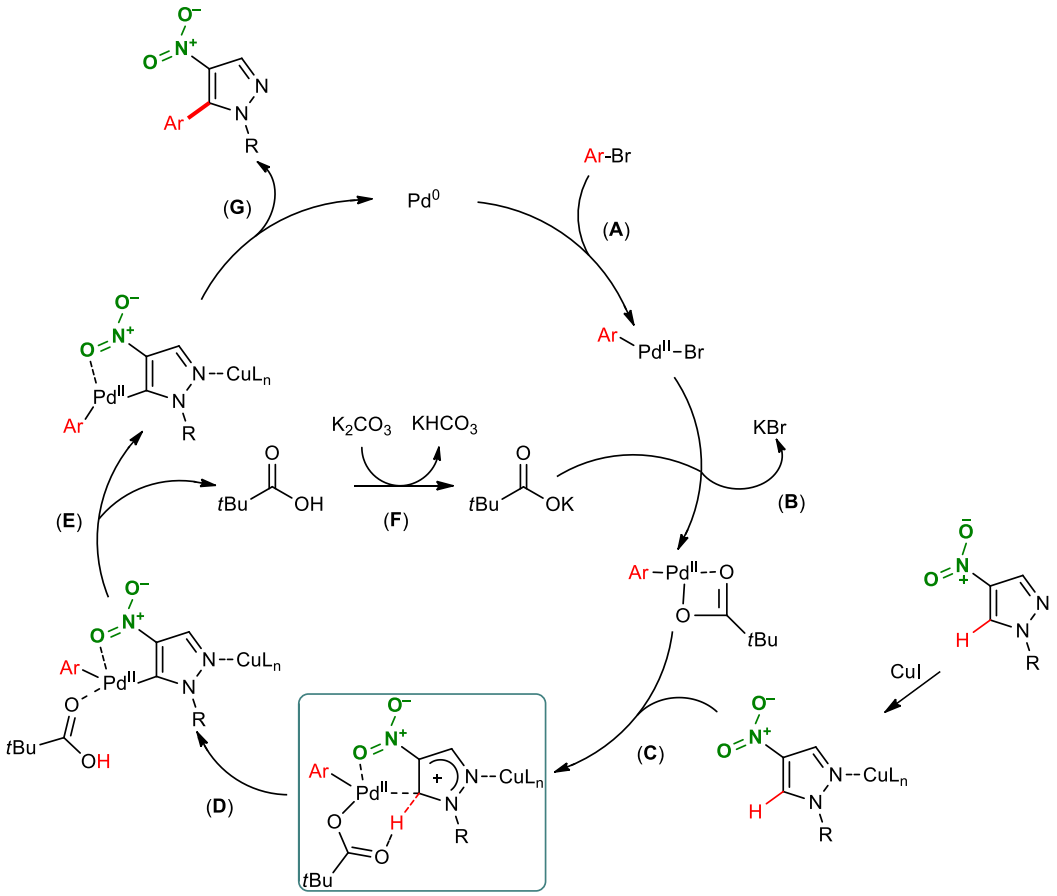


Scheme 5.4.1. Proposed mechanistic explanation of the regioselectivity.

On the other hand, 1-phenyl-1*H*-pyrazoles have a tendency to form thermodynamically stable five-membered metallacycles *via* coordination of the catalyst by N-(2) atom of pyrazole and subsequent cyclometalation (**D**).[167,168] This path may result in direct C-H functionalization of phenyl ring attached to the N-(1) atom of model pyrazole.[153] In this regard, we assume that the high levels of reactivity of Pd(Ni)/Cu catalytic system towards selective C(5)-H arylation could be a result of coordination of the N-(2) atom of pyrazole ring to Cu(I) that would prevent the N-bound coordination mode of the pyrazole substrates with Pd or Ni (**A**, **D**, **E**). This assumption is supported by the obtained observations during the course of optimization of reaction conditions. Namely, in the absence of CuI we observed a product corresponding to C-H arylation at both pyrazole and phenyl rings **5.2.1'** (Table 5.2.1, entry 1).

Based on these considerations we assume that the mechanism of the reaction is very much similar to the mechanism for C(5)-H arylation of 4-nitroimidazoles (Chapter 4.5, Scheme 4.5.2). That is to say, the catalytic cycle starts with oxidative addition of aryl bromide to the catalyst Pd(0) delivering Ar-Pd(II)-Br complex (Scheme 5.4.2, **A**, similar considerations are

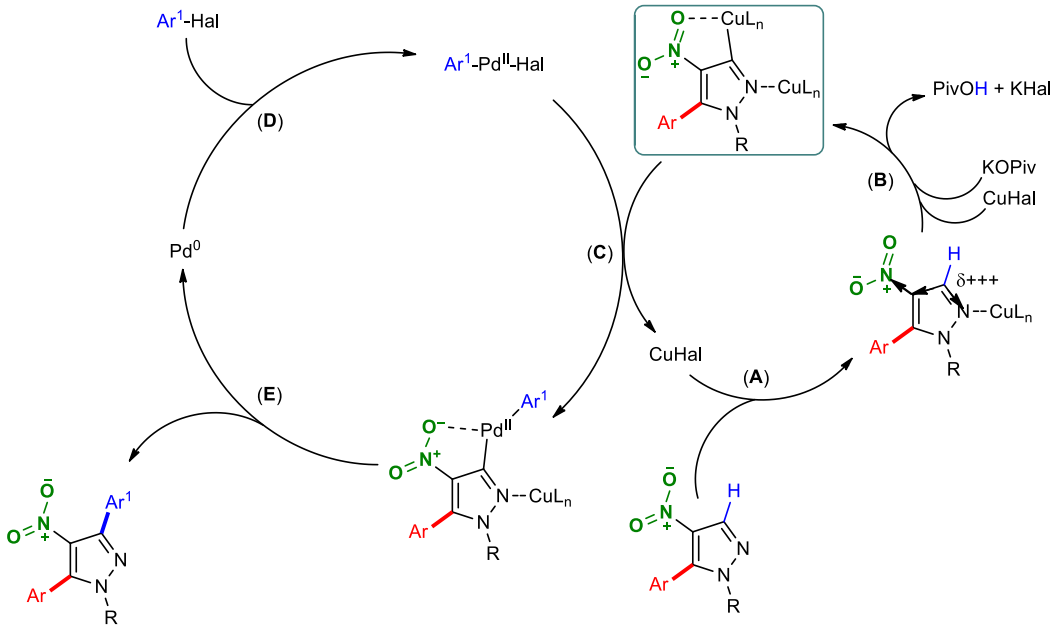
equally true for Ni). In the next step of the process the product of oxidative addition undergoes a ligand exchange reaction with potassium pivalate which is more soluble in the solvent than K_2CO_3 (**B**). Subsequently, the Ar-Pd(II)-OPiv species first coordinates to the nitro group of pyrazole which is followed by a carboxylate-assisted C-H bond cleavage *via* concerted metalation-deprotonation (**C**, **D**). This process is accompanied by regeneration of PivOH and PivOK (**E**, **F**). Finally, the reductive elimination of catalyst Pd(0) leads to the formation of desired arylated 4-nitropyrazole and regeneration of components of catalytic cycle (Scheme 5.4.2, **G**).



Scheme 5.4.2. Possible mechanism of Pd-catalyzed C(5)-H arylation of 4-nitropyrazoles.

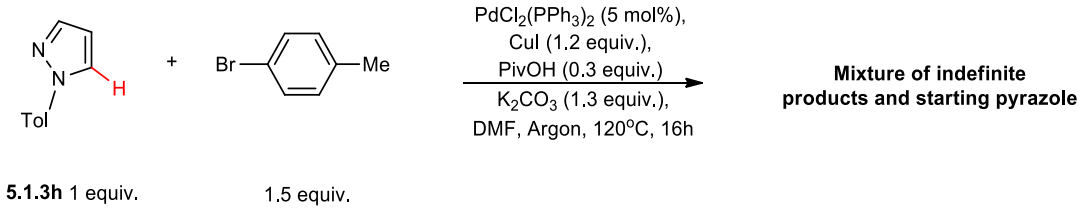
Concerning the Pd-catalyzed C(3)-H arylation of 4-nitropyrazoles, we assume that a cooperative action of Pd and Cu may enable the direct C-H activation *via* appropriate cuprate of pyrazole (Scheme 5.4.1, **F**). Noteworthy, Cu(I) salts alone can initiate the direct C-H arylation of different heteroarenes;[200q,202f,252] nevertheless, in the absence of Pd-catalyst the 5-aryl-4-nitropyrazoles were fully recovered without any conversion. In this respect, recently made DFT calculations by Fu and coworkers, regarding the impact of formation of the Ar-Cu species on concerted C-H activation, fully supports the assumption of cooperative action of

Pd and Cu.[252g] Accordingly, the coordination of Cu to the N-(2) atom of pyrazole ring may increase the C(3)-H acidity due to the enhanced inductive effects (Scheme 5.4.3, **A**). This may be followed by the base induced cupration of pyrazole ring (**B**). Further, the pyrazole can be transferred from Ar-Cu species to the electrophilic Ar^1-Pd(II)-Hal species *via* transmetallation (**D**, **C**). The final step of catalytic cycle constitutes the reductive elimination of arylated 4-nitropyrazole with regeneration of catalytically active Pd(0) complex (**E**). Noteworthy, the final steps of the process are very much similar to the Pd-catalyzed cross-coupling reaction of arylcopper(I) reagents with aryl halides developed by Nilsson and coworkers (Chapter 2.1, Scheme 2.1.16, M = Cu).[109a,110]



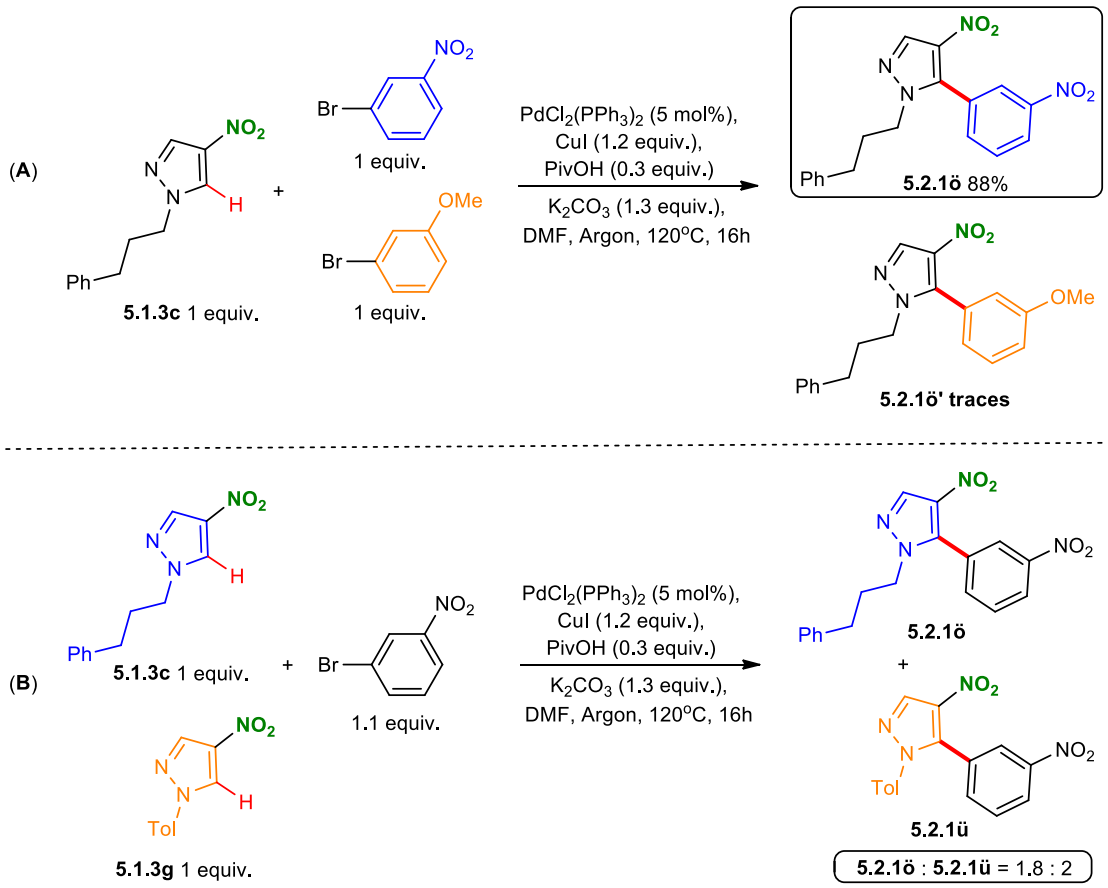
Scheme 5.4.3. Possible mechanism of C(3)-H arylation of 5-aryl-4-nitropyrazoles.

With the aim to obtain more insights into the directing effect of nitro group on TM-catalyzed C-H arylation of 4-nitropyrazoles, the model pyrazole **5.1.3h** was synthesized applying the Cu-induced Ullmann arylation of simple unprotected 1*H*-pyrazole.[237k] Subsequently, the pyrazole **5.1.3h** was subjected to the optimal Pd-catalyzed reaction conditions (Scheme 5.4.4). In this respect, perhaps unsurprisingly, an inseparable mixture of products was observed along with some quantities of starting pyrazole; all attempts to isolate and characterize any product of the reaction were unsuccessful. Noteworthy, the recent works of Doucet and coworkers on Pd-catalyzed direct C-H arylation of unfunctionalized N-substituted pyrazoles revealed on similar reactivities of C(4)-H and C(5)-H bonds of pyrazoles, whereas the C(3)-H bond usually remained intact.[140e,144b,d,h] These results along with our findings clearly show the crucial effect of nitro group on the selectivity and efficiency of the reaction.



Scheme 5.4.4. Exploration of directing ability of nitro group.

On the next stage of the work, in order to get more insights into the reaction pattern, under optimized reaction conditions, the model 4-nitropyrazole **5.1.3c** was treated with two electronically different aryl bromides, namely with 1-bromo-3-methoxybenzene and 1-bromo-3-nitrobenzene (Scheme 5.4.5, **A**). The aim of the competitive experiment was the identification of comparable reactivities of electronically different aryl bromides in Pd-catalyzed direct C-H arylation of 4-nitropyrazoles.



Scheme 5.4.5. The competitive experiments between 4-nitropyrazoles and aryl bromides.

The GC-MS studies of the reaction mixture indicated the preference of electron-deficient aryl bromides over aryl bromides with electron-donating groups (Scheme 5.4.5, **A**). In particular, it was possible to detect the product **5.2.1ö** corresponding to C-H arylation by 1-bromo-3-

nitrobenzene in 88% yield (GC-MS yield). In addition, the GC-MS showed only traces of the product corresponding to C-H arylation by 1-bromo-3-methoxybenzene **5.2.1ö'**.

The related competitive experiment between various 4-nitropyrazoles (**5.1.3c**, **5.1.3g**) and electron-deficient 1-bromo-3-nitrobenzene revealed that the N-(1) substituent of pyrazole ring has no influence on the outcome of the reaction (Scheme 5.4.5, **B**). In particular, a mixture of both arylated 4-nitropyrazoles was observed with almost similar quantities (GC-MS studies).

5.5. Structure Identification

The structures of synthesized compounds were mainly established by NMR, IR spectroscopy and mass spectrometry. Noteworthy, in all arylated 4-nitropyrazoles the aryl groups do not possess bulky functional groups near pyrazole ring which indicates on free rotation around newly formed Ar-Ar C-C bond and absence of atropisomers (at room temperature).[1e,f,253]

In the ^{1}H NMR spectra of starting N-substituted 4-nitropyrazoles **5.1.3** the singlets of C*H* bonds of pyrazole ring appears at 8.03-8.50 ppm and 8.71-9.56 ppm (DMSO-d_6). In the products of C-H arylation **5.2.1**-**5.2.2** at least one of singlets disappear; instead of this, the number of aromatic signals increases (Figure 5.5.1, 5.5.2). In all C(5)-H arylation products **5.2.1a-ä**, the C(3)-H bond appears as a singlet at 8.17-8.40 ppm ($CDCl_3$) (Figure 5.5.1).

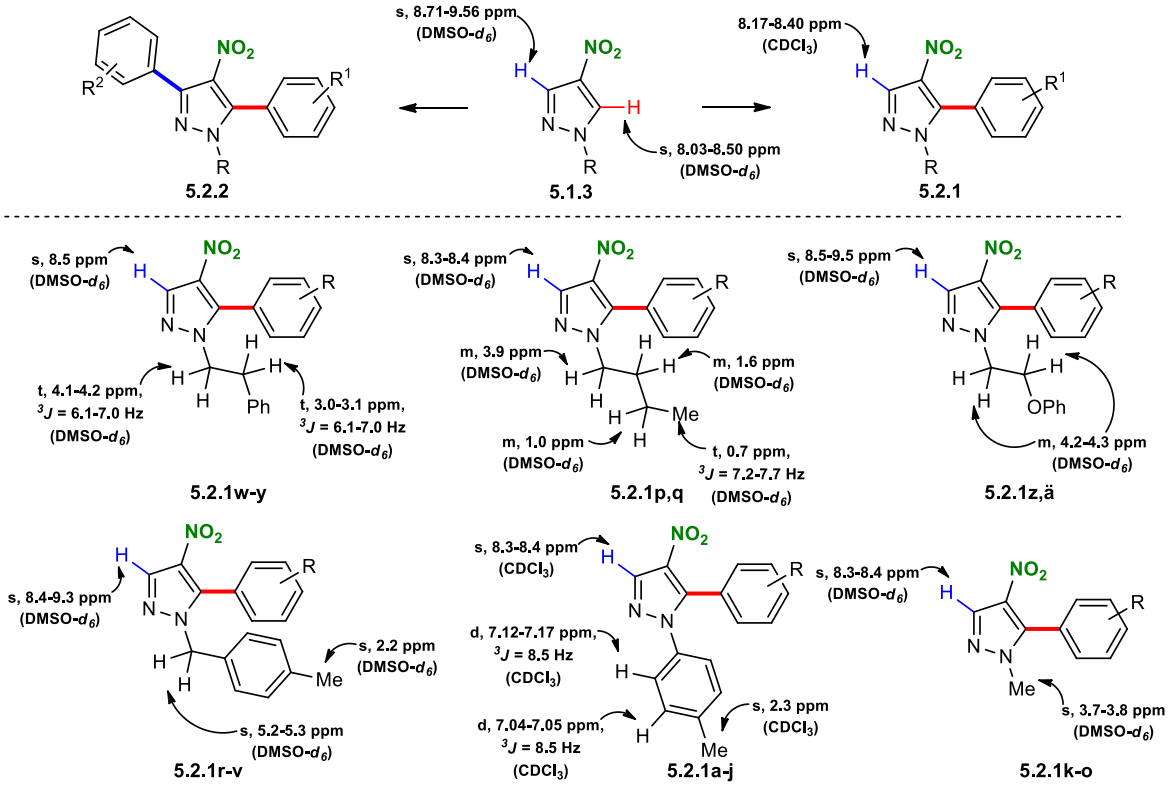


Figure 5.5.1. Observations from NMR experiments.

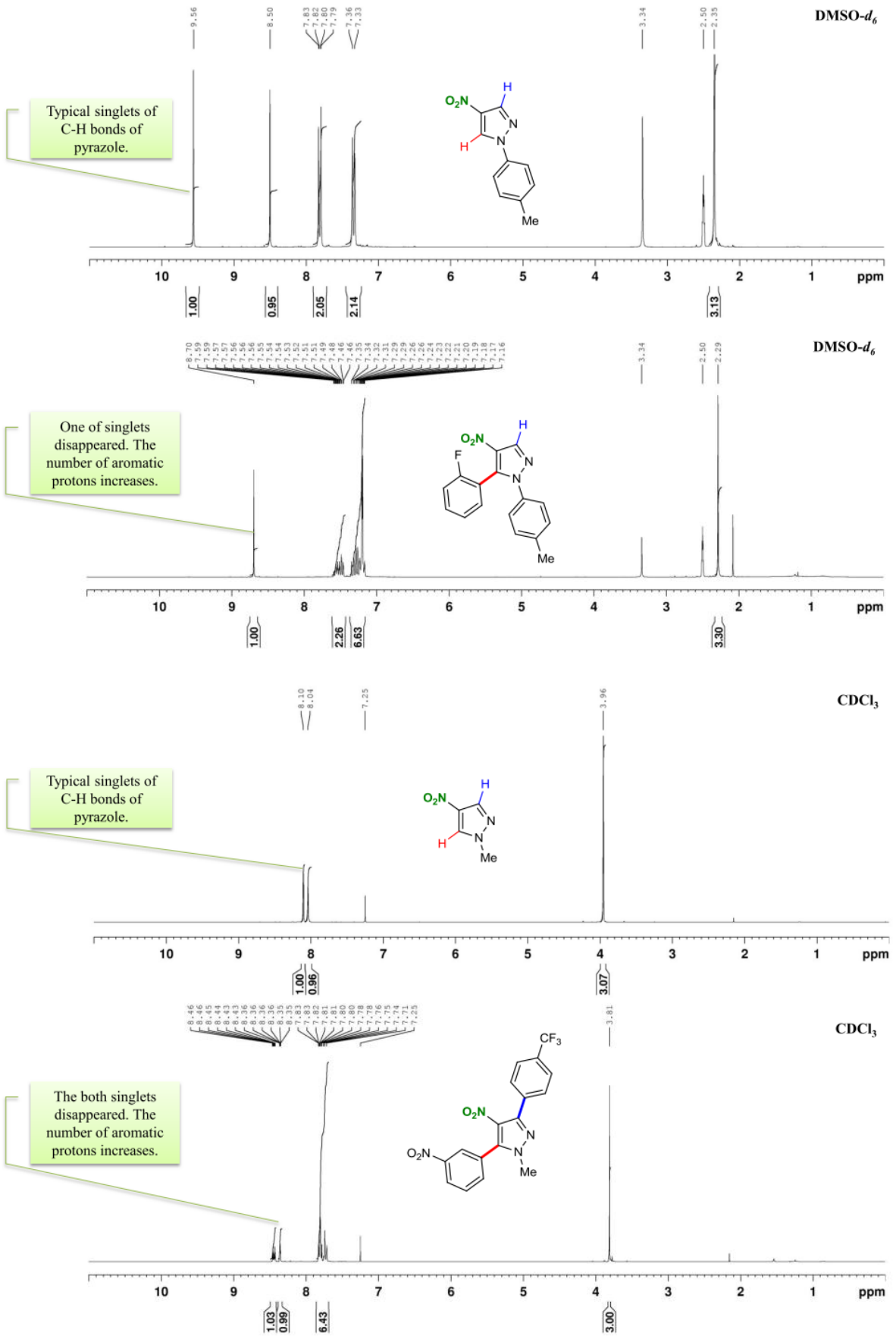
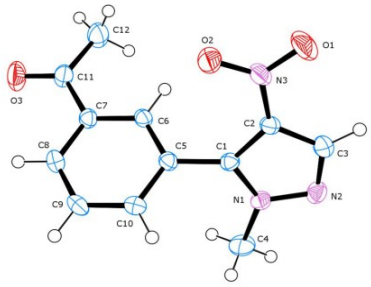
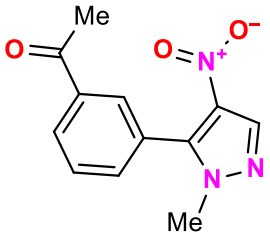


Figure 5.5.2. Comparison of ^{1}H NMR spectra of starting 4-nitropyrazoles **5.1.3f**,**g** and corresponding C-H arylation products **5.2.1g**, **5.2.2c**.

The typical signals of C*H*$_2$ groups of N-alkyl substituents appears at range 0.7-5.3 ppm. In particular, the triplets of C*H*$_2$ groups of phenethyl functionality were detected at 3.0-3.1 ppm (C*H*$_2$Ph) and 4.1-4.2 ppm (NC*H*$_2$) (DMSO-d_6) with a coupling constant ^3J = 6.1-7.0 Hz (Figure 5.5.1, **5.2.1w-y**). The *Me* and C*H*$_2$ groups of *n*-butyl functionality appear at 0.7 ppm (NCH$_2$CH$_2$CH$_2$C*H*$_3$), 1.0 ppm (NCH$_2$CH$_2$C*H*$_2$CH$_3$), 1.6 ppm (NCH$_2$C*H*$_2$CH$_2$CH$_3$) and 3.9 ppm (NC*H*$_2$CH$_2$CH$_2$CH$_3$) respectively (DMSO-d_6) (Figure 5.5.1, **5.2.1p**,**q**). The multiplets of phenoxyethyl C*H*$_2$ groups were seen at 4.2-4.3 ppm (DMSO-d_6) (Figure 5.5.1, **5.2.1z**,**ä**). The singlet of *Me* group of *p*-methylbenzyl functionality along with the singlet of benzyl C*H*$_2$ group appears at 2.2 ppm and 5.2-5.3 ppm respectively (DMSO-d_6) (Figure 5.5.1, **5.2.1r-v**). Accordingly, the singlet of *Me* group of *N*-*p*-tolyl functionality was detected at 2.3 ppm ($CDCl_3$); the aromatic protons of *N*-*p*-tolyl functionality appear at 7.0-7.2 ppm as doublets with a coupling constant ^3J = 8.5 Hz ($CDCl_3$) (Figure 5.5.1, **5.2.1a-j**). The singlet of *Me* group of N-Me functionality was seen at 3.7-3.8 ppm (DMSO-d_6) (Figure 5.5.1, **5.2.1k-o**). The broad singlet of N*H*$_2$ group of reduction products **5.3.1** was detected at 2.9-3.1 ppm ($CDCl_3$). The singlet of N*Me*$_2$ group of reduction products **5.3.2** appears at 2.5 ppm ($CDCl_3$). Additionally, the singlet of C(5)-H bond of pyridine ring of reduction product pyrazolo[4,3-*c*]isoquinolines **5.3.3** was detected at range 8.9-9.1 ppm (DMSO-d_6). Besides, in the ^{13}C NMR spectra of synthesized compounds the *Me* and *C*H$_2$ groups as well as typical quartets of *C*F$_3$ group (^1J = 262-272 Hz, $CDCl_3$) were observed. In the ^{19}F NMR spectra C*F*$_3$ group appears from -62.8 to -62.9 ppm ($CDCl_3$).

Furthermore, in the IR spectra of arylated 4-nitropyrazoles the N-O stretching vibrations of *NO*$_2$ group (medium intensity) were observed at 1480-1554 cm^{-1} (asymmetrical) and 1320-1358 cm^{-1} (symmetrical). On the other hand, in the IR spectra of reduction products the typical peaks of stretching vibrations of *NO*$_2$ group disappeared; instead of these, the two N-H stretches (2920-3321 cm^{-1}) of amino group along with C-N stretch (1238 cm^{-1}) were observed.

Compound	Crystal structure	Structure
5.2.1n		

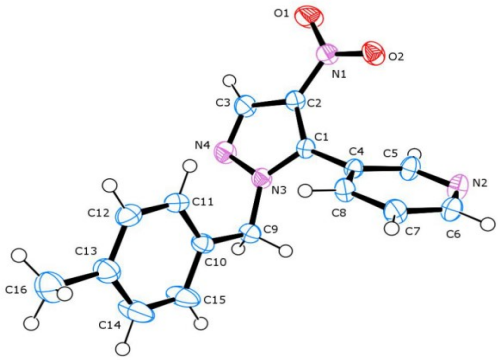
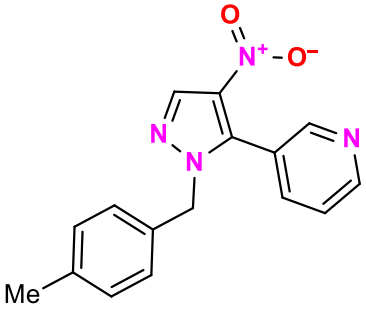
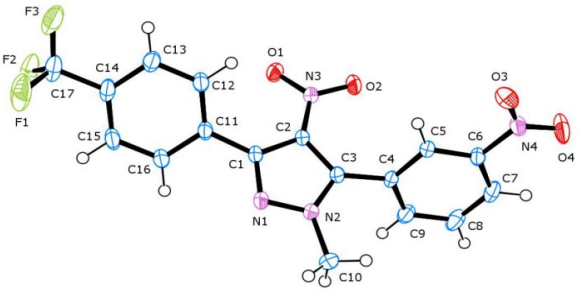
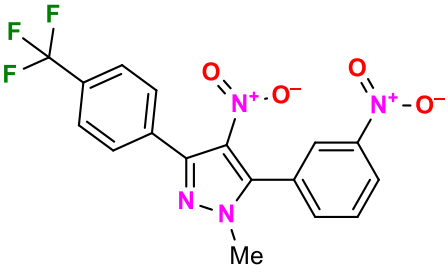
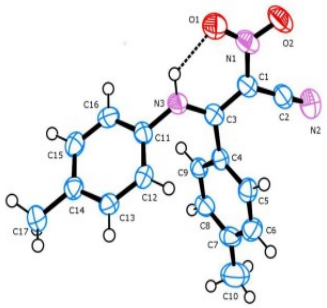
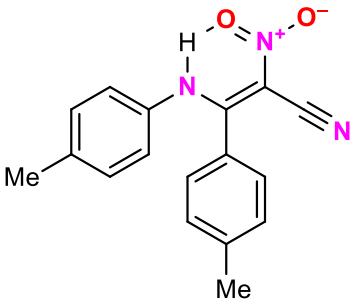
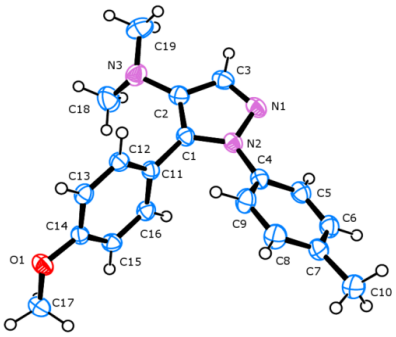
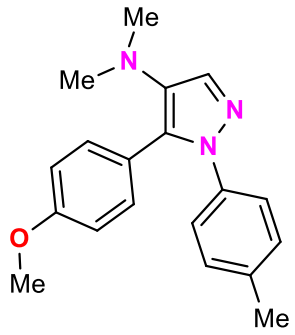
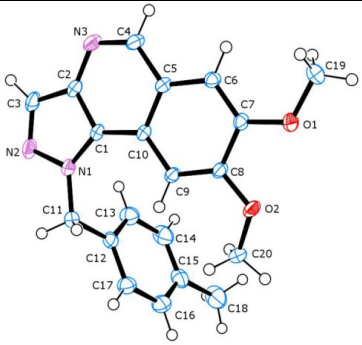
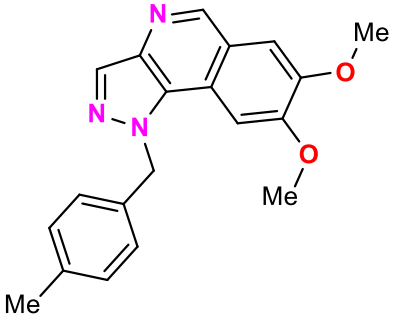
Compound	Crystal structure	Structure
5.2.1v		
5.2.2c		
5.2.1''		
5.3.1c		
5.3.2c		

Table 5.5.1. Crystal structures of compounds **5.2.1n**,**v**, **5.2.1''**, **5.2.2c**, **5.3.1c** and **5.3.2c**.

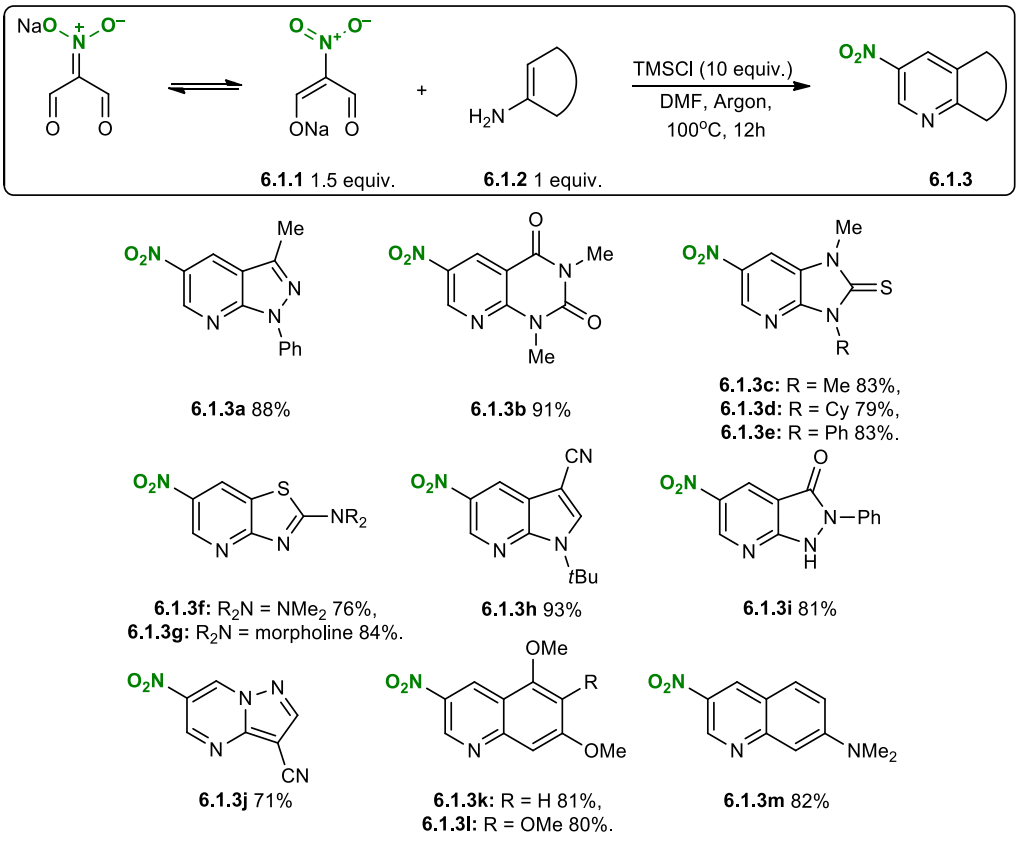
The structures of compounds **5.2.1n**,**v**, **5.2.1''**, **5.2.2c**, **5.3.1c** and **5.3.2c** were confirmed by X-ray single crystal analyses (Table 5.5.1). Thus, the regioselectivity of TM-catalyzed direct C-H arylation was independently proved by X-ray analysis.

6. Direct C-H Arylation of Fused 3-Nitropyridines

6.1. Preparation of Starting Fused 3-Nitropyridines

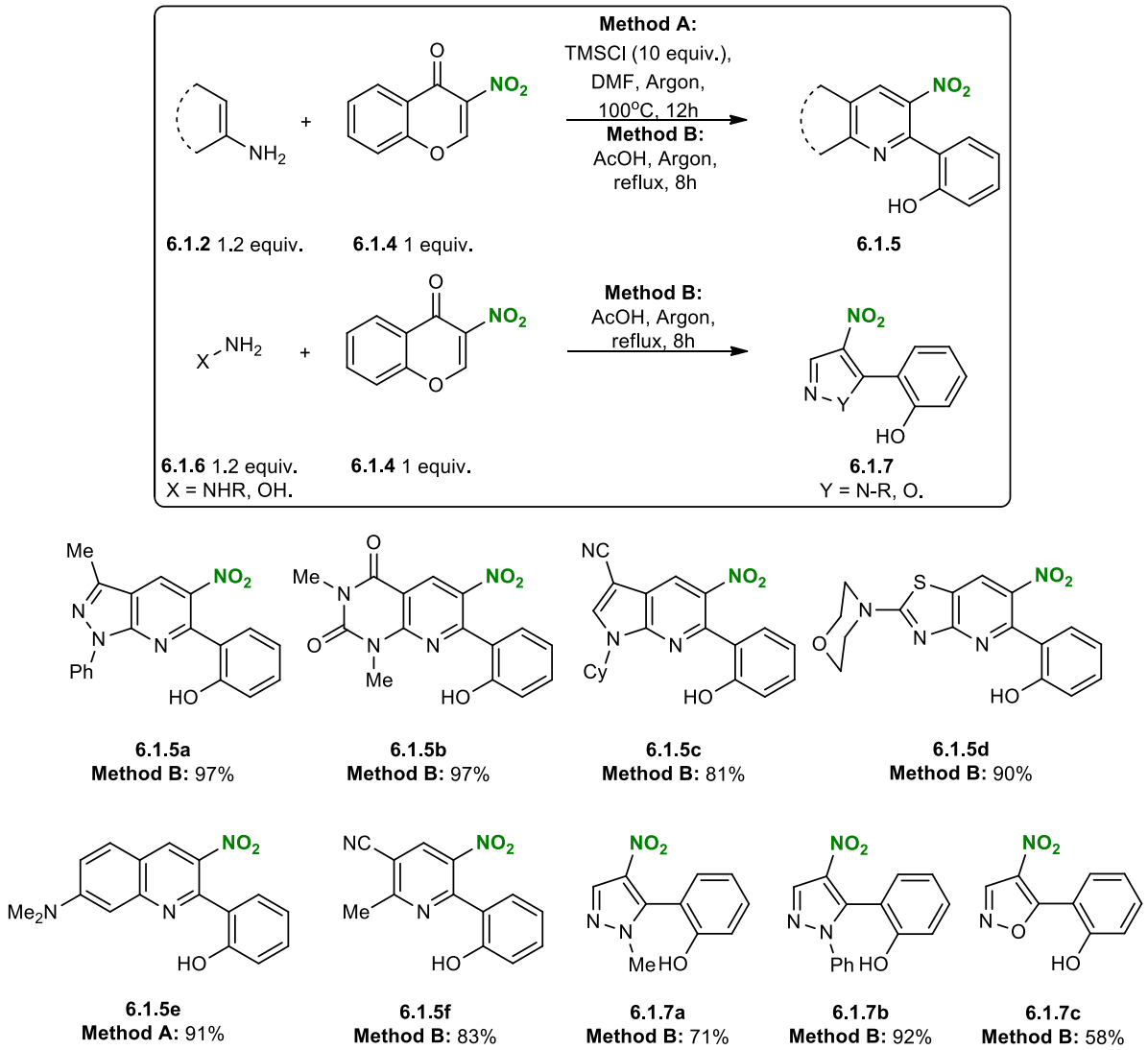
Inspired by previous results on Pd(Ni)-catalyzed direct C-H arylation of 4-nitroimidazoles (Chapter 4)[236] and 4-nitropyrazoles (Chapter 5),[254] we started the present project on TM-catalyzed direct C-H arylation in the range of fused 3-nitropyridines (Scheme 6.1.1, 6.1.2),[260] which represent an important class of purine-like compounds.[234]

Accordingly, the starting fused 3-nitropyridines **6.1.3a-m** were prepared utilizing the reaction of suitable electron-excessive aminoheterocycles and anilines **6.1.2** with the enolate of nitromalonaldehyde **6.1.1** (Scheme 6.1.1).[261] The reaction was performed in DMF under inert atmosphere, at 100°C for 12 hours using TMSCl as water scavenger;[256] thus, it was possible to prepare the desired fused 3-nitropyridines from good to excellent yields.



Scheme 6.1.1. Preparation of starting fused 3-nitropyridines.

In order to extend the substrate scope and applicability of the work, a number of other nitro-substituted heteroarenes were designed and synthesized (**6.1.5** and **6.1.7**) following the methodology previously developed by us (Scheme 6.1.2).[262] In particular, utilizing the reaction of 3-nitrochromone with various binucleophiles, it was possible to prepare a number of nitro-substituted heteroarenes in good yields; the examples include fused pyridines, pyrazoles and isoxazole. As it was shown previously,[262] the reactions can be performed applying two distinct acidic procedures as depicted in Scheme 6.1.2.

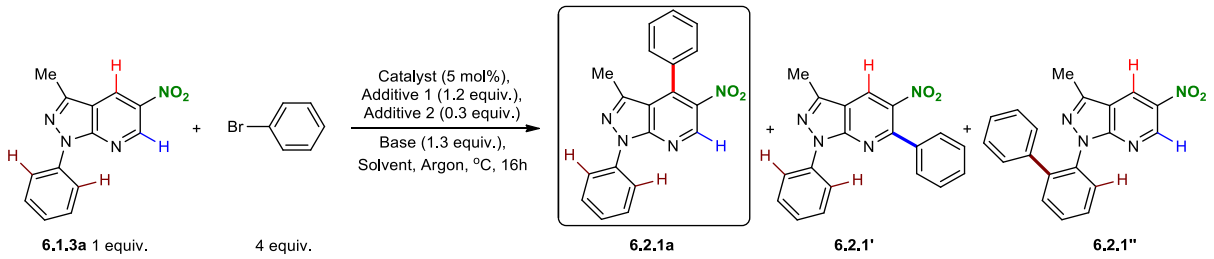


Scheme 6.1.2. Preparation of starting nitro-substituted heteroarenes from 3-nitrochromone.

Noteworthy, these systems are difficult to access by other methodologies due to the electron-deficient nature of pyridines; thus, the developed procedures are of special value.

6.2. C-H Arylation of Fused 3-Nitropyridines: Scope and Limitations

With the set of fused 3-nitropyridines in hand, further, the TM-catalyzed direct C-H arylation of these systems was explored. As a model compound pyrazolo[3,4-*b*]pyridine derivative **6.1.3a** was chosen. This is another interesting substrate, since it has several directing groups and potentially activatable C-H bonds. During the optimization of reaction conditions a number of parameters were thoroughly examined. Some of representative trials are depicted on Table 6.2.1.



6.1.3a 1 equiv. 4 equiv. **6.2.1a** **6.2.1'** **6.2.1''**

Entry	Catalyst	Ligand	Additive 1	Additive 2	Base	Solvent	°C	% of **6.2.1a**[a]
1	$Pd(PPh_3)_4$	-	-	PivOH	K_2CO_3	DMF	130	-
2	$Pd(OAc)_2$	Cy_3PxHBF_4	CuI	PivOH	K_2CO_3	DMF	130	48
3	$Pd(OAc)_2$	-	CuI	PivOH	K_2CO_3	DMF	130	52
4	$Pd(OAc)_2$	-	CuI	PivOH	Cs_2CO_3	DMF	130	43
5	$Pd(OAc)_2$	-	CuI	-	Cs_2CO_3	DMF	130	12
6	$Pd(OAc)_2$	-	CuI	-	K_2CO_3	DMF	130	15
7	$Pd(OAc)_2$	-	CuI	Ph_3CCO_2H	K_2CO_3	DMF	130	40
8	$Pd(OAc)_2$	-	CuI	PivOH	K_3PO_4	DMF	130	8
9	$Pd(OAc)_2$	-	CuI	-	KO*t*Bu	DMF	130	-
10	$Pd(OAc)_2$	-	Ag_2CO_3	PivOH	K_2CO_3	DMF	130	27
11	$Pd(OAc)_2$	-	CuI+Ag_2CO_3	PivOH	K_2CO_3	DMF	130	-
12	$Pd(OAc)_2$	-	AuCl	PivOH	K_2CO_3	DMF	130	-
13	-	-	CuI	PivOH	K_2CO_3	DMF	130	-
14	$Pd(OAc)_2$	-	CuI	PivOH	K_2CO_3	DMA	130	50
15	$Pd(OAc)_2$	-	CuI	PivOH	K_2CO_3	toluene	100	-
16	$Pd(OAc)_2$	-	CuI	-	K_2CO_3	TFA	100	-
17	**$PdCl_2(PPh_3)_2$**	-	**CuI**	**PivOH**	**K_2CO_3**	**DMF**	**130**	**77**
18	**$NiCl_2(PPh_3)_2$**	-	**CuI**	**PivOH**	**K_2CO_3**	**DMF**	**130**	**43**
19	$RuCl_3xH_2O$	Cy_3PxHBF_4	CuI	PivOH	K_2CO_3	DMA	160	-
20	[Ru(*p*-cymene)Cl_2]$_2$	-	- or CuI	PivOH	K_2CO_3	DMA	160	-
21	[Rh(cod)Cl]$_2$	-	- or CuI	PivOH	K_2CO_3	DMA	160	-
22	[Rh(OAc)$_2$]$_2$	-	- or CuI	PivOH	K_2CO_3	DMA	160	-
23	$IrCl_3xH_2O$	Cy_3PxHBF_4	- or CuI	PivOH	K_2CO_3	DMA	160	-

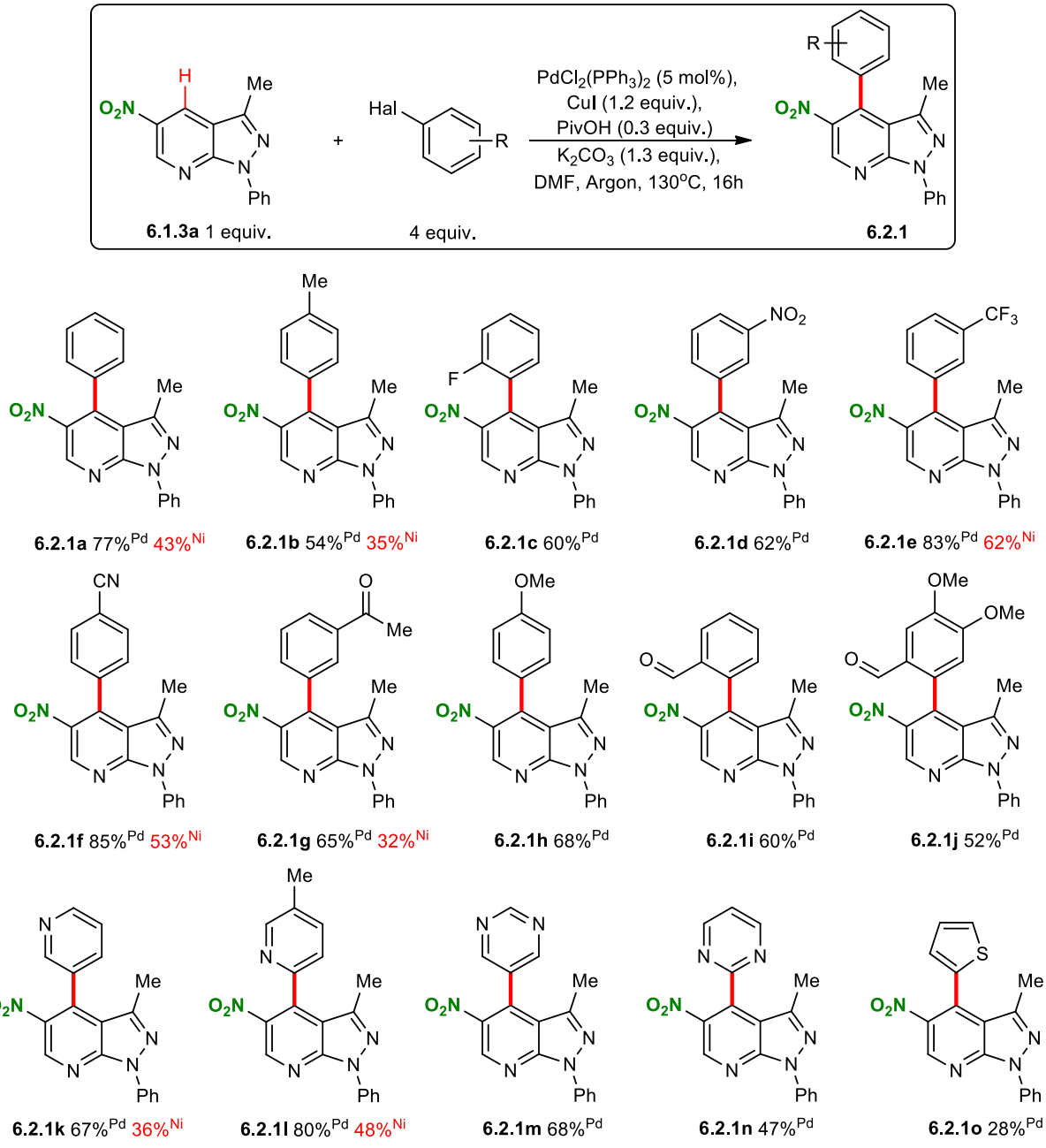
Table 6.2.1. Optimization of reaction conditions; [a] isolated yields.

On the basis of previous results,[236,254] the Pd-based catalysts with CuI as an additive were considered to be the starting point in this study. Gratifyingly, pilot experiments indicated that

indeed the Pd/CuI system is rather efficient for direct γ-C-H arylation of the pyridine ring (Table 6.2.1, entries 2-8, 14, 17). In particular, the best catalyst for direct C-H arylation of model pyrazolo[3,4-*b*]pyridine derivative **6.1.3a** turned to be $PdCl_2(PPh_3)_2$; the desired product **6.2.1a** was isolated in 77% yield as a single regioisomer (entry 17). Further research showed that this regioisomer (**6.2.1a**) is the main product of C-H arylation of pyrazolo[3,4-*b*]pyridine derivative **6.1.3a** within the range of tested conditions.

Further experiments showed that the addition of monodentate phosphine ligands as well as bidentate ligands such as 1,10-phenanthroline have no real impact on the outcome of the reaction (entries 2 and 3). Meanwhile, it should be noted that the use of the salts of coinage metals such as CuI and Ag_2CO_3 in stoichiometric amounts was crucial; in these cases only one regioisomer was observed. Otherwise the conversion of starting pyrazolo[3,4-*b*]pyridine derivative **6.1.3a** was significantly reduced; in addition traces of **6.2.1''** were detected (Table 6.2.1). Interestingly, the use of Lewis acids like CuI or Ag_2CO_3 blocks the formation of this regioisomer. However, the mixture of CuI and Ag_2CO_3 produced an intensive reduction of Ag and oxidation of Cu without any conversion of reactants (entry 11). Exploration of other parameters showed that the best base for the reaction is the K_2CO_3/PivOH system; the replacement of K_2CO_3 by other salts of alkali metals and/or replacement of PivOH by other carboxylic acids decreased the yields of C-H arylation (entries 4-9). On the other hand, the reaction can be effectively performed at 130ºC in DMF (entry 17, 77%) and DMA (entry 14, 50%); however, the use of other solvents such as toluene and TFA turned to be ineffective (entries 15, 16). Afterwards, aiming to obtain another regioisomer and/or the same product with better yields, a number of other transition metal based catalysts were studied; however, the results were quite unsatisfactory (entries 19-23). In this respect, during further examinations it was found that among other transition metals the Ni-based catalysts are also effective under otherwise identical conditions, providing the desired C-H arylation product **6.2.1a** in 43% yield (entry 18). Nevertheless, in this case as well the conversion of starting pyrazolo[3,4-*b*]pyridine derivative **6.1.3a** and overall yield of the reaction was reduced. After the optimization of reaction conditions, next the scope and limitations of the reaction with respect to the aryl halide coupling partners were examined (Scheme 6.2.1). In this context, the results were quite similar to those observed ones for the previous heterocyclic systems (Chapters 4 and 5). Namely, pyrazolo[3,4-*b*]pyridine derivative **6.1.3a** readily react with electron-rich and electron-deficient aryl bromides, as well as heteroaryl bromides, giving rise to the corresponding γ-arylated pyrazolo[3,4-*b*]pyridines **6.2.1a-o** from good to excellent yields. Particularly, as for the previous cases in this case as well a number of functional

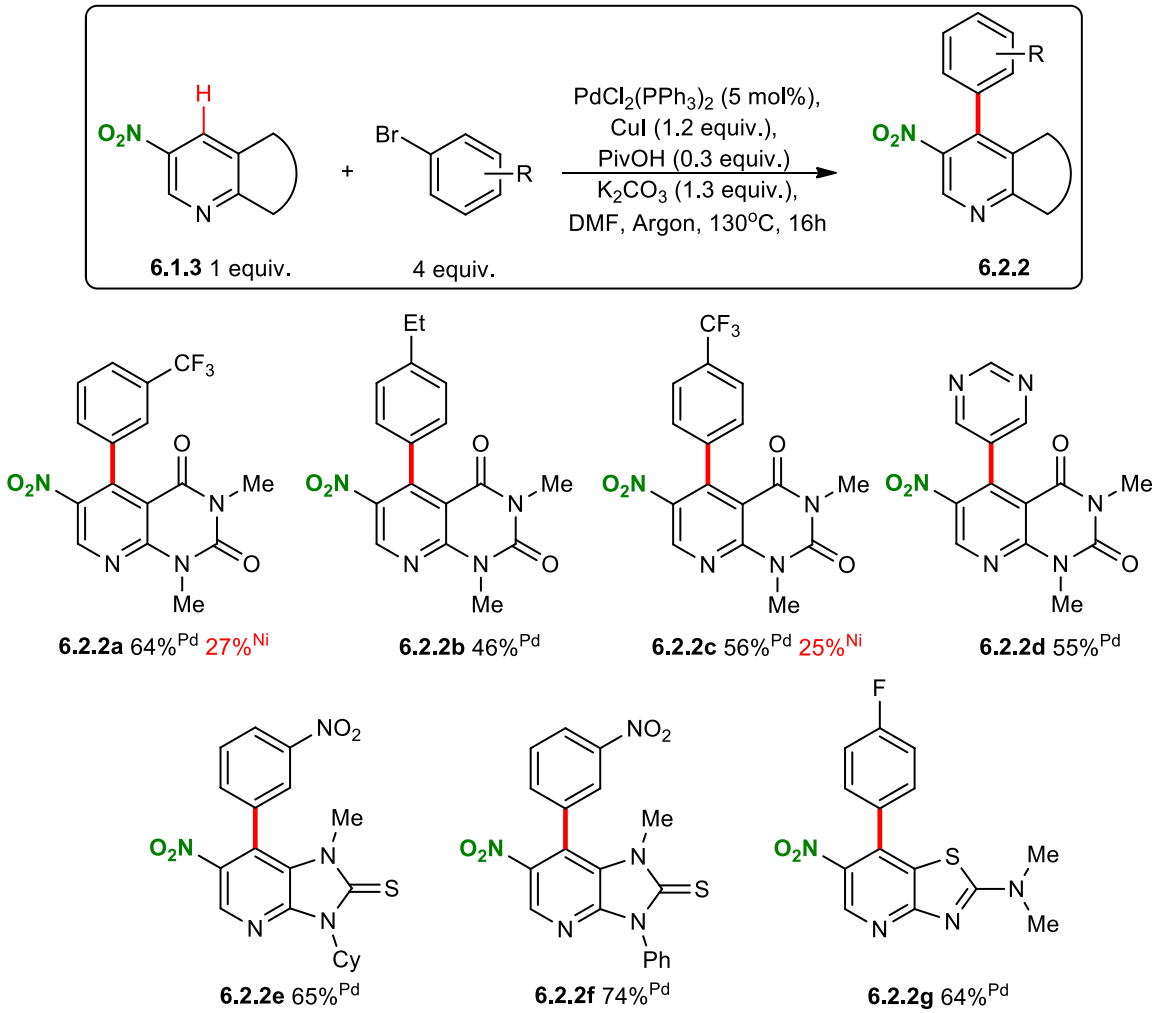
groups including F (**6.2.1c**), NO_2 (**6.2.1d**), CF_3 (**6.2.1e**), CN (**6.2.1f**), Ac (**6.2.1g**), formyl (**6.2.1i**,**j**) and OMe (**6.2.1h**,**j**) were well tolerated under the optimized reaction conditions. At the same time, the use of aryl iodides resulted in the formation of a great amount of symmetrical biaryls *via* homocoupling of aryl iodides induced by CuI.[53] Together with this, under optimized reaction conditions aryl chlorides were not active enough; although, for electron-deficient 2-chloropyrimidine it was possible to isolate the corresponding heteroarylation product **6.2.1n** in 48% yield. Besides, for 5-bromothiophene-2-carboxylic acid, the Pd-catalyzed γ-C-H arylation reaction was accompanied by CuI induced decarboxylation[85d,f,i,186] leading to the arylation product **6.2.1o** in 28% yield.



Scheme 6.2.1. Scope of the reaction with respect to aryl halides.

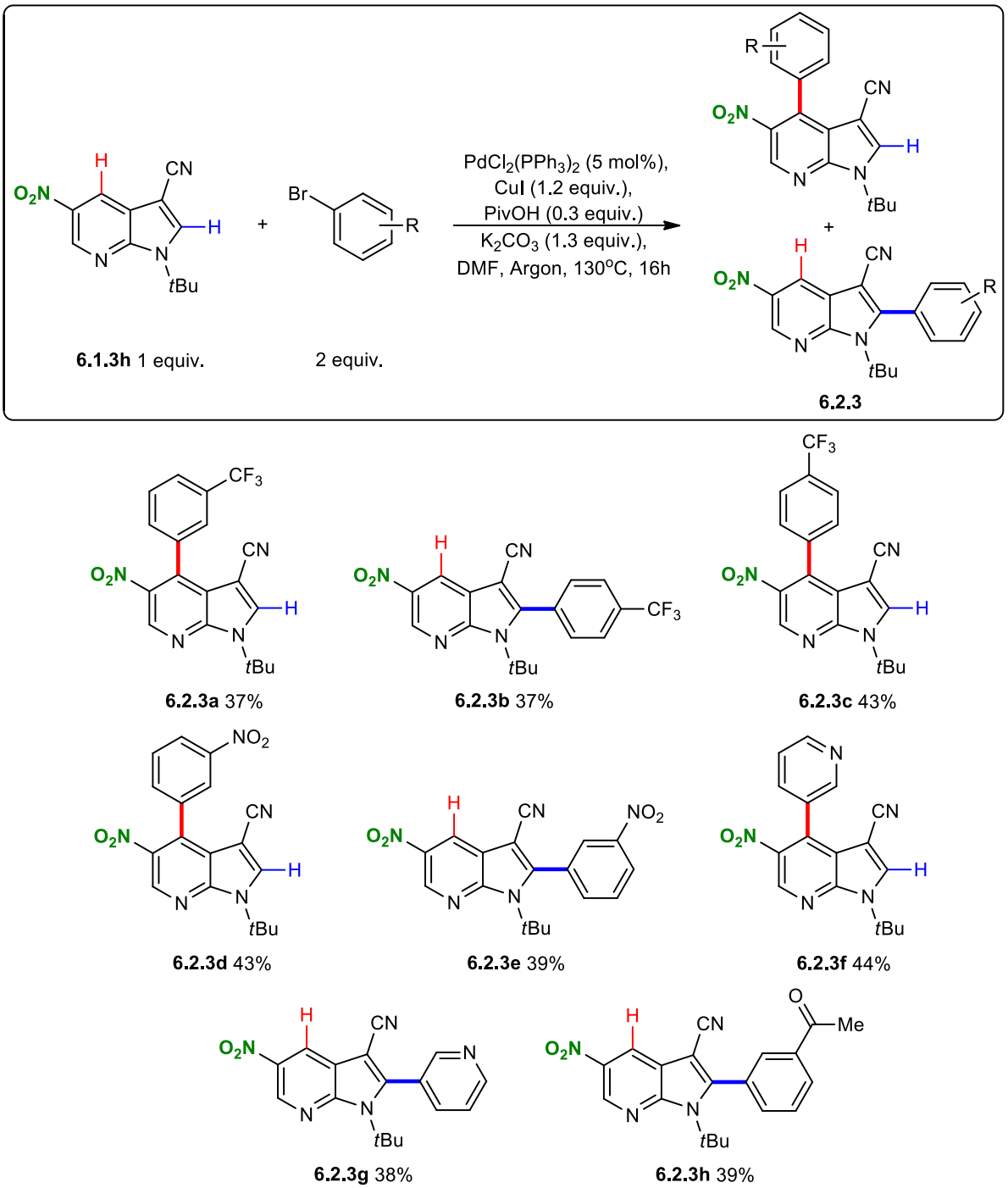
Notably, the Ni-based catalyst was also active with the range of aryl bromides (**6.2.1b**,**e**,**f**,**g**,**k**,**l**) leading to the formation of suitable γ-arylated pyrazolo[3,4-*b*]pyridine derivatives in moderate yields (Scheme 6.2.1).

Once the scope of the reaction towards aryl halide coupling partners was established, it was decided to switched on the examination of the scope of fused 3-nitropyridines. In this regard, it was discovered that the reaction has general character. Particularly, under otherwise similar conditions numerous fused 3-nitropyridines were successfully coupled with different aryl bromides giving rise to the corresponding γ-arylated fused 3-nitropyridines in good yields. That is, 1,3-dimethyl-6-nitropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **6.1.3b**, 6-nitro-1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-thione derivatives **6.1.3d**,**e** and 6-nitrothiazolo[4,5-*b*]pyridine derivative **6.1.3f** react uneventfully with appropriate aryl bromides producing the corresponding γ-C-H arylation products **6.2.2a**-**g** in good yields (Scheme 6.2.2). Notably, in these cases as well the γ-C-H arylation product was the only observed regioisomer. Besides, the reactions can be catalyzed by $NiCl_2(PPh_3)_2$ (**6.2.2a**,**c**); however, with a lower efficiency.



Scheme 6.2.2. Scope of the reaction with respect to fused 3-nitropyridines.

From the target fused 3-nitropyridines, pyrrolo[2,3-*b*]pyridine derivative **6.1.3h** stands out because of two potentially activatable C-H bonds and directing groups. In fact indoles and derivatives are one of the most extensively studied and reactive systems towards TM-catalyzed C-H activation.[170b,181g] Besides, the nitrile group is known to direct the TM-catalyzed C-H activation reactions.[221b,263] Thus, in the process of Pd-catalyzed C-H arylation of pyrrolo[2,3-*b*]pyridine derivative **6.1.3h**, perhaps unsurprisingly, the C-H arylation occurred simultaneously at both pyridine and pyrrole rings (Scheme 6.2.3).

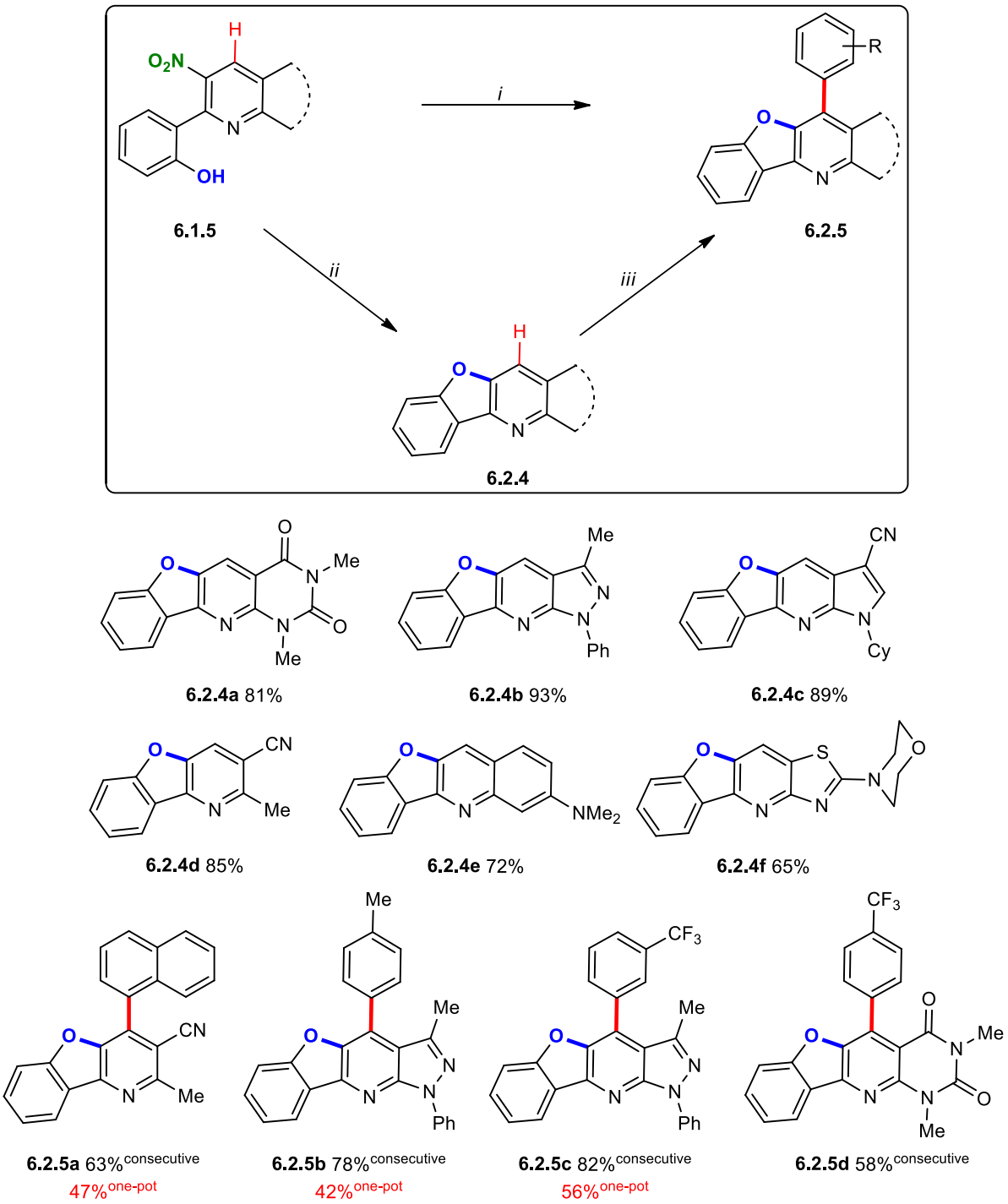


Scheme 6.2.3. Scope of the reaction with respect to pyrrolo[2,3-*b*]pyridine derivative **6.1.3h**.

As a result two regioisomers were isolated, corresponding to the C(2)-H and C(4)-H arylation products **6.2.3a-h** (Scheme 6.2.3). Further exploration of the reaction showed that both C(2)-H and C(4)-H bonds of pyrrolo[2,3-*b*]pyridine **6.1.3h** are approximately equally active towards Pd-catalyzed C-H arylation. Particularly, the use of only 1 equivalent of aryl bromide led to a mixture of regioisomers without full conversion of the reactant **6.1.3h**. Moreover, the reduction of quantities of aryl bromide coupling partner as well as further modifications of the reaction conditions did not affect on the regioselectivity of the reaction, or even in some cases, vice versa, the conversion of starting pyrrolo[2,3-*b*]pyridine **6.1.3h** decreased significantly. After some examinations it was found that quite applicable yields for both regioisomers can be achieved using similar conditions to those used ones for other fused 3-nitropyridines. Additionally, in order to avoid the double arylation and/or disastrous mixtures of products, no more than 2 equivalents of aryl bromide should be used.

On the next stage of the work an attempt was made to arylate α-position of fused 3-nitropyridines (see also Table 6.2.1, **6.2.1'**). Nevertheless, despite numerous efforts on development of a practical approach to α-C-H arylated fused 3-nitropyridines, all trials were unsuccessful. Although, a number of procedures were thoroughly examined, in most cases we obtained complex mixtures of undefined nature and/or poor conversion of reactants. Thereby, to overcome this problem and further extend the substrate scope of the work, it was decided to examine previously synthesized fused 3-nitropyridines **6.1.5** (Scheme 6.1.2), which already possess an aryl substituent at the α-position of pyridine core.

Noteworthy, the synthesized fused 3-nitropyridines **6.1.5** bear a hydroxy group which potentially can be subjected to a TM-catalyzed C-O cross-coupling reaction;[47,264] nevertheless, the reaction of the model fused 3-nitropyridine **6.1.5a** and 4-bromotoluene under standard conditions for C-H activation gave an unexpected result (Scheme 6.2.4). In spite of a complex mixture of products, it was possible to isolate a pure compound, which proved to be the structure **6.2.5b**. Further exploration of the reaction parameters showed that the reaction consists a two-step domino process:[265] initially occurs an intramolecular aromatic nucleophilic substitution of nitro group by hydroxy group which is followed by Pd-catalyzed C-H arylation (Scheme 6.2.4). This assumption was verified by isolation and characterization of intermediate **6.2.4**; further treatment of intermediate **6.2.4** with aryl bromide and other reaction components resulted in the final arylation products **6.2.5** in good yields. It was discovered that the initial step of the domino reaction can occur in the absence of catalyst. Moreover, we excluded reaction components successively to find that CuI and PivOH do not play decisive roles in this transformation and just base (K_2CO_3) can initiate the cyclisation.



Scheme 6.2.4. The domino nitro group substitution-C-H arylation reaction; *i*: ArBr (4 equiv.), $PdCl_2(PPh_3)_2$ (5 mol%), CuI (1.2 equiv.), PivOH (0.3 equiv.), K_2CO_3 (2.3 equiv.), DMF, under argon, 130°C, 16h; *ii*: K_2CO_3 (1.3 equiv.), DMF, under argon, 130°C, 16h; *iii*: ArBr (4 equiv.), $PdCl_2(PPh_3)_2$ (5 mol%), CuI (1.2 equiv.), PivOH (0.3 equiv.), K_2CO_3 (1.3 equiv.), DMF, under argon, 130°C, 16h.

Inspired by these findings, next, the intramolecular nucleophilic substitution of nitro group was performed in a wide range of substrates; in most cases the reaction went uneventful

leading to corresponding furo[3,2-*b*]pyridine derivatives **6.2.4a-f** from good to excellent yields. The only systems which were unreactive and/or unstable under basic conditions were pyrazoles **5.1.7a**,**b** and isoxazole **5.1.7c** (Scheme 6.2.4). With the set of fused furo[3,2-*b*]pyridine derivatives **6.2.4a-f** in hand, the C-H arylation at the pyridine ring was examined. In general it was possible to demonstrate that arylated fused furo[3,2-*b*]pyridines **6.2.5** can be prepared either in one-pot or consecutively. Interestingly, the Pd-catalyzed C-H arylation of starting fused 3-nitropyridines **6.1.5** as well as fused furo[3,2-*b*]pyridines **6.2.4** can occur effectively under the standard conditions which were found to be optimal for previous systems (**6.1.3**). Thus, applying elaborated one-pot and consecutive procedures, a number of arylated fused furo[3,2-*b*]pyridines **6.2.5a-d** were prepared in good yields. Not surprisingly, the consecutive synthesis of arylated fused furo[3,2-*b*]pyridines was more effective (Scheme 6.2.4).

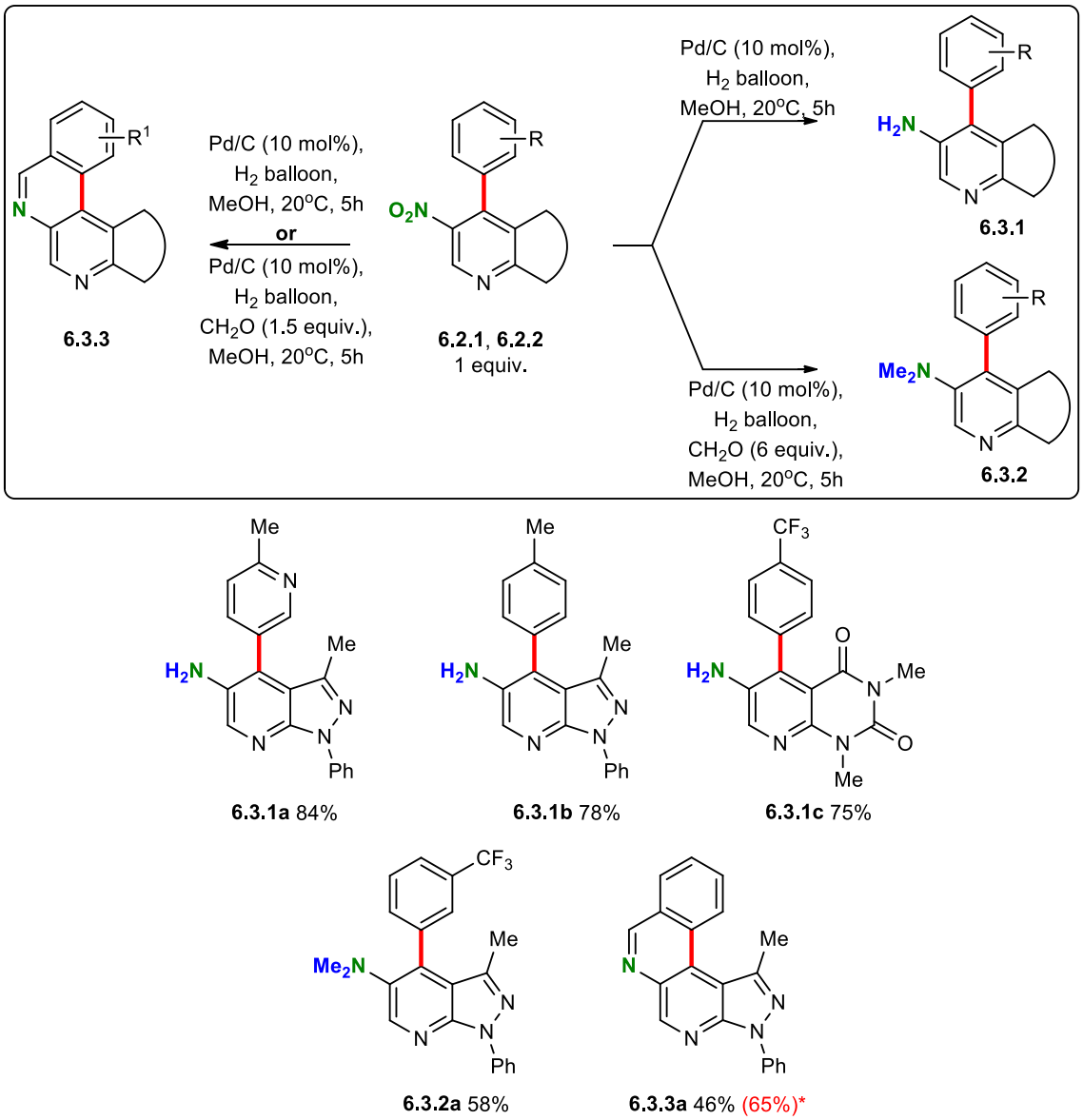
6.3. Exploration of Further Transformations of Nitro Group

On the next stage of the work, in order to fully demonstrate the synthetic capacity of this methodology, the chemical versatility of the directing group was explored. For this purpose, initially the simple reduction of nitro group was examined (Scheme 6.3.1). Thus, it was possible to show that the Pd-catalyzed reduction of the γ-C-H arylation products of fused 3-nitropyridines (**6.2.1**, **6.2.2**) represents a useful approach for the synthesis of arylated fused 3-aminopyridines **6.3.1a-c** which are difficult to access by other methods. The reaction was conducted in distilled technical MeOH under normal pressure of H_2 using Pd/C (10 mol%) as catalyst at ambient temperatures; accordingly, the corresponding 3-aminopyridines were isolated in 75-84% yields (Scheme 6.3.1).

Besides, it was discovered that the Pd-catalyzed reduction of nitro group in the presence of an excess of formaldehyde affords corresponding fused N,N-dimethylaminopyridine **6.3.2a** in 58% yield. Additionally, the Pd-catalyzed reduction of C-H arylation product **6.2.1i** which bear a carbonyl functional group led to the formation of isoquinoline system **6.3.3a** in 65% yield (Scheme 6.3.1). Remarkably, when the reduction of C-H arylation product **6.2.1a** was performed using stoichiometric amounts of formalin (1.5 equivalents), the reduction was followed by isoquinoline ring formation to give **6.3.3a** in 46% yield (Scheme 6.3.1). The new pathway of the reaction can be explained by an assumption that the reduction of nitro group in the presence of stoichiometric amounts of formalin generates an imine which further undergoes a Pd-catalyzed intramolecular hydroarylation followed by aromatisation to form

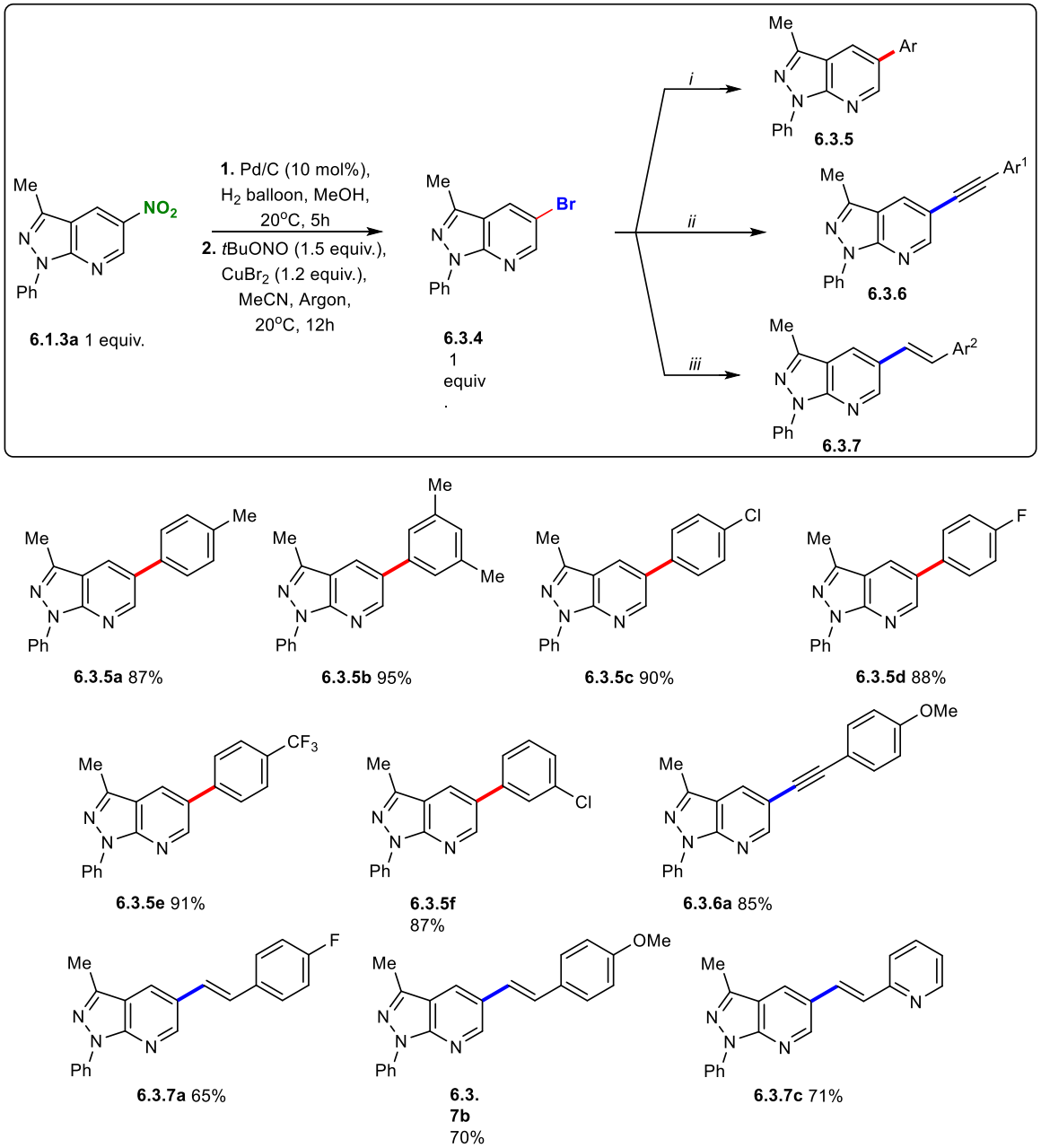
the isoquinoline core. To the best of our knowledge, similar transformations were not observed previously. However, related TM-catalyzed intermolecular hydroarylation of imines is a rapidly growing area in the field of C-H activation.[150p,s,178b,266] Detailed exploration of possible mechanism and further applications of the reaction is underway in our group.

Furthermore, it was possible to transfer the nitro group to bromo substituent (85%) using a semi-one-pot procedure on the basis of modified Sandmeyer halogenation (Scheme 6.3.2).[267] The synthesis of brominated fused pyridine **6.3.4** allowed us to perform some other well-known TM-catalyzed C-C bond forming reactions.[261] Namely, the pyrazolo[3,4-*b*]pyridine system was incorporateed with arenes, alkynes and olefins using Suzuki-Miyaura,[86-88] Sonogashira[268] and Mizoroki-Heck[269] cross-coupling reactions respectively.



Scheme 6.3.1. Reduction of nitro group; * in the brackets on red is the yield of reduction of compound **6.2.1i**.

Firstly, the Suzuki-Miyaura reaction was considered as an efficient approach for incorporation of various arenes in the β-position of the model pyrazolo[3,4-*b*]pyridine. Thus, it was found that brominated pyrazolo[3,4-*b*]pyridine **6.3.4** readily undergo the Pd-catalyzed arylation with the set of diverse boronic acids giving rise to corresponding β-arylated pyrazolo[3,4-*b*]pyridines **6.3.5a-f** in 87-95% yields (Scheme 6.3.2).

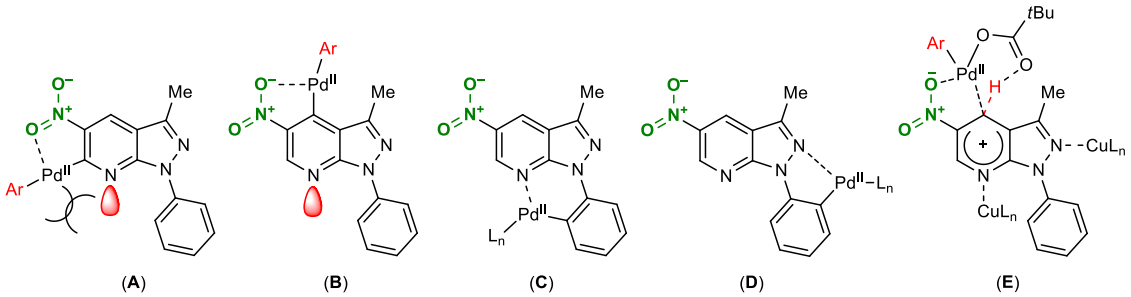


Scheme 6.3.2. Further transformations of nitro group through cross-coupling reactions; *i*: Ar-$B(OH)_2$ (1.5 equiv.), $PdCl_2(PPh_3)_2$ (2 mol%), K_2CO_3 (2 equiv.), 1,4-dioxane, under argon, 90°C, 8h; *ii*: Acetylene (2 equiv.), $PdCl_2(PPh_3)_2$ (2 mol%), CuI (5 mol%), TEA (1.3 equiv.), DMF, under argon, 120°C, 8h; *iii*: Alkene (3 equiv.), $PdCl_2(PPh_3)_2$ (4 mol%), TEA (4 equiv.), DMF, under argon, 140°C, 14h.

Meanwhile, all attempts to shorten the synthetic pathway to β-arylated fused pyridines by usage of appropriate diazonium salt,[85c,k] instead of aryl bromide, were unsuccessful. Although, it was possible to perform the Pd-catalyzed couplings with corresponding diazonium salt, the yields never exceeded 30% due to numerous side processes. Concerning the Sonogashira cross-coupling, it was discovered that the brominated pyrazolo[3,4-*b*]pyridine **6.3.4** can be readily coupled with a commercially available acetylene under the standard conditions for Sonogashira reaction.[268] Namely, conducting the reaction in DMF at 120°C, using $PdCl_2(PPh_3)_2$/CuI catalytic system and TEA as base, suitable pyrazolo[3,4-*b*]pyridine derivative **6.3.6a** was obtained in 85% yield (Scheme 6.3.2). Eventually, the olefination of model pyrazolo[3,4-*b*]pyridine **6.3.4** was performed utilising the Pd-catalyzed reaction with appropriate olefins in DMF at 140°C applying TEA as base. In this way, three examples of alkenylated pyrazolo[3,4-*b*]pyridines **6.3.7a-c** were prepared in 65-71% yields.

6.4. Possible Mechanisms of C-H Arylation and Further Experiments

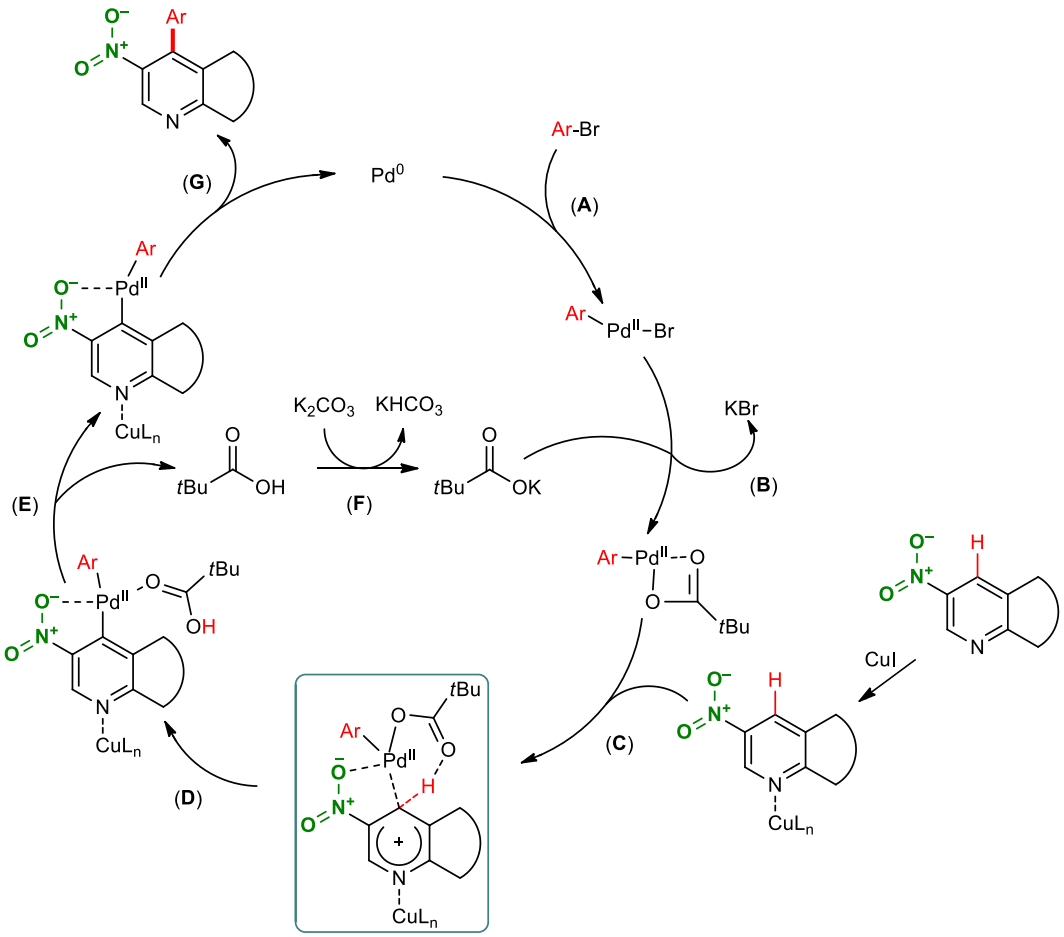
The regioselectivity of the reaction might be explained by the assumption that the free electron pair of the N atom of pyridine shields the α-position which manifests by the electronic repulsion between the electron lone pair of the N atom and the C-Pd bond (Scheme 6.4.1, **A**).[221b] Thus, intermediate (**B**) should be more favourable. On the other hand, pyridine and derivatives have a tendency to form a non-productive N-bound coordination mode with metal centres; thus, poisoning the catalyst (structure **C** or **D** in Scheme 6.4.1, similar considerations are equally applicable for Ni).[167,168] In this respect, the protection of the N atom by conversion to N-oxides[136,147c,g,200d,j] and N-iminopyridinium ylides[147a,b,h] has allowed the development of several TM-catalyzed C(2)-H transformations of pyridines.



Scheme 6.4.1. Proposed mechanistic explanation of the regioselectivity.

On this basis, supposedly the high levels of reactivity of the Pd(Ni)/CuI catalytic system could be a result of the strong coordination of the N atom of the pyridine ring to Cu(I) that would

prevent the N-bound coordination mode of the pyridine substrates with Pd or Ni (**C**, **D**). Noteworthy, very recently two research groups found that the coordination of a strong and bulky Al-based Lewis acid with the N atom of pyridine ring not only activates the pyridine ring but also favours C(4)-H functionalization.[146h,i] Hence, under these circumstances, we suppose that the carboxylate assisted γ-C-H bond cleavage of fused 3-nitropyridines could take place, if the appropriate orientation between the nitro group of the pyridine and Pd (Ni) is assembled (structure **E**, Scheme 6.4.1).

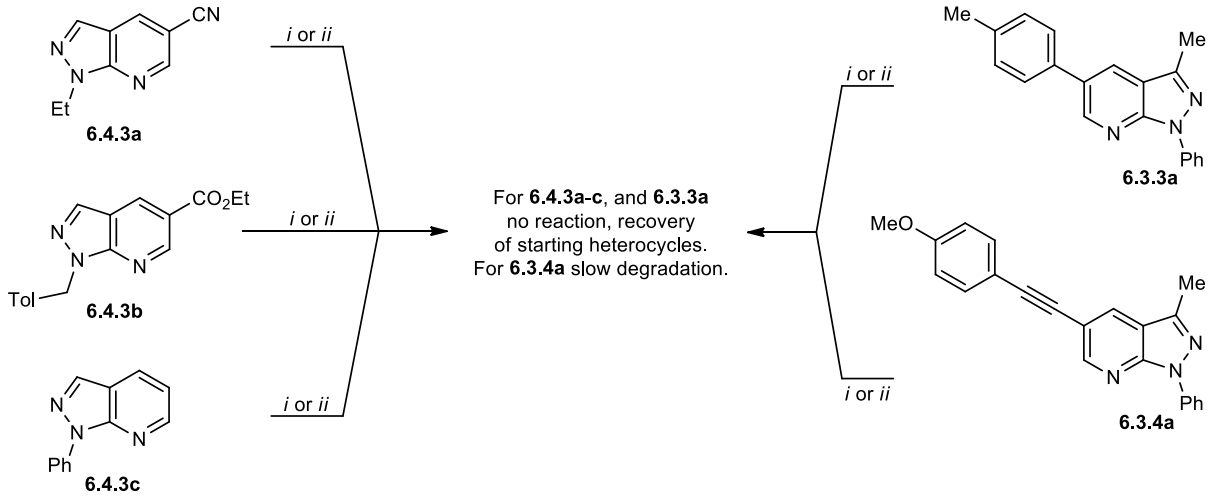


Scheme 6.4.2. Possible mechanism of Pd-catalyzed γ-C-H arylation of fused 3-nitropyridines.

Based on these considerations, we assume that the mechanism of the reaction is very much similar to the mechanisms presented in Chapters 4.5 and 5.4 (Schemes 4.5.2 and 5.4.2). Thus, the catalytic cycle starts with oxidative addition of aryl bromide to the catalyst Pd(0) delivering Ar-Pd(II)-Br complex (Scheme 6.4.2, **A**, similar considerations are equally true for Ni). Subsequently, the product of oxidative addition undergoes a ligand exchange reaction with potassium pivalate which is more soluble in the solvent (DMF) than K_2CO_3 (**B**). On the next stage of the process the Ar-Pd(II)-OPiv species first coordinates to the nitro group of

fused 3-nitropyridine which is followed by γ-C-H bond cleavage *via* carboxylate assisted concerted metalation-deprotonation (**C**, **D**). This process is followed by regeneration of PivOH and PivOK (**E**, **F**). Eventually, the reductive elimination of catalyst leads to the formation of desired γ-arylated fused 3-nitropyridine and regeneration of components of catalytic cycle (Scheme 6.4.2, **G**).

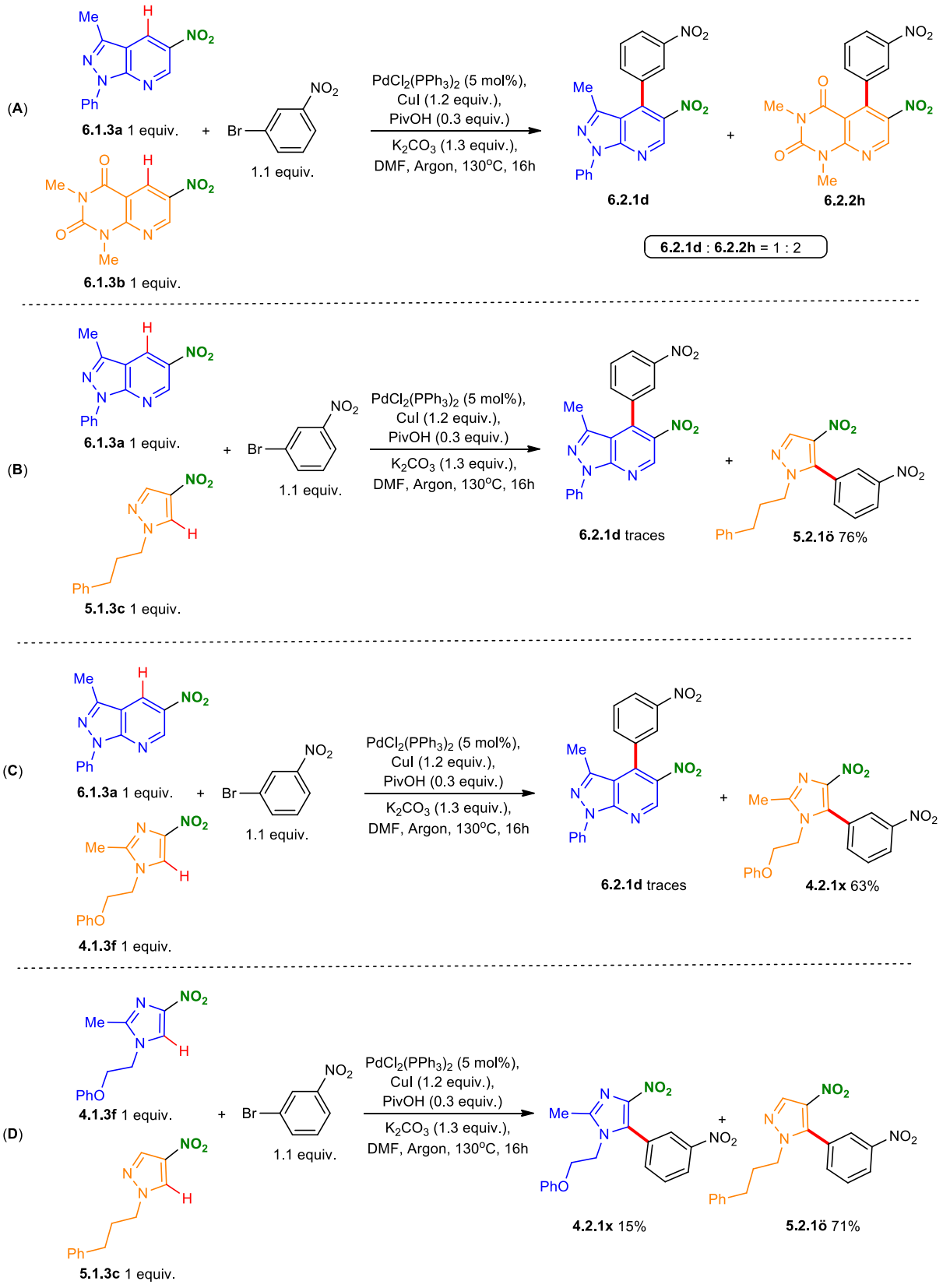
Aiming to shed light on the directing effect of nitro group and to obtain additional insights into the reaction mechanism, the substrates **6.4.3a-c**,[270] **6.3.3a** and **6.3.4a**[261] were subjected to the standard TM-catalyzed reaction conditions (Scheme 6.4.3). However, to our astonishment, the initial testings with model pyrazolo[3,4-*b*]pyridines, bearing a polar CN[270a] **6.4.3a** or CO_2Et[270b] **6.4.3b** substituents instead of nitro group, experienced a failure; substrates **6.4.3a** and **6.4.3b** were recovered completely. The same reactivity pattern was observed for unsubstituted pyrazolo[3,4-*b*]pyridine **6.4.3c**.[270c] Additionally, pyrazolo[3,4-*b*]pyridines bearing a non-coordinating *p*-tolyl **6.3.3a** and CC-Ar **6.3.4a** substituents under otherwise identical conditions did not cause the γ-C-H arylation. In particular, pyrazolo[3,4-*b*]pyridine **6.3.3a** was fully recovered; though, for pyrazolo[3,4-*b*]pyridine **6.3.4a** we observed some conversion resulting in the formation of a mixture of undefined nature, which might be the result of degradation due to the reactivity of the triple bond under TM-catalyzed conditions.



Scheme 6.4.3. Exploration of directing ability of nitro group; *i*: ArBr (4 equiv.), $PdCl_2(PPh_3)_2$ (5 mol%), CuI (1.2 equiv.), PivOH (0.3 equiv.), K_2CO_3 (1.3 equiv.), DMF, under argon, 130°C, 16h; *ii*: ArBr (4 equiv.), $NiCl_2(PPh_3)_2$ (5 mol%), CuI (1.2 equiv.), PivOH (0.3 equiv.), K_2CO_3 (1.3 equiv.), DMF, under argon, 130°C, 16h.

Noteworthy, in previous reports on imidazo[4,5-*b*]pyridines and related heteroannulated pyridines, our colleagues[235] and others[139a,b,h,144f] demonstrated that as a rule the pyridine ring

remains intact under typical C-H activation protocols if the nitro group is replaced by H or electron-withdrawing CF_3 group.



Scheme 6.4.4. The competitive experiments between nitro-substituted heteroarenes.

In addition, Yu and coworkers found that the Pd-catalyzed "*innate*" C-H arylation of unprotected simple pyridines leads to a mixture of isomers (C3/C4/C2) with predominant C(3)-H selectivity.[135] Notably, in the work starting pyridines were used as solvent, otherwise the yields of arylation were significantly reduced which indicates the importance of directing groups on efficient C-H arylation of pyridine and derivatives.

Eventually, we conducted several competitive experiments between various nitro-substituted arenes used in the work (Scheme 6.4.4, **A**-**D**). The aim of the study was the identification of comparable reactivities of nitroarenes in Pd-catalyzed direct C-H arylation. Accordingly, the Pd-catalyzed competitive C-H arylation of two distinct fused 3-nitropyridines was explored (Scheme 6.4.4, **A**). The GC-MS studies of the reaction mixture indicated on the preference of pyrido[2,3-*d*]pyrimidine derivative **6.1.3b** over pyrazolo[3,4-*b*]pyridine derivative **6.1.3a**. In particular, a mixture of both arylated fused 3-nitropyridines was observed in **6.2.1d** : **6.2.2h** = 1 : 2 ratio (GC-MS studies). The related competitive experiment between pyrazolo[3,4-*b*]pyridine derivative **6.1.3a** and 4-nitropyrazole **5.1.3c** revealed that 4-nitropyrazoles are far more reactive towards Pd-catalyzed C-H arylation than fused 3-nitropyridines (Scheme 6.4.4, **B**). Thus, we observed the arylated 4-nitropyrazole **5.2.1ö** in 76% yield and only traces of arylated fused 3-nitropyridine **6.2.1d** (GC-MS studies). Similarly, the competitive experiment between pyrazolo[3,4-*b*]pyridine derivative **6.1.3a** and 4-nitroimidazole **4.1.3f** revealed that 4-nitroimidazoles are also more reactive than fused 3-nitropyridines (Scheme 6.4.4, **C**). Finally, the competitive experiment between 4-nitropyrazole **5.1.3c** and 4-nitroimidazole **4.1.3f** gave a mixture of corresponding arylation products in 71% and 15% yields respectively (Scheme 6.4.4, **D**, GC-MS yields). Hence, from studied nitroarenes 4-nitropyrazoles are the most reactive heterocyclic systems towards Pd-catalyzed direct C-H arylation.

6.5. Structure Identification

The structures of synthesized compounds were mainly established by NMR, IR spectroscopy and mass spectrometry. Noteworthy, in all arylated fused 3-nitropyridines the aryl groups do not possess bulky functional groups near pyridine ring which indicates on free rotation around newly formed Ar-Ar C-C bond and absence of atropisomers (at room temperature).[1e,f,253]

In the ^{1}H NMR spectra of starting fused 3-nitropyridines **6.1.3** the γ- and α-C*H* bonds of pyridine ring appears at 7.62-8.90 ppm and 8.86-9.43 ppm (DMSO-d_6) as doublets with coupling constant ^{4}J = 2.1-2.5 Hz (Figure 6.5.1). In the products of C-H arylation **6.2.1**-**6.2.3** the doublet corresponding to the γ-C*H* bond disappear, the doublet corresponding to the α-C*H*

bond turns to a singlet (9.25-9.42 ppm, DMSO-d_6); in addition, the number of aromatic signals increases (Figure 6.5.1, 6.5.2).

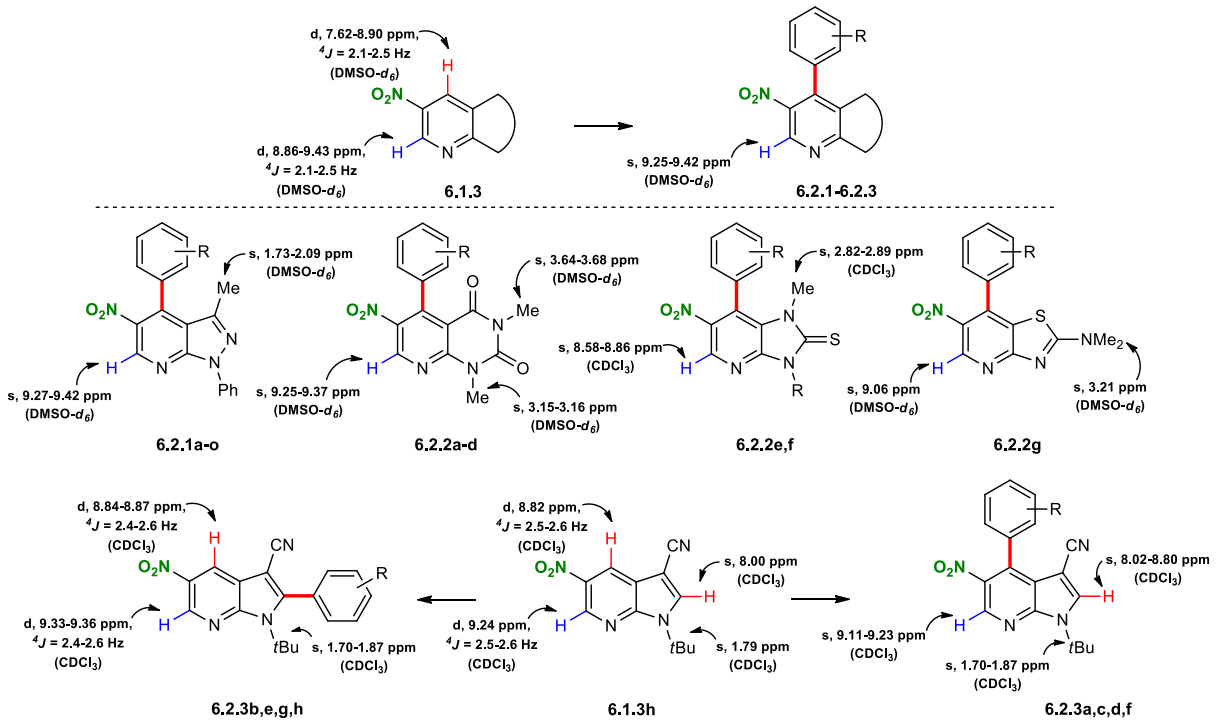


Figure 6.5.1. Observations from NMR experiments.

Accordingly, the singlet of α-C*H* bond of arylated pyrazolo[3,4-*b*]pyridines **6.2.1a-o** appears at range 9.27-9.42 ppm (DMSO-d_6); the singlet of 3-*Me* group of arylated pyrazolo[3,4-*b*]pyridines was seen at 1.73-2.09 ppm (DMSO-d_6) (Figure 6.5.1). Similarly, for arylated pyrido[2,3-*d*]pyrimidines **6.2.2a-d** the singlets of α-C*H* bond and N*Me* groups were seen at 9.25-9.37 ppm, 3.64-3.68 ppm and 3.15-3.16 ppm respectively (DMSO-d_6) (Figure 6.5.1). The typical singlets of α-C*H* bonds of arylated imidazo[4,5-*b*]pyridines **6.2.2e**,**f** and thiazolo[4,5-*b*]pyridine derivative **6.2.2g** appear at 8.58-8.86 ppm ($CDCl_3$) and 9.06 ppm (DMSO-d_6) respectively. Additionally, the singlets of N*Me* group of arylated imidazo[4,5-*b*]pyridines **6.2.2e**,**f** and N*Me*$_2$ group of thiazolo[4,5-*b*]pyridine derivative **6.2.2g** were detected at 2.82-2.89 ppm ($CDCl_3$) and 3.21 ppm (DMSO-d_6) respectively (Figure 6.5.1). In C(2)-H arylated pyrrolo[2,3-*b*]pyridines **6.2.3b**,**e**,**g**,**h** the γ- and α-C*H* bonds of pyridine core appear as doublets at range 8.84-8.87 ppm and 9.33-9.36 ppm with a coupling constant ^4J = 2.4-2.6 Hz ($CDCl_3$). On the other hand, in C(4)-H arylated pyrrolo[2,3-*b*]pyridines **6.2.3a**,**c**,**d**,**f** the C*H* bonds of pyrrole and pyridine rings appear as singlets at range 8.02-8.80 ppm and 9.11-9.23 ppm respectively ($CDCl_3$). The *tert*-butyl group of arylated pyrrolo[2,3-*b*]pyridines **6.2.3** appears as a singlet at range 1.70-1.87 ppm ($CDCl_3$) (Figure 6.5.1).

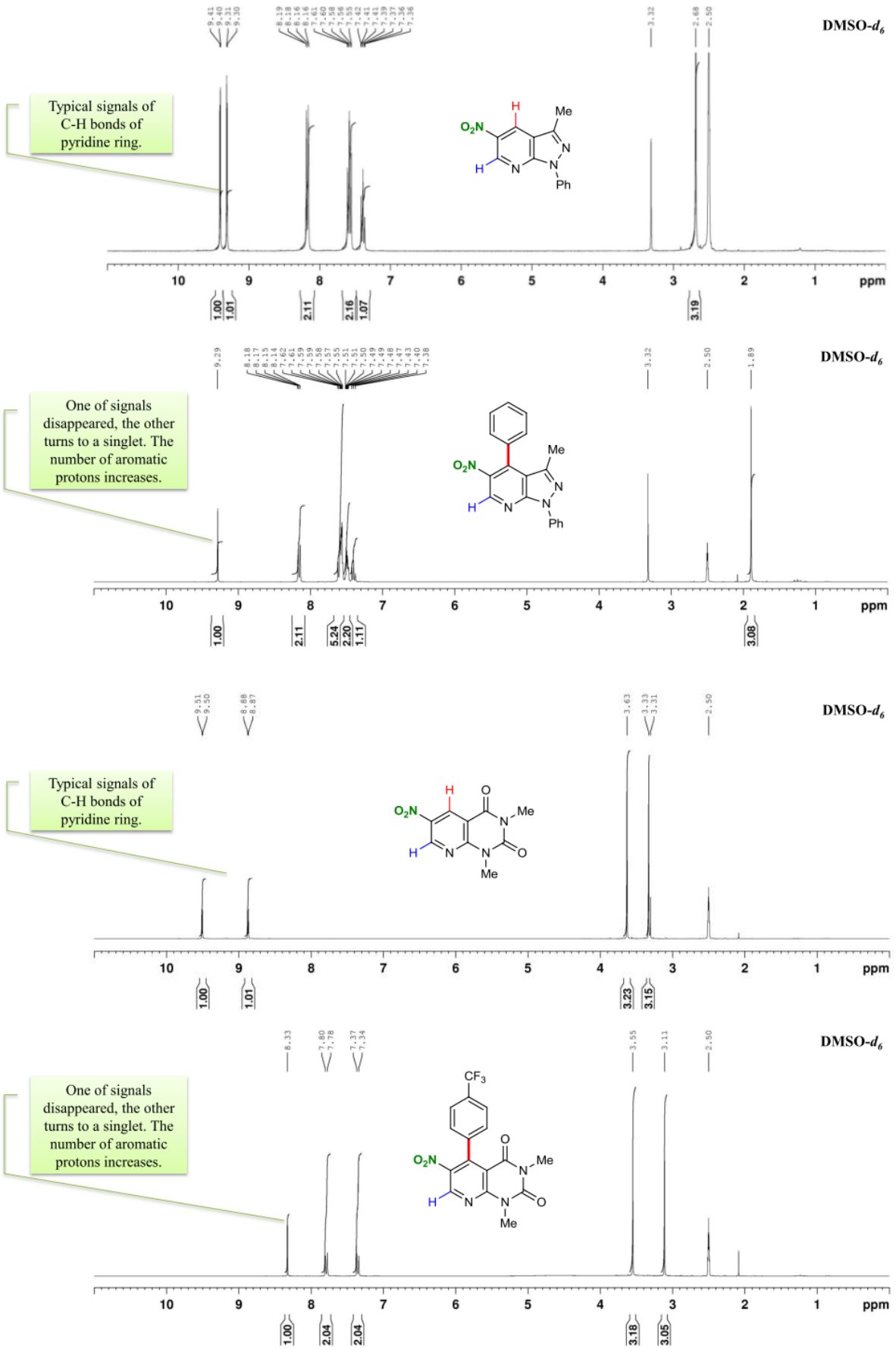
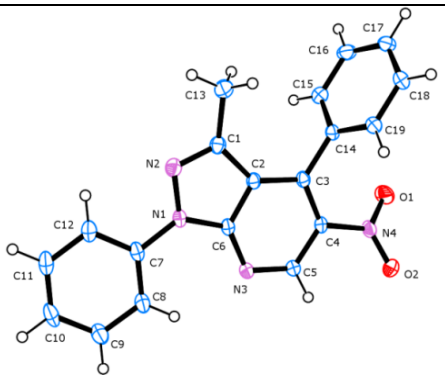
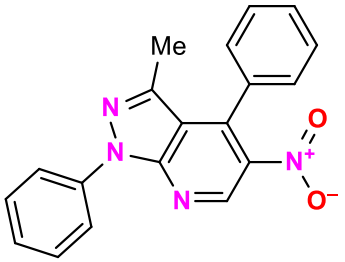
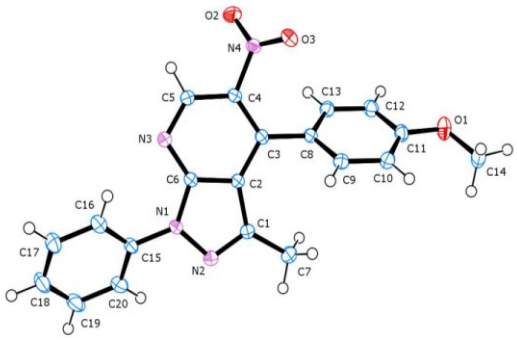
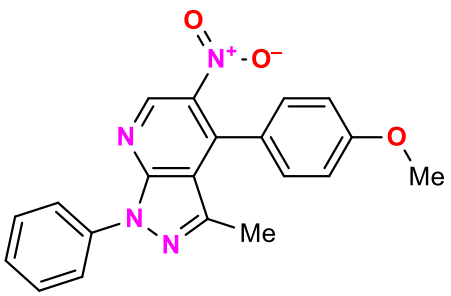


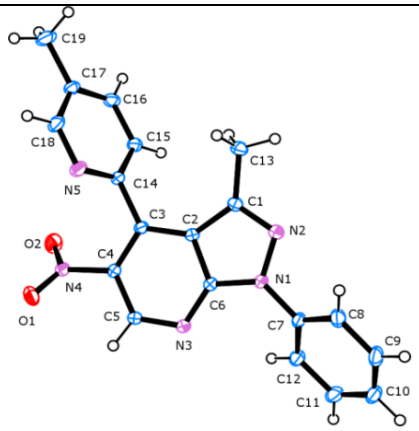
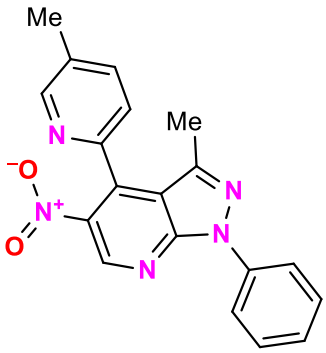
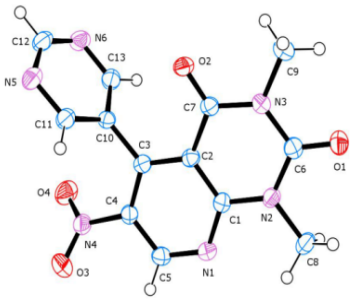
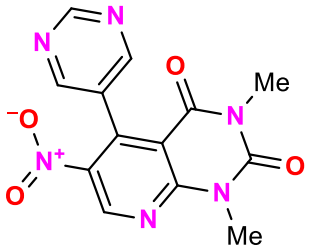
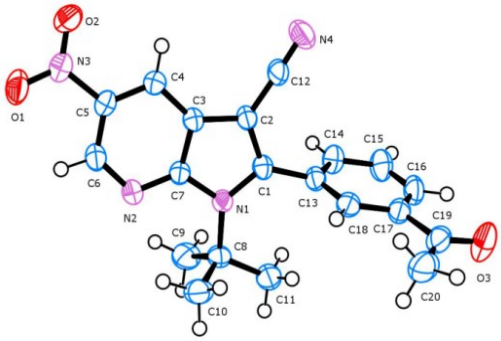
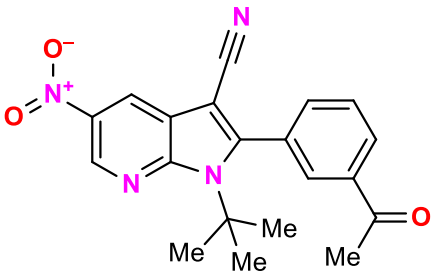
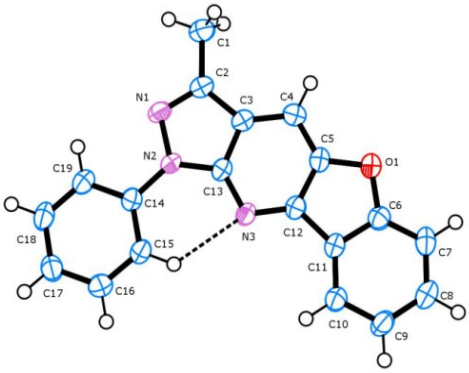
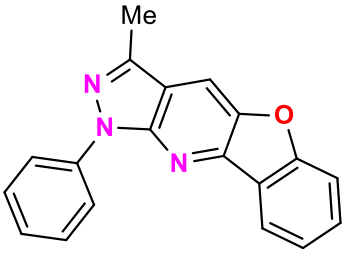
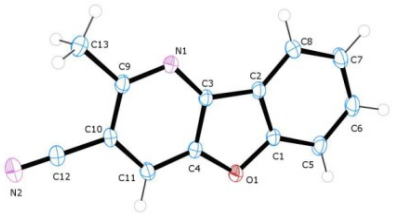
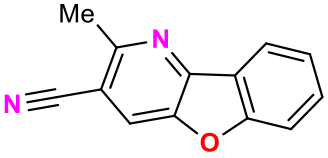
Figure 6.5.2. Comparison of ^{1}H NMR spectra of starting fused 3-nitropyridines **6.1.3a**,**b** and corresponding C-H arylation products **6.2.1a**, **6.2.2c**.

The singlet of γ-C*H* bond of pyridine core in furo[3,2-*b*]pyridine derivatives **6.2.4a-f** was seen at 7.98-8.78 ppm (DMSO-d_6); in corresponding C-H arylation products **6.2.5a-d** the singlet disappeared. The broad singlet of NH_2 group of reduction products **6.3.1a-c** was detected at 4.20-4.31 ppm ($CDCl_3$).

Besides, in the ^{13}C NMR spectra of pyrido[2,3-*d*]pyrimidines **6.2.2a-d** and imidazo[4,5-*b*]pyridines **6.2.2e**,**f** the carbonyl groups and thione (C=S) were detected at 152.9-153.4 ppm, 158.9-159.5 ppm (DMSO-d_6) and 147.8 ppm ($CDCl_3$) respectively. In addition, the typical quartets of CF_3 group were observed (^1J = 240-274 Hz, DMSO-d_6). In the ^{19}F NMR spectra CF_3 group appears from -60.9 to -62.8 ppm (DMSO-d_6).

Furthermore, in the IR spectra of arylated fused 3-nitropyridines **6.2.1-6.2.3** the N-O stretching vibrations of NO_2 group (medium intensity) were observed at 1430-1590 cm^{-1} (asymmetrical) and 1290-1358 cm^{-1} (symmetrical). On the other hand, in the IR spectra of reduction products **6.3.1** the typical peaks of stretching vibrations of NO_2 group disappeared; instead of these the two N-H stretches (3330-3442 cm^{-1}) of amino group along with C-N stretch (1280-1290 cm^{-1}) were observed. In addition, in the IR spectra of pyrrolo[2,3-*b*]pyridines **6.2.3** and pyrido[2,3-*d*]pyrimidines **6.2.2a-d** the typical peaks of stretching vibrations of *CN* and carbonyl groups were observed at ranges 2223-2228 cm^{-1} and 1660-1722 cm^{-1} respectively (from medium to strong intensity).

Compound	Crystal structure	Structure
6.2.1a		
6.2.1h		

Compound	Crystal structure	Structure
6.2.1l		
6.2.2d		
6.2.3h		
6.2.4b		
6.2.4d		

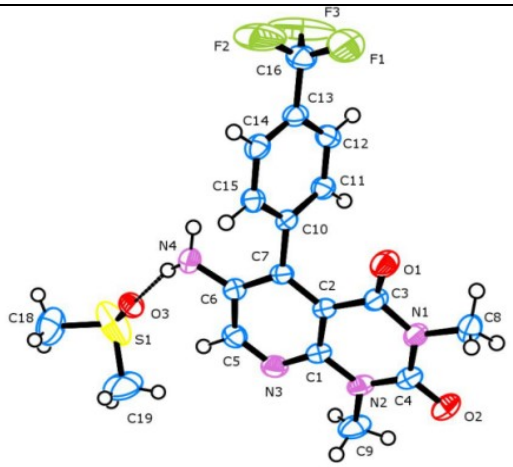
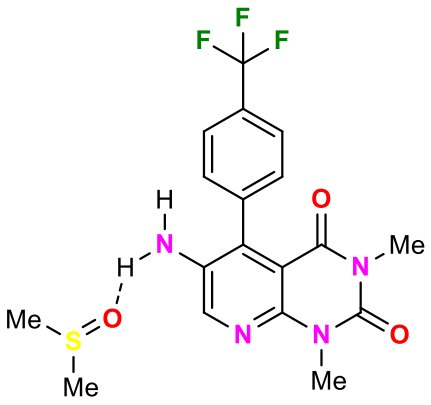
Compound	Crystal structure	Structure
6.3.1c		

Table 6.5.1. Crystal structures of compounds **6.2.1a**,**h**,**l**, **6.2.2d**, **6.2.3h**, **6.2.4b**,**d** and **6.3.1c**.

The structures of compounds **6.2.1a**,**h**,**l**, **6.2.2d**, **6.2.3h**, **6.2.4b**,**d** and **6.3.1c** were confirmed by X-ray single crystal analyses (Table 6.5.1). Thus, the regioselectivity of TM-catalyzed direct C-H arylation was independently proved by X-ray analysis.

7. Exploration of Other Nitroarenes Towards Direct C-H Arylation

To extend our methodology, a number of variously substituted nitroarenes were synthesized and studied applying the conditions developed for previous systems. Among others, 3-nitro-2*H*-chromen-2-one **7.1a**,[271] 3-nitro-4*H*-chromen-4-one **7.1b**,[262] 5-nitropyrimidine derivatives **7.1c-e**,[272] 4-nitroisoxazole **7.1f**,[273] methyl 4-nitrofuran-2-carboxylate **7.1g**[274] (Figure 7.1) as well as some of fused 3-nitropyridines **6.1.3i**,**j** and quinolines **6.1.3k-m**[261] (Scheme 6.1.1) were unreactive and/or unstable in our typical reaction protocol.

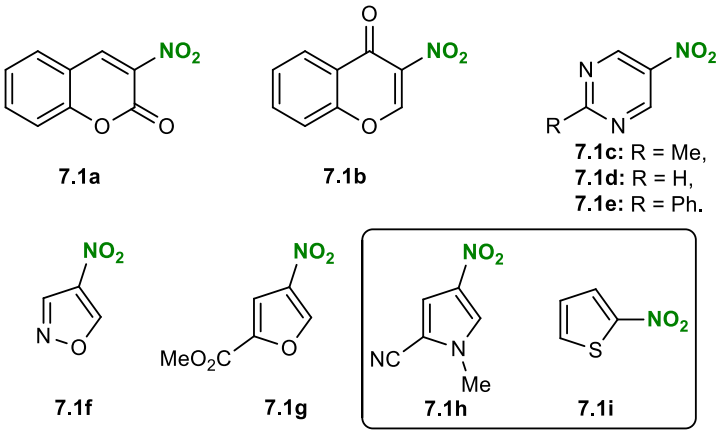
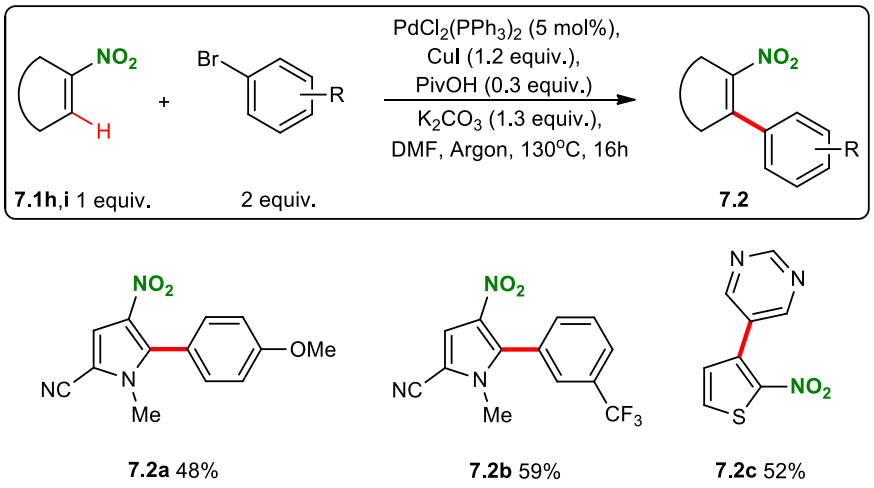


Figure 7.1. The list of nitroarenes explored in the work.

Gratifyingly, in contrast to these unsuccessful trials, further experiments showed that 1-methyl-4-nitro-1*H*-pyrrole-2-carbonitrile **7.1h**[275] and commercially available 2-nitrothiophene **7.1i** under otherwise identical conditions are prone to react with suitable aryl bromides leading to the formation of corresponding biaryls **7.2a-c** in good yields (Scheme 7.1). In all cases, the product of the arylation of the β-C-H bond to the nitro group was the only observed regioisomer. Further optimization of reaction conditions and exploration of new methods for TM-catalyzed C-H activation of nitroarenes will be studied in our ongoing research program.



Scheme 7.1. Scope of the reaction with respect to other nitroarenes.

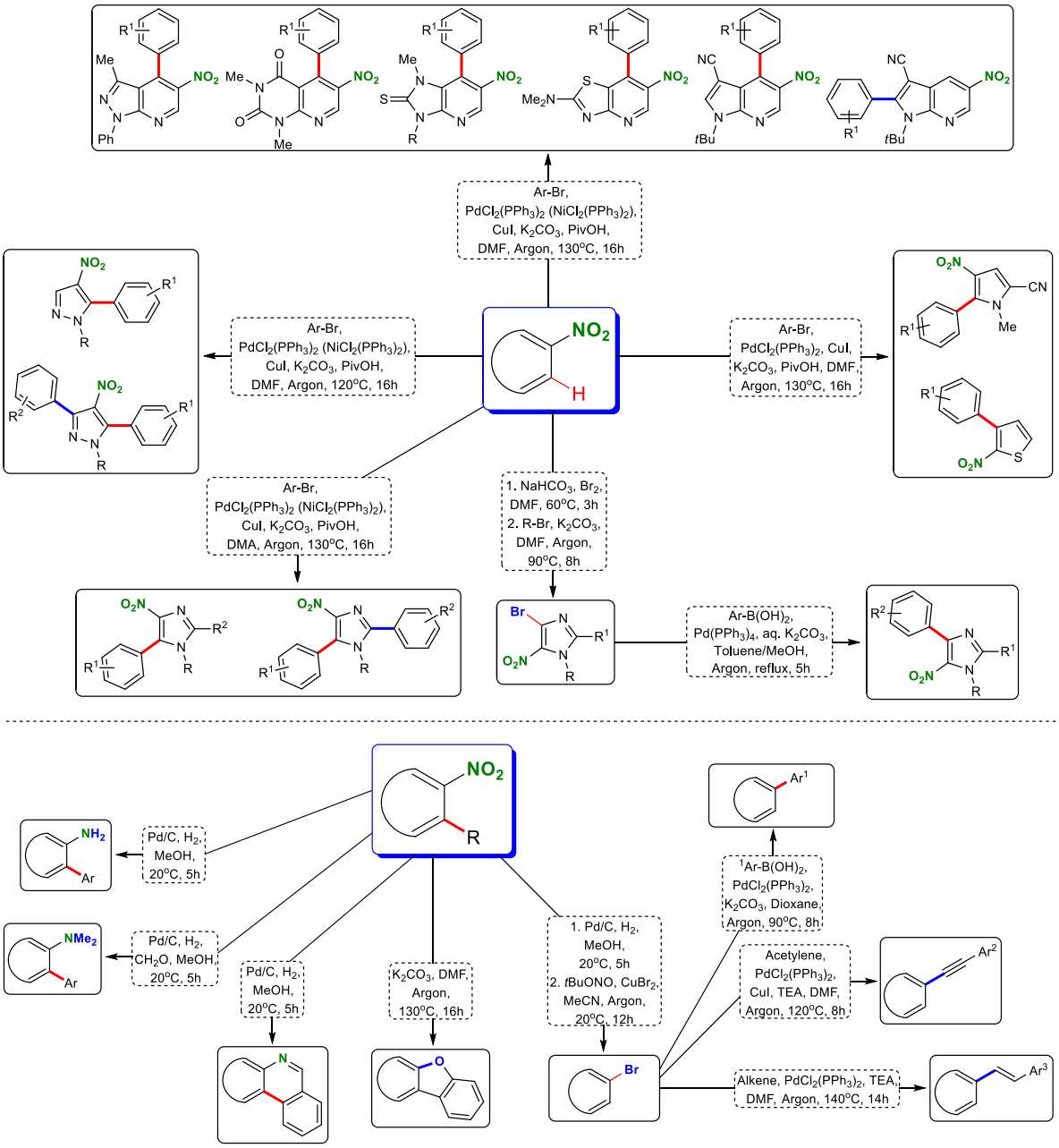
8. Summary and Outlook

In conclusion, the TM-catalyzed C-H arylation of a broad range of nitro-substituted heteroarenes was studied in detail (Scheme 8.1). Namely, in case of 4-nitroimidazoles it was possible to arylate the C(5)-H and C(2)-H bonds regioselectively. For arylation of position 4 of imidazole ring an efficient Pd-catalyzed Suzuki-Miyaura cross-coupling reaction of 4-bromo-5-nitroimidazoles was developed. In addition, it was possible to demonstrate that the yields of Suzuki-Miyaura cross-coupling reaction of 5-bromo-4-nitroimidazoles were slightly lower in comparison to the yields obtained for similar compounds in direct C(5)-H arylation.

In case of 4-nitropyrazoles the reactions proceeded with exclusive C(5)-H regioselectivity; however, additional experiments showed that the C(5)-H arylation products can be further arylated at position 3 of pyrazole ring in the presence of an excess of CuI.

In case of purine-like fused 3-nitropyridines we were successful with pyrazolo[3,4-*b*]pyridine, pyrido[2,3-*d*]pyrimidine, imidazo[4,5-*b*]pyridine, thiazolo[4,5-*b*]pyridine and pyrrolo[2,3-*b*]pyridine derivatives. In all cases except pyrrolo[2,3-*b*]pyridine derivative, the main

regioisomer appeared to be the γ-C-H arylation product. For the pyrrolo[2,3-*b*]pyridine derivative, it was possible to show that the positions 2 and 4 are almost equally active.



Scheme 8.1. Scope of the work.

The scope of the reactions with respect to the aryl halide coupling partner as well as for nitro-substituted heteroarenes was examined. For all systems the C-H arylation can be performed by two different d-metals, namely Pd and Ni, using CuI as additive. The use of Pd-based catalysts proved to give better yields than Ni. Furthermore, it was possible to optimize the reaction conditions, so that only stoichiometric amounts of coupling partners can be used. The competitive experiments showed that aryl bromides with an electron-withdrawing group are

much more reactive than the respective aryl bromides with an electron-donating group. Besides, the competitive experiments between different nitro-substituted heteroarenes showed that 4-nitropyrazoles are the most reactive heterocyclic system towards Pd-catalyzed direct C-H arylation.

Additionally, it was discovered that among others, nitropyrrole derivatives and 2-nitrothiophene under otherwise identical conditions are prone to react with suitable aryl bromides leading to the formation of corresponding biaryls. Many other nitro-substituted heteroarenes were also examined; nevertheless, the results were unsatisfactory.

Within the course of study the multipurpose nature of nitro group as directing group was demonstrated (Scheme 8.1). In particular, *via* reduction of nitro group in different conditions it was possible to prepare various aminoarenes, N,N-dimethylamino arenes and isoquinolines fused with different heteroarenes. It was possible to perform a domino nitro group substitution-C-H arylation reaction which leads to the formation of benzofuran derivatives. Eventually, we could transform the nitro group to bromo substituent, using a semi-one-pot procedure, which allowed us to perform some further C-C bond forming reactions *via* cross-coupling reactions.

A mechanistic explanation of results was proposed. The developed methods show a number of advantages, including high experimental simplicity, catalyst efficiency, functional group compatibility, low cost of the catalytic system and starting materials.

Regarding the future development of the field, it is difficult to predict anything since 15 years ago nobody really knew about C-H activation (Chapter 2.2, Figure 2.2.1); nevertheless, especially during the last four years the field of TM-catalyzed direct C-H transformations has been growing enormously (Chapter 2.2, Figure 2.2.1). A number of crucial chemical transformations were and will be modified to corresponding efficient direct C-H transformations; thus, making the synthesis of targeted substances less time consuming and inexpensive.

Appendix

A.1. Experimental Section

A.1.1. Equipment

^{1}H NMR Spectroscopy: Bruker AM 250, Bruker ARX 300, Bruker ARX 500; δ = 0.00 ppm for tetramethylsilane; δ = 7.25 ppm for ($CDCl_3$); δ = 2.50 ppm for DMSO-d_6. Characterization of the signals: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, t = triplet, dt = double of triplet, q = quartet, quint = quintet, m = multiplet, br = broad. Spectra were evaluated according to first order rules. All coupling constants are indicated as (*J*).

^{13}C NMR Spectroscopy: Bruker AM 250, (62.9 MHz); Bruker ARX 300, (75 MHz), Bruker ARX 500, (125 MHz); Ref: δ = 77.00 ppm for $CDCl_3$; δ = 39.7 ppm for DMSO-d_6. The multiplicity of the carbon atoms was determined by the DEPT 135 and APT technique (APT = Attached Proton Test) and quoted as Me, CH_2, CH and C for primary, secondary, tertiary and quaternary carbon atoms, respectively. Characterization of the signal: q = quartet. The multiplicity of the signals was determined by the DEPT and/or the APT recording technologies.

Mass Spectrometry (MS): AMD MS40, AMD 402 (AMD Intectra), Varian MAT CH 7, MAT 731.

High Resolution Mass Spectrometry (HRMS): Finnigan MAT 95 or Varian MAT 311; Bruker FT CIR, AMD 402 (AMD Intectra).

Infrared Spectroscopy (IR): Bruker IFS 66 (FT IR), Nicolet 205 FT IR; Nicolet Protege 460, Nicolet 360 Smart rbit (ATR); KBr, KAP, Nujol, and ATR; Abbreviations for signal allocations: w = weak, m = medium, s = strong.

X-ray Crystal Structure Analysis: Bruker X8Apex Diffractometer with CCD-Kamera (Mo - 100 Kα and graphite monochromator, λ = 0.71073 Å).

Melting Points: Micro heating table HMK 67/1825 Kuestner (Büchi apparatus); Melting points are uncorrected.

Column Chromatography: Chromatography was performed over Merck silica gel 60 (0,063 - 0,200 mm, 70 - 230 mesh) as normal and/or over silica gel 60 (0,040 - 0,063 mm, 200 -400 mesh) as flash chromatography. All solvents were distilled before use.

Thin Layer Chromatography (TLC): Merck DC finished aluminum foils silica gel 60 F254 and Macherey finished foils Alugram® Sil G/UV254. Detection under UV light at 254 nm and/or 366 nm without dipping reagent, as well as with vanillin-sulfuric acid reagent (1 mL vanillin in 100 mL stock solution of 85% methanol, 14% acetic acid and 1% sulfuric acid).

Chemicals and work technique: All solvents for using were distilled by standard methods. Most of the starting chemicals are standard, commercially available from Merck®, Aldrich®, Arcos® and others.

A.1.2. General procedures and spectroscopic data

General Procedure for the Synthesis of *N*-Substituted Imidazoles by Alkylation. Synthesis of Compounds 4.1.3a-i, 4.1.6a-c, and 4.1.7a-c. The corresponding imidazole (1 equiv.) and K_2CO_3 (3 equiv.) successively were weighed in air and placed in a Schlenk flask equipped with a magnetic stir bar, which then was capped with a rubber septum. The reaction vessel was evacuated and back filled with argon. The dry DMF (8 mL for 10 mmol of imidazole) and corresponding alkyl bromide (1.3 equiv.) were added *via* syringe, and the reaction was heated to 90°C for 8h. Upon completion, the reaction was cooled to room temperature and concentrated under vacuum. The crude mass was washed with water, which was extracted with chloroform. Finally, the organic phase was dried (Na_2SO_4), filtered, and evaporated to dryness, or (if necessary) the residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired alkylated product.

General Procedure for Direct C-H Arylation of *N*-Substituted 4-Nitroimidazoles. Synthesis of Compounds 4.2.1a-t and 4.2.5a. The corresponding *N*-substituted 4-nitroimidazole **4.1.3b**,**c**,**e-g** or **4.2.4c** (1 equiv.), CuI (1.2 equiv.), K_2CO_3 (1.3 equiv.), $(CH_3)_3CCO_2H$ (0.3 equiv.), and $PdCl_2(PPh_3)_2$ (or $NiCl_2(PPh_3)_2$) (0.05 equiv.) successively

were weighed in air and placed in a Schlenk flask equipped with a magnetic stir bar, which then was capped with a rubber septum. The reaction vessel was evacuated and back filled with argon (three times). The dry DMA (8 mL for 1 mmol of *N*-substituted 4-nitroimidazole) and aryl bromide (2 equiv.) were added *via* syringe (in the case of solid aryl bromide, first it was dissolved in dry DMA under inert atmosphere), and the reaction was heated to 130°C for 14h. Upon completion, the reaction was cooled to room temperature and concentrated under vacuum. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired arylated product.

General Procedure for Pd-Catalyzed Intramolecular Dehydrogenative Twofold C-H Cross-Coupling Reaction. Synthesis of Compounds 4.2.2a-c. The corresponding *N*-substituted 4-nitro-imidazole **4.1.3c**,**e**,**f** (1 equiv.), Ag_2CO_3 (1.2 equiv.), K_2CO_3 (1.3 equiv.), $(CH_3)_3CCO_2H$ (0.3 equiv.), and $PdCl_2(PPh_3)_2$ (0.05 equiv.) successively were weighed in air and placed in a Schlenk flask, equipped with a magnetic stir bar, which then was capped with a rubber septum. The reaction vessel was evacuated and back filled with argon (three times). The dry DMA (8 mL for 1 mmol of *N*-substituted 4-nitroimidazole) was added *via* a syringe, and the reaction was heated to 130°C for 14h. Upon completion, the reaction was cooled to room temperature and concentrated under vacuum. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired product.

General Procedure for Direct C-H Arylation of 2,5-Unsubstituted 4-Nitroimidazole. Synthesis of Compounds 4.2.3a-c. The corresponding *N*-substituted 4-nitroimidazole **4.1.3d** (1 equiv.), CuI (1.2 equiv.), K_2CO_3 (2.3 equiv.), $(CH_3)_3CCO_2H$ (0.3 equiv.), and $PdCl_2(PPh_3)_2$ (0.05 equiv.) successively were weighed in air and placed in a Schlenk flask, equipped with a magnetic stir bar, which then was capped with a rubber septum. The reaction vessel was evacuated and back filled with argon (three times). The dry DMA (8 mL for 1 mmol of *N*-substituted 4-nitroimidazole) and aryl bromide (2.5 equiv.) were added *via* syringe (in the case of solid aryl bromide, first it was dissolved in dry DMA under inert atmosphere), and the reaction was heated to 130°C for 14h. Upon completion, the reaction was cooled to room temperature and concentrated under vacuum. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired arylated product.

General Procedure for Regioselective C(5)-H Arylation of 2,5-Unsubstituted 4-

Nitroimidazole. Synthesis of Compounds 4.2.4a-c. The corresponding *N*-substituted 4-nitroimidazole **4.1.3d** (1 equiv.), CuI (1.2 equiv.), K_2CO_3 (1.3 equiv.), $(CH_3)_3CCO_2H$ (0.3 equiv.), and $PdCl_2(PPh_3)_2$ (0.05 equiv.) successively were weighed in air and placed in a Schlenk flask, equipped with a magnetic stir bar, which then was capped with a rubber septum. The reaction vessel was evacuated and back filled with argon (three times). The dry DMA (8 mL for 1 mmol of *N*-substituted 4-nitroimidazole) and aryl bromide (1.1 equiv.) were added *via* syringe (in case of solid aryl bromide, first it was dissolved in dry DMA under inert atmosphere), and the reaction was heated to 130ºC for 14h. Upon completion, the reaction was cooled to room temperature and concentrated under vacuum. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired arylated product.

General Procedure for Pd-Catalyzed Suzuki-Miyaura Cross-Coupling Reaction of 5(4)-Bromo-4(5)-nitroimidazoles. Synthesis of Compounds 4.3.1a-f and 4.3.2a-e. The corresponding 5(4)-bromo-4(5)-nitroimidazole **4.1.6** or **4.1.7** (1 equiv.), arylboronic acid (1.3 equiv.), and $Pd(PPh_3)_4$ (0.10 equiv.) successively were weighed in air and placed in a Schlenk flask (under the flow of argon), equipped with a magnetic stir bar, which then was set with reflux and capped with a rubber septum. The toluene/MeOH (5 : 1) system (8 mL for 1 mmol of 5(4)-bromo-4(5)-nitroimidazole) and 2 M aqueous K_2CO_3 (1 mL for 1 mmol of starting nitroimidazole) were added *via* syringe (under the flow of argon), and the reaction mixture was refluxed for 5h in inert atmosphere (argon balloon). Upon completion, the reaction was cooled to room temperature and concentrated under vacuum. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired arylated product.

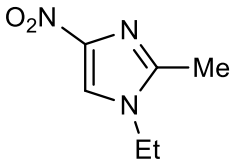
General Procedure for Reduction of Arylated Nitroimidazoles Containing a Carbonyl Group. Synthesis of Compounds 4.4.3a-e. To a Schlenk flask equipped with a magnetic stir bar and filled with corresponding arylated nitroimidazole **4.2.1t**, **4.3.1a**,**b**, **4.3.2a**,**e** (1 equiv.) was added 10% Pd/C (0.1 equiv.). The flask was fitted with a rubber septum and then held under vacuum for 3min; it was then filled with MeOH (25 mL for 1 mmol of arylated nitroimidazole) and hydrogen. Holding under vacuum was repeated one more time, and after sequential filling with hydrogen, the reaction mixture was stirred for 5h under H_2 atmosphere (H_2 balloon). After the reaction was stopped, the mixture was filtered through a Celite pad. The filtrate was evaporated to dryness and purified by column chromatography typically

using heptane/ethyl acetate mixtures to provide the desired product.

Competitive Experiment Between Imidazole 4.1.3c and Electronically Different Aryl Bromides. Synthesis of Compound 4.2.1u. The corresponding *N*-substituted 4-nitroimidazole **4.1.3c** (1 equiv.), CuI (1.2 equiv.), K_2CO_3 (1.3 equiv.), $(CH_3)_3CCO_2H$ (0.3 equiv.), and $PdCl_2(PPh_3)_2$ (0.05 equiv.) successively were weighed in air and placed in a Schlenk flask, equipped with a magnetic stir bar, which then was capped with a rubber septum. The reaction vessel was evacuated and back filled with argon (three times). The dry DMA (8 mL for 1 mmol of *N*-substituted 4-nitroimidazole) and aryl bromides (from each 1 equiv.) were added *via* syringe (in case of solid aryl bromide, first it was dissolved in dry DMA under inert atmosphere), and the reaction was heated to 130°C for 14h. Upon completion, the reaction was cooled to room temperature and concentrated under vacuum. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures.

Competitive Experiment Between Two Various Imidazoles. Synthesis of Compounds 4.2.1u and 4.2.1w. The corresponding *N*-substituted 4-nitroimidazoles **4.1.3c** and **4.1.3g** (from each 1 equiv.), CuI (1.2 equiv.), K_2CO_3 (1.3 equiv.), $(CH_3)_3CCO_2H$ (0.3 equiv.), and $PdCl_2(PPh_3)_2$ (0.05 equiv.) successively were weighed in air and placed in a Schlenk flask, equipped with a magnetic stir bar, which then was capped with a rubber septum. The reaction vessel was evacuated and back filled with argon (three times). The dry DMA (8 mL for 2 mmol of *N*-substituted 4-nitroimidazoles) and aryl bromide (1.1 equiv.) were added *via* syringe (in the case of solid aryl bromide, first it was dissolved in dry DMA under inert atmosphere), and the reaction was heated to 130°C for 14h. Upon completion, the reaction was cooled to room temperature and concentrated under vacuum. The mixture of compounds **4.2.1u** and **4.2.1w** was purified by column chromatography typically using heptane/ethyl acetate mixtures.

1-Ethyl-2-methyl-4-nitro-1*H*-imidazole (4.1.3a).



Starting from 2-methyl-4(5)-nitro-1*H*-imidazole **4.1.1a** (1.27 g, 10 mmol), bromoethane (1.41 g, 13 mmol) and K_2CO_3 (4.14 g, 30 mmol) in 8 mL DMF, the product **4.1.3a** was isolated as a white solid (1.271 g, 82%). Mp: 64-65°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (t, 3H, ^3J = 7.0 Hz, CH_2CH_3), 2.42 (s, 3H, Me), 3.96 (t,

2H, ^{3}J = 7.0 Hz, *CH*$_2$CH$_3$), 7.69 (s, 1H, imidazole).

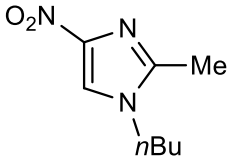
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.0, 15.5 (Me), 42.0 (CH_2), 118.9 (CH), 144.4 (C).

MS (GC, 70 eV): *m/z* (%) = 155 (M^+, 61), 83 (20), 56 (41), 43 (100).

HRMS (EI): calcd for $C_6H_9N_3O_2$ (M^+) 155.06893, found 155.06894.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3108 (w), 1532 (s), 1495 (m), 1453 (w), 1423 (m), 1399 (s), 1332 (s), 1292 (s), 1259 (s), 1190 (w), 1149 (m), 1082 (m), 1034 (w), 991 (m), 964 (m), 835 (s), 803 (m), 757 (s), 681 (s), 639 (w).

1-Butyl-2-methyl-4-nitro-1*H*-imidazole (4.1.3b).



Starting from 2-methyl-4(5)-nitro-1*H*-imidazole **4.1.1a** (1.27 g, 10 mmol), 1-bromobutane (1.78 g, 13 mmol) and K_2CO_3 (4.14 g, 30 mmol) in 8 mL DMF, the product **4.1.3b** was isolated as a white solid (1.610 g, 88%). Mp: 55-57°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 (t, 3H, ^{3}J = 6.7 Hz, $CH_2CH_2CH_2CH_3$), 1.18-1.31 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.56-1.70 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.29 (s, 3H, Me), 3.81 (t, 2H, ^{3}J = 7.3 Hz, $CH_2CH_2CH_2CH_3$), 7.59 (s, 1H, imidazole).

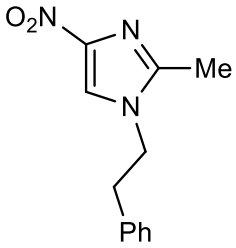
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 12.7, 13.1 (Me), 19.3, 31.9, 46.6 (CH_2), 119.5 (CH), 144.4, 145.9 (C).

MS (GC, 70 eV): *m/z* (%) = 183 (M^+, 58), 168 (21), 141 (64), 43 (100).

HRMS (EI): calcd for $C_8H_{13}N_3O_2$ (M^+) 183.10023, found 183.100133.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3119 (w), 2960 (m), 2874 (w), 1531 (s), 1496 (m), 1466 (s), 1379 (m), 1330 (s), 1290 (s), 1261 (s), 1186 (m), 1135 (m), 1095 (m), 994 (m), 827 (s), 757 (s), 682 (m), 663 (m).

2-Methyl-4-nitro-1-phenethyl-1*H*-imidazole (4.1.3c).



Starting from 2-methyl-4(5)-nitro-1*H*-imidazole **4.1.1a** (1.27 g, 10 mmol), (2-bromoethyl)benzene (2.40 g, 13 mmol) and K_2CO_3 (4.14 g, 30 mmol) in 8 mL DMF, the product **4.1.3c** was isolated as a white solid (2.150 g, 93%). Mp: 111-113°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.08 (s, 3H, Me), 3.07 (t, 2H, ^{3}J = 6.8 Hz, CH_2), 4.24 (t, 2H, ^{3}J = 6.8 Hz, CH_2), 7.00-7.03 (m, 2H, CH_{Ar}), 7.16-7.17 (m, 1H, CH_{Ar}), 7.23-7.30 (m, 3H, CH_{Ar}), 7.48 (s, 1H, imidazole).

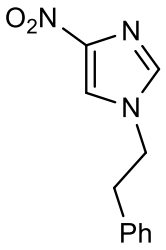
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 11.8 (Me), 37.2, 49.8 (CH_2), 119.1, 127.5, 128.4 (CH), 128.6, 128.9 (C), 129.0, 135.9, 136.0 (CH), 147.9 (C).

MS (GC, 70 eV): *m/z* (%) = 231 (M^+, 40), 105 (25), 91 (100).

HRMS (EI): calcd for $C_{12}H_{13}N_3O_2$ (M^+) 231.10023, found 231.100263.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3115 (w), 1516 (m), 1481 (s), 1438 (m), 1404 (m), 1377 (s), 1333 (s), 1286 (s), 1159 (w), 1124 (m), 1048 (w), 1015 (w), 982 (m), 863 (m), 822 (s), 751 (s), 698 (s), 654 (s), 621 (w), 564 (m).

4-Nitro-1-phenethyl-1*H*-imidazole (4.1.3d).



Starting from 4(5)-nitro-1*H*-imidazole **4.1.1b** (1.13 g, 10 mmol), (2-bromoethyl)benzene (2.40 g, 13 mmol) and K_2CO_3 (4.14 g, 30 mmol) in 8 mL DMF, the product **4.1.3d** was isolated as a white solid (1.736 g, 80%). Mp: 81-83°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.07 (t, 2H, ^3J = 6.9 Hz, CH_2), 4.24 (t, 2H, ^3J = 6.9 Hz, CH_2), 7.00-7.03 (m, 2H, CH_{Ar}), 7.17 (d, 1H, ^4J = 1.4 Hz, imidazole), 7.21-7.27 (m, 3H, CH_{Ar}), 7.58 (d, 1H, ^4J = 1.4 Hz, imidazole).

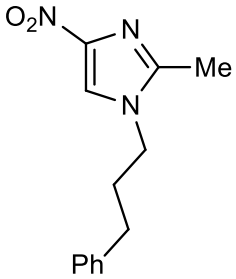
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 37.2, 49.8 (CH_2), 119.1, 127.5, 128.4 (CH), 128.6, 128.9 (C), 129.1, 135.9 (CH), 136.0, 147.9 (C).

MS (GC, 70 eV): *m/z* (%) = 217 (M^+, 40), 105 (25), 91 (100).

HRMS (EI): calcd for $C_{11}H_{11}N_3O_2$ (M^+) 217.22394, found 217.22396.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3115 (w), 1516 (m), 1481 (s), 1438 (m), 1404 (m), 1377 (m), 1333 (s), 1286 (s), 1159 (w), 1124 (m), 1079 (w), 1048 (w), 982 (m), 932 (w), 863 (m), 822 (s), 751 (s), 698 (s), 672 (m), 654 (s), 564 (m).

2-Methyl-4-nitro-1-(3-phenylpropyl)-1*H*-imidazole (4.1.3e).



Starting from 2-methyl-4(5)-nitro-1*H*-imidazole **4.1.1a** (1.27 g, 10 mmol), (3-bromopropyl)benzene (2.59 g, 13 mmol) and K_2CO_3 (4.14 g, 30 mmol) in 8 mL DMF, the product **4.1.3e** was isolated as a white solid (1.911 g, 78%). Mp: 82-84°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.17-2.29 (m, 2H, CH_2), 2.42 (s, 3H, Me), 2.77 (t, 2H, ^3J = 7.4 Hz, CH_2), 3.97 (t, 2H, ^3J = 7.4 Hz, CH_2), 7.22-7.24 (m, 2H, CH_{Ar}), 7.31-7.43 (m, 3H, CH_{Ar}), 7.74 (s, 1H, imidazole).

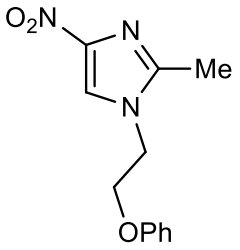
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.0 (Me), 31.3, 32.3, 46.3 (CH_2), 119.4, 126.7, 128.2, 128.8 (CH), 139.4, 144.7, 146.5 (C).

MS (GC, 70 eV): *m/z* (%) = 245 (M^+, 34), 141 (100), 117 (25), 91 (76), 43 (68).

HRMS (EI): calcd for $C_{13}H_{15}N_3O_2$ (M^+) 245.11588, found 245.11586.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3104 (w), 3023 (w), 1531 (s), 1494 (s), 1464 (m), 1454 (m), 1419 (m), 1401 (m), 1358 (s), 1326 (s), 1289 (s), 1233 (w), 4498 (w), 1143 (m), 1039 (w), 991 (m), 910 (w), 833 (s), 747 (s), 698 (s), 681 (m), 641 (w), 618 (w), 591 (w), 572 (m).

2-Methyl-4-nitro-1-(2-phenoxyethyl)-1*H*-imidazole (4.1.3f).



Starting from 2-methyl-4(5)-nitro-1*H*-imidazole **4.1.1a** (1.27 g, 10 mmol), (2-bromoethoxy)benzene (2.61 g, 13 mmol) and K_2CO_3 (4.14 g, 30 mmol) in 8 mL DMF, the product **4.1.3f** was isolated as a white solid (2.198 g, 89%). Mp: 100-101°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.48 (s, 3H, Me), 4.24-4.30 (m, 4H, 2×CH_2), 6.80-6.83 (m, 2H, CH_{Ar}), 6.93-6.98 (m, 1H, CH_{Ar}), 7.22-7.27 (m, 2H, CH_{Ar}), 7.81 (s, 1H, imidazole).

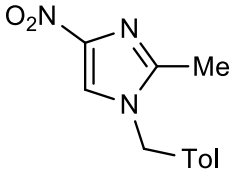
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.1 (Me), 46.5, 66.1 (CH_2), 114.3, 120.2, 121.8, 129.6 (CH), 145.2, 146.4, 157.4 (C).

MS (GC, 70 eV): *m/z* (%) = 247 (M^+, 100), 120 (60), 107 (72), 77 (73).

HRMS (EI): calcd for $C_{12}H_{13}N_3O_3$ (M^+) 247.09514, found 247.09556.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3118 (w), 1588 (w), 1531 (m), 1495 (m), 1469 (m), 1385 (m), 1329 (s), 1290 (s), 1237 (s), 1161 (m), 1079 (m), 1050 (m), 993 (m), 907 (m), 827 (m), 787 (m), 753 (s), 690 (s), 678 (m), 617 (w), 599 (m), 568 (w).

1-(4-Methylbenzyl)-2-methyl-4-nitro-1*H*-imidazole (4.1.3g).



Starting from 2-methyl-4(5)-nitro-1*H*-imidazole **4.1.1a** (1.27 g, 10 mmol), 1-(bromomethyl)-4-methylbenzene (2.40 g, 13 mmol) and K_2CO_3 (4.14 g, 30 mmol) in 8 mL DMF, the product **4.1.3g** was isolated as a white solid (1.917 g, 83%). Mp: 104-105°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3H, Me), 2.38 (s, 3H, Me), 5.03 (s, 2H, CH_2), 7.02 (d, 2H, ^3J = 8.1 Hz, CH_{Ar}), 7.18 (d, 2H, ^3J = 8.1 Hz, CH_{Ar}), 7.60 (s, 1H, imidazole).

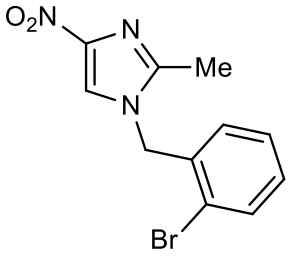
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.3, 21.1 (Me), 50.8 (CH_2), 120.0, 127.3, 130.1 (CH), 130.7, 139.0, 145.0, 146.4 (C).

MS (GC, 70 eV): *m/z* (%) = 231 (M^+, 11), 105 (100).

HRMS (EI): calcd for $C_{12}H_{13}N_3O_2$ (M^+) 231.10023, found 231.10038.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3099 (w), 1533 (s), 1493 (m), 1462 (m), 145 (w), 1396 (s), 1350 (m), 1329 (s), 1314 (m), 1286 (s), 1226 (m), 1141 (m), 1036n (w), 993 (m), 833 (m), 756 (s), 681 (s), 662 (m), 616 (w), 574 (m).

1-(2-Brombenzyl)-2-methyl-4-nitro-1*H*-imidazole (4.1.3h).



Starting from 2-methyl-4(5)-nitro-1*H*-imidazole **4.1.1a** (1.27 g, 10 mmol), 1-bromo-2-(bromomethyl)benzene (3.25 g, 13 mmol) and K_2CO_3 (4.14 g, 30 mmol) in 8 mL DMF, the product **4.1.3h** was isolated as a brown solid (2.449 g, 83%). Mp: 91-92°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 3H, Me), 5.15 (s, 2H, CH_2), 6.95 (dd, 1H, ^3J = 7.6 Hz, ^4J = 1.7 Hz, CH_{Ar}), 7.24-7.34 (m, 2H, CH_{Ar}), 7.56 (s, 1H, CH_{Ar}), 7.64 (dd, 1H, ^3J = 7.8 Hz, ^4J = 1.3 Hz, CH_{Ar}).

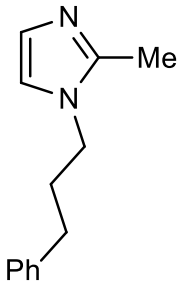
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.3 (Me), 51.0 (CH_2), 119.8 (CH), 123.3 (C), 128.5, 129.2, 130.8 (CH), 133.1 (C), 133.7 (CH), 145.2, 146.5 (C).

MS (GC, 70 eV): *m/z* (%) = 296 (M^+, 9), 296 (1), 295 (10), 171 (100), 169 (97), 90 (34), 89 (32).

HRMS (EI): calcd for $C_{11}H_{10}N_3O_2Br$ (M^+) 296.12000, found 296.12012.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3127 (w), 1588 (w), 1532 (s), 1493 (s), 1438 (m), 1413 (m), 1380 (m), 1358 (m), 1324 (m), 1291 (s), 1268 (s), 1142 (m), 1127 (m), 1030 (m), 992 (m), 943 (w), 829 (m), 783 (m), 752 (s), 659 (m).

2-Methyl-1-(3-phenylpropyl)-1*H*-imidazole (4.1.3i).



Starting from 2-methyl-1*H*-imidazole (0.82 g, 10 mmol), (3-bromopropyl)benzene (2.59 g, 13 mmol) and K_2CO_3 (4.14 g, 30 mmol) in 8 mL DMF, the product **4.1.3i** was isolated as a white viscous oil (0.821 g, 41%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.02-2.12 (m, 2H, CH_2), 2.32 (s, 3H, Me), 2.64 (t, 2H, ^3J = 7.4 Hz, CH_2), 3.82 (t, 2H, ^3J = 7.2 Hz, CH_2), 6.81-6.82 (m, 1H, imidazole), 6.91-6.92 (m, 1H, imidazole), 7.13-7.32 (m, 5H, CH_{Ar}).

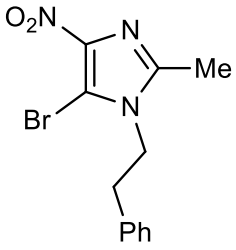
^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 13.0 (Me), 32.0, 32.6, 45.3 (CH_2), 119.0, 126.4, 127.0, 128.3, 128.6 (CH), 140.4, 144.4, (C).

MS (GC, 70 eV): *m/z* (%) = 200 (M^+, 50), 117 (17), 117 (25), 96 (76), 91 (45).

HRMS (ESI): calcd for $C_{13}H_{16}N_2$ (M+H) 201.13862, found 201.13866.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3034 (w), 2928 (w), 1589 (w), 1531 (m), 1492 (m), 1423 (m), 1349 (w), 1277 (w), 1232 (w), 1153 (w), 1095 (w), 1045 (w), 926 (w), 857 (w), 768 (s), 738 (s), 704 (s), 669 (s), 619 (w), 577 (m).

5-Bromo-2-methyl-4-nitro-1-phenethyl-1*H*-imidazole (4.1.6a).



Starting from 5(4)-bromo-2-methyl-4(5)-nitro-1*H*-imidazole **4.1.5** (2.06 g, 10 mmol), (2-bromoethyl)benzene (2.40 g, 13 mmol) and K_2CO_3 (4.14 g, 30 mmol) in 8 mL DMF, the product **4.1.6a** was isolated as a brown solid (1.767 g, 57%). Mp: 127-129°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.01 (s, 3H, Me), 3.02 (t, 2H, ^3J = 7.0 Hz, CH_2), 4.18 (t, 2H, ^3J = 7.0 Hz, CH_2), 6.98-7.01 (m, 2H, CH_{Ar}), 7.25-7.27 (m, 3H, CH_{Ar}).

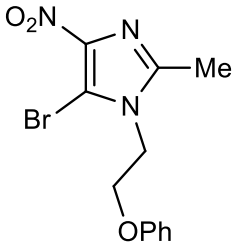
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.5 (Me), 35.6, 48.0 (CH_2), 104.2 (C), 127.5, 128.7, 129.1 (CH), 136.0, 145.3 (C).

MS (GC, 70 eV): *m/z* (%) = 309 (M^+, 4), 230 (100), 213 (50), 105 (70), 91 (99), 77 (35).

HRMS (EI): calcd for $C_{12}H_{12}N_3BrO_2$ (M^+) 309.01074, found 309.010864.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2927 (w), 1724 (w), 1632 (w), 1599 (w), 1537 (w), 1515 (s), 1476 (m), 1453 (m), 1381 (s), 1281 (s), 1239 (m), 1181 (w), 1153 (m), 1082 (w), 1040 (m), 1013 (m), 930 (w), 899 (w), 842 (m), 759 (m), 750 (s), 673 (m), 634 (m), 570 (m).

5-Bromo-2-methyl-4-nitro-1-(2-phenoxyethyl)-1*H*-imidazole (4.1.6b).



Starting from 5(4)-bromo-2-methyl-4(5)-nitro-1*H*-imidazole **4.1.5** (2.06 g, 10 mmol), (2-bromoethoxy)benzene (2.61 g, 13 mmol) and K_2CO_3 (4.14 g, 30 mmol) in 8 mL DMF, the product **4.1.6b** was isolated as a brown solid (1.891 g, 58%). Mp: 93-95°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.63 (s, 3H, Me), 4.28 (t, 2H, ^3J = 5.0 Hz, CH_2), 4.44 (t, 2H, ^3J = 5.0 Hz, CH_2), 6.81-6.85 (m, 2H, CH_{Ar}), 6.95-7.02 (m, 1H, CH_{Ar}), 7.25-7.31 (m, 2H, CH_{Ar}).

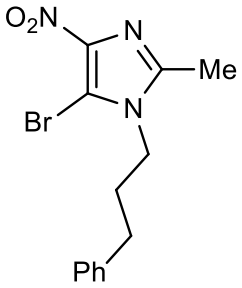
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.3 (Me), 45.8, 65.3 (CH_2), 104.4 (C), 114.0, 121.6, 129.5 (CH), 146.2, 157.3 (C).

MS (GC, 70 eV): *m/z* (%) = 325 (M^+, 1), 246 (100), 107 (15), 77 (31).

HRMS (ESI): calcd for $C_{12}H_{12}N_3BrO_3$ (M+H) 326.01348, found 326.0141.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2931 (w), 1587 (w), 1526 (s), 1494 (s), 1466 (m), 1376 (m), 1336 (s), 1279 (m), 1244 (s), 1157 (w), 1080 (m), 1057 (m), 1038 (m), 916 (m), 882 (w), 842 (m), 788 (m), 753 (s), 687 (s), 603 (m).

5-Bromo-2-methyl-4-nitro-1-(3-phenylpropyl)-1*H*-imidazole (4.1.6c).



Starting from 5(4)-bromo-2-methyl-4(5)-nitro-1*H*-imidazole **4.1.5** (2.06 g, 10 mmol), (3-bromopropyl)benzene (2.59 g, 13 mmol) and K_2CO_3 (4.14 g, 30 mmol) in 8 mL DMF, the product **4.1.6c** was isolated as a brown solid (1.782 g, 55%). Mp: 62-64°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.01-2.12 (m, 2H, CH_2), 2.37 (s, 3H, Me), 2.72 (t, 2H, ^3J = 7.5 Hz, CH_2), 3.93-3.98 (m, 2H, CH_2), 7.16-7.34 (m, 5H, CH_{Ar}).

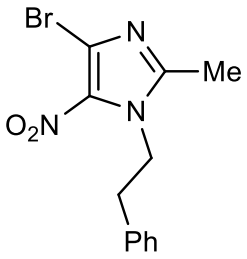
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.9 (Me), 30.7, 32.5, 45.7 (CH_2), 104.5 (C), 126.6, 128.1, 128.7 (CH), 139.4, 144.6 (C).

MS (GC, 70 eV): *m/z* (%) = 323 (M^+, 1), 244 (24), 198 (100), 117 (18), 91 (64).

HRMS (EI): calcd for $C_{13}H_{14}N_3BrO_2$ (M^+) 323.02639, found 323.02638.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1519 (s), 1479 (m), 1384 (s), 1334 (s), 1285 (s), 1254 (s), 1173 (w), 1148 (m), 1084 (w), 1028 (m), 907 (w), 867 (m), 834 (m), 752 (m), 718 (s), 693 (s), 670 (m), 631 (w).

4-Bromo-2-methyl-5-nitro-1-phenethyl-1*H*-imidazole (4.1.7a).



Starting from 5(4)-bromo-2-methyl-4(5)-nitro-1*H*-imidazole **4.1.5** (2.06 g, 10 mmol), (2-bromoethyl)benzene (2.40 g, 13 mmol) and K_2CO_3 (4.14 g, 30 mmol) in 8 mL DMF, the product **4.1.7a** was isolated as a brown solid (0.960 g, 31%). Mp: 125-127°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.01 (s, 3H, Me), 3.03 (t, 2H, ^3J = 7.0 Hz, CH_2), 4.49 (t, 2H, ^3J = 7.0 Hz, CH_2), 7.02-7.05 (m, 2H, CH_{Ar}), 7.27-7.29 (m, 3H, CH_{Ar}).

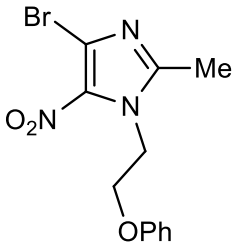
^{13}C NMR (62.96 MHz, $CDCl_3$): δ = 13.6 (Me), 36.4, 49.2 (CH_2), 120.8 (C), 127.4, 128.7, 129.0 (CH), 136.4, 149.1 (C).

MS (GC, 70 eV): *m/z* (%) = 309 (M^+, 1), 263 (44), 184 (100), 104 (72), 91 (76), 77 (41).

HRMS (EI): calcd for $C_{12}H_{12}N_3BrO_2$ (M^+) 309.01074, found 309.011022.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2931 (w), 1526 (s), 1497 (w), 1462 (m), 1415 (m), 1384 (m), 1357 (s), 1332 (s), 1275 (w), 1249(s), 1192 (m), 1175 (s), 1085 (w), 1032 (w), 1002 (m), 852 (w), 830 (s), 802 (w), 755 (s), 741 (m), 704 (s), 686 (m), 671 (m), 630 (w), 610 (w), 563 (m).

4-Bromo-2-methyl-5-nitro-1-(2-phenoxyethyl)-1*H*-imidazole (4.1.7b).



Starting from 5(4)-bromo-2-methyl-4(5)-nitro-1*H*-imidazole **4.1.5** (2.06 g, 10 mmol), (2-bromoethoxy)benzene (2.61 g, 13 mmol) and K_2CO_3 (4.14 g, 30 mmol) in 8 mL DMF, the product **4.1.7b** was isolated as a brown solid (1.239 g, 38%). Mp: 100-102°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.60 (s, 3H, Me), 4.29 (t, 2H, ^3J = 5.0 Hz, CH_2), 4.70 (t, 2H, ^3J = 5.0 Hz, CH_2), 6.76-6.80 (m, 2H, CH_{Ar}), 6.92-6.98 (m, 1H, CH_{Ar}), 7.22-7.28 (m, 2H, CH_{Ar}).

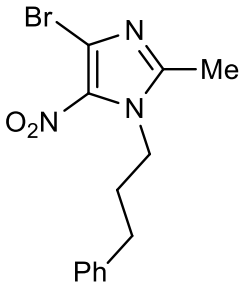
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.6 (Me), 47.2, 66.3 (CH_2), 114.1 (CH), 121.2 (C), 121.7, 129.6 (CH), 150.4, 157.5 (C).

MS (GC, 70 eV): *m/z* (%) = 325 (M^+, 5), 263 (44), 281 (85), 232 (71), 200 (56), 107 (26), 77 (100).

HRMS (EI): calcd for $C_{12}H_{12}N_3BrO_3$ (M+H) 326.01348, found 326.0141.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2930 (w), 1586 (w), 1516 (s), 1488 (m), 1454 (s), 1413 (s), 1355 (s), 1329 (s), 1235 (s), 1172 (s), 1083 (m), 1063 (m), 1022 (m), 912 (m), 890 (w), 829 (m), 758 (s), 693 (s), 632 (w), 591 (m).

4-Bromo-2-methyl-5-nitro-1-(3-phenylpropyl)-1*H*-imidazole (4.1.7c).



Starting from 5(4)-bromo-2-methyl-4(5)-nitro-1*H*-imidazole **4.1.5** (2.06 g, 10 mmol), (3-bromopropyl)benzene (2.59 g, 13 mmol) and K_2CO_3 (4.14 g, 30 mmol) in 8 mL DMF, the product **4.1.7c** was isolated as a brown solid (1.296 g, 40%). Mp: 50-52°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.94-2.06 (m, 2H, CH_2), 2.24 (s, 3H, Me), 2.64 (t, 2H, ^3J = 7.5 Hz, CH_2), 4.18 (t, 2H, ^3J = 7.5 Hz, CH_2), 7.09-7.25 (m, 5H, CH_{Ar}).

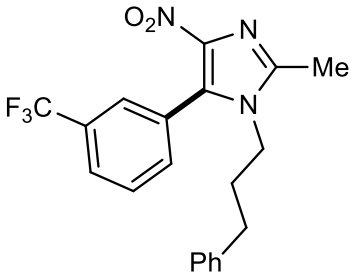
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.7 (Me), 31.0, 32.4, 46.8 (CH_2), 120.3 (C), 126.3, 128.0, 128.5 (CH), 139.5, 148.4 (C).

MS (GC, 70 eV): *m/z* (%) = 323 (M^+, 1), 277 (52), 198 (50), 175 (32), 117 (51), 91 (100).

HRMS (ESI): Calcd for $C_{13}H_{15}N_3BrO_2$ (M+H) 324.03422. Found 324.03456.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1514 (s), 1495 (m), 1452 (s), 1409 (s), 1378 (m), 1343 (s), 1250 (s), 1230 (s), 1170 (s), 1032 (m), 910 (w), 885 (w), 830 (s), 765 (s), 745 (s), 721 (s), 695 (s), 643 (w), 585 (w).

5-(4-(Trifluoromethyl)phenyl)-2-methyl-4-nitro-1-(3-phenylpropyl)-1*H*-imidazole (4.2.1a).



Starting from 2-methyl-4-nitro-1-(3-phenylpropyl)-1*H*-imidazole **4.1.3e** (0.245 g, 1 mmol), 1-bromo-3-(trifluoromethyl)benzene (0.450 g, 2 mmol), (1-iodo-3-(trifluoromethyl)benzene (0.544 g, 2 mmol)), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMA, the product **4.2.1a** was isolated as a green solid (0.373 g, 96%^{Pd}), (0.276 g, 71%$^{Ar-I}$). Mp: 118-120°C.

^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 1.77-1.87 (m, 2H, CH_2), 2.31 (s, 3H, Me), 2.71-2.77 (m, 2H, CH_2), 3.99-4.05 (m, 2H, CH_2), 65.8-6.88 (m, 2H, CH_{Ar}), 7.19-7.22 (m, 3H, CH_{Ar}), 7.62-7.77 (m, 3H, CH_{Ar}), 7.88-7.91 (m, 1H, CH_{Ar}).

^{19}F NMR (235 MHz, DMSO-*d*$_6$): δ = -62.7 (CF_3).

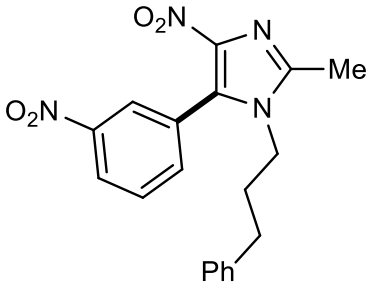
^{13}C NMR (62.9 MHz, DMSO-*d*$_6$): δ = 13.4 (Me), 31.3, 32.4, 44.2 (CH_2), 123.5 (q, ^1J = 274.3 Hz, CF_3), 126.7 (CH), 126.8 (q, ^3J = 8 Hz, C), 127.9 (CH), 128.4 (C), 128.7, 129.5 (CH), 130.2 (C), 131.3 (q, ^2J = 32.8 Hz, CCF_3), 133.5 (CH), 139.1, 143.5, 143.9 (C).

MS (GC, 70 eV): *m/z* (%) = 389 (M^+, 100), 285 (12), 211 (20), 198 (39), 178 (11), 117 (11), 91 (55).

HRMS (EI): calcd for $C_{20}H_{18}N_3O_2F_3$ (M^+) 389.13456, found 389.13444.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956 (w), 1602 (w), 1573 (w), 1533 (w), 1504 (s), 1437 (m), 1402 (m), 1331 (s), 1291 (s), 1245 (m), 1222 (w), 1190 (m), 1163 (m), 1120 (s), 1081 (s), 1020 (w), 930 (w), 872 (m), 804 (m), 778 (w), 750 (m), 732 (m), 698 (s), 674 (m), 565 (m).

2-Methyl-4-nitro-5-(3-nitrophenyl)-1-(3-phenylpropyl)-1*H*-imidazole (4.2.1b).



Starting from 2-methyl-4-nitro-1-(3-phenylpropyl)-1*H*-imidazole **4.1.3e** (0.245 g, 1 mmol), 1-bromo-3-nitrobenzene (0.404 g, 2 mmol), (1-iodo-3-nitrobenzene (0.498 g, 2 mmol)), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), ($NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMA, the product **4.2.1b** was isolated as a green solid (0.296 g, 81%^{Pd}), (0.157 g, 48%^{Ni}), (0.216 g, 59%$^{Ar-I}$). Mp: 164-166°C.

^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 1.69-1.79 (m, 2H, CH_2), 2.41-2.46 (m, 5H, Me, CH_2), 3.72-3.78 (m, 2H, CH_2), 6.94-6.97 (m, 2H, CH_{Ar}), 7.06-7.17 (m, 3H, CH_{Ar}), 7.74-7.80 (m, 1H, CH_{Ar}), 7.92-7.95 (m, 1H, CH_{Ar}), 8.33-8.37 (m, 2H, CH_{Ar}).

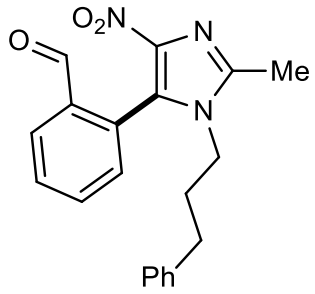
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 13.0 (Me), 30.3, 31.5, 43.7 (CH_2), 124.5, 124.9, 125.8, 127.9, 128.1 (CH), 129.4, 130.1 (C), 130.2, 137.0 (CH), 140.1, 142.7, 144.3, 147.6 (C).

MS (GC, 70 eV): *m/z* (%) = 366 (M^+, 47), 175 (25), 117 (18), 91 (100).

HRMS (EI): calcd for $C_{19}H_{18}N_4O_4$ (M^+) 366.37062, found 366.37064.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3060 (w), 1526 (s), 1504 (m), 1441 (w), 1402 (w), 1349 (s), 1290 (s), 1242 (m), 1099 (m), 1018 (w), 932 (w), 890 (w), 861 (w), 814 (m), 755 (s), 733 (m), 694 (s), 668 (m), 578 (w).

2-(2-Methyl-4-nitro-1-(3-phenylpropyl)-1*H*-imidazol-5-yl)benzaldehyde (4.2.1c).



Starting from 2-methyl-4-nitro-1-(3-phenylpropyl)-1*H*-imidazole **4.1.3e** (0.245 g, 1 mmol), 2-bromobenzaldehyde (0.370 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMA, the product **4.2.1c** was isolated as a yellow solid (0.314 g, 90%^{Pd}). Mp: 126-128°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.71-1.82 (m, 2H, CH_2), 2.40 (s, 3H, Me), 2.44 (t, 2H, ^3J = 7.3 Hz, CH_2), 3.47-3.71 (m, 2H, CH_2), 6.88-6.92 (m, 2H, CH_{Ar}), 7.11-7.18 (m, 2H, CH_{Ar}), 7.27-7.31 (m, 1H, CH_{Ar}), 7.37-7.55 (m, 1H, CH_{Ar}), 7.66-7.74 (m, 2H, CH_{Ar}), 7.94-8.00 (m, 1H, CH_{Ar}), 9.85 (s, 1H, CHO).

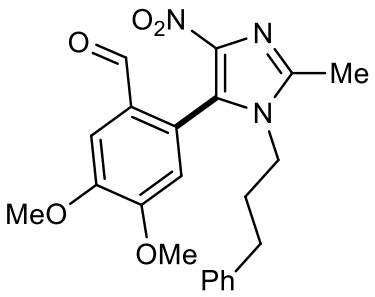
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.4 (Me), 30.9, 32.3, 44.2 (CH_2), 126.4, 127.9 (CH), 128.3 (C), 128.6, 130.7 (CH), 131.7 (C), 131.9, 132.1, 134.0, 135.1 (CH), 139.2, 143.6 (C), 190.4 (CH).

MS (GC, 70 eV): *m/z* (%) = 349 (M^+, 1), 303 (100), 91 (44).

HRMS (ESI): calcd for $C_{20}H_{20}N_3O_3$ (M+H) 350.14992, found 350.15086.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1683 (s), 1599 (w), 1564 (w), 1542 (m), 1490 (s), 1453 (m), 1398 (m), 1353 (m), 1337 (s), 1294 (s), 1269 (m), 1254 (m), 1225 (m), 1197 (m), 1120 (w), 1032 (w), 1005 (w), 978 (w), 850 (m), 823 (m), 764 (m), 738 (s), 698 (s), 671 (s), 614 (m), 540 (m).

4,5-Dimethoxy-2-(2-methyl-4-nitro-1-(3-phenylpropyl)-1*H*-imidazol-5-yl)benzaldehyde (4.2.1d).



Starting from 2-methyl-4-nitro-1-(3-phenylpropyl)-1*H*-imidazole **4.1.3e** (0.245 g, 1 mmol), 2-bromo-4,5-dimethoxybenzaldehyde (0.490 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMA, the product **4.2.1d** was isolated as a yellow solid (0.360 g, 88%^{Pd}). Mp: 165-167°C.

^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 1.77-1.82 (m, 2H, CH_2), 2.41-2.51 (m, 5H, Me, CH_2), 3.56-3.72 (m, 2H, CH_2), 3.87 (s, 3H, OMe), 4.02 (s, 3H, OMe), 6.67 (s, 1H, CH_{Ar}), 6.89-6.92 (m, 3H, CH_{Ar}), 7.17-7.19 (m, 2H, CH_{Ar}), 7.46 (br s, 1H, CH_{Ar}), 9.63 (s, 1H, CHO).

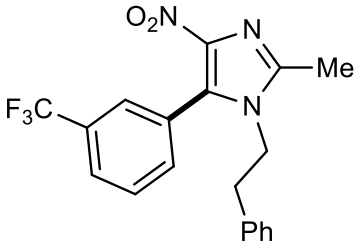
^{13}C NMR (62.9 MHz, DMSO-*d*$_6$): δ = 13.6 (Me), 30.3, 31.5, 43.8 (CH_2), 55.7, 56.2 (OMe), 111.5, 113.8 (CH), 123.3, 125.8 (C), 127.9, 128.1, 128.8 (CH), 129.6 (C), 131.4, 131.5 (CH), 132.0, 140.2, 143.4, 144.3, 149.7, 153.2 (C), 190.0 (CHO).

MS (GC, 70 eV): *m/z* (%) = 409 (M^+, 1), 363 (100), 91 (25).

HRMS (ESI): calcd for $C_{22}H_{24}N_3O_5$ (M+H) 410.17105, found 410.17082.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2938 (w), 1681 (m), 1591 (m), 1514 (s), 1494 (m), 1441 (m), 1397 (m), 1352 (m), 1329 (m), 1268 (s), 1227 (m), 1145 (s), 1100 (m), 1021 (m), 866 (w), 824 (w), 749 (m), 699 (s), 641 (w), 586 (m), 540 (w).

5-(3-(Trifluoromethyl)phenyl)-2-methyl-4-nitro-1-phenethyl-1*H*-imidazole (4.2.1e).



Starting from 2-methyl-4-nitro-1-phenethyl-1*H*-imidazole **4.1.3c** (0.231 g, 1 mmol), 1-bromo-3-(trifluoromethyl)benzene (0.450 g, 2 mmol), (1-iodo-3-(trifluoromethyl)benzene (0.544 g, 2 mmol)), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), ($NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMA, the product **4.2.1e** was isolated as a green solid (0.368 g, 98%^{Pd}), (0.274 g, 73%^{Ni}), (0.281 g, 75%$^{Ar\text{-}I}$). Mp: 164-166°C.

^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 2.31 (s, 3H, Me), 2.71-2.77 (m, 2H, CH_2), 3.99-4.05 (m, 2H, CH_2), 6.58-6.88 (m, 2H, CH_{Ar}), 7.19-7.22 (m, 3H, CH_{Ar}), 7.62-7.77 (m, 3H, CH_{Ar}), 7.88-7.91 (m, 1H, CH_{Ar}).

^{19}F NMR (235 MHz, DMSO-*d*$_6$): δ = -61.03 (CF_3).

^{13}C NMR (62.9 MHz, DMSO-*d*$_6$): δ = 12.9 (Me), 34.8, 46.0 (CH_2), 123.8 (q, ^1J = 271 Hz, CF_3), 126.3, 126.8, 127.0, 128.5, 128.5 (CH), 129.3 (q, ^2J = 31 Hz, CCF_3), 129.7 (CH), 131.0

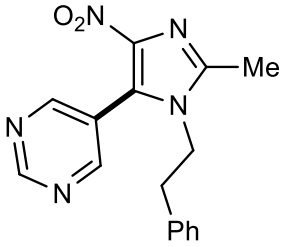
(C), 134.0 (CH), 137.0, 142.6, 144.4 (C).

MS (GC, 70 eV): *m/z* (%) = 375 (M^+, 94), 105 (100), 91 (80).

HRMS (EI): calcd for $C_{19}H_{16}N_3O_2F_3$ (M^+) 375.11891, found 375.11871.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1565 (w), 1533 (w), 1498 (m), 1440 (w), 1388 (w), 1354 (m), 1329 (s), 1308 (s), 1288 (s), 1254 (m), 1224 (w), 1201 (w), 1167 (m), 1117 (s), 1073 (s), 1020 (w), 935 (m), 900 (w), 856 (m), 806 (s), 755 (m), 698 (s), 672 (m), 649 (w).

5-(2-Methyl-4-nitro-1-phenethyl-1*H*-imidazol-5-yl)pyrimidine (4.2.1f).



Starting from 2-methyl-4-nitro-1-phenethyl-1*H*-imidazole **4.1.3c** (0.231 g, 1 mmol), 5-bromopyrimidine (0.318 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), ($NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMA, the product **4.2.1f** was isolated as a yellow solid (0.247 g, 80%^{Pd}), (0.163 g, 53%^{Ni}). Mp: 183-185°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.45 (s, 3H, Me), 2.86 (t, 2H, ^3J = 6.4 Hz, CH_2), 4.10 (t, 2H, ^3J = 6.4 Hz, CH_2), 6.76-6.78 (m, 2H, CH_{Ar}), 7.22-7.32 (m, 3H, CH_{Ar}), 8.37 (s, 2H, CH_{Ar}), 9.29 (s, 1H, CH_{Ar}).

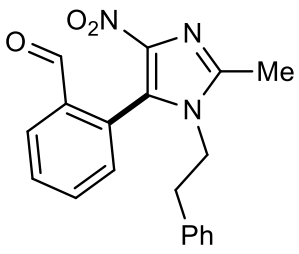
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.5 (Me), 35.9, 46.3 (CH_2), 122.7, 125.5 (C), 127.8, 128.5, 129.2 (CH), 131.9, 135.3, 144.2, 145.2 (C), 157.4, 158.9 (CH).

MS (GC, 70 eV): *m/z* (%) = 309 (M^+, 98), 105 (90), 91 (100), 77 (33).

HRMS (EI): calcd for $C_{16}H_{15}N_5O_2$ (M^+) 309.12203, found 309.12208.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2920 (w), 1609 (w), 1549 (w), 1505 (s), 1453 (w), 1408 (s), 1342 (s), 1298 (m), 1253 (m), 1187 (m), 1119 (w), 997 (m), 919 (m), 865 (m), 754 (m), 724 (s), 705 (s), 665 (m), 625 (s), 564 (m).

2-(2-Methyl-4-nitro-1-phenethyl-1*H*-imidazol-5-yl)benzaldehyde (4.2.1g).



Starting from 2-methyl-4-nitro-1-phenethyl-1*H*-imidazole **4.1.3c** (0.231 g, 1 mmol), 2-bromobenzaldehyde (0.370 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), ($NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMA, the product **4.2.1g** was isolated as a yellow solid (0.322 g, 96%^{Pd}), (0.218 g, 65%^{Ni}). Mp: 162-164°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.26 (s, 3H, Me), 2.70 (t, 2H, ^3J = 7.1 Hz, CH_2), 3.72-3.81 (m, 1H, CH_2), 3.96-4.06 (m, 2H, CH_2), 6.78-6.81 (m, 2H, CH_{Ar}), 7.11-7.13 (m, 1H, CH_{Ar}),

7.17-7.22 (m, 2H, CH_{Ar}), 7.42-7.53 (m, 2H, CH_{Ar}), 7.62-7.73 (m, 1H, CH_{Ar}), 8.00-8.03 (m, 1H, CH_{Ar}), 9.81 (s, 1H, CHO).

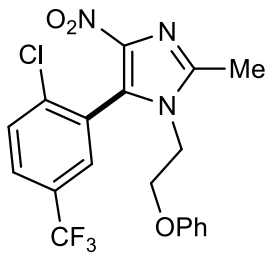
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.4 (Me), 36.0, 46.5 (CH_2), 127.4 (CH), 128.4 (C), 128.6, 129.0, 130.6, 131.7, 132.1 (CH), 133.9, 135.1, 136.1 (C), 190.4 (CH).

MS (GC, 70 eV): *m/z* (%) = 335 (M^+, 1), 289 (100), 105 (39), 91 (15), 77 (14).

HRMS (ESI): calcd for $C_{19}H_{18}N_3O_3$ (M+H) 336.13427, found 336.1346.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1695 (m), 1599 (w), 1531 (m), 1496 (s), 1437 (m), 1384 (m), 1319 (s), 1293 (s), 1270 (m), 1236 (s), 1201 (m), 1120 (w), 1092 (w), 1003 (w), 931 (w), 850 (m), 824 (m), 757 (s), 702 (s), 673 (m), 569 (m).

5-(2-Chloro-5-(trifluoromethyl)phenyl)-2-methyl-4-nitro-1-(2-phenoxyethyl)-1*H*-imidazole (4.2.1h).



Starting from 2-methyl-4-nitro-1-(2-phenoxyethyl)-1*H*-imidazole **4.1.3f** (0.247 g, 1 mmol), 2-bromo-1-chloro-4-(trifluoromethyl)benzene (0.520 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMA, the product **4.2.1h** was isolated as a green solid (0.318 g, 30%^{Pd}). Mp: 180-181°C.

^1H NMR (300 MHz, DMSO-*d*$_6$): δ = 2.63 (s, 3H, Me), 3.93-4.19 (m, 4H, 2×CH_2), 6.69-6.72 (m, 2H, CH_{Ar}), 6.94-6.98 (m, 1H, CH_{Ar}), 7.21-7.26 (m, 2H, CH_{Ar}), 7.67-7.76 (m, 3H, CH_{Ar}).

^{19}F NMR (235 MHz, DMSO-*d*$_6$): δ = -62.5 (CF_3).

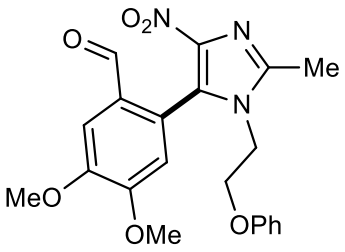
^{13}C NMR (62.9 MHz, DMSO-*d*$_6$): δ = 13.9 (Me), 44.7, 65.6 (CH_2), 114.1, 121.9 (CH), 123.4 (q, ^1J = 273 Hz, CF_3), 127.5, 128.1 (C), 128.5 (q, ^3J = 4 Hz, CH), 129.3 (q, ^3J = 4 Hz, CH), 129.7 (CH), 130.2 (C), 130.8 (CH), 138.9, 144.1, 145.5, 157.4 (C).

MS (GC, 70 eV): *m/z* (%) = 425 (M^+, 16), 390 (59), 360 (100), 77 (39).

HRMS (ESI): calcd for $C_{19}H_{16}N_3O_3F_3Cl$ (M+H) 426.08249, found 426.08249.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1738 (w), 1673 (w), 1588 (w), 1532 (w), 1504 (s), 1406 (m), 1329 (s), 1285 (m), 1239 (s), 1168 (s), 1121 (s), 1078 (s), 1017 (m), 918 (m), 859 (m), 814 (m), 791 (m), 753 (s), 689 (m), 605 (w), 535 (m).

4,5-Dimethoxy-2-(2-methyl-4-nitro-1-(2-phenoxyethyl)-1*H*-imidazol-5-yl)benzaldehyde (4.2.1i).



Starting from 2-methyl-4-nitro-1-(2-phenoxyethyl)-1*H*-imidazole **4.1.3f** (0.247 g, 1 mmol), 2-bromo-4,5-dimethoxybenzaldehyde (0.490 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMA, the product **4.2.1i** was isolated as a yellow solid (0.333 g, 81%^{Pd}). Mp: 141-143°C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.56 (s, 3H, Me), 3.85 (s, 3H, OMe), 3.93 (s, 3H, OMe), 3.96-4.26 (m, 4H, 2×CH_2), 6.73 (d, 2H, ^3J = 8.0 Hz, CH_{Ar}), 6.91 (t, 1H, ^3J = 7.1 Hz, CH_{Ar}), 7.19-7.25 (m, 3H, CH_{Ar}), 7.56 (s, 1H, CH_{Ar}), 9.67 (s, 1H, CHO).

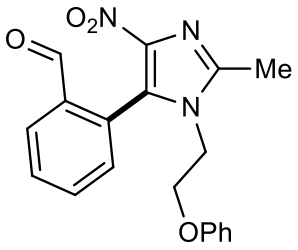
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 13.0 (Me), 43.6 (CH_2), 55.2, 55.8 (OMe), 65.2 (CH_2), 110.7, 113.7, 120.5 (CH), 123.0, 127.9, 128.1, 128.3, 128.9 (C), 129.4 (CH), 143.2, 144.6, 149.3, 152.7, 157.1 (C), 189.4 (CHO).

MS (GC, 70 eV): *m/z* (%) = 411 (M^+, 1), 365 (100), 77 (18).

HRMS (ESI): calcd for $C_{21}H_{22}N_3O_6$ (M+H) 412.15031, found 412.15044.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2933 (w), 1737 (w), 1678 (m), 1586 (m), 1537 (m), 1495 (s), 1445 (m), 1398 (m), 1353 (m), 1329 (m), 1283 (s), 1222 (s), 1155 (s), 1119 (m), 1036 (m), 1016 (m), 882 (s), 856 (m), 815 (m), 743 (s), 691 (m), 585 (m).

2-(2-Methyl-4-nitro-1-(2-phenoxyethyl)-1*H*-imidazol-5-yl)benzaldehyde (4.2.1j).



Starting from 2-methyl-4-nitro-1-(2-phenoxyethyl)-1*H*-imidazole **4.1.3f** (0.247 g, 1 mmol), 2-bromobenzaldehyde (0.370 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMA, the product **4.2.1j** was isolated as a yellow solid (0.263 g, 75%^{Pd}). Mp: 148-150°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.57 (s, 3H, Me), 3.96-4.24 (m, 4H, 2×CH_2), 6.70-6.74 (m, 2H, CH_{Ar}), 6.88-6.93 (m, 1H, CH_{Ar}), 7.19-7.25 (m, 2H, CH_{Ar}), 7.59-7.64 (m, 1H, CH_{Ar}), 7.77-7.89 (m, 2H, CH_{Ar}), 8.10 (dd, 1H, ^3J = 7.3 Hz, ^4J = 1.2 Hz, CH_{Ar}), 9.86 (s, 1H, CHO).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.4 (Me), 44.1, 65.6 (CH_2), 114.2, 121.0, 128.7, 129.4 (CH), 130.6 (C), 130.7, 131.4, 131.5, 132.0, 134.2 (CH), 135.0, 143.3, 145.2, 157.5 (C), 194.8 (CHO).

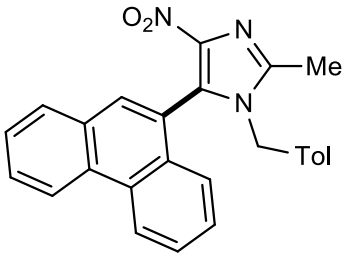
MS (GC, 70 eV): *m/z* (%) = 351 (M^+, 1), 305 (21), 44 (100).

HRMS (EI): calcd for $C_{19}H_{17}N_3O_4$ (M^+) 351.35598, found 351.35599.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2927 (w), 1690 (m), 1600 (m), 1565 (w), 1538 (w), 1496 (s), 1396 (m),

1353 (m), 1330 (s), 1293 (m), 1269 (m), 1230 (s), 1179 (m), 1119 (w), 1085 (m), 1051 (m), 962 (w), 908 (w), 886 (w), 849 (m), 828 (m), 757 (s), 721 (m), 692 (s), 670 (m), 631 (w), 592 (w), 539 (m).

1-(4-Methylbenzyl)-2-methyl-4-nitro-5-(phenanthren-10-yl)-1*H*-imidazole (4.2.1k).



Starting from 2-methyl-1-(4-methylbenzyl)-4-nitro-1*H*-imidazole **4.1.3g** (0.231 g, 1 mmol), 9-bromophenanthrene (0.514 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), ($NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMA, the product **4.2.1k** was isolated as a dark brown viscous oil (0.258 g, 80%^{Pd}), (0.162 g, 40%^{Ni}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.15 (s, 3H, Me), 2.39 (s, 3H, Me), 4.62 (d, 1H, ^3J = 15.0 Hz, CH_2), 4.84 (d, 1H, ^3J = 15.0 Hz, CH_2), 6.55 (d, 2H, ^3J = 7.9 Hz, CH_{Ar}), 6.86 (d, 2H, ^3J = 7.9 Hz, CH_{Ar}), 7.36-7.67 (m, 7H, CH_{Ar}), 8.60 (t, 2H, ^3J = 9.8 Hz, CH_{Ar}).

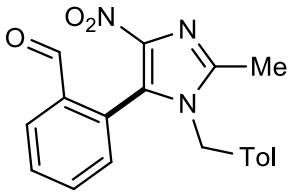
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.7, 18.4, 20.9 (Me), 48.1 (CH_2), 126.3, 127.0, 129.5 (CH), 130.7, 131.7 (C), 134.2 (CH), 137.1, 137.9, 143.4, 144.1, 144.7 (C) 149.9 (CH).

MS (GC, 70 eV): *m/z* (%) = 407 (M^+, 53), 105 (100).

HRMS (EI): calcd for $C_{26}H_{21}N_3O_2$ (M^+) 407.16283, found 407.16301.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1537 (m), 1504 (s), 1446 (m), 1385 (m), 1336(s), 1293 (s), 1222 (m), 1124 (w), 1018 (m), 933 (w), 859 (s), 796 (s), 766 (m), 756 (m), 719 (m), 665 (m), 624 (m), 594 (w).

3-(1-(4-Methylbenzyl)-2-methyl-4-nitro-1*H*-imidazol-5-yl)benzaldehyde (4.2.1l).



Starting from 2-methyl-1-(4-methylbenzyl)-4-nitro-1*H*-imidazole **4.1.3g** (0.231 g, 1 mmol), 2-bromobenzaldehyde (0.370 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMA, the product **4.2.1l** was isolated as a yellow solid (0.285 g, 85%^{Pd}). Mp: 139-141°C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.21 (s, 3H, Me), 2.39 (s, 3H, Me), 4.88-5.03 (m, 2H, CH_2), 6.74 (d, 2H, ^3J = 8.0 Hz, CH_{Ar}), 7.03 (d, 2H, ^3J = 8.0 Hz, CH_{Ar}), 7.48-7.51 (m, 1H, CH_{Ar}), 7.72-7.77 (m, 2H, CH_{Ar}), 7.95-7.99 (m, 1H, CH_{Ar}), 9.73 (s, 1H, CHO).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 13.4, 20.5 (Me), 47.6 (CH_2), 126.4, 127.5 (CH), 128.4 (C), 129.1, 129.5, 130.5 (CH), 130.6 (C), 130.9, 131.5 (CH), 132.0 (C), 134.0, 134.7 (CH),

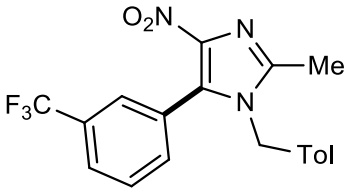
137.0, 143.4, 144.8 (C), 191.4 (CHO).

MS (GC, 70 eV): *m/z* (%) = 335 (M^+, 1), 105 (100).

HRMS (ESI): calcd for $C_{19}H_{18}N_3O_3$ (M+H) 336.13427, found 336.1342.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2841 (w), 2751 (w), 1699 (m), 1601 (w), 1568 (w) 1533 (m), 1494 (s), 1435 (m), 1397 (m), 1377 (s), 1328 (s), 1288 (s), 1249 (s), 1199 (m), 1121 (m), 1036 (w), 1003 (w), 859 (m), 813 (s), 785 (s), 765 (s), 723 (m), 670 (m), 610 (m), 541 (s).

1-(4-Methylbenzyl)-5-(3-(trifluoromethyl)phenyl)-2-methyl-4-nitro-1*H*-imidazole (4.2.1m).



Starting from 2-methyl-1-(4-methylbenzyl)-4-nitro-1*H*-imidazole **4.1.3g** (0.231 g, 1 mmol), 1-bromo-3-(trifluoromethyl)benzene (0.450 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), ($NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMA, the product **4.2.1m** was isolated as a green solid (0.368 g, 92%^{Pd}), (0.191 g, 62%^{Ni}). Mp: 152-154°C.

^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 2.31 (s, 3H, Me), 2.43 (s, 3H, Me), 4.90 (s, 2H, CH_2), 6.71 (d, 2H, ^3J = 6.0 Hz, CH_{Ar}), 7.45 (d, 2H, ^3J = 6.0 Hz, CH_{Ar}), 7.45-7.56 (m, 3H, CH_{Ar}), 7.68-7.71 (m, 1H, CH_{Ar}).

^{19}F NMR (235 MHz, DMSO-*d*$_6$): δ = -62.9 (CF_3).

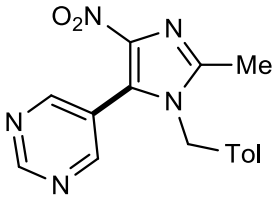
^{13}C NMR (62.9 MHz, DMSO-*d*$_6$): δ = 13.7, 21.0 (Me), 48.2 (CH_2), 123.4 (q, ^1J = 273.2 Hz, CF_3), 125.7 (CH), 126.7 (q, ^3J = 4.1 Hz, CH), 127.1 (q, ^3J = 4.1 Hz, CH), 128.2 (C), 129.3 (CH), 129.9 (C), 130.7 (CH), 131.1 (q, ^2J = 32.6 Hz, CCF_3), 131.3 (C), 133.5 (CH), 138.4, 143.5, 144.7 (C).

MS (GC, 70 eV): *m/z* (%) = 375 (M^+, 10), 105 (100).

HRMS (EI): calcd for $C_{19}H_{16}N_3O_2F_3$ (M^+) 375.11891, found 375.11887.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1538 (m), 1499 (m), 1429 (w), 1399 (m), 1328 (s), 1288 (s), 1252 (m), 1184 (m), 1164 (s), 1111 (s), 1076 (s), 1024 (m), 926 (m), 857 (m), 812 (m), 796 (s), 766 (m), 726 (m), 700 (m), 663 (m), 644 (w), 599 (w).

5-(1-(4-Methylbenzyl)-2-methyl-4-nitro-1*H*-imidazol-5-yl)pyrimidine (4.2.1n).



Starting from 2-methyl-1-(4-methylbenzyl)-4-nitro-1*H*-imidazole **4.1.3g** (0.231 g, 1 mmol), 5-bromopyrimidine (0.318 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), ($NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMA, the product **4.2.1n** was isolated as a yellow solid (0.253 g, 82%^{Pd}), (0.157 g, 51%^{Ni}). Mp: 183-185°C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.25 (s, 3H, Me), 2.39 (s, 3H, Me), 5.14 (s, 2H, CH_2), 6.82 (d, 2H, ^3J = 8.1 Hz, CH_{Ar}), 7.10 (d, 2H, ^3J = 8.1 Hz, CH_{Ar}), 8.84 (s, 2H, CH_{Ar}), 9.25 (s, 1H, CH_{Ar}).

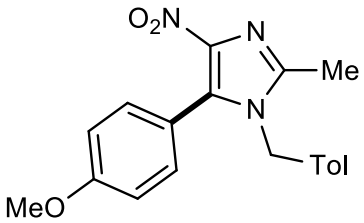
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 13.2, 20.6 (Me), 47.5 (CH_2), 123.0 (C), 126.1 (CH), 126.8 (C), 128.6, 129.4, 131.4, 131.5 (CH), 132.0, 137.1, 143.8, 145.5 (C), 157.7, 158.7 (CH).

MS (GC, 70 eV): *m/z* (%) = 309 (M^+, 10), 105 (100).

HRMS (EI): calcd for $C_{16}H_{15}N_5O_2$ (M^+) 309.12203, found 309.12176.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2965 (w), 1551 (w), 1529 (w), 1501 (s), 1432 (m), 1401 (m), 1339 (s), 1299 (m), 1271 (m), 1189 (m), 1120 (m), 1002 (m), 917 (w), 858 (m), 789 (m), 756 (w), 723 (s), 694 (m), 665 (m), 628 (m), 537 (m).

1-(4-Methylbenzyl)-5-(4-methoxyphenyl)-2-methyl-4-nitro-1*H*-imidazole (4.2.1o).



Starting from 2-methyl-1-(4-methylbenzyl)-4-nitro-1*H*-imidazole **4.1.3g** (0.231 g, 1 mmol), 1-bromo-4-methoxybenzene (0.374 g, 2 mmol), (1-iodo-4-methoxybenzene (0.468 g, 2 mmol)), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMA, the product **4.2.1o** was isolated as a yellow viscous oil (0.226 g, 67%^{Pd}), (0.155 g, 46%$^{Ar\text{-}I}$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29 (s, 3H, Me), 2.33 (s, 3H, Me), 3.79 (s, 3H, OMe), 4.91 (s, 2H, CH_2), 6.75 (d, 2H, ^3J = 7.6 Hz, CH_{Ar}), 6.90 (d, 2H, ^3J = 8.5 Hz, CH_{Ar}), 7.09 (d, 2H, ^3J = 7.6 Hz, CH_{Ar}), 7.19 (d, 2H, ^3J = 8.5 Hz, CH_{Ar}).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.8, 21.0 (Me), 47.8 (CH_2), 55.3 (OMe), 114.2 (CH), 115.4, 119.0 (C), 125.8, 128.7, 129.8, 130.1, 131.6 (CH), 133.1, 138.1, 143.2, 144.1, 160.8 (C).

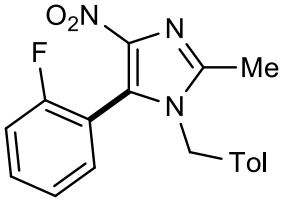
MS (GC, 70 eV): *m/z* (%) = 337 (M^+, 32), 105 (100).

HRMS (EI): calcd for $C_{19}H_{19}N_3O_3$ (M^+) 337.14209, found 337.14203.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2926 (w), 1666 (w), 1613 (w), 1506 (s), 1441 (w), 1335 (s), 1288 (s),

1247 (s), 1176 (s), 1110 (w), 1032 (m), 856 (s), 797 (m), 717 (m), 669 (w), 620 (w), 596 (m), 529 (m).

1-(4-Methylbenzyl)-5-(2-fluorophenyl)-2-methyl-4-nitro-1*H*-imidazole (4.2.1p).



Starting from 2-methyl-1-(4-methylbenzyl)-4-nitro-1*H*-imidazole **4.1.3g** (0.231 g, 1 mmol), 1-bromo-2-fluorobenzene (0.350 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMA, the product **4.2.1p** was isolated as a green solid (0.166 g, 51%^{Pd}). Mp: 115-117°C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.26 (s, 3H, Me), 2.34 (s, 3H, Me), 4.82-4.99 (m, 2H, CH_2), 6.72 (d, 2H, ^3J = 8.0 Hz, CH_{Ar}), 7.05 (d, 2H, ^3J = 8.0 Hz, CH_{Ar}), 7.09-7.22 (m, 3H, CH_{Ar}), 7.39-7.46 (m, 1H, CH_{Ar}).

^{19}F NMR (235 MHz, DMSO-d_6): δ = -111.23 (CF).

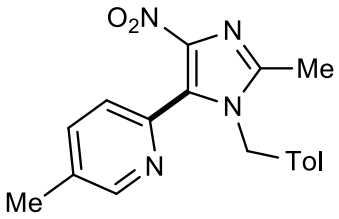
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 13.4, 20.8 (Me), 48.0 (CH_2), 115.2 (d, ^3J = 15.4 Hz, C), 115.9 (d, ^2J = 22.2 Hz, CH), 124.3 (d, J = 4.1 Hz, C), 125.8 (CH), 126.5 (C), 129.5, 131.1, 131.5, 132.1, 132.3 (CH), 137.9, 143.9, 144.9 (C), 159.3 (d, ^1J = 249.7 Hz, CF).

MS (GC, 70 eV): *m/z* (%) = 325 (M^+, 21), 105 (100).

HRMS (ESI): calcd for $C_{18}H_{17}N_3O_2F$ (M+H) 326.12993, found 326.13006.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1532 (m), 1495 (s), 1444 (m), 1397 (m), 1378 (m), 1328 (s), 1288 (m), 1269 (m), 1251 (m), 1221 (m), 1116 (w), 1095 (w), 1007 (w), 863 (w), 840 (m), 808 (s), 765 (s), 716 (m), 665 (m), 607 (m).

2-Methyl-5-(2-methyl-1-(4-methylbenzyl)-4-nitro-1*H*-imidazol-5-yl)pyridine (4.2.1q).



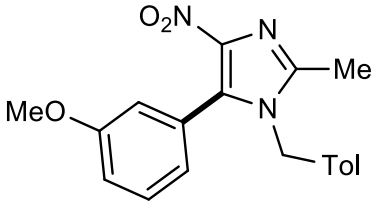
Starting from 2-methyl-1-(4-methylbenzyl)-4-nitro-1*H*-imidazole **4.1.3g** (0.231 g, 1 mmol), 2-bromo-5-methylpyridine (0.344 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMA, the product **4.2.1q** was isolated as a yellow viscous oil (0.220 g, 54%^{Pd}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.25 (s, 3H, Me), 2.36 (s, 6H, Me), 5.16 (s, 2H, CH_2), 6.76 (d, 2H, ^3J = 8.0 Hz, CH_{Ar}), 7.02 (d, 2H, ^3J = 8.0 Hz, CH_{Ar}), 7.45 (d, 1H, ^3J = 8.0 Hz, CH_{Ar}), 7.53-7.56 (m, 1H, CH_{Ar}), 8.51 (s, 1H, CH_{Ar}).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.7, 18.4, 20.6 (Me), 48.0 (CH_2), 126.3, 127.1, 129.5

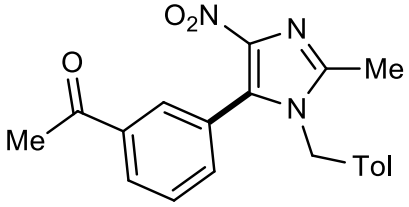
(CH), 130.8, 131.8, 134.2 (C), 137.1 (CH), 137.9, 143.5, 144.1, 144.8 (C), 150.0 (CH).
MS (GC, 70 eV): *m/z* (%) = 322 (M^+, 10), 305 (100), 263 (34), 146 (26), 119 (23), 105 (52).
HRMS (EI): calcd for $C_{18}H_{18}N_4O_2$ (M^+) 322.14243, found 322.14228.
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1733 (w), 1668 (w), 1564 (w), 1497 (s), 1441 (m), 1384 (m), 1336 (s), 1282 (m), 1226 (w), 1136 (m), 1039 (w), 901 (m), 864 (w), 839 (w), 810 (w), 749 (s), 725 (s), 616 (m).

1-(4-Methylbenzyl)-5-(3-methoxyphenyl)-2-methyl-4-nitro-1*H*-imidazole (4.2.1r).



Starting from 2-methyl-1-(4-methylbenzyl)-4-nitro-1*H*-imidazole **4.1.3g** (0.231 g, 1 mmol), 1-bromo-3-methoxybenzene (0.374 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), ($NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMA, the product **4.2.1r** was isolated as a yellow solid (0.263 g, 78%^{Pd}), (0.145 g, 43%^{Ni}). Mp: 146-148°C.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.31 (s, 3H, Me), 2.35 (s, 3H, Me), 3.67 (s, 3H, OMe), 4.91 (s, 2H, CH_2), 6.75-6.77 (m, 3H, CH_{Ar}), 6.84-6.87 (m, 1H, CH_{Ar}), 6.95-6.99 (m, 1H, CH_{Ar}), 7.09-7.12 (m, 2H, CH_{Ar}), 7.29-7.34 (m, 1H, CH_{Ar}).
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.8, 21.0 (Me), 47.9 (CH_2), 55.2 (OMe), 115.4, 115.9, 122.2, 125.8 (CH), 128.3 (C), 129.7, 129.8 (CH), 131.8, 132.8, 138.1, 144.2, 159.5 (C).
MS (GC, 70 eV): *m/z* (%) = 337 (M^+, 24), 105 (100).
HRMS (EI): calcd for $C_{19}H_{19}N_3O_3$ (M^+) 337.14209, found 337.14198.
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2919 (w), 1589 (m), 1568 (m), 1536 (m), 1503 (s), 1451 (m), 1398 (s), 1344 (s), 1292 (s), 1223 (s), 1180 (m), 1125 (m), 1039 (m), 1016 (m), 897 (m), 873 (m), 829 (m), 786 (s), 765 (m), 706 (m), 689 (m), 665 (m), 555 (w).

1-(3-(2-Methyl-1-(4-methylbenzyl)-4-nitro-1*H*-imidazol-5-yl)phenyl)ethanone (4.2.1s).



Starting from 2-methyl-1-(4-methylbenzyl)-4-nitro-1*H*-imidazole **4.1.3g** (0.231 g, 1 mmol), 1-(3-bromophenyl)ethanone (0.398 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMA, the product **4.2.1s** was isolated as a yellow solid (0.251 g, 72%^{Pd}). Mp: 173-174°C.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.23 (s, 3H, Me), 2.34 (s, 3H, Me), 2.49 (s, 3H, Me),

5.03 (s, 2H, CH_2), 6.80 (d, 2H, ^3J = 7.5 Hz, CH_{Ar}), 7.09 (d, 2H, ^3J = 7.5 Hz, CH_{Ar}), 7.58-7.70 (m, 2H, CH_{Ar}), 7.91 (br s, 1H, CH_{Ar}), 8.01-8.05 (m, 1H, CH_{Ar}).

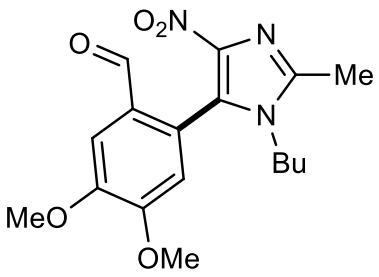
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 13.2, 20.5, 26.6 (Me), 47.3 (CH_2), 126.0 (CH), 128.0 (C), 129.0, 129.1, 129.3, 130.0 (CH), 132.2, 132.4 (C), 134.8 (CH), 136.8, 136.9, 142.7, 144.4 (C), 197.2 (CO).

MS (GC, 70 eV): *m/z* (%) = 349 (M^+, 8), 105 (100).

HRMS (EI): calcd for $C_{20}H_{19}N_3O_3$ (M^+) 349.14209, found 349.14266.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2921 (w), 1683 (s), 1564 (w), 1535 (w), 1501 (s), 1424 (w), 1396 (m), 1335 (s), 1274 (s), 1231 (s), 1122 (w), 1020 (w), 958 (w), 904 (w), 796 (m), 766 (m), 693 (m), 588 (m).

2-(1-Butyl-2-methyl-4-nitro-1*H*-imidazol-5-yl)-4,5-dimethoxybenzaldehyde (4.2.1t).



Starting from 1-butyl-2-methyl-4-nitro-1*H*-imidazole **4.1.3b** (0.183 g, 1 mmol), 2-bromo-4,5-dimethoxybenzaldehyde (0.490 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMA, the product **4.2.1t** was isolated as a brown solid (0.295 g, 85%^{Pd}). Mp: 212-214°C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.67 (t, 3H, ^3J = 7.3 Hz, $CH_2CH_2CH_2CH_3$), 1.04-1.17 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.33-1.42 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.46 (s, 3H, Me), 3.61-3.82 (m, 2H, $CH_2CH_2CH_2CH_3$), 3.85 (s, 3H, OMe), 3.92 (s, 3H, OMe), 7.19 (s, 1H, CH_{Ar}), 7.58 (s, 1H, CH_{Ar}), 9.70 (s, 1H, CHO).

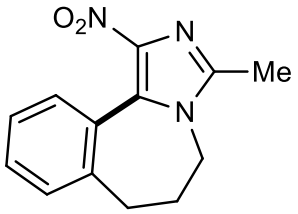
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 13.1, 13.2 (Me), 18.9, 31.1, 44.2 (CH_2), 55.7, 56.3 (OMe), 111.6, 114.5 (CH), 123.5, 128.2, 129.6, 132.0, 143.4, 149.8, 153.2 (C), 189.9 (CHO).

MS (GC, 70 eV): *m/z* (%) = 347 (M^+, 1), 303 (100), 91 (44).

HRMS (ESI): calcd for $C_{17}H_{21}N_3O_5$ (M+H) 348.1554, found 348.1560.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2957 (w), 1666 (m), 1582 (m), 1498 (s), 1447 (w), 14023 (m), 1351 (m), 1291 (m), 1276 (s), 1222 (s), 1132 (s), 1132 (s), 1077 (m), 1019 (m), 978 (w), 889 (m), 859 (w), 814 (m), 749 (m), 720 (m), 698 (m), 585 (m), 539 (m).

3-Methyl-1-nitro-6,7-dihydro-5*H*-benzo[*c*]imidazo[1,5-*a*]azepine (4.2.2a).



Starting from 2-methyl-4-nitro-1-(3-phenylpropyl)-1*H*-imidazole **4.1.3e** (0.245 g, 1 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), Ag_2CO_3 (0.331 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMA, the product **4.2.2a** was isolated as a yellow viscous oil (0.199 g, 82%^{Pd}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.23 (t, 2H, ^3J = 6.8 Hz, CH_2), 2.48 (s, 3H, Me), 2.64 (t, 2H, ^3J = 6.6 Hz, CH_2), 3.76 (br s, 2H, CH_2), 7.27-7.31 (m, 1H, CH_{Ar}), 7.38-7.42 (m, 2H, CH_{Ar}), 7.74-7.78 (m, 1H, CH_{Ar}).

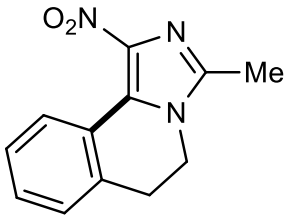
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.1 (Me), 29.9, 30.8, 42.5 (CH_2), 126.9 (CH), 127.3 (C), 129.0, 130.5, 131.5 (CH), 132.2, 138.3, 142.3 (C).

MS (GC, 70 eV): *m/z* (%) = 243 (M^+, 100), 212 (11), 156 (22), 144 (45), 128 (31), 116 (66).

HRMS (EI): calcd for $C_{13}H_{13}N_3O_2$ (M^+) 243.10023, found 243.10027.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2922 (w), 2854 (w), 1577 (w), 1562 (w), 1529 (m), 1494 (s), 1454 (m), 1399 (m), 1380 (m), 1329 (s), 1316 (s), 1279 (s), 1238 (m), 1120 (w), 1025 (w), 1004 (m), 956 (w), 855 (s), 822 (m), 772 (m), 757 (s), 722 (m), 690 (m), 665 (m).

3-Methyl-1-nitro-5,6-dihydroimidazo[5,1-*a*]isoquinoline (4.2.2b).



Starting from 2-methyl-4-nitro-1-phenethyl-1*H*-imidazole **4.1.3c** (0.231 g, 1 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), Ag_2CO_3 (0.331 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMA, the product **4.2.2b** was isolated as a yellow solid (0.222 g, 97%^{Pd}). Mp: 151-152°C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.40 (s, 3H, Me), 3.09 (t, 2H, ^3J = 6.6 Hz, CH_2), 4.08 (t, 2H, ^3J = 6.8 Hz, CH_2), 7.36-7.44 (m, 2H, CH_{Ar}), 8.25-8.29 (m, 2H, CH_{Ar}).

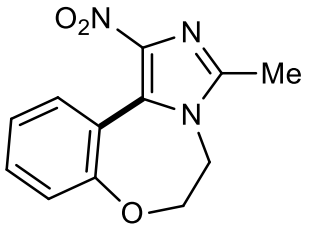
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 12.6 (Me), 28.4, 40.8 (CH_2), 124.2 (C), 127.0, 127.4, 128.2, 129.9 (CH), 134.8, 142.9 (C).

MS (GC, 70 eV): *m/z* (%) = 229 (M^+, 85), 159 (15), 140 (34), 130 (100), 115 (41), 103 (29).

HRMS (EI): calcd for $C_{12}H_{11}N_3O_2$ (M^+) 229.08458, found 229.08425.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2957 (w), 1741 (w), 1610 (w), 1531 (m), 1480 (m), 1403 (m), 1375 (m), 1344 (m), 1309 (w), 1269 (s), 1066 (m), 1131 (m), 1043 (m), 1002 (m), 937 (m), 845 (s), 780 (s), 761 (s), 700 (m), 683 (m), 650 (m).

3-Methyl-1-nitro-5,6-dihydrobenzo[*f*]imidazo[1,5-*d*][1,4]-oxazepine (4.2.2c).



Starting from 2-methyl-4-nitro-1-(2-phenoxyethyl)-1*H*-imidazole **4.1.3f** (0.247 g, 1 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), Ag_2CO_3 (0.331 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMA, the product **4.2.2c** was isolated as a yellow viscous oil (0.186 g, 76%^{Pd}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.51 (s, 3H, Me), 4.01 (t, 2H, ^3J = 5.9 Hz, CH_2), 4.49 (t, 2H, ^3J = 5.9 Hz, CH_2), 7.20 (dd, 1H, ^3J = 8.0 Hz, ^4J = 1.1 Hz, CH_{Ar}), 7.31 (dt, 1H, ^3J = 7.6 Hz, ^4J = 1.3 Hz, CH_{Ar}), 7.47 (dt, 1H, ^3J = 7.6 Hz, ^4J = 1.9 Hz, CH_{Ar}), 7.84 (dd, 1H, ^3J = 7.8 Hz, ^4J = 1.7 Hz, CH_{Ar}).

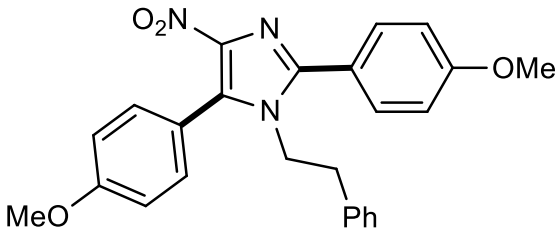
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.0 (Me), 42.7, 73.8 (CH_2), 121.8 (CH), 122.6 (C), 125.0 (CH), 130.1 (C), 132.1, 132.2 (CH), 142.0, 153.3 (C).

MS (GC, 70 eV): *m/z* (%) = 245 (M^+, 100).

HRMS (EI): calcd for $C_{12}H_{11}N_3O_3$ (M^+) 245.08004, found 245.08010.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2881 (w), 1743 (w), 1531 (m), 1504 (m), 1450 (m), 1402 (m), 1380 (m), 1329 (s), 1275 (s), 1231 (m), 1145 (w), 1109 (w), 1043 (m), 884 (w), 837 (m), 799 (m), 753 (m), 663 (w).

2,5-Bis(4-methoxyphenyl)-4-nitro-1-phenethyl-1*H*-imidazole (4.2.3a).



Starting from 4-nitro-1-phenethyl-1*H*-imidazole **4.1.3d** (0.217 g, 1 mmol), 1-bromo-4-methoxybenzene (0.374 g, 2.5 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.320 g, 2.3 mmol) in 8 mL DMA, the product **4.2.3a** was isolated as a yellow solid (0.249 g, 58%^{Pd}). Mp: 153-155°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.47-2.51 (m, 2H, CH_2), 3.04 (s, 3H, OMe), 3.85 (s, 3H, OMe), 4.16 (t, 2H, ^3J = 7.2 Hz, CH_2), 6.64-6.67 (m, 2H, CH_{Ar}), 7.07-7.17 (m, 7H, CH_{Ar}), 7.32-7.34 (m, 2H, CH_{Ar}), 7.55 (d, 2H, ^3J = 9.0 Hz, CH_{Ar}).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 34.5, 46.7 (CH_2), 55.2, 55.3 (OMe), 114.0, 114.2 (CH), 119.3, 121.4 (C), 126.7, 128.3, 128.5, 130.4, 131.7 (CH), 133.6, 136.7, 143.2, 145.4, 160.2, 160.3 (C).

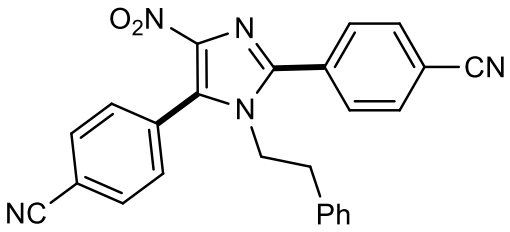
MS (GC, 70 eV): *m/z* (%) = 429 (M^+, 100), 135 (27), 105 (60).

HRMS (EI): calcd for $C_{25}H_{23}N_3O_4$ (M^+) 429.46782, found 429.46784.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1613 (m), 1575 (w), 1505 (m), 1489 (m), 1454 (m), 1379 (m), 1341 (m),

1289 (m), 1245 (s), 1171 (s), 1110 (m), 1020 (m), 861 (m), 833 (s), 797 (m), 739 (s), 697 (s), 645 (m), 535 (m).

4,4′-(4-Nitro-1-phenethyl-1*H*-imidazole-2,5-diyl)dibenzonitrile (4.2.3b).



Starting from 4-nitro-1-phenethyl-1*H*-imidazole **4.1.3d** (0.217 g, 1 mmol), 4-bromobenzonitrile (0.455 g, 2.5 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.320 g, 2.3 mmol) in 8 mL DMA, the product **4.2.3b** was isolated as a brown solid (0.264 g, 63%^{Pd}). Mp: 224-226°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.46 (t, 2H, ^3J = 6.8 Hz, CH_2), 4.15 (t, 2H, ^3J = 6.8 Hz, CH_2), 6.47-6.50 (m, 2H, CH_{Ar}), 7.05-7.19 (m, 3H, CH_{Ar}), 7.25-7.29 (m, 2H, CH_{Ar}), 7.55-7.58 (m, 2H, CH_{Ar}), 7.69-7.74 (m, 4H, CH_{Ar}).

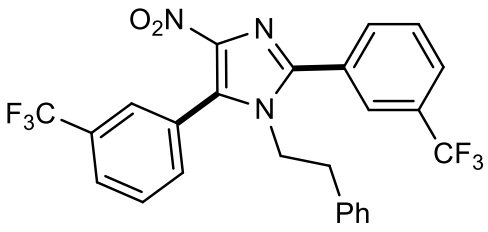
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 35.9, 47.5 (CH_2), 114.1, 114.3, 117.8 (C), 127.7, 128.3, 129.1, 129.6, 131.1 (CH), 131.4 (C), 131.6 (CH), 132.6 (C), 132.6 (CH), 132.9, 135.1, 144.5, 144.9 (C).

MS (GC, 70 eV): *m/z* (%) = 419 (M^+, 86), 389 (22), 128 (22), 105 (100), 91 (62).

HRMS (ESI): calcd for $C_{25}H_{18}N_5O_2$ (M+H) 420.1455, found 420.14487.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2233 (m), 1514 (s), 1480 (m), 1453 (w), 1393 (m), 1346 (s), 1308 (m), 1260 (m), 1181 (w), 1078 (w), 1007 (w), 918 (w), 858 (m), 845 (s), 754 (m), 746 (m), 699 (s), 659 (m), 557 (s), 549 (s).

2,5-Bis(3-(trifluoromethyl)phenyl)-4-nitro-1-phenethyl-1*H*-imidazole (4.2.3c).



Starting from 4-nitro-1-phenethyl-1*H*-imidazole **4.1.3d** (0.217 g, 1 mmol), 1-bromo-3-(trifluoromethyl)benzene (0.562 g, 2.5 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.320 g, 2.3 mmol) in 8 mL DMA, the product **4.2.3c** was isolated as a yellow solid (0.308 g, 61%^{Pd}). Mp: 184-185°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.53 (t, 2H, ^3J = 6.7 Hz, CH_2), 4.20 (t, 2H, ^3J = 6.7 Hz, CH_2), 6.54-6.57 (m, 2H, CH_{Ar}), 7.10-7.20 (m, 3H, CH_{Ar}), 7.46-7.53 (m, 2H, CH_{Ar}), 7.62-7.82 (m, 6H, CH_{Ar}).

^{19}F NMR (235 MHz, DMSO-d_6): δ = -62.7 (CF_3).

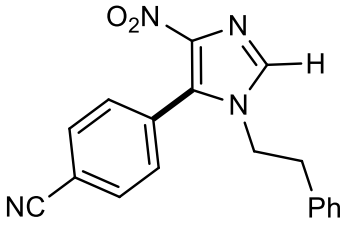
^{13}C NMR: due to bed solubility it was not possible to measure.

MS (GC, 70 eV): *m/z* (%) = 505 (M^+, 51), 173 (14), 145 (13), 105 (100), 91 (24).

HRMS (EI): calcd for $C_{25}H_{17}N_3O_2F_6$ (M^+) 505.12195, found 505.12226.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1568 (w), 1505 (s), 1456 (w), 1381 (w), 1325 (s), 1311 (s), 1240 (m), 1167 (s), 1120 (s), 1072 (s), 923 (m), 900 (m), 851 (m), 811 (m), 795 (s), 751 (m), 728 (w), 715 (m), 695 (s), 671 (m), 648 (m).

4-(4-Nitro-1-phenethyl-1*H*-imidazol-5-yl)benzonitrile (4.2.4a).



Starting from 4-nitro-1-phenethyl-1*H*-imidazole **4.1.3d** (0.217 g, 1 mmol), 4-bromobenzonitrile (0.200 g, 1.1 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.180 g, 1.3 mmol) in 8 mL DMA, the product **4.2.4a** was isolated as a yellow solid (0.267 g, 84%^{Pd}). Mp: 131-133°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.90 (t, 2H, ^3J = 6.8 Hz, CH_2), 4.07 (t, 2H, ^3J = 6.8 Hz, CH_2), 6.82-6.85 (m, 2H, CH_{Ar}), 7.18-7.29 (m, 3H, CH_{Ar}), 7.43-7.67 (m, 3H, CH_{Ar}), 7.72-7.74 (m, 2H, CH_{Ar}).

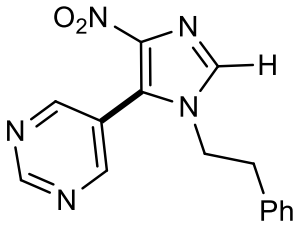
^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 37.0, 47.6 (CH_2), 113.8 (CH), 118.0 (C), 127.5 (CH), 128.2 (C), 128.4, 128.5 (CH), 128.7 (C), 128.8, 129.1, 129.7 (CH), 130.3, 130.7 (C), 131.0, 132.4, 132.6 (CH), 133.0 (C).

MS (GC, 70 eV): *m/z* (%) = 318 (M^+, 83), 105 (56), 91 (100).

HRMS (EI): calcd for $C_{18}H_{14}N_4O_2$ (M^+) 318.11113, found 318.111300.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2233 (m), 1574 (w), 1514 (s), 1496 (s), 1437 (m), 1405 (w), 1337 (s), 1275 (m), 1226 (m), 1190 (m), 1112 (m), 1028 (w), 1000 (m), 933 (w), 845 (s), 748 (s), 720 (m), 697 (s), 655 (s), 566 (m), 541 (s).

5-(4-Nitro-1-phenethyl-1*H*-imidazol-5-yl)pyrimidine (4.2.4b).



Starting from 4-nitro-1-phenethyl-1*H*-imidazole **4.1.3d** (0.217 g, 1 mmol), 5-bromopyrimidine (0.175 g, 1.1 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.180 g, 1.3 mmol) in 8 mL DMA, the product **4.2.4b** was isolated as a yellow solid (0.242 g, 82%^{Pd}). Mp: 137-139°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.90 (t, 2H, ^3J = 6.6 Hz, CH_2), 4.20 (t, 2H, ^3J = 6.6 Hz,

CH_2), 6.94-6.97 (m, 2H, CH_{Ar}), 7.21-7.23 (m, 2H, CH_{Ar}), 7.57-7.63 (m, 1H, CH_{Ar}), 8.07 (s, 1H, CH_{Ar}), 8.74 (s, 2H, CH_{Ar}), 9.31 (s, 1H, CH_{Ar}).

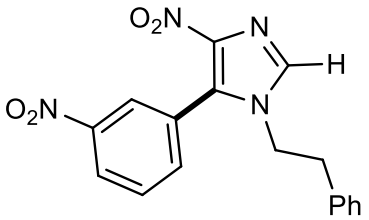
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 35.8, 47.0 (CH_2), 122.3, 126.2 (C), 126.8, 128.6, 128.8, 131.4, 131.5 (CH), 136.9 (C), 137.5 (CH), 144.5 (C) 157.7, 158.8 (CH).

MS (GC, 70 eV): *m/z* (%) = 295 (M^+, 38), 278 (12), 105 (40), 91 (100), 77 (27).

HRMS (EI): calcd for $C_{15}H_{13}N_5O_2$ (M^+) 295.10638, found 295.10607.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3127 (w), 1714 (w), 1599 (w), 1552 (m), 1495 (s), 1454 (m), 1408 (m), 1371 (s), 1333 (s), 1266 (s), 1223 (m), 1189 (m), 1156 (m), 1119 (m), 1080 (w), 996 (m), 913 (w), 864 (w), 831 (s), 760 (s), 725 (s), 702 (s), 652 (m), 628 (s), 588 (w), 566 (m), 539 (s).

4-Nitro-5-(3-nitrophenyl)-1-phenethyl-1*H*-imidazole (4.2.4c).



Starting from 4-nitro-1-phenethyl-1*H*-imidazole **4.1.3d** (0.217 g, 1 mmol), 1-bromo-3-nitrobenzene (0.222 g, 1.1 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.180 g, 1.3 mmol) in 8 mL DMA, the product **4.2.4c** was isolated as a yellow solid (0.220 g, 65%^{Pd}). Mp: 128-130°C.

^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 2.85 (t, 2H, ^3J = 6.7 Hz, CH_2), 4.13 (t, 2H, ^3J = 6.7 Hz, CH_2), 6.89-6.92 (m, 2H, CH_{Ar}), 7.17-7.19 (m, 3H, CH_{Ar}), 7.74-7.81 (m, 2H, CH_{Ar}), 8.03 (br s, 1H, CH_{Ar}), 8.09 (br s, 1H, CH_{Ar}), 8.35-8.37 (m, 1H, CH_{Ar}).

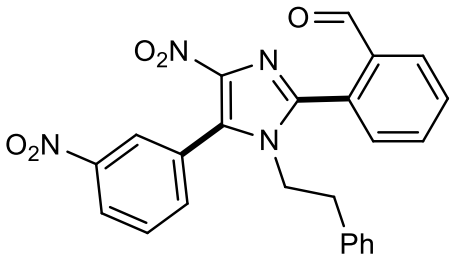
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 35.7, 46.9 (CH_2), 124.5, 125.2, 126.7, 128.4 (CH), 128.4 (C), 128.5, 128.8 (CH), 130.0 (C), 130.1, 131.5 (CH), 132.0 (C), 136.7, 136.8 (CH), 137.0, 147.7 (C).

MS (GC, 70 eV): *m/z* (%) = 338 (M^+, 70), 105 (46), 91 (100).

HRMS (EI): calcd for $C_{17}H_{14}N_4O_4$ (M^+) 338.10096, found 338.10087.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3126 (w), 1526 (s), 1496 (s), 1436 (m), 1383 (w), 1345 (s), 1296 (s), 1249 (w), 1212 (m), 1158 (m), 1103 (m), 1028 (w), 1004 (m), 902 (m), 829 (s), 763 (m), 731 (s), 692 (s), 647 (s), 538 (s).

2-(4-Nitro-5-(3-nitrophenyl)-1-phenethyl-1*H*-imidazol-2-yl)benzaldehyde (4.2.5a).



Starting from 4-nitro-5-(3-nitrophenyl)-1-phenethyl-1*H*-imidazole **4.2.4c** (0.338 g, 1 mmol), 2-bromobenzaldehyde (0.370 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.180 g, 1.3 mmol) in 8 mL DMA, the product **4.2.5a** was isolated as a yellow solid (0.345 g, 78%^{Pd}). Mp: 152-154°C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.84 (t, 2H, ^3J = 6.6 Hz, CH_2), 3.98 (t, 2H, ^3J = 6.6 Hz, CH_2), 6.52-6.55 (m, 2H, CH_{Ar}), 7.04-7.15 (m, 3H, CH_{Ar}), 7.33-7.36 (m, 1H, CH_{Ar}), 7.61-7.74 (m, 4H, CH_{Ar}), 7.96-7.99 (m, 1H, CH_{Ar}), 8.12-8.13 (m, 1H, CH_{Ar}), 8.30-8.34 (m, 1H, CH_{Ar}), 9.90 (s, 1H, CHO).

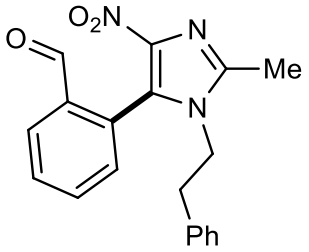
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 35.8, 47.1 (CH_2), 123.9, 124.8, 125.4, 127.5, 127.6, 138.4 (CH), 128.7 (C), 129.0, 130.0 (CH), 130.2 (C) 131.2 (CH), 132.0 (C), 134.0, 134.9, 135.1 (CH), 135.6 (C), 136.4 (CH), 144.2, 144.6, 148.2 (C), 190.9 (CHO).

MS (GC, 70 eV): *m/z* (%) = 442 (M^+, 70), 310 (77), 264 (22), 105 (100).

HRMS (ESI): calcd for $C_{24}H_{18}N_4O_5$ (M+H) 443.1350, found 443.13495.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3084 (w), 2858 (w), 1693 (m), 1600 (w), 1525 (s), 1470 (m), 1453 (m), 1389 (m), 1346 (s), 1246 (m), 1196 (m), 1137 (w), 1078 (w), 906 (w), 876 (w), 829 (m), 776 (m), 739 (s), 698 (s), 573 (w).

2-(2-Methyl-4-nitro-1-phenethyl-1*H*-imidazol-5-yl)benzaldehyde (4.3.1a).



Starting from 5-bromo-2-methyl-4-nitro-1-phenethyl-1*H*-imidazole **4.1.6a** (0.310 g, 1 mmol), (2-formylphenyl)boronic acid (0.195 g, 1.3 mmol), $Pd(PPh_3)_4$ (0.115 g, 0.10 mmol) and 2M aq. K_2CO_3 (1 mL) in 8 mL Toluene/MeOH (5:1), the product **4.3.1a** was isolated as a yellow solid (0.208 g, 62%). Mp: 162-164°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.26 (s, 3H, Me), 2.70 (t, 2H, ^3J = 7.1 Hz, CH_2), 3.72-3.81 (m, 1H, CH_2), 3.96-4.06 (m, 2H, CH_2), 6.78-6.81 (m, 2H, CH_{Ar}), 7.11-7.13 (m, 1H, CH_{Ar}), 7.17-7.22 (m, 2H, CH_{Ar}), 7.42-7.53 (m, 2H, CH_{Ar}), 7.62-7.73 (m, 1H, CH_{Ar}), 8.00-8.03 (m, 1H, CH_{Ar}), 9.81 (s, 1H, CHO).

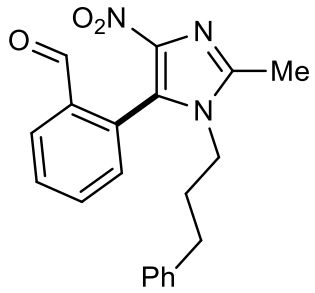
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.4 (Me), 36.0, 46.5 (CH_2), 127.4 (CH), 128.4 (C), 128.6, 129.0, 130.6, 131.7, 132.1 (CH), 133.9, 135.1, 136.1 (C), 190.4 (CH).

MS (GC, 70 eV): *m/z* (%) = 335 (M^+, 1), 289 (100), 105 (39), 91 (15), 77 (14).

HRMS (ESI): calcd for $C_{19}H_{18}N_3O_3$ (M+H) 336.13427, found 336.1346.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1695 (m), 1599 (w), 1531 (m), 1496 (s), 1437 (m), 1384 (m), 1319 (s), 1293 (s), 1270 (m), 1236 (s), 1201 (m), 1120 (w), 1092 (w), 1003 (w), 931 (w), 850 (m), 824 (m), 757 (s), 702 (s), 673 (m), 569 (m).

2-(2-Methyl-4-nitro-1-(3-phenylpropyl)-1*H*-imidazol-5-yl)benzaldehyde (4.3.1b).



Starting from 5-bromo-2-methyl-4-nitro-1-(3-phenylpropyl)-1*H*-imidazole **4.1.6c** (0.324 g, 1 mmol), (2-formylphenyl)boronic acid (0.195 g, 1.3 mmol), $Pd(PPh_3)_4$ (0.115 g, 0.10 mmol) and 2M aq. K_2CO_3 (1 mL) in 8 mL Toluene/MeOH (5:1), the product **4.3.1b** was isolated as a yellow solid (0.196 g, 56%). Mp: 126-128°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.71-1.82 (m, 2H, CH_2), 2.40 (s, 3H, Me), 2.44 (t, 2H, ^3J = 7.3 Hz, CH_2), 3.47-3.71 (m, 2H, CH_2), 6.88-6.92 (m, 2H, CH_{Ar}), 7.11-7.18 (m, 2H, CH_{Ar}), 7.27-7.31 (m, 1H, CH_{Ar}), 7.37-7.55 (m, 1H, CH_{Ar}), 7.66-7.74 (m, 2H, CH_{Ar}), 7.94-8.00 (m, 1H, CH_{Ar}), 9.85 (s, 1H, CHO).

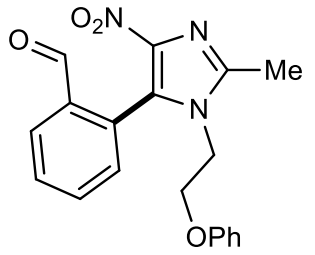
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.4 (Me), 30.9, 32.3, 44.2 (CH_2), 126.4, 127.9 (CH), 128.3 (C), 128.6, 130.7 (CH), 131.7 (C), 131.9, 132.1, 134.0, 135.1 (CH), 139.2, 143.6 (C), 190.4 (CH).

MS (GC, 70 eV): *m/z* (%) = 349 (M^+, 1), 303 (100), 91 (44).

HRMS (ESI): calcd for $C_{20}H_{20}N_3O_3$ (M+H) 350.14992, found 350.15086.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1683 (s), 1599 (w), 1564 (w), 1542 (m), 1490 (s), 1453 (m), 1398 (m), 1353 (m), 1337 (s), 1294 (s), 1269 (m), 1254 (m), 1225 (m), 1197 (m), 1120 (w), 1032 (w), 1005 (w), 978 (w), 850 (m), 823 (m), 764 (m), 738 (s), 698 (s), 671 (s), 614 (m), 540 (m).

2-(2-Methyl-4-nitro-1-(2-phenoxyethyl)-1*H*-imidazol-5-yl)benzaldehyde (4.3.1c).



Starting from 5-bromo-2-methyl-4-nitro-1-(2-phenoxyethyl)-1*H*-imidazole **4.1.6b** (0.326 g, 1 mmol), (2-formylphenyl)boronic acid (0.195 g, 1.3 mmol), $Pd(PPh_3)_4$ (0.115 g, 0.10 mmol) and 2M aq. K_2CO_3 (1 mL) in 8 mL Toluene/MeOH (5:1), the product **4.3.1c** was isolated as a yellow solid (0.240 g, 68%). Mp: 148-150°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.57 (s, 3H, Me), 3.96-4.24 (m, 4H, 2×CH_2), 6.70-6.74 (m, 2H, CH_{Ar}), 6.88-6.93 (m, 1H, CH_{Ar}), 7.19-7.25 (m, 2H, CH_{Ar}), 7.59-7.64 (m, 1H, CH_{Ar}), 7.77-7.89 (m, 2H, CH_{Ar}), 8.10 (dd, 1H, ^3J = 7.3 Hz, ^4J = 1.2 Hz, CH_{Ar}), 9.86 (s, 1H, CHO).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.4 (Me), 44.1, 65.6 (CH_2), 114.2, 121.0, 128.7, 129.4 (CH), 130.6 (C), 130.7, 131.4, 131.5, 132.0, 134.2 (CH), 135.0, 143.3, 145.2, 157.5 (C), 194.8

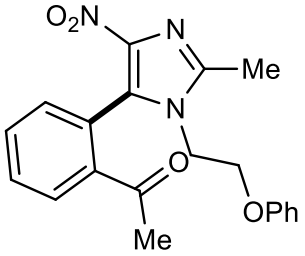
(CHO).

MS (GC, 70 eV): *m/z* (%) = 351 (M^+, 1), 305 (21), 44 (100).

HRMS (EI): calcd for $C_{19}H_{17}N_3O_4$ (M^+) 351.35598, found 351.35599.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2927 (w), 1690 (m), 1600 (m), 1565 (w), 1538 (w), 1496 (s), 1396 (m), 1353 (m), 1330 (s), 1293 (m), 1269 (m), 1230 (s), 1179 (m), 1119 (w), 1085 (m), 1051 (m), 962 (w), 908 (w), 886 (w), 849 (m), 828 (m), 757 (s), 721 (m), 692 (s), 670 (m), 631 (w), 592 (w), 539 (m).

1-(2-(2-Methyl-4-nitro-1-(2-phenoxyethyl)-1*H*-imidazol-5-yl)phenyl)ethanone (4.3.1d).



Starting from 5-bromo-2-methyl-4-nitro-1-(2-phenoxyethyl)-1*H*-imidazole **4.1.6b** (0.326 g, 1 mmol), (2-acetylphenyl)boronic acid (0.213 g, 1.3 mmol), $Pd(PPh_3)_4$ (0.115 g, 0.10 mmol) and 2M aq. K_2CO_3 (1 mL) in 8 mL Toluene/MeOH (5:1), the product **4.3.1d** was isolated as a yellow viscous oil (0.233 g, 37%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.11 (s, 3H, Me), 2.49 (s, 3H, Me), 2.70-2.76 (m, 2H, CH_2), 3.69-3.79 (m, 1H, CH_2), 3.94-4.12 (m, 1H, CH_2), 6.89-6.97 (m, 2H, CH_{Ar}), 7.04-7.07 (m, 1H, CH_{Ar}), 7.18-7.24 (m, 3H, CH_{Ar}), 7.51-7.62 (m, 2H, CH_{Ar}), 7.89-7.92 (m, 1H, CH_{Ar}).

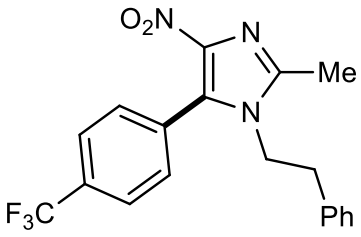
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.1, 27.8 (Me), 35.4, 46.7 (CH_2), 127.0 (C), 128.5, 128.6, 128.7, 129.3 (CH), 129.3 (C), 130.1, 131.4, 131.8 (CH), 132.6, 136.8, 138.9, 143.9, 199.3 (C).

MS (GC, 70 eV): *m/z* (%) = 365 (M^+, 1), 319 (100).

HRMS (ESI): calcd for $C_{20}H_{20}N_3O_4$ (M+H) 366.14483, found 366.14499.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1699 (m), 1601 (w), 1531 (m), 1496 (s), 1442 (m), 1384 (m), 1319 (s), 1293 (s), 1275 (m), 1236 (s), 1205 (m), 1120 (w), 1092 (w), 1000 (w), 931 (w), 852 (s), 824 (m), 759 (m), 702 (s), 673 (m), 569 (m).

2-Methyl-4-nitro-1-phenethyl-5-(4-(trifluoromethyl)phenyl)-1*H*-imidazole (4.3.1e).



Starting from 5-bromo-2-methyl-4-nitro-1-phenethyl-1*H*-imidazole **4.1.6a** (0.310 g, 1 mmol), (4-(trifluoromethyl)phenyl)boronic acid (0.247 g, 1.3 mmol), $Pd(PPh_3)_4$ (0.115 g, 0.10 mmol) and 2M aq. K_2CO_3 (1 mL) in 8 mL Toluene/MeOH (5:1), the product **4.3.1e** was isolated as a green solid (0.326 g, 87%). Mp: 155-156°C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.17 (s, 3H, Me), 3.10 (t, 2H, ^3J = 7.1 Hz, CH_2), 4.52 (t, 2H, ^3J = 7.1 Hz, CH_2), 7.08-7.11 (m, 2H, CH_{Ar}), 7.27-7.31 (m, 3H, CH_{Ar}), 7.69 (d, 2H, ^3J =

8.0 Hz, CH_{Ar}), 7.87 (d, 2H, ^{3}J = 8.0 Hz, CH_{Ar}).

^{19}F NMR (235 MHz, DMSO-d_6): δ = -62.8 (CF_3).

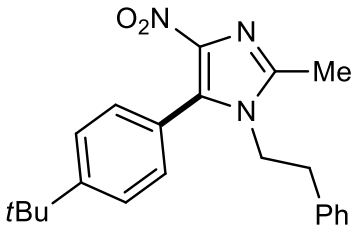
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 13.8 (Me), 36.5, 48.8 (CH_2), 124.8 (q, ^{1}J = 270.5 Hz, CF_3), 125.0 (q, ^{4}J = 3.7 Hz, $CHCCF_3$), 127.5, 128.8, 129.1, 130.0 (CH), 131.3 (q, ^{2}J = 33.2 Hz, CCF_3), 134.9, 136.5, 141.9, 148.7 (C).

MS (GC, 70 eV): *m/z* (%) = 375 (M^+, 10), 329 (100), 105 (58), 91 (49), 77 (26).

HRMS (EI): calcd for $C_{19}H_{16}N_3O_2F_3$ (M^+) 375.11891, found 375.11984.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1714 (w), 1558 (w), 1506 (w), 1468 (m), 1359 (m), 1317 (s), 1186 (m), 1108 (s), 1067 (s), 1018 (m), 848 (s), 746 (s), 701 (s), 661 (w), 593 (m).

5-(4-*Tert*-Butylphenyl)-2-methyl-4-nitro-1-phenethyl-1*H*-imidazole (4.3.1f).



Starting from 5-bromo-2-methyl-4-nitro-1-phenethyl-1*H*-imidazole **4.1.6a** (0.310 g, 1 mmol), (4-(*tert*-butyl)phenyl)boronic acid (0.232 g, 1.3 mmol), $Pd(PPh_3)_4$ (0.115 g, 0.10 mmol) and 2M aq. K_2CO_3 (1 mL) in 8 mL Toluene/MeOH (5:1), the product **4.3.1f** was isolated as a yellow viscous oil (0.258 g, 71%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (s, 9H, *t*Bu), 2.55 (s, 3H, Me), 2.70 (t, 2H, ^{3}J = 7.2 Hz, CH_2), 3.97 (t, 2H, ^{3}J = 7.2 Hz, CH_2), 6.76-6.80 (m, 2H, CH_{Ar}), 7.19-7.21 (m, 5H, CH_{Ar}), 7.50 (d, 2H, ^{3}J = 8.5 Hz, CH_{Ar}).

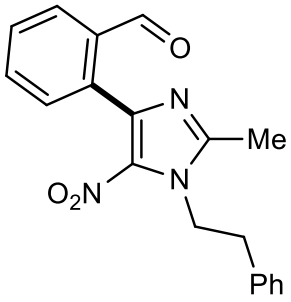
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.3 (Me), 31.2 (*t*Bu), 34.9 (C*t*Bu), 36.2, 46.4 (CH_2), 124.1 (C), 125.8, 127.3, 128.6, 129.0, 129.7 (CH), 132.5, 136.3, 143.7, 153.2 (C).

MS (GC, 70 eV): *m/z* (%) = 363 (M^+, 100), 348 (89), 244 (15), 115 (11), 105 (97), 91 (28), 77 (27).

HRMS (ESI): calcd for $C_{22}H_{26}N_3O_2$ (M+H) 364.20195, found 364.2019.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2960 (w), 1575 (w), 1544 (w), 1504 (s), 1452 (m), 1398 (m), 1383 (s), 1331 (s), 1294 (s), 1248 (s), 1201 (w), 1100 (w), 1048 (w), 1029 (w), 1003 (m), 867 (s), 832 (m), 769 (m), 744 (s), 698 (s), 669 (m), 629 (w), 577 (m), 558 (m).

2-(2-Methyl-5-nitro-1-phenethyl-1*H*-imidazol-4-yl)benzaldehyde (4.3.2a).



Starting from 4-bromo-2-methyl-5-nitro-1-phenethyl-1*H*-imidazole **4.1.7a** (0.310 g, 1 mmol), (2-formylphenyl)boronic acid (0.195 g, 1.3 mmol), $Pd(PPh_3)_4$ (0.115 g, 0.10 mmol) and 2M aq. K_2CO_3 (1 mL) in 8 mL Toluene/MeOH (5:1), the product **4.3.2a** was isolated as a brown viscous oil (0.262 g, 78%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.06 (s, 3H, Me), 3.07 (t, 2H, ^3J = 6.8 Hz, CH_2), 4.53 (t, 2H, ^3J = 6.8 Hz, CH_2), 7.06-7.09 (m, 1H, CH_{Ar}), 7.24-7.27 (m, 1H, CH_{Ar}), 7.41-7.44 (m, 2H, CH_{Ar}), 7.46-7.51 (m, 2H, CH_{Ar}), 7.54-7.56 (m, 1H, CH_{Ar}), 7.64-7.67 (m, 1H, CH_{Ar}) 7.95 (dd, 1H, ^3J = 7.5 Hz, ^4J = 1.47 Hz, CH_{Ar}), 9.91 (s, 1H, CHO).

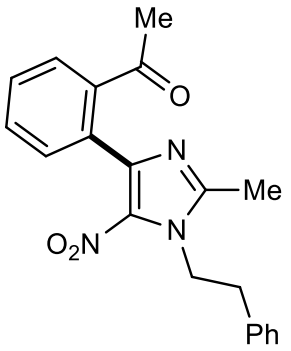
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.6 (Me), 36.3, 48.5 (CH_2), 127.3 (CH), 128.3 (C), 128.5 (CH), 128.7 (C), 128.9 (CH), 129.1 (C), 129.4 (CH), 130.9 (C), 131.8, 132.0, 133.2 (CH), 134.4, 136.5 (C), 190.8 (CHO).

MS (GC, 70 eV): *m/z* (%) = 335 (M^+, 100).

HRMS (ESI): calcd for $C_{19}H_{18}N_3O_3$ (M+H) 336.13427, found 336.13499.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1697 (m), 1600 (w), 1531 (m), 1496 (s), 1440 (m), 1384 (m), 1319 (s), 1293 (s), 1271 (m), 1236 (s), 1201 (m), 1120 (w), 1092 (w), 1005 (w), 931 (w), 850 (m), 825 (m), 757 (s), 700 (s), 673 (m), 569 (m).

1-(2-(2-Methyl-5-nitro-1-phenethyl-1*H*-imidazol-4-yl)phenyl)ethanone (4.3.2b).



Starting from 4-bromo-2-methyl-5-nitro-1-phenethyl-1*H*-imidazole **4.1.7a** (0.310 g, 1 mmol), (2-acetylphenyl)boronic acid (0.213 g, 1.3 mmol), $Pd(PPh_3)_4$ (0.115 g, 0.10 mmol) and 2M aq. K_2CO_3 (1 mL) in 8 mL Toluene/MeOH (5:1), the product **4.3.2b** was isolated as a red solid (0.265 g, 76%). Mp: 123-125°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.00 (s, 3H, Me), 2.56 (s, 3H, Me), 3.07 (t, 2H, ^3J = 6.6 Hz, CH_2), 4.50 (t, 2H, ^3J = 6.6 Hz, CH_2), 7.14-7.16 (m, 2H, CH_{Ar}), 7.25-7.34 (m, 3H, CH_{Ar}), 7.45-7.56 (m, 3H, CH_{Ar}), 7.77-7.80 (m, 1H, CH_{Ar}).

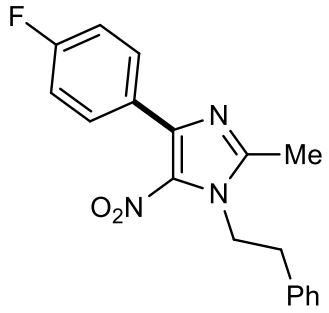
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.4, 27.6 (Me), 36.3, 48.4 (CH_2), 126.9, 128.0, 128.7, 128.8, 128.9, 131.0, 131.1 (CH), 131.9, 133.3, 136.7, 138.7, 145.1, 149.0, 199.6 (C).

MS (GC, 70 eV): *m/z* (%) = 349 (M^+, 1), 303 (100), 199 (17), 105 (71).

HRMS (ESI): calcd for $C_{20}H_{20}N_3O_3$ (M+H) 350.14992, found 350.15029.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1694 (s), 1549 (m), 1498 (m), 1462 (s), 1418 (s), 1353 (s), 1327 (s), 1308 (s), 1249 (s), 1186 (s), 998 (w), 836 (m), 779 (m), 754 (s), 701 (s), 633 (w), 593 (s).

4-(4-Fluorophenyl)-2-methyl-5-nitro-1-phenethyl-1*H*-imidazole (4.3.2c).



Starting from 4-bromo-2-methyl-5-nitro-1-phenethyl-1*H*-imidazole **4.1.7a** (0.310 g, 1 mmol), (4-fluorophenyl)boronic acid (0.182 g, 1.3 mmol), $Pd(PPh_3)_4$ (0.115 g, 0.10 mmol) and 2M aq. K_2CO_3 (1 mL) in 8 mL Toluene/MeOH (5:1), the product **4.3.2c** was isolated as a brown viscous oil (0.238 g, 73%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.15 (s, 3H, Me), 3.08 (t, 2H, ^3J = 7.4 Hz, CH_2), 4.52 (t, 2H, ^3J = 7.4 Hz, CH_2), 7.08-7.15 (m, 4H, CH_{Ar}), 7.26-7.31 (m, 3H, CH_{Ar}), 7.75-7.80 (m, 2H, CH_{Ar}).

^{19}F NMR (235 MHz, DMSO-d_6): δ = -110.8 (CF).

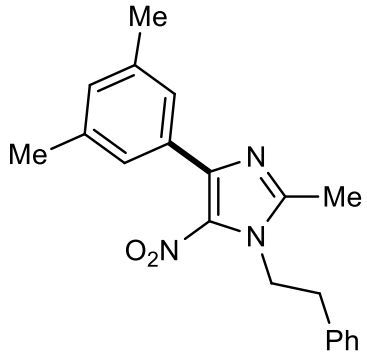
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.6 (Me), 36.5, 48.7 (CH_2), 115.2 (d, ^3J = 20 Hz, CH), 127.4 (CH), 127.5 (C), 128.8, 129.0 (CH), 131.7 (d, ^3J = 8 Hz, CH), 136.6, 142.9, 148.5 (C), 163.4 (d, ^1J = 249.9 Hz, CF).

MS (GC, 70 eV): *m/z* (%) = 325 (M^+, 30), 279 (100), 238 (15), 133 (14), 105 (48), 91 (40) 77 (19).

HRMS (ESI): calcd for $C_{18}H_{17}FN_3O_2$ (M+H) 326.12993, found 326.13008.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1499 (w), 1456 (w), 1409 (w), 1376 (w), 1351 (w), 1329 (m), 1312 (m), 1261 (w), 1219 (m), 1183 (m), 1156 (m), 1083 (m), 1016 (m), 841 (s), 795 (s), 759 (s), 708 (s), 643 (w), 593 (m).

2-Methyl-4-(3,5-dimethylphenyl)-5-nitro-1-phenethyl-1*H*-imidazole (4.3.2d).



Starting from 4-bromo-2-methyl-5-nitro-1-phenethyl-1*H*-imidazole **4.1.7a** (0.310 g, 1 mmol), (3,5-dimethylphenyl)boronic acid (0.195 g, 1.3 mmol), $Pd(PPh_3)_4$ (0.115 g, 0.10 mmol) and 2M aq. K_2CO_3 (1 mL) in 8 mL Toluene/MeOH (5:1), the product **4.3.2d** was isolated as a brown viscous oil (0.252 g, 75%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.09 (s, 3H, Me), 2.33 (s, 6H, 2xMe), 3.05 (t, 2H, ^3J = 7.0 Hz, CH_2), 4.46 (t, 2H, ^3J = 7.0 Hz, CH_2), 7.02-7.09 (m, 3H, CH_{Ar}), 7.22-7.32 (m, 5H, CH_{Ar}).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.8 (Me), 21.3 (2xMe), 36.6, 48.6 (CH_2), 125.0, 127.1 (C), 127.3, 128.7, 128.8, 129.0 (CH), 131.3 (C), 131.4 133.8, 136.8 (CH), 137.6, 138.0, 144.4, 148.3 (C).

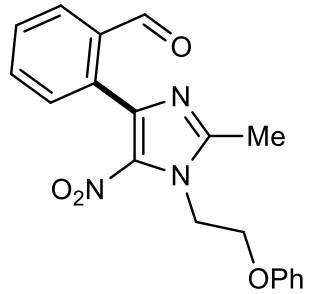
MS (GC, 70 eV): *m/z* (%) = 335 (M^+, 64), 305 (14), 289 (90), 233 (22), 160 (15), 132 (24),

115 (27), 105 (100), 91 (57), 77 (42).

HRMS (ESI): calcd for $C_{20}H_{22}N_3O_2$ (M+H) 336.17065, found 336.17099.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2959 (w), 1602 (w), 1537 (w), 1501 (m), 1454 (m), 1417 (s), 1376 (w), 1354 (s), 1323 (s), 1245 (m), 1178 (s), 1085 (w), 1031 (w), 903 (w), 892 (w), 854 (m), 816 (m), 752 (s), 700 (s), 656 (w), 632 (m), 571 (w), 536 (w).

2-(2-Methyl-5-nitro-1-(2-phenoxyethyl)-1*H*-imidazol-4-yl)-benzaldehyde (4.3.2e).



Starting from 4-bromo-2-methyl-5-nitro-1-(2-phenoxyethyl)-1*H*-imidazole **4.1.7b** (0.326 g, 1 mmol), (2-formylphenyl)boronic acid (0.195 g, 1.3 mmol), $Pd(PPh_3)_4$ (0.115 g, 0.10 mmol) and 2M aq. K_2CO_3 (1 mL) in 8 mL Toluene/MeOH (5:1), the product **4.3.2e** was isolated as a brown viscous oil (0.281 g, 80%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.66 (s, 3H, Me), 4.38 (t, 2H, ^3J = 4.8 Hz, CH_2), 4.76 (t, 2H, ^3J = 4.8 Hz, CH_2), 6.82-6.86 (m, 2H, CH_{Ar}), 6.95-7.00 (m, 1H, CH_{Ar}), 7.25-7.30 (m, 2H, CH_{Ar}), 7.50-7.66 (m, 3H, CH_{Ar}), 7.98 (dd, 1H, ^3J = 7.4 Hz, ^4J = 1.1 Hz, CH_{Ar}), 9.92 (s, 1H, CHO).

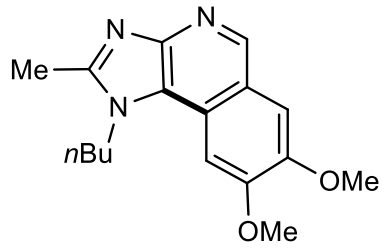
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.6 (Me), 46.7, 66.5 (CH_2), 114.2, 121.6, 128.8, 129.6, 131.0, 133.2, 134.5 (CH), 141.6, 150.2, 157.7 (C), 190.9 (CHO).

MS (GC, 70 eV): *m/z* (%) = 351 (M^+, 1), 305 (100), 183 (24), 77 (46).

HRMS (ESI): calcd for $C_{19}H_{18}N_3O_4$ (M+H) 352.121914, found 352.121963.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1693 (m), 1598 (m), 1491 (s), 1459 (m), 1413 (s), 1354 (m), 1323 (s), 1296 (m), 1240 (s), 1186 (s), 1082 (m), 1062 (m), 912 (m), 823 (m), 770 (s), 751 (s), 696 (m), 677 (m), 637 (m), 610 (m).

1-Butyl-7,8-dimethoxy-2-methyl-1*H*-imidazo[4,5-*c*]isoquinoline (4.4.3a).



Starting from 2-(1-butyl-2-methyl-4-nitro-1*H*-imidazol-5-yl)-4,5-dimethoxybenzaldehyde **4.2.1t** (0.347 g, 1 mmol), Pd/C (0.030 g, 0.10 mmol) and H_2 balloon in 25 mL MeOH, the product **4.4.3a** was isolated as a brown viscous oil (0.203 g, 68%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.71 (t, 3H, ^3J = 7.1 Hz, $CH_2CH_2CH_2\mathit{CH_3}$), 1.09-1.15 (m, 2H, $CH_2CH_2\mathit{CH_2}CH_3$), 1.42-1.44 (m, 2H, $CH_2\mathit{CH_2}CH_2CH_3$), 2.54 (s, 3H, Me), 3.66-3.84 (m, 2H, $\mathit{CH_2}CH_2CH_2CH_3$), 3.90 (s, 3H, OMe), 3.97 (s, 3H, OMe), 7.23 (s, 1H, CH_{Ar}), 7.62 (s, 1H, CH_{Ar}), 9.74 (s, 1H, isoquinoline).

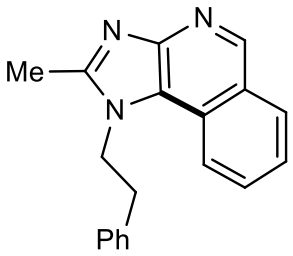
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 13.1, 13.2 (Me), 18.9, 31.1, 44.2 (CH_2), 55.7, 56.3 (OMe), 111.5, 114.5 (CH), 123.5, 128.2, 129.6, 143.4, 144.3, 149.8, 153.2 (C), 189.9 (CH).

MS (GC, 70 eV): *m/z* (%) = 299 (M^+, 100).

HRMS (EI): calcd for $C_{17}H_{21}N_3O_2$ (M^+) 299.36754, found 299.36755.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2933 (w), 1665 (m), 1582 (m), 1498 (s), 1448 (m), 1351 (s), 1291 (m), 1267 (s), 1059 (w), 1132 (s), 1077 (s), 1019 (s), 978 (w), 889 (m), 859 (m), 814 (m), 749 (m), 675 (w), 639 (w), 585 (m).

2-Methyl-1-phenethyl-1*H*-imidazo[4,5-*c*]isoquinoline (4.4.3b).



Starting from 2-(2-methyl-4-nitro-1-phenethyl-1*H*-imidazol-5-yl)benzaldehyde **4.2.1g** (0.335 g, 1 mmol), Pd/C (0.030 g, 0.10 mmol) and H_2 balloon in 25 mL MeOH, the product **4.4.3b** was isolated as a brown solid (0.186 g, 65%). Mp: 262-264°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.12 (s, 3H, Me), 3.20 (br s, 2H, CH_2), 4.70 (br s, 2H, CH_2), 6.88-6.91 (m, 2H, CH_{Ar}), 7.22-7.25 (m, 3H, CH_{Ar}), 7.52 (t, 1H, ^3J = 7.3 Hz, CH_{Ar}), 7.66 (t, 1H, ^3J = 7.3 Hz, CH_{Ar}), 7.79 (d, 1H, ^3J = 8.3 Hz, CH_{Ar}), 8.11 (d, 1H, ^3J = 7.8 Hz, ^4J = 0.8 Hz, CH_{Ar}), 8.68 (s, 1H, isoquinoline).

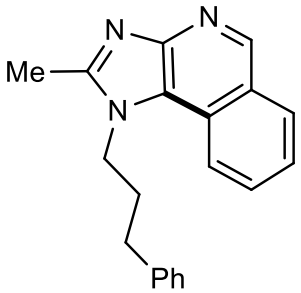
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.4 (Me), 36.0, 47.9 (CH_2), 120.9, 118.8 (CH), 119.4, 122.9, 126.2 (C), 126.3, 126.9, 127.5, 128.7, 128.8, 129.1, 132.1 (CH), 136.4, 143.1, 151.4 (C).

MS (GC, 70 eV): *m/z* (%) = 287 (M^+, 81), 196 (100), 128 (36).

HRMS (EI): calcd for $C_{19}H_{17}N_3$ (M^+) 287.14170, found 287.14121.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2999 (w), 1526 (m), 1499 (m), 1454 (m), 1414 (m), 1362 (m), 1337 (m), 1304 (s), 1228 (m), 1190 (m), 1135 (m), 994 (m), 928 (w), 885 (m), 804 (w), 775 (s), 752 (s), 670 (s), 665 (m), 649 (m), 619 (s), 569 (m).

2-Methyl-1-(3-phenylpropyl)-1*H*-imidazo[4,5-*c*]isoquinoline (4.4.3c).



Starting from 2-(2-methyl-4-nitro-1-(3-phenylpropyl)-1*H*-imidazol-5-yl)benzaldehyde **4.2.1c** (0.349 g, 1 mmol), Pd/C (0.030 g, 0.10 mmol) and H_2 balloon in 25 mL MeOH, the product **4.4.3c** was isolated as a yellow solid (0.222 g, 74%). Mp: 126-128°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.07 (br s, 2H, CH_2), 2.51 (s, 3H, Me), 2.70 (t, 2H, ^3J = 6.6 Hz, CH_2), 4.28 (br s, 2H, CH_2), 7.10-7.15 (m, 2H, CH_{Ar}), 7.17-7.35 (m, 6H, CH_{Ar}), 7.57-7.59 (m, 1H, CH_{Ar}), 8.52 (s, 1H, isoquinoline).

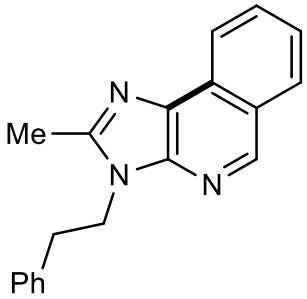
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.8 (Me), 31.2, 32.8, 45.1 (CH_2), 118.6 (CH), 119.0 (C), 124.3, 124.4 (CH), 125.8 (C), 128.5, 128.7, 129.6, 130.3 (CH), 139.9 (C), 148.3 (CH), 150.3, 150.4 (C).

MS (GC, 70 eV): *m/z* (%) = 301 (M^+, 100), 196 (39), 182 (39), 169 (15), 128 (24), 91 (29).

HRMS (EI): calcd for $C_{20}H_{19}N_3$ (M^+) 301.15735, found 301.15740.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1578 (w), 1529 (m), 1503 (m), 1454 (m), 1415 (m), 1309 (s), 1284 (m), 1231 (m), 1189 (s), 1127 (m), 1044 (w), 991 (m), 903 (m), 829 (w), 776 (m), 754 (s), 702 (s), 669 (m), 654 (s), 577 (s).

2-Methyl-3-phenethyl-3*H*-imidazo[4,5-*c*]isoquinoline (4.4.3d).



Starting from 2-(2-methyl-5-nitro-1-phenethyl-1*H*-imidazol-4-yl)benzaldehyde **4.3.2a** (0.335 g, 1 mmol), Pd/C (0.030 g, 0.10 mmol) and H_2 balloon in 25 mL MeOH, the product **4.4.3d** was isolated as a red solid (0.195 g, 68%). Mp: 138-140°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24 (s, 3H, Me), 3.20 (t, 2H, ^3J = 6.8 Hz, CH_2), 4.56 (t, 2H, ^3J = 6.8 Hz, CH_2), 6.97-7.00 (m, 2H, CH_{Ar}), 7.20-7.24 (m, 3H, CH_{Ar}), 7.51-7.57 (m, 1H, CH_{Ar}), 7.75-7.80 (m, 1H, CH_{Ar}), 8.07 (d, 1H, ^3J = 8.3 Hz, CH_{Ar}), 8.51 (dd, 1H, ^3J = 8.3 Hz, ^4J = 0.8 Hz, CH_{Ar}), 8.95 (s, 1H, isoquinoline).

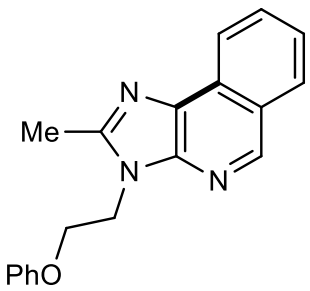
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.8 (Me), 36.2, 44.7 (CH_2), 120.9, 124.8 (CH), 126.3 (C), 126.9, 128.4, 128.7, 128.9 (CH), 129.4 (C), 130.4, 132.0, 132.2 (CH), 138.0, 142.4 (C), 146.5 (CH), 149.8 (C).

MS (GC, 70 eV): *m/z* (%) = 287 (M^+, 79), 196 (72), 183 (100), 128 (33), 116 (24), 77 (16).

HRMS (ESI): calcd for $C_{19}H_{18}N_3$ (M+H) 288.14952, found 288.14934.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2971 (w), 1630 (m), 1572 (m), 1491 (w), 1453 (m), 1436 (m), 1360 (s), 1225 (m), 1118 (m), 1024 (m), 1003 (m), 895 (w), 796 (w), 751 (s), 694 (s), 665 (m), 580 (m).

2-Methyl-3-(2-phenoxyethyl)-3*H*-imidazo[4,5-*c*]isoquinoline (4.4.3e).



Starting from 2-(2-methyl-5-nitro-1-(2-phenoxyethyl)-1*H*-imidazol-4-yl)benzaldehyde **4.3.2e** (0.351 g, 1 mmol), Pd/C (0.030 g, 0.10 mmol) and H_2 balloon in 25 mL MeOH, the product **4.4.3e** was isolated as a brown viscous oil (0.188 g, 62%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.83 (s, 3H, Me), 4.39 (t, 2H, ^3J = 5.2 Hz, CH_2), 4.74 (t, 2H, ^3J = 5.2 Hz, CH_2), 6.78-6.81 (m, 2H,

CH_{Ar}), 6.87-6.92 (m, 1H, CH_{Ar}), 7.18-7.23 (m, 2H, CH_{Ar}), 7.49-7.54 (m, 1H, CH_{Ar}), 7.73-7.79 (m, 1H, CH_{Ar}), 8.03 (d, 1H, ^3J = 8.3 Hz, CH_{Ar}), 8.50 (dd, 1H, ^3J = 8.3 Hz, ^4J = 0.7 Hz, CH_{Ar}), 8.90 (s, 1H, isoquinoline).

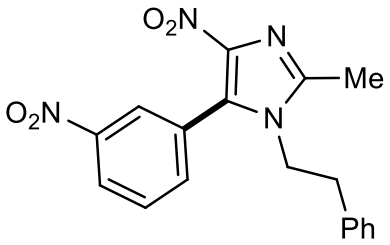
^{13}C NMR(62.9 MHz, $CDCl_3$): δ = 14.6 (Me), 42.5, 66.3 (CH_2), 114.2, 120.8, 121.2, 124.9 (CH), 126.3 (C), 128.3 (CH), 128.7 (C), 129.5, 130.5 (CH), 142.3 (C), 146.4 (CH), 150.5, 158.0 (C).

MS (GC, 70 eV): *m/z* (%) = 303 (M^+, 26), 183 (100).

HRMS (ESI): calcd for $C_{19}H_{18}N_3O$ (M+H) 304.14444, found 304.14427.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2928 (w), 1724 (w), 1633 (w), 1597 (m), 1496 (m), 1458 (m), 1438 (m), 1403 (m), 1358 (s), 1291 (m), 1237 (s), 1176 (m), 1082 (m), 1059 (m), 996 (m), 890 (m), 748 (s), 690 (s), 668 (s), 577 (m).

5-(3-(Nitrophenyl)-2-methyl-4-nitro-1-phenethyl-1*H*-imidazole (4.2.1u).



Starting from 2-methyl-4-nitro-1-phenethyl-1*H*-imidazole **4.1.3c** (0.231 g, 1 mmol), 1-bromo-3-nitrobenzene (0.202 g, 1 mmol), 1-bromo-3-methoxybenzene (0.187 g, 1 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMA, the product **4.2.1u** was isolated as a green solid (0.290 g, 82%^{Pd}). Mp: 132-133°C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.31 (s, 3H, Me), 2.74 (d, 2H, ^3J = 7.0 Hz, CH_2), 4.07 (d, 2H, ^3J = 7.0 Hz, CH_2), 6.84-6.88 (m, 2H, CH_{Ar}), 7.15-7.17 (m, 3H, CH_{Ar}), 7.75-7.77 (m, 2H, CH_{Ar}), 8.04-8.05 (m, 1H, CH_{Ar}), 8.33-8.36 (m, 1H, CH_{Ar}).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 12.9 (Me), 34.9, 46.0 (CH_2), 124.3, 125.3, 126.7, 128.4, 128.6, 128.8 (CH), 129.1 (C), 130.1, 131.5 (CH), 132.0 (C), 136.7 (CH), 137.0, 142.6, 144.6, 147.7 (C).

MS (GC, 70 eV): *m/z* (%) = 352 (M^+, 100), 105 (85), 91 (80).

HRMS (EI): calcd for $C_{18}H_{16}N_4O_4$ (M^+) 352.34404, found 352.34406.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3056 (w), 1520 (s), 1494 (m), 1402 (w), 1342 (s), 1291 (s), 1247 (m), 1162 (w), 1120 (w), 1086 (w), 1019 (w), 929 (w), 884 (w), 856 (s), 837 (w), 810 (w), 767 (w), 745 (s), 735 (s), 693 (s), 667 (m), 566 (w), 540 (m).

General Procedure for the Synthesis of 4-Nitropyrazoles by Alkylation. Synthesis of Compounds 5.1.3a-e: Corresponding 4-nitro-1*H*-pyrazole **5.1.1** (1 equiv.) and K_2CO_3 (2.3

equiv.) successively were weighed to air and placed in a Schlenk flask, equipped with a magnetic stir bar, which then was capped with a rubber septum. The reaction vessel was evacuated and back filled with argon. The dry DMF (8 mL for 10 mmol of 4-nitro-1*H*-pyrazole) and corresponding alkyl bromide **5.1.2** (1.3 equiv.) were added *via* a syringe, and the reaction was heated to 90°C for 8h. Upon completion, the reaction was cooled to room temperature and concentrated under vacuum. The crude mass was washed with water, which was extracted with chloroform afterward. Finally, the organic phase was dried (Na_2SO_4), filtered, and evaporated to dryness, or (if necessary) the residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired alkylated product.

General Procedure for the Synthesis of 4-Nitropyrazoles by Cyclocondensation. Synthesis of Compounds 5.1.3f,g: Corresponding hydrazine **5.1.5** (1 equiv.) and nitromalonaldehyde **5.1.4** (1.5 equiv.) were placed in a pressure tube under the flow of dry argon and dissolved in dry DMF (10 mL for 10 mmol of hydrazine) containing TMSCl (10 equiv.). The mixture was heated at 120°C for 6h. Then the solution was evaporated under reduced pressure. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired 4-nitropyrazole.

General Procedure for Direct C(5)-H Arylation of 4-Nitropyrazoles. Synthesis of Compounds 5.2.1a-ä: Corresponding 4-nitropyrazole **5.1.3** (1 equiv.), CuI (1.2 equiv.), K_2CO_3 (1.3 equiv.), $(CH_3)_3CCO_2H$ (0.3 equiv.), and $PdCl_2(PPh_3)_2$ (or $NiCl_2(PPh_3)_2$) (0.05 equiv.) successively were weighed to air and placed in a Schlenk flask, equipped with a magnetic stir bar, which then was capped with a rubber septum. The reaction vessel was evacuated and back filled with argon (three times). The dry DMF (8 mL for 1 mmol of 4-nitropyrazole) and aryl bromide (4 equiv.) were added *via* a syringe (in the case of solid aryl bromide, first it was dissolved in dry DMF under inert atmosphere), and the reaction was heated to 120°C for 16h. Upon completion, the reaction was cooled to room temperature and concentrated under vacuum. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired arylated product.

General Procedure for Synthesis of Compounds 5.2.1′ and 5.2.1′′: Corresponding 4-nitropyrazole **5.1.3g** (1 equiv.), K_2CO_3 (1.3 equiv.), $(CH_3)_3CCO_2H$ (0.3 equiv.), and $PdCl_2(PPh_3)_2$ (0.05 equiv.) successively were weighed to air and placed in a Schlenk flask,

equipped with a magnetic stir bar, which then was capped with a rubber septum. The reaction vessel was evacuated and back filled with argon (three times). The dry DMF (8 mL for 1 mmol of 4-nitropyrazole) and aryl bromide (4 equiv.) were added *via* a syringe (in the case of solid aryl bromide, first it was dissolved in dry DMF under inert atmosphere), and the reaction was heated to 120°C for 16h. Upon completion, the reaction was cooled to room temperature and concentrated under vacuum. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures.

General Procedure for One-Pot Double C-H Arylation of 4-Nitropyrazoles. Synthesis of Compounds 5.2.2a,b: Corresponding 4-nitropyrazole **5.1.3** (1 equiv.), CuI (6 equiv.), K_2CO_3 (2.3 equiv.), $(CH_3)_3CCO_2H$ (0.3 equiv.), and $PdCl_2(PPh_3)_2$ (0.05 equiv.) successively were weighed to air and placed in a Schlenk flask, equipped with a magnetic stir bar, which then was capped with a rubber septum. The reaction vessel was evacuated and back filled with argon (three times). The dry DMF (8 mL for 1 mmol of 4-nitropyrazole) and aryl bromide (6 equiv.) were added *via* a syringe (in the case of solid aryl bromide, first it was dissolved in dry DMF under inert atmosphere), and the reaction was heated to 120°C for 16h. Upon completion, the reaction was cooled to room temperature and concentrated under vacuum. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired arylated product.

General Procedure for C-H Arylation of the Third Position of 4-Nitropyrazoles. Synthesis of Compounds 5.2.2a-d: Corresponding 4-nitro-5-arylpyrazole **5.2.1** (1 equiv.), CuI (4 equiv.), K_2CO_3 (1.3 equiv.), $(CH_3)_3CCO_2H$ (0.3 equiv.), and $PdCl_2(PPh_3)_2$ (0.05 equiv.) successively were weighed to air and placed in a Schlenk flask, equipped with a magnetic stir bar, which then was capped with a rubber septum. The reaction vessel was evacuated and back filled with argon (three times). The dry DMF (8 mL for 1 mmol of 4-nitro-5-arylpyrazole) and aryl bromide (4 equiv.) were added *via* a syringe (in the case of solid aryl bromide, first it was dissolved in dry DMF under inert atmosphere), and the reaction was heated to 120°C for 16h. Upon completion, the reaction was cooled to room temperature and concentrated under vacuum. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired arylated product.

General Procedure for Reduction of 4-Nitropyrazoles. Synthesis of Compounds 5.3.1a,b and 5.3.3a-e: To a Schlenk flask equipped with a magnetic stir bar and filled with

corresponding 4-nitro-5-arylpyrazole **5.2.1** (1 equiv.) was added 10% Pd/C (0.1 equiv.). The flask was fitted with a rubber septum and then held under vacuum for 3min, after that, it was filled with MeOH (25 mL for 1 mmol of 4-nitropyrazole) and hydrogen. Holding under vacuum was repeated one more time, and after sequential filling with hydrogen, the reaction mixture was stirred for 5h under H_2 atmosphere (H_2 balloon). After the reaction was stopped, the mixture was filtered through a Celite pad, and the filtrate was evaporated to dryness or (if necessary) was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired product.

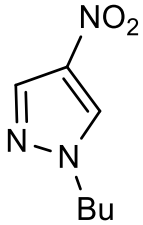
General Procedure for Reduction of 4-Nitropyrazoles with Formaldehyde. Synthesis of Compounds 5.3.2a-c: To a Schlenk flask equipped with a magnetic stir bar and filled with corresponding 4-nitro-5-arylpyrazole **5.2.1** (1 equiv.) was added 10% Pd/C (0.1 equiv.). The flask was fitted with a rubber septum and then held under vacuum for 3min, after that, it was filled with MeOH (25 mL for 1 mmol of 4-nitropyrazole), formaldehyde solution (6 equiv., 37 wt % in H_2O, contains 10-15% methanol as stabilizer), and hydrogen. Holding under vacuum was repeated one more time, and after sequential filling with hydrogen, the reaction mixture was stirred for 5h under H_2 atmosphere (H_2 balloon). After the reaction was stopped, the mixture was filtered through Celite pad and filtrate was evaporated to dryness or (if necessary) was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired product.

Competitive Experiment Between Pyrazole 5.1.3c and Electronically Different Aryl Bromides. The corresponding *N*-substituted 4-nitropyrazole **5.1.3c** (1 equiv.), CuI (1.2 equiv.), K_2CO_3 (1.3 equiv.), $(CH_3)_3CCO_2H$ (0.3 equiv.), and $PdCl_2(PPh_3)_2$ (0.05 equiv.) successively were weighed in air and placed in a Schlenk flask, equipped with a magnetic stir bar, which then was capped with a rubber septum. The reaction vessel was evacuated and back filled with argon (three times). The dry DMF (8 mL for 1 mmol of *N*-substituted 4-nitropyrazole) and aryl bromides (from each 1 equiv.) were added *via* syringe (in case of solid aryl bromide, first it was dissolved in dry DMF under inert atmosphere), and the reaction was heated to 120°C for 16h. After the reaction was stopped, the mixture was filtered through Celite pad and the filtrate was submitted to GC/MS analysis.

Competitive Experiment Between Two Various Pyrazoles. The corresponding *N*-substituted 4-nitropyrazoles **5.1.3c** and **5.1.3g** (from each 1 equiv.), CuI (1.2 equiv.), K_2CO_3

(1.3 equiv.), $(CH_3)_3CCO_2H$ (0.3 equiv.), and $PdCl_2(PPh_3)_2$ (0.05 equiv.) successively were weighed in air and placed in a Schlenk flask, equipped with a magnetic stir bar, which then was capped with a rubber septum. The reaction vessel was evacuated and back filled with argon (three times). The dry DMF (8 mL for 2 mmol of *N*-substituted 4-nitropyrazoles) and aryl bromide (1.1 equiv.) were added *via* syringe (in the case of solid aryl bromide, first it was dissolved in dry DMF under inert atmosphere), and the reaction was heated to 120°C for 16h. After the reaction was stopped, the mixture was filtered through Celite pad and the filtrate was submitted to GC/MS analysis.

1-Butyl-4-nitro-1*H*-pyrazole (5.1.3a).



Starting from 4-nitro-1*H*-pyrazole **5.1.1** (1.13 g, 10 mmol), 1-bromobutane (1.78 g, 13 mmol) and K_2CO_3 (3.20 g, 23 mmol) in 8 mL DMF, the product **5.1.3a** was isolated as a brown solid (1.42 g, 84%). Mp: 92-93°C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 0.88 (t, 3H, ^3J = 7.4 Hz, $CH_2CH_2CH_2\mathit{CH_3}$), 1.18-1.27 (m, 2H, $CH_2CH_2\mathit{CH_2}CH_3$), 1.72-1.84 (m, 2H, $CH_2\mathit{CH_2}CH_2CH_3$), 4.17 (t, 2H, ^3J = 7.2 Hz, $\mathit{CH_2}CH_2CH_2CH_3$), 8.24 (s, 1H, pyrazole), 8.90 (s, 1H, pyrazole).

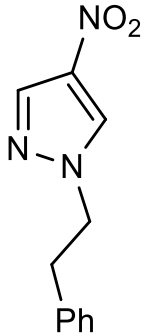
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 13.2 (Me), 18.9, 31.1, 52.0 (CH_2), 130.3 (CH), 134.7 (C), 135.4 (CH).

MS (GC, 70 eV): *m/z* (%) = 169 (M^+, 9), 126 (100), 114 (10), 97 (25), 80 (14), 52 (53), 41 (80).

HRMS (ESI): calcd for $C_7H_{11}N_3O_2$ (M+H) 170.0924, found 170.09227.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3112 (m), 2931 (m), 2868 (w), 1502 (s), 1458 (m), 1405 (s), 1368 (w), 1304 (s), 1191 (w), 1129 (m), 999 (m), 957 (w), 892 (m), 817 (s), 754 (s), 659 (w), 599 (m), 560 (m).

4-Nitro-1-phenethyl-1*H*-pyrazole (5.1.3b).



Starting from 4-nitro-1*H*-pyrazole **5.1.1** (1.13 g, 10 mmol), (2-bromoethyl)benzene (2.40 g, 13 mmol) and K_2CO_3 (3.20 g, 23 mmol) in 8 mL DMF, the product **5.1.3b** was isolated as a white solid (1.93 g, 89%). Mp: 128-130°C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.14 (d, 2H, ^3J = 7.2 Hz, CH_2), 4.43 (d, 2H, ^3J = 7.0 Hz, CH_2), 7.14-7.31 (m, 5H, CH_{Ar}), 8.25 (s, 1H, pyrazole), 8.75 (s, 1H, pyrazole).

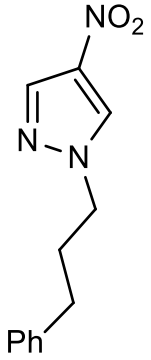
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 35.1, 53.4 (CH_2), 126.6, 128.4, 128.6, 130.4 (CH), 134.6 (C), 135.5 (CH), 137.5 (C).

MS (GC, 70 eV): *m/z* (%) = 217 (M^+, 1), 104 (100), 91 (75), 77 (20), 65 (28), 52 (23), 41 (10).

HRMS (EI): calcd for $C_{11}H_{11}N_3O_2$ (M^+) 217.08458, found 217.08471.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3104 (m), 3030 (w), 2931 (w), 1529 (m), 1498 (s), 1453 (m), 1408 (s), 1327 (m), 1299 (s), 1146 (w), 1005 (m), 966 (w), 880 (m), 817 (m), 756 (s), 726 (s), 697 (s), 601 (m), 572 (m), 546 (m).

4-nitro-1-(3-phenylpropyl)-1*H*-pyrazole (5.1.3c).



Starting from 4-nitro-1*H*-pyrazole **5.1.1** (1.13 g, 10 mmol), (3-bromopropyl)benzene (2.60 g, 13 mmol) and K_2CO_3 (3.20 g, 23 mmol) in 8 mL DMF, the product **5.1.3c** was isolated as a white viscous oil (2.01 g, 87%).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.16-2.31 (m, 2H, CH_2), 2.62-2.70 (m, 2H, CH_2), 4.13 (t, ^3J = 7.1 Hz, CH_2), 7.14-7.34 (m, 5H, CH_{Ar}), 8.06-8.10 (m, 2H, pyrazole).

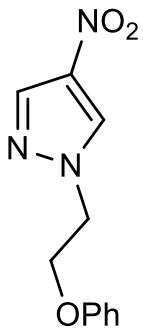
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 30.9, 32.4, 52.6 (CH_2), 126.1, 128.3, 128.5, 128.7 (CH), 135.8 (C), 140.0 (CH), 140.5 (C).

MS (GC, 70 eV): *m/z* (%) = 231 (M^+, 11), 126 (41), 117 (100), 103 (16), 91 (89), 65 (38), 41 (14).

HRMS (EI): calcd for $C_{12}H_{13}N_3O_2$ (M^+) 231.10023, found 231.10023.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3115 (w), 3024 (w), 2923 (w), 1601 (w), 1496 (s), 1446 (m), 1410 (s), 1365 (m), 1301 (s), 1143 (w), 1031 (w), 1000 (m), 956 (m), 884 (m), 816 (s), 779 (m), 739 (s), 697 (s), 601 (m), 554 (m).

4-Nitro-1-(2-phenoxyethyl)-1*H*-pyrazole (5.1.3d).



Starting from 4-nitro-1*H*-pyrazole **5.1.1** (1.13 g, 10 mmol), (2-bromoethoxy)benzene (2.61 g, 13 mmol) and K_2CO_3 (3.20 g, 23 mmol) in 8 mL DMF, the product **5.1.3d** was isolated as a white solid (2.16 g, 93%). Mp: 127-128°C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 4.15 (d, 2H, ^3J = 5.3 Hz, CH_2), 4.34 (d, 2H, ^3J = 5.3 Hz, CH_2), 6.64-6.71 (m, 3H, CH_{Ar}), 6.98-7.05 (m, 2H, CH_{Ar}), 8.03 (s, 1H, pyrazole), 8.71 (s, 1H, pyrazole).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 52.0, 65.4 (CH_2), 114.5, 121.0, 131.0 (CH), 134.9 (C),

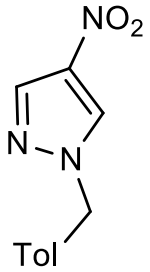
135.7 (CH), 157.8 (C).

MS (GC, 70 eV): *m/z* (%) = 233 (M^+, 16), 140 (35), 120 (85), 107 (14), 94 (47), 77 (100), 65 (58).

HRMS (EI): calcd for $C_{11}H_{11}N_3O_3$ (M^+) 233.07949, found 233.07995.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3118 (m), 3040 (w), 2919 (w), 1598 (w), 1527 (m), 1478 (s), 1435 (m), 1416 (m), 1360 (w), 1321 (m), 1296 (s), 1244 (s), 1136 (w), 1079 (m), 1000 (m), 869 (m), 818 (s), 745 (s), 682 (s), 609 (s), 552 (m).

1-(4-Methylbenzyl)-4-nitro-1*H*-pyrazole (5.1.3e).



Starting from 4-nitro-1*H*-pyrazole **5.1.1** (1.13 g, 10 mmol), 1-(bromomethyl)-4-methylbenzene (2.41 g, 13 mmol) and K_2CO_3 (3.20 g, 23 mmol) in 8 mL DMF, the product **5.1.3e** was isolated as a white solid (1.81 g, 83%). Mp: 112-113°C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.27 (s, 3H, Me), 5.34 (s, 2H, CH_2), 7.14-7.25 (m, 4H, CH_{Ar}), 8.25 (s, 1H, pyrazole), 9.00 (s, 1H, pyrazole).

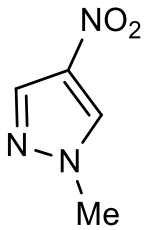
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 20.6 (Me), 55.6 (CH_2), 128.0, 129.2, 130.3 (CH), 132.2, 132.7, 135.0 (C), 135.8, 137.5 (CH).

MS (GC, 70 eV): *m/z* (%) = 217 (M^+, 26), 105 (100), 91 (11), 79 (23), 65 (11), 52 (16), 39 (15).

HRMS (EI): calcd for $C_{11}H_{11}N_3O_2$ (M^+) 217.08458, found 217.08410.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3130 (w), 2962 (w), 1558 (w), 1503 (s), 1423 (m), 1403 (s), 1325 (m), 1291 (m), 1163 (w), 1114 (m), 1000 (m), 926 (w), 866 (m), 812 (s), 755 (s), 694 (w), 590 (m), 554 (m).

1-Methyl-4-nitro-1*H*-pyrazole (5.1.3f).



Starting from methylhydrazine (0.460 g, 10 mmol), enolate of nitromalonaldehyde **5.1.4** (2.08 g, 15 mmol) and TMSCl (10.86 g, 100 mmol) in 10 mL DMF, the product **5.1.3f** was isolated as a yellow solid (1.02 g, 81%). Mp: 96-97°C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.91 (s, 3H, Me), 8.22 (s, 1H, pyrazole), 8.83 (s, 1H, pyrazole).

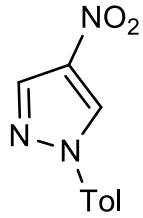
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 39.6 (Me), 130.9 (CH), 134.8 (C), 135.4 (CH).

MS (GC, 70 eV): *m/z* (%) = 127 (M^+, 33), 97 (14), 52 (18), 46 (10), 42 (100), 38 (19), 30 (25).

HRMS (EI): calcd for $C_4H_5N_3O_2$ (M^+) 127.03763, found 127.03757.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3112 (m), 2962 (w), 1720 (w), 1529 (m), 1505 (s), 1447 (m), 1400 (s), 1310 (s), 1191 (w), 1130 (m), 1068 (w), 999 (m), 885 (s), 819 (s), 753 (s), 692 (w), 684 (m), 591 (s), 548 (m).

4-Nitro-1-*p*-tolyl-1*H*-pyrazole (5.1.3g).



Starting from *p*-tolylhydrazine (1.22 g, 10 mmol), enolate of nitromalonaldehyde **5.1.4** (2.08 g, 15 mmol) and TMSCl (10.86 g, 100 mmol) in 10 mL DMF, the product **5.1.3g** was isolated as a brown solid (1.76 g, 87%). Mp: 98-99°C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.35 (s, 3H, Me), 7.34 (d, 2H, ^3J = 8.4 Hz, CH_{Ar}), 7.81 (d, 2H, ^3J = 8.4 Hz, CH_{Ar}), 8.50 (s, 1H, pyrazole), 9.56 (s, 1H, pyrazole).

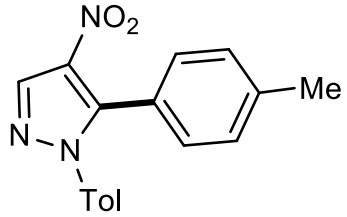
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 20.5 (Me), 119.3, 127.7, 130.0 (CH), 136.1 (C), 136.7 (CH), 137.9 (C).

MS (GC, 70 eV): *m/z* (%) = 203 (M^+, 100), 142 (10), 128 (24), 118 (34), 103 (12), 91 (73), 65 (49), 51 (24).

HRMS (EI): calcd for $C_{10}H_9N_3O_2$ (M^+) 203.06893, found 203.06907.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3130 (m), 3035 (w), 2924 (w), 1902 (w), 1503 (s), 1405 (s), 1348 (w), 1312 (s), 1236 (w), 1170 (m), 1107 (w), 1025 (w), 1002 (m), 947 (m), 886 (m), 810 (s), 750 (s), 657 (w), 594 (m), 563 (m).

4-Nitro-1,5-di-*p*-tolyl-1*H*-pyrazole (5.2.1a).



Starting from 4-nitro-1-(*p*-tolyl)-1*H*-pyrazole **5.1.3g** (0.203 g, 1 mmol), 1-bromo-4-methylbenzene (0.684 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), ($NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1a** was isolated as a brown viscous oil (0.246 g, 83%^{Pd}), (0.132 g, 45%^{Ni}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3H, Me), 2.37 (s, 3H, Me), 7.05-7.12 (m, 4H, CH_{Ar}), 7.20 (br s, 4H, CH_{Ar}), 8.36 (s, 1H, pyrazole).

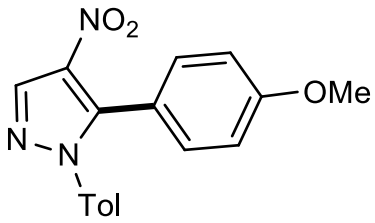
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.1, 21.5 (Me), 123.4 (C), 125.1, 128.5, 129.2, 130.2, 130.4 (CH), 133.7, 136.2 (C), 137.4 (CH), 138.8, 140.3, 141.0 (C).

MS (GC, 70 eV): *m/z* (%) = 293 (M^+, 100), 249 (11), 246 (15), 209 (13), 208 (21), 91 (39), 89 (11), 65 (28).

HRMS (ESI): calcd for $C_{17}H_{16}N_3O_2$ (M+H) 294.1237, found 294.12351.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3041 (w), 1557 (w), 1505 (s), 1388 (s), 1321 (s), 1178 (w), 1112 (w), 1020 (w), 945 (w), 875 (w), 827 (s), 763 (s), 698 (m), 629 (w), 592 (m).

5-(4-Methoxyphenyl)-4-nitro-1-*p*-tolyl-1*H*-pyrazole (5.2.1b).



Starting from 4-nitro-1-(*p*-tolyl)-1*H*-pyrazole **5.1.3g** (0.203 g, 1 mmol), 1-bromo-4-methoxybenzene (0.748 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), ($NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1b** was isolated as a brown viscous oil (0.188 g, 61%^{Pd}), (0.123 g, 40%^{Ni}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32 (s, 3H, Me), 3.81 (s, 3H, OMe), 6.86-6.89 (m, 2H, CH_{Ar}), 7.05-7.12 (m, 4H, CH_{Ar}), 7.20-7.23 (m, 2H, CH_{Ar}), 8.35 (s, 1H, pyrazole).

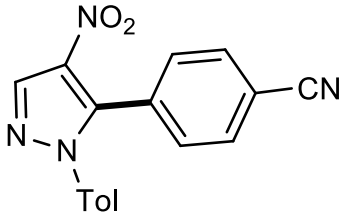
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.1 (Me), 55.3 (OMe), 114 (CH), 118.3 (C), 125.1, 129.9, 131.9 (CH), 133.2, 136.2 (C), 137.4 (CH), 138.8, 140.8, 160.8 (C).

MS (GC, 70 eV): *m/z* (%) = 309 (M^+, 100), 224 (11), 91 (21), 65 (14).

HRMS (ESI): calcd for $C_{17}H_{16}N_3O_3$ (M+H) 310.11862, found 310.11868.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3021 (w), 1611 (m), 1558 (w), 1506 (s), 1455 (m), 1392 (s), 1324 (s), 1291 (m), 1250 (m), 1176 (s), 1113 (w), 1026 (m), 1014 (m), 954 (m), 862 (w), 842 (s), 821 (s), 762 (s), 713 (w), 615 (m), 595 (m).

4-(4-Nitro-1-*p*-tolyl-1*H*-pyrazol-5-yl)benzonitrile (5.2.1c).



Starting from 4-nitro-1-(*p*-tolyl)-1*H*-pyrazole **5.1.3g** (0.203 g, 1 mmol), 4-bromobenzonitrile (0.728 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), ($NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1c** was isolated as a brown viscous oil (0.258 g, 85%^{Pd}), (0.152 g, 50%^{Ni}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3H, Me), 7.01 (d, 2H, ^3J = 8.3 Hz, CH_{Ar}), 7.12 (d, 2H, ^3J = 8.3 Hz, CH_{Ar}), 7.42 (d, 2H, ^3J = 8.6 Hz, CH_{Ar}), 7.64 (d, 2H, ^3J = 8.6 Hz, CH_{Ar}), 8.35 (s, 1H, pyrazole).

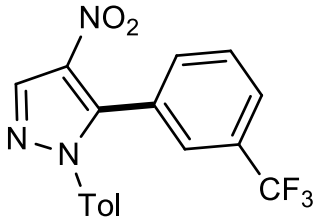
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21 (Me), 113.8, 117.8 (C), 125.1, 127.8, 129.9, 131.2, 132.0, 132.8 (CH), 134.0, 135.3 (C), 137.3 (CH), 138.6, 139.6, 143.4 (C).

MS (GC, 70 eV): *m/z* (%) = 304 (M^+, 100), 303(13), 257 (16), 219 (10) 91 (35), 65 (20).

HRMS (ESI): calcd for $C_{17}H_{13}N_4O_2$ (M+H) 305.1033, found 305.10312.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3042 (w), 1557 (w), 1508 (s), 1455 (m), 1390 (s), 1322 (s), 1200 (w), 1179 (w), 1112 (w) 1007 (w), 955 (m), 909 (m), 820 (s), 728 (s), 649 (m), 630 (w), 595 (m), 552 (s).

5-(3-(Trifluoromethyl)phenyl)-4-nitro-1-*p*-tolyl-1*H*-pyrazole (5.2.1d).



Starting from 4-nitro-1-(*p*-tolyl)-1*H*-pyrazole **5.1.3g** (0.203 g, 1 mmol), 1-bromo-3-(trifluoromethyl)benzene (0.900 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), ($NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1d** was isolated as a brown viscous oil (0.256 g, 74%^{Pd}), (0.156 g, 45%^{Ni}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32 (s, 3H, Me), 7.04 (d, 2H, ^3J = 8.5 Hz, CH_{Ar}), 7.12 (d, 2H, ^3J = 8.5 Hz, CH_{Ar}), 7.49-7.56 (m, 3H, CH_{Ar}), 7.66-7.70 (m, 1H, CH_{Ar}), 8.38 (s, 1H, pyrazole).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -62.9 (CF_3).

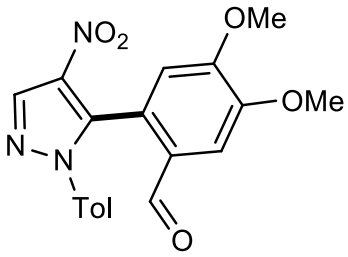
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21 (Me), 123.4 (q, ^1J = 262 Hz, CF_3), 126.7 (q, ^3J = 4 Hz, $CHCCF_3$), 127.5 (q, ^3J = 4 Hz, $CHCCF_3$), 129.0, 129.8, 130.0, 130.9 (CH), 131.0 (q, ^2J = 33 Hz, CCF_3), 133.8 (CH), 134.0, 135.5 (C), 137.3 (CH), 139.1, 139.5 (C).

MS (GC, 70 eV): *m/z* (%) = 347 (M^+, 100), 300 (16), 346 (14), 262 (11), 91 (25), 65 (14).

HRMS (EI): calcd for $C_{17}H_{12}N_3O_2F_3$ (M^+) 347.08761, found 347.08784.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3043 (w), 1556 (w), 1505 (s), 1391 (s), 1311(s), 1266 (m), 1124 (s), 1073 (s), 1024 (m), 904 (m), 868 (w), 830 (s), 699 (s), 646 (m), 529 (m).

4,5-Dimethoxy-2-(4-nitro-1-*p*-tolyl-1*H*-pyrazol-5-yl)benzaldehyde (5.2.1e).



Starting from 4-nitro-1-(*p*-tolyl)-1*H*-pyrazole **5.1.3g** (0.203 g, 1 mmol), 2-bromo-4,5-dimethoxybenzaldehyde (0.980 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1e** was isolated as a brown viscous oil (0.176 g, 48%^{Pd}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.31 (s, 3H, Me), 3.82 (s, 3H, OMe), 3.97 (s, 3H, OMe), 6.72 (s, 1H, CH_{Ar}), 7.02-7.10 (m, 4H, CH_{Ar}), 7.41 (s, 1H, CH_{Ar}), 8.41 (s, 1H, pyrazole), 9.66 (s, 1H, CHO).

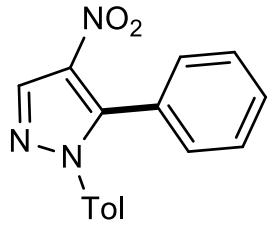
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.1 (Me), 56.2 (OMe), 56.4 (OMe), 111.3, 113.5 (CH), 122.7 (C), 124.7 (CH), 128.5 (C), 129.8 (CH), 135.7 (C), 137.2 (CH), 137.9, 139.3, 150.6, 153.4 (C), 188.1 (CH).

MS (GC, 70 eV): *m/z* (%) = 367 (M^+, 16), 367 (16), 350 (12), 322 (34), 321 (100), 309 (12), 308 (15), 305 (13), 277 (13), 91 (22), 65 (17).

HRMS (ESI): calcd for $C_{19}H_{18}N_3O_5$ (M+H) 368.1241, found 368.12386.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3010 (w), 1683 (m), 1592 (w), 1557 (w), 1505 (s), 1456 (m), 1394 (s), 1316 (s), 1281 (s), 1221 (m), 1163 (m), 1118 (s), 1016 (s), 976 (w), 875 (m) 817 (s), 785 (m), 763 (w), 746 (m), 716 (w), 629 (w), 584 (w).

4-Nitro-5-phenyl-1-*p*-tolyl-1*H*-pyrazole (5.2.1f).



Starting from 4-nitro-1-(*p*-tolyl)-1*H*-pyrazole **5.1.3g** (0.203 g, 1 mmol), bromobenzene (0.628 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), ($NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1f** was isolated as a brown viscous oil (0.206 g, 74%^{Pd}), (0.106 g, 38%^{Ni}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32 (s, 3H, Me), 7.04-7.11 (m, 4H, CH_{Ar}), 7.27-7.31 (m, 2H, CH_{Ar}), 7.34-7.43 (m, 3H, CH_{Ar}), 8.37 (s, 1H, pyrazole).

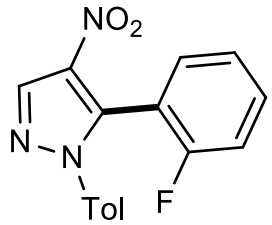
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.1 (Me), 125.1 (CH), 126.6 (C), 128.5, 129.6, 130.0, 130.4 (CH), 136.1 (C), 137.4 (CH), 138.9, 140.8 (C).

MS (GC, 70 eV): *m/z* (%) = 279 (M^+, 100), 279 (100), 235 (11), 232 (16), 194 (14), 91 (34), 89 (11), 65 (23).

HRMS (ESI): calcd for $C_{16}H_{14}N_3O_2$ (M+H) 280.10805, found 280.10789.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3056 (w), 1606 (w), 1556 (w), 1504 (s), 1446 (m), 1386 (s), 1322 (s), 1184 (m), 1116 (w), 1069 (w), 1034 (w), 1007 (w), 949 (m), 915 (m), 861 (m) 821 (s), 754 (s), 709 (m), 690 (s), 646 (m), 594 (m), 528 (s).

5-(2-Fluorophenyl)-4-nitro-1-*p*-tolyl-1*H*-pyrazole (5.2.1g).



Starting from 4-nitro-1-(*p*-tolyl)-1*H*-pyrazole **5.1.3g** (0.203 g, 1 mmol), 1-bromo-2-fluorobenzene (0.700 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), ($NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1g** was isolated as a brown

viscous oil (0.130 g, 44%^{Pd}), (0.056 g, 19%^{Ni}).

^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 2.29 (s, 3H, Me), 7.16-7.22 (m, 4H, CH_{Ar}), 7.23-7.35 (m, 2H, CH_{Ar}), 7.46-7.59 (m, 2H, CH_{Ar}), 8.69 (s, 1H, pyrazole).

^{19}F NMR (282 MHz, DMSO-*d*$_6$): δ = -112.7 (CF).

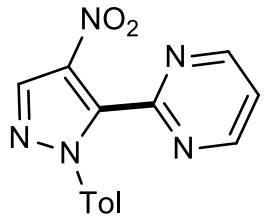
^{13}C NMR (75.5 MHz, DMSO-*d*$_6$): δ = 20.5 (Me), 114.6 (d, *J* = 14 Hz, C), 115.7 (d, *J* = 24 Hz, CH), 124.6 (d, *J* = 3 Hz, CH), 125.0, 129.6, 132.2 (CH), 133.0 (d, *J* = 8 Hz, CH), 134.7 (d, *J* = 79 Hz, CF), 135.5 (C), 137.2 (CH), 139.1, 157.6, 160.9 (C).

MS (GC, 70 eV): *m/z* (%) = 297 (M^+, 100), 132 (17), 91 (66), 65 (44).

HRMS (ESI): calcd for $C_{16}H_{12}N_3O_2F$ (M+H) 298.09863, found 298.09895.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2923 (w), 1711 (w), 1623 (w), 1559 (w), 1507 (s), 1460 (m), 1392 (s), 1324 (s), 1265 (w), 1224 (m), 1178 (w), 1109 (w), 1035 (w), 957 (w), 866 (w), 815 (s), 757 (s), 710 (w), 646 (w), 595 (w), 550 (w).

2-(4-Nitro-1-*p*-tolyl-1*H*-pyrazol-5-yl)pyrimidine (5.2.1h).



Starting from 4-nitro-1-(*p*-tolyl)-1*H*-pyrazole **5.1.3g** (0.203 g, 1 mmol), 2-bromopyrimidine (0.636 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1h** was isolated as a yellow solid (0.123 g, 44%^{Pd}). Mp: 204-206°C.

^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 2.28 (s, 3H, Me), 7.15-7.23 (m, 4H, CH_{Ar}), 7.65 (t, 1H, ^{3}J = 4.9 Hz, CH_{Ar}), 8.69 (s, 1H, pyrazole), 8.96 (d, 2H, ^{3}J = 4.9 Hz, pyrimidine).

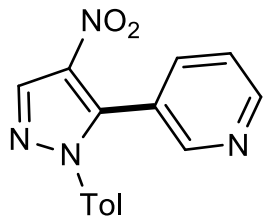
^{13}C NMR (62.9 MHz, DMSO-*d*$_6$): δ =20.5 (Me), 122.0, 124.3, 129.8 (CH), 134.2, 135.6 (C), 136.7 (CH), 138.2, 139.1, 155.8 (C), 158.1 (CH).

MS (GC, 70 eV): *m/z* (%) = 281 (M^+, 50), 264 (77), 234 (100), 91 (41).

HRMS (EI): calcd for $C_{14}H_{11}N_5O_2$ (M^+) 281.09073, found 281.09078.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1558 (w), 1512 (s), 1465 (m), 1394 (s), 1324 (s), 1288 (m), 1218 (w), 1176 (w), 1099 (w), 1042 (w), 988 (w), 960 (m), 868 (w), 818 (s), 758 (m), 732 (w), 709 (m), 667 (w), 650 (w), 625 (m), 596 (m), 534 (m).

3-(4-Nitro-1-*p*-tolyl-1*H*-pyrazol-5-yl)pyridine (5.2.1i).



Starting from 4-nitro-1-(*p*-tolyl)-1*H*-pyrazole **5.1.3g** (0.203 g, 1 mmol), 3-bromopyridine (0.632 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), $(NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in

8 mL DMF, the product **5.2.1i** was isolated as a brown viscous oil (0.235 g, 84%^{Pd}), (0.092g, 33%^{Ni}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32 (s, 3H, Me), 7.04 (d, 2H, ^{3}J = 8.5 Hz, CH_{Ar}), 7.12 (d, 2H, ^{3}J = 8.5 Hz, CH_{Ar}),7.32-7.36 (m, 1H, pyridine), 7.67-7.71 (m, 1H, pyridine), 8.39 (s, 1H, pyrazole) 8.47 (s, 1H, pyridine), 8.64 (d, ^{3}J = 4.02 Hz,1H, pyridine).

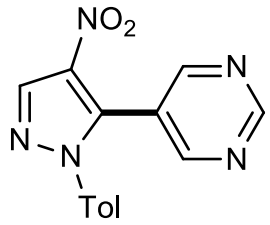
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.1 (Me), 123.2, 125.3, 130.0 (CH), 134.4, 135.5 (C), 137.5 (CH), 137.6 (C), 138.1 (CH), 139.6 (C), 150.5, 150.7 (CH).

MS (GC, 70 eV): *m/z* (%) = 280 (M^+, 100), 280 (100), 279 (70), 236 (16), 234 (14), 233 (52), 232 (17), 220 (11), 195 (11), 91 (33), 65 (26).

HRMS (ESI): calcd for $C_{15}H_{13}N_4O_2$ (M+H) 281.1033, found 281.1033.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3054 (w), 1599 (w), 1549 (w), 1494 (s), 1471 (m), 1392 (s), 1318 (s), 1192 (m), 1179 (w), 1110 (w), 1031 (m), 1005 (w), 955 (m), 920 (w), 861 (m) 824 (s), 761 (s), 706 (s), 620 (m), 533 (s).

5-(4-Nitro-1-*p*-tolyl-1*H*-pyrazol-5-yl)pyrimidine (5.2.1j).



Starting from 4-nitro-1-(*p*-tolyl)-1*H*-pyrazole **5.1.3g** (0.203 g, 1 mmol), 5-bromopyrimidine (0.636 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1j** was isolated as a brown viscous oil (0.230 g, 82%^{Pd}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3H, Me), 7.05 (d, 2H, ^{3}J = 8.5 Hz, CH_{Ar}), 7.17 (d, 2H, ^{3}J = 8.5 Hz, CH_{Ar}), 8.42 (s, 1H, pyrazole), 8.68 (s, 2H, pyrimidine), 9.22 (s, 1H, pyrimidine).

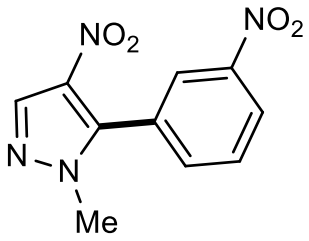
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.2 (Me), 122.1 (C), 125.5, 130.3 (CH), 134.4, 134.7, 135.0 (C), 137.6 (CH), 140.3 (C), 157.8, 159.1 (CH).

MS (GC, 70 eV): *m/z* (%) = 281 (M^+, 100), 280 (16), 264 (26), 237 (22), 235 (13), 234 (68), 221 (12), 207 (18), 91 (49), 65 (33).

HRMS (EI): calcd for $C_{14}H_{11}N_5O_2$ (M^+) 281.09073, found 281.09048.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3046 (w), 1598 (w), 1556 (m), 1495 (s), 1463 (m), 1396 (s), 1320 (s), 1286 (m), 1212 (m), 1165 (w), 1111 (w), 1039 (w), 1002 (w), 957 (m), 918 (w), 862 (w) 825 (s), 762 (s), 743 (w), 723 (s), 628 (s), 539 (m).

1-Methyl-4-nitro-5-(3-nitrophenyl)-1*H*-pyrazole (5.2.1k).



Starting from 1-methyl-4-nitro-1*H*-pyrazole **5.1.3f** (0.127 g, 1 mmol), 1-bromo-3-nitrobenzene (0.808 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1k** was isolated as a brown solid (0.235 g, 95%^{Pd}).

Mp: 126-128°C.

^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 3.73 (s, 3H, Me), 7.85-7.95 (m, 1H, CH_{Ar}), 8.05-8.09 (m, 1H, CH_{Ar}), 8.41-8.45 (m, 2H, CH_{Ar}, pyrazole), 8.53-8.54 (m, 1H, CH_{Ar}).

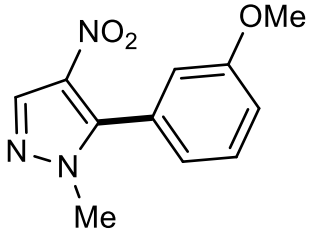
^{13}C NMR (62.9 MHz, DMSO-*d*$_6$): δ = 38.1 (Me), 125.0, 125.2 (CH), 128.2 (C), 130.2 (CH), 132.4 (C), 135.9, 136.7 (CH), 138.8, 147.8, 162.3 (C).

MS (GC, 70 eV): *m/z* (%) = 248 (M^+, 100), 163 (26), 117 (52).

HRMS (EI): calcd for $C_{10}H_8N_4O_4$ (M^+) 248.05401, found 248.05381.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3068 (w), 1673 (w), 1526 (m), 1505 (m), 1472 (m), 1388 (m), 1349 (s), 1322 (m), 1239 (m) 1172 (w), 1087 (m), 979 (w), 919 (w), 826 (m), 758 (m), 726 (m), 694 (m), 675 (m), 640 (m), 592 (w).

5-(3-Methoxyphenyl)-1-methyl-4-nitro-1*H*-pyrazole (5.2.1l).



Starting from 1-methyl-4-nitro-1*H*-pyrazole **5.1.3f** (0.127 g, 1 mmol), 1-bromo-3-methoxybenzene (0.748 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1l** was isolated as a yellow viscous oil (0.193 g, 83%^{Pd}).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.73 (s, 3H, NMe), 3.84 (s, 3H, OMe), 6.89-6.95 (m, 2H, CH_{Ar}), 7.05-7.09 (m, 1H, CH_{Ar}), 7.44 (t, 1H, ^3J = 7.5 Hz, CH_{Ar}), 8.17 (s, 1H, pyrazole).

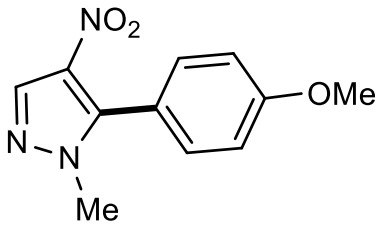
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 38.0 (NMe), 55.4 (OMe), 115.3, 115.9, 121.7 (CH), 127.7 (C), 130.0, 136.3 (CH), 141.3, 159.7 (C).

MS (GC, 70 eV): *m/z* (%) = 233 (M^+, 100), 148 (30), 133 (30), 115 (30), 95 (76).

HRMS (EI): calcd for $C_{11}H_{11}N_3O_3$ (M^+) 233.07949, found 233.07921.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2923 (w), 1582 (w), 1555 (w), 1499 (m), 1465 (m), 1390 (m), 1348 (m), 1323 (s), 1285 (m), 1257 (m), 1208 (m), 1168 (m), 1044 (m), 1021 (m), 975 (w), 824 (s), 786 (m), 761 (m), 737 (m), 691 (m), 640 (w).

5-(4-Methoxyphenyl)-1-methyl-4-nitro-1*H*-pyrazole (5.2.1m).



Starting from 1-methyl-4-nitro-1*H*-pyrazole **5.1.3f** (0.127 g, 1 mmol), 1-bromo-4-methoxybenzene (0.748 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), ($NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1m** was isolated as a brown solid (0.144 g, 62%^{Pd}), (0.051 g, 22%^{Ni}). Mp: 67-68°C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.70 (s, 3H, NMe), 3.85 (s, 3H, OMe), 7.09 (d, 2H, ^3J = 8.6 Hz, CH_{Ar}), 7.50 (d, 2H, ^3J = 8.6 Hz, CH_{Ar}), 8.35 (s, 1H, pyrazole).

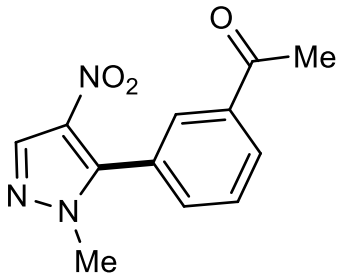
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 37.9 (NMe), 55.3 (OMe), 114.0 (CH), 118.1 (C), 131.6 (CH), 132.2 (C), 136.0 (CH), 141.1, 160.5 (C).

MS (GC, 70 eV): *m/z* (%) = 233 (M^+, 100), 148 (25), 133 (28), 101 (15).

HRMS (ESI): calcd for $C_{11}H_{12}N_3O_3$ (M+H) 234.08732, found 234.08738.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2837 (w), 1609 (m), 1575 (w), 1505 (s), 1459 (m), 1440 (m), 1391 (s), 1321 (s), 1297 (m), 1259 (s), 1175 (s), 1111 (m), 1034 (m), 970 (m), 945 (w), 867 (m), 834 (s), 798 (m), 762 (s), 696 (w), 642 (m), 615 (m), 586 (s), 530 (m).

1-(3-(1-Methyl-4-nitro-1*H*-pyrazol-5-yl)phenyl)ethanone (5.2.1n).



Starting from 1-methyl-4-nitro-1*H*-pyrazole **5.1.3f** (0.127 g, 1 mmol), 1-(3-bromophenyl)ethanone (0.796 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1n** was isolated as a brown solid (0.198 g, 78%^{Pd}). Mp: 109-111°C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.63 (s, 3H, COMe), 3.71 (s, 3H, Me), 7.70-7.75 (m, 1H, CH_{Ar}), 7.83-7.87 (m, 1H, CH_{Ar}), 8.12-8.17 (m, 2H, CH_{Ar}), 8.41 (s, 1H, pyrazole).

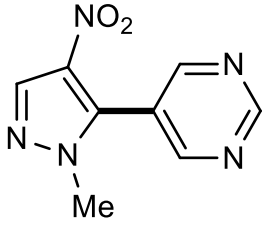
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 26.8, 38.0 (Me), 127.1 (C), 129.1, 129.7, 129.8 (CH), 132.6 (C), 134.5, 136.0 (CH), 137.0, 140.3, 197.4 (C).

MS (GC, 70 eV): *m/z* (%) = 245 (M^+, 37), 230 (100), 43 (42).

HRMS (EI): calcd for $C_{12}H_{11}N_3O_3$ (M^+) 245.07949, found 245.07931.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3064 (w), 1678 (s), 1605 (m), 1552 (w), 1483 (s), 1423 (m), 1392 (s), 1220 (s), 1169 (m), 1037 (w), 962 (w), 944 (w), 860 (m), 828 (s), 802 (s), 761 (s), 693 (m), 588 (m).

5-(1-Methyl-4-nitro-1*H*-pyrazol-5-yl)pyrimidine (5.2.1o).



Starting from 1-methyl-4-nitro-1*H*-pyrazole **5.1.3f** (0.127 g, 1 mmol), 5-bromopyrimidine (0.636 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1o** was isolated as a brown solid (0.188 g, 92%^{Pd}). Mp: 177-179°C.

^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 3.82 (s, 3H, Me), 8.47 (s, 1H, pyrazole), 9.11 (s, 2H, pyrimidine), 9.37 (s, 1H, pyrimidine).

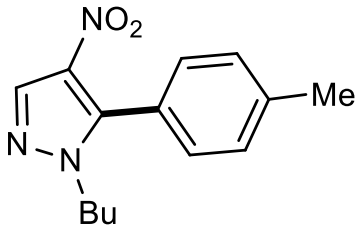
^{13}C NMR (62.9 MHz, DMSO-*d*$_6$): δ = 38.3 (Me), 122.0 (C), 128.6, 131.4 (CH), 131.9, 135.4 (C), 136.1, 157.8, 159.1 (CH).

MS (GC, 70 eV): *m/z* (%) = 205 (M^+, 100), 175 (27), 161 (25), 134 (42), 120 (31), 79 (27), 62 (78).

HRMS (EI): calcd for $C_8H_7N_5O_2$ (M^+) 205.05943, found 205.05932.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2961 (w), 1713 (w), 1674 (w), 1598 (w), 1556 (m), 1496 (m), 1471 (m), 1392 (s), 1320 (s), 1248 (m), 1193 (m), 1154 (m), 1119 (m), 1052 (w), 999 (w), 972 (m), 920 (m), 878 (m), 828 (m), 761 (m), 716 (s), 694 (m), 641 (m), 628 (m), 594 (m), 539 (s).

1-Butyl-4-nitro-5-*p*-tolyl-1*H*-pyrazole (5.2.1p).



Starting from 1-butyl-4-nitro-1*H*-pyrazole **5.1.3a** (0.169 g, 1 mmol), 1-bromo-4-methylbenzene (0.684 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1p** was isolated as a yellow solid (0.215 g, 83%^{Pd}). Mp: 163-164°C.

^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 0.73 (t, 3H, ^3J = 7.7 Hz, $CH_2CH_2CH_2\mathit{CH_3}$), 1.05-1.17 (m, 2H, $CH_2CH_2\mathit{CH_2}CH_3$), 1.59-1.68 (m, 2H, $CH_2\mathit{CH_2}CH_2CH_3$), 2.41 (s, 3H, Me), 3.93 (t, 3H, ^3J = 6.7 Hz, $\mathit{CH_2}CH_2CH_2CH_3$), 7.35-7.42 (m, 4H, CH_{Ar}), 8.38 (s, 1H, pyrazole).

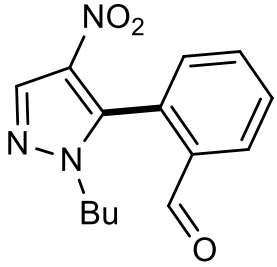
^{13}C NMR (62.9 MHz, DMSO-*d*$_6$): δ = 13.2 (Me), 18.7 (CH_2), 21.0 (Me), 30.9, 49.4 (CH_2), 123.5 (C), 129.2, 129.6 (CH), 132.2 (C), 136.17 (CH), 139.8, 141.3 (C).

MS (GC, 70 eV): *m/z* (%) = 259 (M^+, 17), 227 (100).

HRMS (ESI): calcd for $C_{14}H_{18}N_3O_2$ (M+H) 260.13935, found 260.13948.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3126 (w), 2953 (w), 2232 (m), 1555 (w), 1500 (s), 1496 (m), 1396 (s), 1320 (s), 1251 (m), 1195 (m), 1113 (w), 1027 (w), 983 (w), 880 (w), 846 (s), 763 (s), 685 (w), 595 (w), 569 (m), 548 (s).

2-(1-Butyl-4-nitro-1*H*-pyrazol-5-yl)benzaldehyde (5.2.1q).



Starting from 1-butyl-4-nitro-1*H*-pyrazole **5.1.3a** (0.169 g, 1 mmol), 2-bromobenzaldehyde (0.740 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1q** was isolated as a brown viscous oil (0.174 g, 64%^{Pd}).

^{1}H NMR (250 MHz, DMSO-*d*$_6$): δ = 0.70 (t, 3H, ^3J = 7.2 Hz, $CH_2CH_2CH_2\mathit{CH_3}$), 1.05-1.17 (m, 2H, $CH_2CH_2\mathit{CH_2}CH_3$), 1.53-1.64 (m, 2H, $CH_2\mathit{CH_2}CH_2CH_3$), 3.78-3.85 (m, 2H, $\mathit{CH_2}CH_2CH_2CH_3$), 7.61-7.64 (m, 1H, CH_{Ar}), 7.86-7.90 (m, 2H, CH_{Ar}), 8.15-8.18 (m, 1H, CH_{Ar}), 8.44 (s, 1H, pyrazole), 9.92 (s, 1H, CHO).

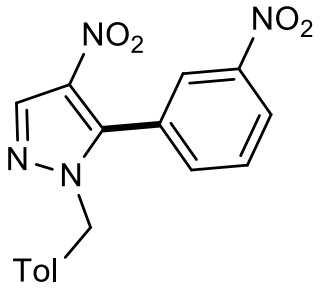
^{13}C NMR (62.9 MHz, DMSO-*d*$_6$): δ = 13.1 (Me), 18.7, 30.6, 49.5 (CH_2), 126.6 (C), 131.2, 131.4 (CH), 132.2 (C), 132.7 (CH), 133.0 (C), 134.3 (CH), 134.5 (C), 136.0 (CH), 139.3 (C), 192.0 (CHO).

MS (GC, 70 eV): *m/z* (%) = 273 (M^+, 1), 227 (100), 183 (18), 171 (55), 129 (29), 115 (23), 102 (26).

HRMS (EI): calcd for $C_{14}H_{15}O_3N_3$ (M^+) 273.11079, found 273.11081.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3391 (w), 2958 (w), 1703 (m), 1599 (w), 1558 (w), 1500 (s), 1461 (m), 1401 (s9, 1321 (s), 1271 (m), 1242 (m), 1197 (m), 1023 (w), 845 (w), 826 (s), 758 (s), 605 (w).

1-(4-Methylbenzyl)-4-nitro-5-(3-nitrophenyl)-1*H*-pyrazole (5.2.1r).



Starting from 1-(4-methylbenzyl)-4-nitro-1*H*-pyrazole **5.1.3e** (0.217 g, 1 mmol), 1-bromo-3-nitrobenzene (0.808 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1r** was isolated as a yellow solid (0.246 g, 73%^{Pd}). Mp: 157-158°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 3H, Me), 5.13 (s, 2H, CH_2), 6.86 (d, 2H, ^3J = 7.9 Hz, CH_{Ar}), 7.08 (d, 2H, ^3J = 7.9 Hz, CH_{Ar}), 7.56-7.60 (m, 1H, CH_{Ar}), 7.67 (t, 1H, ^3J = 8.0 Hz, CH_{Ar}), 8.08-8.10 (m, 1H, CH_{Ar}), 8.26 (s, 1H, pyrazole), 8.36-8.40 (m, 1H, CH_{Ar}).

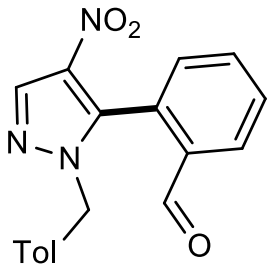
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.1 (Me), 54.8 (CH_2), 125.0, 125.1, 127.3 (CH), 128.3 (C), 129.7, 129.9 (CH), 131.5, 133.9 (C), 135.9, 136.5 (CH), 138.7, 148.1 (C).

MS (GC, 70 eV): *m/z* (%) = 338 (M^+, 1), 105 (100).

HRMS (EI): calcd for $C_{17}H_{14}N_4O_4$ (M^+) 338.10096, found 338.10021.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3117 (w), 2919 (w), 1620 (w), 1565 (w), 1530 (s), 1498 (s), 1477 (s), 1453 (m), 1400 (s), 1344 (s), 1322 (s), 1247 (m), 1184 (m), 1085 (w), 1035 (w), 1006 (w), 900 (m), 871 (m), 829 (s), 773 (s), 740 (s), 696 (m), 680 (m), 651 (w), 607 (m), 534 (w).

2-(1-(4-Methylbenzyl)-4-nitro-1*H*-pyrazol-5-yl)benzaldehyde (5.2.1s).



Starting from 1-(4-methylbenzyl)-4-nitro-1*H*-pyrazole **5.1.3e** (0.217 g, 1 mmol), 2-bromobenzaldehyde (0.740 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1s** was isolated as a yellow viscous oil (0.215 g, 67%^{Pd}).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.22 (s, 3H, Me), 5.05-5.06 (m, 2H, CH_2), 6.81 (d, 2H, ^3J = 8.0 Hz, CH_{Ar}), 7.03 (d, 2H, ^3J = 8.0 Hz, CH_{Ar}), 7.51-7.54 (m, 1H, CH_{Ar}), 7.81-7.84 (m, 2H, CH_{Ar}), 8.06-8.09 (m, 1H, CH_{Ar}), 8.47 (s, 1H, pyrazole), 9.73 (s, 1H, CHO).

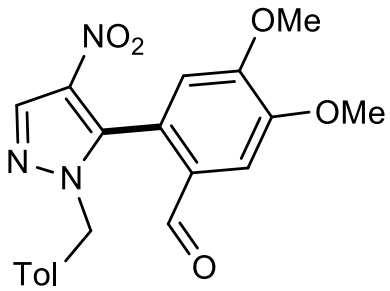
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 20.6 (Me), 53.7 (CH_2), 126.6 (C), 127.5, 128.9, 131.1, 131.3 (CH), 132.1 (C), 132.2 (CH), 133.6 (C), 134.1 (CH), 134.4 (C), 136.1 (CH), 137.2, 139.4 (C), 191.4 (CHO).

MS (GC, 70 eV): *m/z* (%) = 321 (M^+, 100), 77 (18).

HRMS (ESI): calcd for $C_{18}H_{15}N_3O_3$ (M+H) 322.11862, found 322.11825.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3129 (w), 1706 (s), 1564 (m), 1497 (s), 1459 (m), 1399 (s), 1350 (m), 1321 (s), 1295 (m), 1268 (m), 1244 (m), 1195 (m), 1133 (w), 1042 (w), 1021 (w), 922 (w), 879 (w), 831 (s), 811 (m), 781 (s), 762 (s), 732 (m), 667 (m), 602 (m), 534 (m).

2-(1-(4-Methylbenzyl)-4-nitro-1*H*-pyrazol-5-yl)-4,5-dimethoxybenzaldehyde (5.2.1t).



Starting from 1-(4-methylbenzyl)-4-nitro-1*H*-pyrazole **5.1.3e** (0.217 g, 1 mmol), 2-bromo-4,5-dimethoxybenzaldehyde (0.980 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1t** was isolated as a yellow solid (0.205 g, 54%^{Pd}). Mp: 68-69°C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.28 (s, 3H, Me), 3.82 (s, 3H, OMe), 3.90 (s, 3H, OMe), 5.34 (s, 2H, CH_2), 7.16-7.24 (m, 4H, CH_{Ar}), 7.32 (d, 2H, ^4J = 3.9 Hz, CH_{Ar}), 8.25 (s, 1H, CH_{Ar}), 9.0 (s, 1H, pyrazole), 10.07 (s, 1H, CHO).

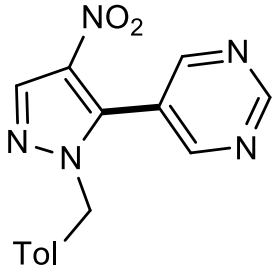
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 20.7 (Me), 55.6 (CH_2), 55.7, 56.5 (OMe), 110.5, 116.0 (CH), 119.3, 125.7 (C), 128.0, 129.2, 130.4 (CH), 132.7 (C), 135.8 (CH), 137.5, 148.6, 154.5 (C), 190.2 (CHO).

MS (GC, 70 eV): *m/z* (%) = 381 (M^+, 58), 335 (34), 105 (100).

HRMS (EI): calcd for $C_{20}H_{19}N_3O_5$ (M^+) 381.13192, found 381.13183.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1667 (m), 1584 (m), 1504 (s), 1470 (m), 1444 (m), 1385 (m), 1340 (w), 1311 (w), 1269 (s), 1217 (m), 1154 (s), 1041 (m), 1014 (m), 979 (m), 866 (s), 811 (s), 756 (m), 737 (s), 654 (m), 588 (s), 555 (m).

5-(1-(4-Methylbenzyl)-4-nitro-1*H*-pyrazol-5-yl)pyrimidine (5.2.1u).



Starting from 1-(4-methylbenzyl)-4-nitro-1*H*-pyrazole **5.1.3e** (0.217 g, 1 mmol), 5-bromopyrimidine (0.636 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1u** was isolated as a yellow solid (0.230 g, 78%^{Pd}). Mp: 106-108°C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.25 (s, 3H, Me), 5.31 (s, 2H, CH_2), 6.90 (d, 2H, ^3J = 8.3 Hz, CH_{Ar}), 7.09 (d, 2H, ^3J = 8.3 Hz, CH_{Ar}), 8.54 (s, 1H, pyrimidine), 8.94 (s, 2H, pyrimidine), 9.33 (s, 1H, pyrazole).

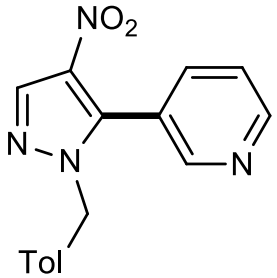
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 20.6 (Me), 53.9 (CH_2), 122.0 (C), 127.2, 129.2 (CH), 132.2, 134.0, 135.6 (C), 136.5 (CH), 137.3 (C), 157.5, 159.2 (CH).

MS (GC, 70 eV): *m/z* (%) = 295 (M^+, 78), 105 (100), 77 (28).

HRMS (EI): calcd for $C_{15}H_{13}N_5O_2$ (M^+) 295.10638, found 295.10704.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3128 (w), 1599 (w), 1549 (m), 1514 (m), 1470 (m), 1441 (w), 1399 (s), 1354 (m), 1324 (m), 1260 (m), 1187 (m), 1009 (w), 1055 (w), 987 (w), 913 (w), 870 (m), 824 (m), 772 (m), 757 (s), 722 (s), 629 (m), 612 (s), 538 (m).

3-(1-(4-Methylbenzyl)-4-nitro-1*H*-pyrazol-5-yl)pyridine (5.2.1v).



Starting from 1-(4-methylbenzyl)-4-nitro-1*H*-pyrazole **5.1.3e** (0.217 g, 1 mmol), 3-bromopyridine (0.632 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1v** was isolated as a yellow solid (0.244 g, 83%^{Pd}). Mp: 113-115°C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.24 (s, 3H, Me), 5.21 (s, 2H,

CH_2), 6.87 (d, 2H, ^3J = 8.1 Hz, CH_{Ar}), 7.08 (d, 2H, ^3J = 8.1 Hz, CH_{Ar}), 7.54-7.58 (m, 1H, CH_{Ar}), 7.92-7.96 (m, 1H, CH_{Ar}), 8.50 (s, 1H, pyrazole), 8.65-8.73 (m, 2H, CH_{Ar}).

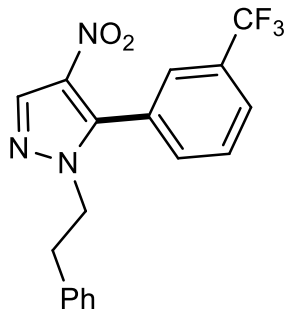
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 20.6 (Me), 53.5 (CH_2), 123.5, 127.1, 129.1 (CH), 132.4, 133.4 (C), 136.5 (CH), 137.2 (C), 137.7 (CH), 138.6 (C), 149.8, 151.0 (CH).

MS (GC, 70 eV): *m/z* (%) = 294 (M^+, 84), 105 (100).

HRMS (EI): calcd for $C_{16}H_{14}N_4O_2$ (M^+) 294.11113, found 294.11093.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2918 (w), 1602 (w), 1573 (w), 1552 (w), 1498 (s), 1466 (m), 1400 (s), 1355 (w), 1324 (s), 1258 (m); 1190 (m), 1101 (w), 1029 (m), 996 (m), 873 (w), 839 (m), 813 (m), 798 (s), 763 (m), 708 (m), 614 (m).

5-(3-(Trifluoromethyl)phenyl)-4-nitro-1-phenethyl-1*H*-pyrazole (5.2.1w).



Starting from 4-nitro-1-phenethyl-1*H*-pyrazole **5.1.3b** (0.217 g, 1 mmol), 1-bromo-3-(trifluoromethyl)benzene (0.900 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1w** was isolated as a yellow viscous oil (0.281 g, 78%^{Pd}).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.04 (d, 2H, ^3J = 6.3 Hz, CH_2), 4.14 (d, 2H, ^3J = 6.3 Hz, CH_2), 6.81-6.85 (m, 2H, CH_{Ar}), 7.17-7.22 (m, 3H, CH_{Ar}), 7.34-7.38 (m, 2H, CH_{Ar}), 7.67 (t, 1H, ^3J = 7.9 Hz, CH_{Ar}), 7.88 (d, 1H, ^3J = 8.0 Hz, CH_{Ar}), 8.52 (s, 1H, pyrazole).

^{19}F NMR (282 MHz, DMSO-d_6): δ = -61.0 (CF_3).

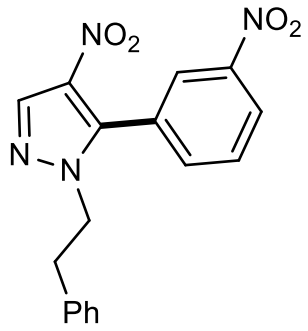
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 34.9, 51.3 (CH_2), 123.7 (q, ^1J = 272 Hz, CF_3), 126.4 (q, ^3J = 4 Hz, CH), 126.7 (CH), 126.8 (q, ^3J = 4 Hz, CH), 127.3 (C), 128.5 (CH), 129.0 (q, ^2J = 32 Hz, CCF_3), 129.6 (CH), 132.5 (C), 133.8, 136.5 (CH), 137.4, 140.1 (C).

MS (GC, 70 eV): *m/z* (%) = 361 (M^+, 1), 104 (100), 91 (24).

HRMS (ESI): calcd for $C_{18}H_{15}N_3O_2F_3$ (M+H) 362.11109, found 362.11081.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1558 (w), 1506 (s), 1462 (m), 1399 (m), 1309 (s), 1245 (m), 1163 (s), 1123 (s), 1096 (m), 1074 (s), 1028 (m), 932 (w), 902 (m), 869 (m), 829 (s), 809 (m), 758 (s), 700 (s), 645 (w), 593 (m), 558 (m).

4-Nitro-5-(3-nitrophenyl)-1-phenethyl-1*H*-pyrazol (5.2.1x).



Starting from 4-nitro-1-phenethyl-1*H*-pyrazole **5.1.3b** (0.217 g, 1 mmol), 1-bromo-3-nitrobenzene (0.808 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), ($NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1x** was isolated as a brown viscous oil (0.321 g, 95%^{Pd}), (0.169g, 50%^{Ni}).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.13 (t, 2H, ^3J = 6.1 Hz, CH_2), 4.16 (t, 2H, ^3J = 6.1 Hz, CH_2), 6.73-6.78 (m, 2H, CH_{Ar}), 6.95-6.99 (m, 1H, CH_{Ar}), 7.15-7.28 (m, 3H, CH_{Ar}), 7.51 (t, 1H, ^3J = 8.0 Hz, CH_{Ar}), 7.62 (t, 1H, ^4J = 1.4 Hz, CH_{Ar}), 8.26-8.31 (m, 2H, CH_{Ar}, pyrazole).

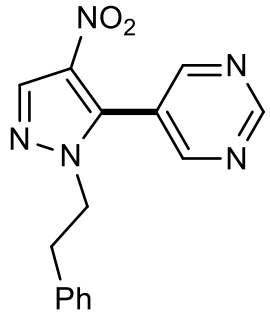
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 35.9, 51.9 (CH_2), 124.8, 127.4 (CH), 127.9 (C), 128.6, 128.9, 129.6, 135.5 (CH), 136.7 (C), 136.8 (CH), 139.6, 148.0 (C).

MS (GC, 70 eV): *m/z* (%) = 338 (M^+, 1), 104 (100), 91 (29).

HRMS (ESI): calcd for $C_{17}H_{14}N_4O_4$ (M+H) 339.109, found 339.109.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2923 (w), 1559 (w), 1525 (s), 1499 (s), 1455 (m), 1398 (s), 1346 (s), 1322 (s), 1254 (m), 1178 (m), 1098 (w), 1077 (w), 1030 (w), 978 (w), 904 (w), 871 (m), 825 (s), 736 (s), 697 (s), 647 (m), 560 (m).

5-(4-Nitro-1-phenethyl-1*H*-pyrazol-5-yl)pyrimidine (5.2.1y).



Starting from 4-nitro-1-phenethyl-1*H*-pyrazole **5.1.3b** (0.217 g, 1 mmol), 5-bromopyrimidine (0.636 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1y** was isolated as a yellow viscous oil (0.256 g, 87%^{Pd}).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.05 (d, 2H, ^3J = 7.0 Hz, CH_2), 4.25 (d, 2H, ^3J = 7.0 Hz, CH_2), 6.86-6.89 (m, 2H, CH_{Ar}), 7.18-7.23 (m, 3H, CH_{Ar}), 8.47 (s, 2H, pyrimidine), 8.57 (s, 1H, pyrazole), 9.29 (s, 1H, pyrimidine).

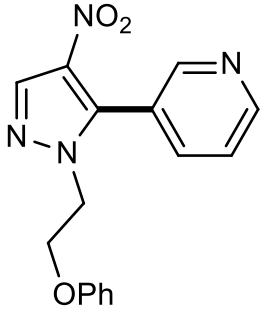
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 35.1, 51.6 (CH_2), 121.6 (C), 126.8, 128.6 (CH), 133.2, 135.8 (C), 136.7 (CH), 137.3 (C), 157.2, 159.0 (CH).

MS (GC, 70 eV): *m/z* (%) = 295 (M^+, 1), 104 (100), 91 (45).

HRMS (ESI): calcd for $C_{15}H_{14}N_5O_2$ (M+H) 296.1142, found 296.11452.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2929 (w), 2223 (m), 1599 (w), 1550 (m), 1499 (s), 1465 (m), 1399 (s), 1322 (s), 1263 (m), 1178 (m), 1077 (w), 1031 (w), 974 (w), 915 (w), 867 (w), 826 (s), 748 (m), 724 (m), 701 (s), 627 (m), 561 (w).

3-(4-Nitro-1-(2-phenoxyethyl)-1*H*-pyrazol-5-yl)pyridine (5.2.1z).



Starting from 4-nitro-1-(2-phenoxyethyl)-1*H*-pyrazole **5.1.3d** (0.233 g, 1 mmol), 3-bromopyridine (0.632 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), ($NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1z** was isolated as a brown viscous oil (0.282 g, 91%^{Pd}), (0.130g, 42%^{Ni}).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 4.32 (br s, 4H, 2xCH_2), 6.81-6.94 (m, 3H, CH_{Ar}), 7.21-7.27 (m, 2H, CH_{Ar}), 7.55-7.66 (m, 2H, CH_{Ar}), 8.13 (br s, 1H, CH_{Ar}), 8.51 (s, 1H, pyrazole).

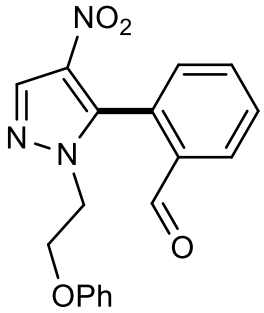
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 49.4, 65.3 (CH_2), 114.2, 120.9, 128.5, 128.7, 129.4 (CH), 131.3 (C), 131.4, 131.9 (CH), 133.1 (C), 136.7 (CH), 157.5 (C).

MS (GC, 70 eV): *m/z* (%) = 310 (M^+, 22), 217 (51), 170 (16), 120 (100), 77 (66).

HRMS (EI): calcd for $C_{16}H_{14}N_4O_3$ (M^+) 310.10604, found 310.10655.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3076 (w), 1598 (w), 1552 (w), 1496 (s), 1405 (m), 1361 (w), 1321 (m), 1272 (w), 1248 (m), 1178 (w), 1151 (w), 1082 (w), 1048 (w), 1011 (w), 995 (w), 906 (w), 830 (m), 753 (s), 708 (m), 693 (s), 615 (m), 539 (w).

2-(4-Nitro-1-(2-phenoxyethyl)-1*H*-pyrazol-5-yl)benzaldehyde (5.2.1ä).



Starting from 4-nitro-1-(2-phenoxyethyl)-1*H*-pyrazole **5.1.3d** (0.233 g, 1 mmol), 2-bromobenzaldehyde (0.740 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1ä** was isolated as a yellow solid (0.219 g, 65%^{Pd}). Mp: 98-100°C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 4.21-4.28 (m, 4H, 2xCH_2), 6.75-6.78 (m, 2H, CH_{Ar}), 6.87-6.93 (m, 1H, CH_{Ar}), 7.19-7.26 (m, 2H, CH_{Ar}), 7.64-7.67 (m, 1H, CH_{Ar}), 7.81-7.91 (m, 2H, CH_{Ar}), 9.51 (s, 1H, pyrazole), 9.89 (s, 1H, CHO).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 49.4, 65.2 (CH_2), 114.2, 121.0 (CH), 127.0 (C), 129.4, 131.1, 131.4, 131.6 (CH), 133.4 (C), 134.1 (CH), 136.5 (CH), 140.0, 157.6 (C), 191.7 (CHO).

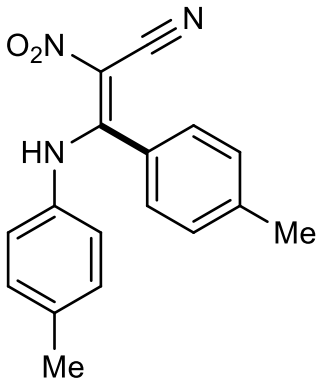
MS (GC, 70 eV): *m/z* (%) = 337 (M^+, 1), 231 (100), 146 (65), 120 (43), 75 (63).

HRMS (ESI): calcd for $C_{18}H_{15}N_3O_4$ (M+H) 338.11353, found 338.11364.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1713 (w), 1600 (w), 1553 (w), 1497 (s), 1475 (m), 1394 (m), 1320 (s), 1234 (s), 1159 (m), 1079 (m), 1045 (m), 1002 (m), 897 (w), 869 (m), 823 (s), 795 (m), 748

(s), 683 (m), 610 (m), 577 (m), 533 (m).

(*Z*)-2-nitro-3-(*p*-tolyl)-3-(*p*-tolylamino)acrylonitrile (5.2.1′′).



Starting from 4-nitro-1-(*p*-tolyl)-1*H*-pyrazole **5.1.3g** (0.203 g, 1 mmol), 1-bromo-4-methylbenzene (0.684 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), Cy_3PxHBF_4 (0.044 g, 0.12 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1′′** was isolated as a yellow solid (0.088 g, 30%^{Pd}). Mp: 171-173°C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.19 (s, 3H, Me), 2.27 (s, 3H, Me), 6.95-7.04 (m, 4H, CH_{Ar}), 7.19 (d, 2H, ^3J = 8.0 Hz, CH_{Ar}), 7.35 (d, 2H, ^3J = 8.0 Hz, CH_{Ar}), 12.07 (s, 1H, NH).

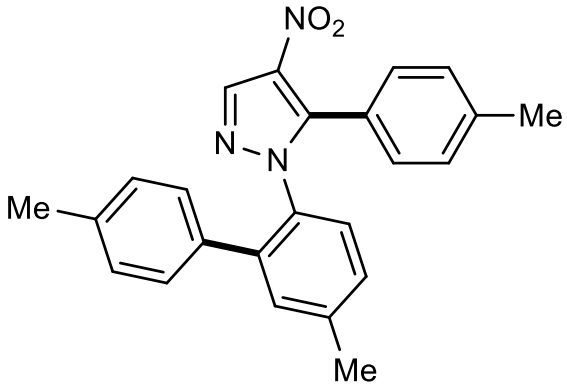
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 20.4, 20.9 (Me), 104.1, 114.0 (C), 126.0, 126.1 (CH), 127.2 (C), 128.5, 129.1, 129.2 (CH), 134.5, 136.8, 141.0 (C).

MS (GC, 70 eV): *m/z* (%) = 293 (M^+, 100).

HRMS (ESI): calcd for $C_{17}H_{16}N_3O_2$ (M+H) 294.1237, found 293.12375.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3208 (w), 2920 (w), 2217 (w), 1707 (w), 1590 (m), 1559 (s), 1506 (s), 1426 (m), 1362 (m), 1324 (w), 1274 (s), 1195 (s), 1159 (s), 1111 (m), 1020 (m), 955 (w), 818 (s), 765 (m), 719 (m), 700 (m), 665 (w), 572 (w).

1-(4',5-dimethyl-[1,1'-biphenyl]-2-yl)-4-nitro-5-(*p*-tolyl)-1*H*-pyrazole (5.2.1′).



Starting from 4-nitro-1-(*p*-tolyl)-1*H*-pyrazole **5.1.3g** (0.203 g, 1 mmol), 1-bromo-4-methylbenzene (0.684 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), Cy_3PxHBF_4 (0.044 g, 0.12 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **5.2.1′** was isolated as a yellow viscous oil (0.046 g, 12%^{Pd}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.44 (s, 3H, Me), 2.50 (s, 3H, Me), 2.53 (s, 3H, Me), 7.20-7.40 (m, 10H, CH_{Ar}), 7.73-7.76 (m, 2H, CH_{Ar}).

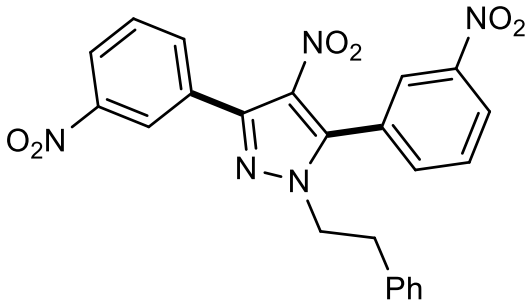
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.1, 21.4, 21.5 (Me), 124.1 (C), 125.2 (CH), 127.5 (C), 128.9, 129.1, 129.3, 129.6, 130.1 (CH), 136.2, 138.6, 139.3, 140.1, 142.1, 147.8 (C).

MS (GC, 70 eV): *m/z* (%) = 383 (M^+, 100), 233 (20), 219 (13), 208 (43), 202 (25), 91 (45), 65 (29).

HRMS (EI): calcd for $C_{24}H_{21}N_3O_2$ (M^+) 383.16338, found 383.16340.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3027 (w), 2917 (w), 2860 (w), 1615 (w), 1558 (w), 1508 (s), 1426 (m), 1355 (s), 1270 (w), 1182 (w) 1116 (w), 1019 (w), 967 (w), 829 (s), 743 (m), 650 (w), 535 (m).

4-Nitro-3,5-bis(3-nitrophenyl)-1-phenethyl-1*H*-pyrazole (5.2.2a).



Starting from 4-nitro-1-phenethyl-1*H*-pyrazole **5.1.3b** (0.217 g, 1 mmol)$^{one\text{-}pot}$, (4-nitro-5-(3-nitrophenyl)-1-phenethyl-1*H*-pyrazole **5.2.1x** (0.338 g, 1 mmol))^{consecutive}, 1-bromo-3-nitrobenzene (1.21 g, 6 mmol)$^{one\text{-}pot}$, (1-bromo-3-nitrobenzene (0.808 g, 4 mmol))^{consecutive}, $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (1.14 g, 6 mmol)$^{one\text{-}pot}$, (CuI (0.762 g, 4 mmol))^{consecutive}, PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.320 g, 2.3 mmol)$^{one\text{-}pot}$, (K_2CO_3 (0.179 g, 1.3 mmol))^{consecutive}, in 8 mL DMF, the product **5.2.2a** was isolated as a yellow solid (0.220 g, 48%$^{one\text{-}pot}$), (0.284 g, 62%^{consecutive}). Mp: 148-150°C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.18 (t, 2H, ^3J = 6.4 Hz, CH_2), 4.21 (t, 2H, ^3J = 6.4 Hz, CH_2), 6.80-6.84 (m, 2H, CH_{Ar}), 7.07-7.11 (m, 1H, CH_{Ar}), 7.19-7.32 (m, 3H, CH_{Ar}), 7.56 (t, 1H, ^3J = 8.0 Hz, CH_{Ar}), 7.69 (t, 2H, ^3J = 8.0 Hz, CH_{Ar}), 7.74 (t, 1H, ^4J = 1.7 Hz, CH_{Ar}), 8.06-8.10 (m, 2H, CH_{Ar}), 8.30-8.38 (m, 1H, CH_{Ar}).

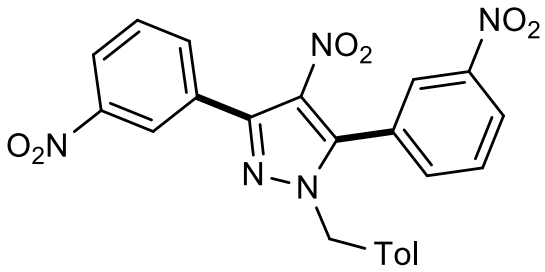
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 34.9, 51.2 (CH_2), 123.2, 123.5, 123.8, 124.1, 126.5 (CH), 127.1 (C), 127.6, 128.0, 128.3, 128.8 (CH), 131.0 (C), 134.4, 134.5 (CH), 135.6, 140.6, 144.7, 147.1, 147.2 (C).

MS (GC, 70 eV): *m/z* (%) = 459 (M^+, 1), 104 (100).

HRMS (EI): calcd for $C_{23}H_{17}N_5O_6$ (M^+) 459.11733, found 459.11773.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2923 (w), 1525 (s), 1499 (s), 1477 (m), 1455 (m), 1398 (s), 1346 (s), 1322 (s), 1254 (m), 1178 (m), 1098 (w), 1077 (w), 1030 (w), 978 (w), 931 (w), 904 (w), 871 (m), 825 (s), 736 (s), 697 (s), 676 (s), 647 (m), 607 (w), 560 (m).

1-(4-Methylbenzyl)-4-nitro-3,5-bis(3-nitrophenyl)-1*H*-pyrazole (5.2.2b).



Starting from 1-(4-methylbenzyl)-4-nitro-1*H*-pyrazole **5.1.3e** (0.217 g, 1 mmol)$^{one\text{-}pot}$, (1-(4-methylbenzyl)-4-nitro-5-(3-nitrophenyl)-1*H*-pyrazole **5.2.1r** (0.338 g, 1 mmol))^{consecutive}, 1-bromo-3-nitrobenzene (1.21 g, 6 mmol)$^{one\text{-}pot}$, (1-bromo-3-nitrobenzene (0.808 g, 4 mmol))^{consecutive}, $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (1.14 g, 6 mmol)$^{one\text{-}pot}$, (CuI (0.762 g, 4 mmol))^{consecutive}, PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.320 g, 2.3 mmol)$^{one\text{-}pot}$, (K_2CO_3 (0.179 g, 1.3 mmol))^{consecutive}, in 8 mL DMF, the product **5.2.2b** was isolated as a yellow solid (0.243 g, 53%$^{one\text{-}pot}$), (0.312 g, 68%^{consecutive}). Mp: 131-132°C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.31 (s, 3H, Me), 5.18 (s, 2H, CH_2), 6.90 (d, 2H, ^3J = 8.0 Hz, CH_{Ar}), 7.09 (d, 2H, ^3J = 8.0 Hz, CH_{Ar}), 7.59-7.74 (m, 3H, CH_{Ar}), 8.04-8.14 (m, 2H, CH_{Ar}), 8.31-8.44 (m, 2H, CH_{Ar}), 8.62-8.64 (m, 1H, CH_{Ar}).

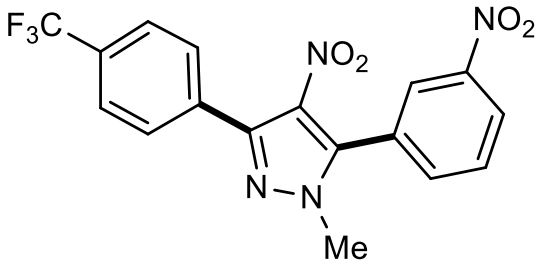
^{13}C NMR: due to bed solubility it was not possible to measure.

MS (GC, 70 eV): *m/z* (%) = 459 (M^+, 62), 105 (100).

HRMS (EI): calcd for $C_{23}H_{17}N_5O_6$ (M^+) 459.11733, found 459.11682.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3086 (w), 2922 (s), 2852 (w), 1620 (w), 1524 (s), 1454 (m), 1345 (s), 1244 (w), 1201 (w), 1097 (m), 1041 (w), 909 (m), 870 (w), 842 (m), 808 (m), 736 (s), 677 (s), 570 (w).

3-(4-(Trifluoromethyl)phenyl)-1-methyl-4-nitro-5-(3-nitrophenyl)-1*H*-pyrazole (5.2.2c).



Starting from 1-methyl-4-nitro-5-(3-nitrophenyl)-1*H*-pyrazole **5.2.1k** (0.248 g, 1 mmol), 1-bromo-4-(trifluoromethyl)benzene (0.900 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.762 g, 4 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol), in 8 mL DMF, the product **5.2.2c** was isolated as a white solid (0.333 g, 85%^{consecutive}). Mp: 202-204°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.81 (s, 3H, Me), 7.71-7.77 (m, 2H, CH_{Ar}), 7.78-7.93 (m, 4H, CH_{Ar}), 8.35-8.36 (m, 1H, CH_{Ar}), 8.44 (dt, 1H, ^3J = 7.1 Hz, ^4J = 2.5 Hz, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -62.8 (CF_3).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 38.3 (Me), 124.0 (q, ^1J = 272 Hz, CF_3), 124.9 (CH), 125.2 (C), 125.2, 125.3, 125.4 (CH), 128.6 (C), 129.6, 130.2 (CH), 131.4 (q, ^2J = 33 Hz, CH), 133.6

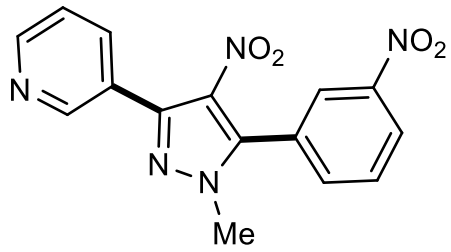
(C), 135.7 (CH), 140.6, 146.3, 148.4 (C).

MS (GC, 70 eV): *m/z* (%) = 392 (M^+, 100), 373 (16), 316 (14), 174 (28), 163 (40), 117 (40).

HRMS (EI): calcd for $C_{17}H_{11}N_4O_4F_3$ (M^+) 392.07269, found 392.07271.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3087 (w), 1525 (m), 1505 (m), 1451 (m), 1350 (s), 1321 (s), 1239 (m), 1191 (w), 1166 (m), 1108 (s), 1063 (s), 1013 (m), 964 (w), 916 (m), 877 (w), 849 (s), 815 (m), 800 (m), 769 (w), 731 (s), 697 (s), 678 (m), 656 (m), 647 (m), 595 (m).

3-(1-Methyl-4-nitro-5-(3-nitrophenyl)-1*H*-pyrazol-3-yl)pyridine (5.2.2d).



Starting from 1-methyl-4-nitro-5-(3-nitrophenyl)-1*H*-pyrazole **5.2.1k** (0.248 g, 1 mmol), 3-bromopyridine (0.632 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.762 g, 4 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol), in 8 mL DMF, the product **5.2.2d** was isolated as a brown solid (0.201 g, 62%^{consecutive}). Mp: 202-204°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.77 (s, 3H, NMe), 7.57-7.63 (m, 1H, CH_{Ar}), 7.74-7.76 (m, 2H, CH_{Ar}), 7.96-7.99 (m, 1H, CH_{Ar}), 8.25-8.31 (m, 2H, CH_{Ar}), 8.38-8.42 (m, 1H, CH_{Ar}), 8.54 (t, 1H, ^4J = 1.9 Hz, CH_{Ar}).

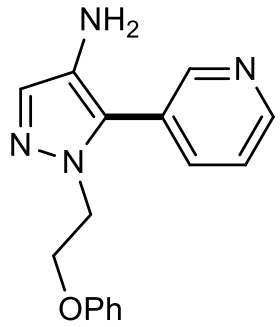
^{13}C NMR: due to bed solubility it was not possible to measure.

MS (GC, 70 eV): *m/z* (%) = 325 (M^+, 100), 163 (23), 117 (25).

HRMS (EI): calcd for $C_{15}H_{11}N_5O_4$ (M^+) 325.0811, found 325.08113.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3098 (w), 2929 (w), 1620 (w), 1524 (s), 1503 (m), 1454 (m), 1379 (w), 1346 (s), 1235 (m), 1087 (m), 1002 (w), 901 (m), 840 (m), 799 (m), 768 (w), 737 (s), 720 (m), 696 (s), 673 (m), 646 (m).

1-(2-Phenoxyethyl)-5-(pyridin-3-yl)-1*H*-pyrazol-4-amine (5.3.1a).



Starting from 3-(4-nitro-1-(2-phenoxyethyl)-1*H*-pyrazol-5-yl)pyridine **5.2.1z** (0.310 g, 1 mmol), Pd/C (0.030 g, 0.10 mmol) and H_2 balloon in 25 mL MeOH, the product **5.3.1a** was isolated as a brown viscous oil (0.246 g, 88%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.99-3.14 (br s, 2H, NH_2), 4.21-4.35 (m, 4H, 2xCH_2), 6.66-6.70 (m, 2H, CH_{Ar}), 6.82-6.88 (m, 1H, CH_{Ar}), 7.12-7.19 (m, 3H, CH_{Ar}), 7.34-7.39 (m, 1H, CH_{Ar}), 7.74-7.77 (m, 1H, CH_{Ar}).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 49.1, 66.6 (CH_2), 114.4, 121.2, 123.8 (CH), 125.9, 127.6,

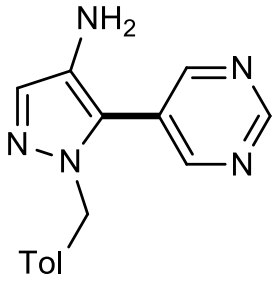
128.2 (C), 129.5, 131.3, 137.4, 149.3, 150.4 (CH) 158.1 (C).

MS (GC, 70 eV): *m/z* (%) = 280 (M^+, 100), 173 (34), 160 (81), 105 (28), 77 (30).

HRMS (EI): calcd for $C_{16}H_{16}N_4O$ (M^+) 280.13186, found 280.13186.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3321 (w), 2929 (w), 1666 (w), 1597 (m), 1494 (m), 1460 (w), 1411 (m), 1370 (m), 1291 (w), 1238 (s), 1172 (m), 1081 (w), 1054 (m), 1003 (w), 959 (w), 903 (w), 814 (m), 789 (w), 753 (s), 711 (s), 690 (s), 618 (m).

1-(4-Methylbenzyl)-5-(pyrimidin-5-yl)-1*H*-pyrazol-4-amine (5.3.1b).



Starting from 5-(1-(4-methylbenzyl)-4-nitro-1*H*-pyrazol-5-yl)pyrimidine **5.2.1u** (0.295 g, 1 mmol), Pd/C (0.030 g, 0.10 mmol) and H_2 balloon in 25 mL MeOH, the product **5.3.1b** was isolated as a brown viscous oil (0.220 g, 83%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.19 (br s, 5H, NH_2, Me), 5.08 (s, 2H, CH_2), 6.74 (d, 2H, ^3J = 8.0 Hz, CH_{Ar}), 6.95 (d, 2H, ^3J = 8.0 Hz, CH_{Ar}), 7.17 (s, 1H, pyrazole), 8.52 (s, 2H, pyrimidine), 9.08 (s, 1H, pyrimidine).

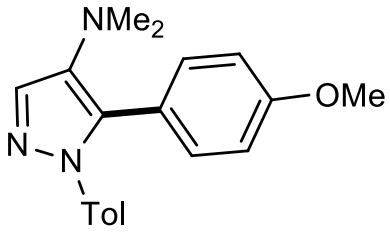
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.0 (Me), 54.1 (CH_2), 123.7, 124.6 (C), 126.5 (CH) 129.1, 129.5, 131.0 (CH), 133.8, 137.7 (C), 156.9 (CH), 158.0 (C).

MS (GC, 70 eV): *m/z* (%) = 265 (M^+, 87), 105 (100).

HRMS (EI): calcd for $C_{15}H_{15}N_5$ (M^+) 265.13220, found 265.13228.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2922 (w), 1682 (w), 1545 (m), 1515 (m), 1406 (s), 1315 (m), 1187 (m), 1119 (w), 1038 (w), 998 (m), 912 (w), 793 (s), 752 (m), 724 (s), 657 (m), 627 (s).

5-(4-Methoxyphenyl)-*N*,*N*-dimethyl-1-*p*-tolyl-1*H*-pyrazol-4-amine (5.3.2a).



Starting from 5-(4-methoxyphenyl)-4-nitro-1-(*p*-tolyl)-1*H*-pyrazole **5.2.1b** (0.309 g, 1 mmol), CH_2O (0.180 g, 6 mmol (37 wt % in H_2O)), Pd/C (0.030 g, 0.10 mmol) and H_2 balloon in 25 mL MeOH, the product **5.3.2a** was isolated as an orange viscous oil (0.273 g, 89%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 3H, Me), 2.56 (s, 6H, NMe_2), 3.80 (s, 3H, OMe), 6.84 (d, 2H, ^3J = 8.5 Hz, CH_{Ar}), 7.06 (br s, 4H, CH_{Ar}), 7.20 (d, 2H, ^3J = 8.5 Hz, CH_{Ar}), 7.51 (s, 1H, pyrazole).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.0 (Me), 44.7 (NMe_2), 55.2 (OMe), 113.8 (CH), 123.0 (C), 124.8, 129.2 (CH) 131.2 (C), 131.2 (CH), 131.6, 136.6, 136.9, 138.1, 159.2 (C).

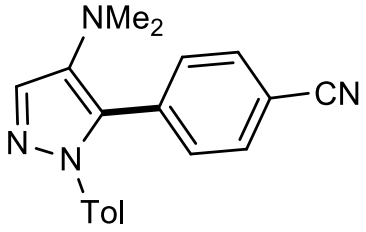
MS (GC, 70 eV): *m/z* (%) = 307 (M^+, 100), 307 (100), 306 (10), 224 (40), 146 (13), 132 (19),

91 (18), 65 (13).

HRMS (ESI): calcd for $C_{16}H_{15}N_3O_2$ (M+H) 308.17600, found 308.17655.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3011 (w), 1614 (w), 1565 (w), 1513 (s), 1456 (m), 1384 (m), 1287 (w), 1245 (s), 1176 (m), 1086 (w), 1035 (m), 962 (s), 926 (w), 813 (s), 740 (w) 661 (m), 631 (m), 576 (m), 528 (m).

4-(4-(Dimethylamino)-1-*p*-tolyl-1*H*-pyrazol-5-yl)benzonitrile (5.3.2b).



Starting from 4-(4-nitro-1-(*p*-tolyl)-1*H*-pyrazol-5-yl)benzonitrile **5.2.1c** (0.304 g, 1 mmol), CH_2O (0.180 g, 6 mmol (37 wt % in H_2O)), Pd/C (0.030 g, 0.10 mmol) and H_2 balloon in 25 mL MeOH, the product **5.3.2b** was isolated as an orange viscous oil (0.257 g, 85%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3H, Me), 2.56 (s, 6H, NMe_2), 7.02 (d, 2H, ^3J = 8.3 Hz, CH_{Ar}), 7.10 (d, 2H, ^3J = 8.3 Hz, CH_{Ar}), 7.42 (d, 2H, ^3J = 8.3 Hz, CH_{Ar}), 7.56 (d, 2H, ^3J = 8.3 Hz, CH_{Ar}), 7.57 (s, 1H, pyrazole).

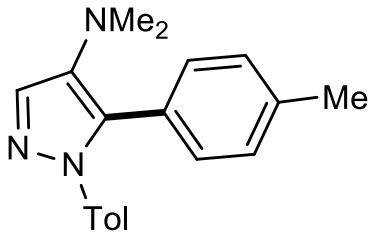
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.1 (Me), 44.9 (NMe_2), 111.2, 118.6 (C), 125.1, 129.6 (CH), 130.0 (C), 130.2, 131.8, 132.0 (CH), 135.2, 137,6. 138,1 (C).

MS (GC, 70 eV): *m/z* (%) = 302 (M^+, 100), 303 (23), 302 (100), 301 (13), 276 (11), 260 (10), 219 (34), 146 (12), 132 (20), 91 (25), 65 (14).

HRMS (ESI): calcd for $C_{19}H_{19}N_4$ (M+H) 303.1610, found 303.16064.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2942 (w), 2777 (w), 1558 (w), 1513 (s), 1452 (w), 1411 (w), 1382 (m), 1312 (w), 1232 (w), 1180 (w), 1149 (w), 1086 (w), 1031 (w), 1015 (w), 961 (m), 926 (w), 818 (s), 771 (w), 729 (w), 700 (w), 660 (w), 629 (w), 593 (w), 573 (w).

***N*,*N*-Dimethyl-1,5-di-*p*-tolyl-1*H*-pyrazol-4-amine (5.3.2c).**



Starting from 4-nitro-1,5-di-*p*-tolyl-1*H*-pyrazole **5.2.1a** (0.293 g, 1 mmol), CH_2O (0.180 g, 6 mmol (37 wt % in H_2O)), Pd/C (0.030 g, 0.10 mmol) and H_2 balloon in 25 mL MeOH, the product **5.3.2c** was isolated as an orange viscous oil (0.250 g, 86%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 3H, Me), 2.33 (s, 3H, Me), 2.56 (s, 6H, NMe_2), 6.99-7.21 (m, 8H, CH_{Ar}), 7.49 (s, 1H, pyrazole).

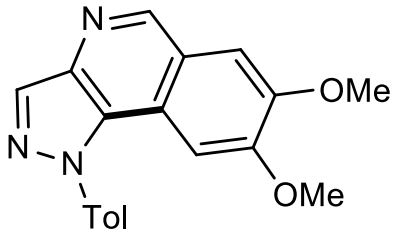
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.0 (Me), 21.3 (Me), 44.8 (NMe_2), 124.8 (CH), 127.7 (C), 129.0, 129.2, 129.9, 131.2 (CH) 131.7, 136.6, 136.7, 138.0, 138.1 (C).

MS (GC, 70 eV): *m/z* (%) = 291 (M^+, 100), 291 (100), 290 (10), 276 (11), 208 (36), 146 (11), 132 (20), 91 (19), 65 (11).

HRMS (ESI): calcd for $C_{19}H_{22}N_3$ (M+H) 292.17355, found 292.18126.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2946 (w), 1558 (w), 1515 (m), 1556 (w), 1420 (w), 1382 (m), 1327 (s), 1271 (w), 1230 (w), 1175 (m), 1148 (m), 1121 (s), 1095 (m), 1073 (m), 1031 (m), 971 (m), 926 (m), 908 (m), 810 (s), 717 (m), 702 (m), 694 (m), 658 (m), 582 (m).

7,8-Dimethoxy-1-*p*-tolyl-1*H*-pyrazolo[4,3-*c*]isoquinoline (5.3.3a).



Starting from 4,5-dimethoxy-2-(4-nitro-1-(*p*-tolyl)-1*H*-pyrazol-5-yl)benzaldehyde **5.2.1e** (0.367 g, 1 mmol), Pd/C (0.030 g, 0.10 mmol) and H_2 balloon in 25 mL MeOH, the product **5.3.3a** was isolated as a gray solid (0.297 g, 93%). Mp: 180-182°C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.46 (s, 3H, Me), 3.51 (s, 3H, OMe), 3.92 (s, 3H, OMe), 6.83 (s, 1H, CH_{Ar}), 7.48 (d, 2H, ^3J = 8.1 Hz, CH_{Ar}), 7.54 (d, 2H, ^3J = 8.1 Hz, CH_{Ar}), 7.73 (s, 1H, CH_{Ar}), 8.45 (s, 1H, pyrazole), 8.95 (s, 1H, Py).

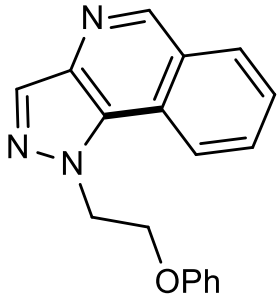
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 20.8 (Me), 55.0, 55.7 (OMe), 100.8, 108.6 (CH), 117.6, 122.7 (C), 126.9, 127.9 (CH), 129.8 (C), 135.3 (CH), 135.9, 138.1, 138.9 (C), 147.9 (CH), 149.3, 151.8 (C).

MS (GC, 70 eV): *m/z* (%) = 319 (M^+, 100).

HRMS (EI): calcd for $C_{19}H_{17}N_3O_2$ (M^+) 319.13153, found 319.13144.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2905 (w), 1622 (w), 1518 (w), 1492 (s), 1455 (m), 1437 (m), 1385 (m), 1295 (w), 1258 (s), 1205 (m), 1174 (m), 1137 (s), 1084 (m), 944 (m), 925 (m), 865 (m), 824 (s), 796 (s), 713 (m), 664 (w), 630 (w), 573 (m), 563 (m).

1-(2-Phenoxyethyl)-1*H*-pyrazolo[4,3-*c*]isoquinoline (5.3.3b).



Starting from 2-(4-nitro-1-(2-phenoxyethyl)-1*H*-pyrazol-5-yl)benzaldehyde **5.2.1ä** (0.337 g, 1 mmol), Pd/C (0.030 g, 0.10 mmol) and H_2 balloon in 25 mL MeOH, the product **5.3.3b** was isolated as a yellow solid (0.254 g, 88%). Mp: 117-119°C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.51 (t, 2H, ^3J = 5.3 Hz, CH_2), 5.24 (t, 2H, ^3J = 5.3 Hz, CH_2), 6.68-6.72 (m, 2H, CH_{Ar}), 6.82-6.88 (m, 1H, CH_{Ar}), 7.13-7.20 (m, 1H, CH_{Ar}), 7.78-7.83 (m, 1H, CH_{Ar}), 7.93-7.99 (m, 1H, CH_{Ar}), 8.29-8.32 (m, 1H, CH_{Ar}), 8.37 (s, 1H, pyrazole), 9.07 (s, 1H, Py).

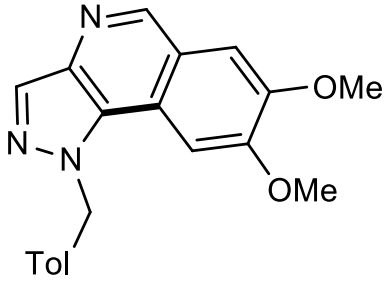
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 51.5, 66.8 (CH_2), 114.2, 120.8, 122.0 (CH), 122.6, 126.8 (C), 127.3 (CH), 128.1 (C), 129.3, 129.4, 130.8, 134.2 (CH), 136.3 (C), 149.4 (CH), 157.9 (C).

MS (GC, 70 eV): *m/z* (%) = 289 (M^+, 24), 196 (26), 182 (31), 169 (100), 128 (51), 77 (47).

HRMS (ESI): calcd for $C_{18}H_{16}N_3O$ (M+H) 290.12879, found 290.1288.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3033 (w), 1622 (w), 1588 (m), 1531 (w), 1496 (m), 1445 (m), 1416 (m), 1350 (w), 1286 (m), 1241 (s), 1133 (w), 1061 (m), 1021 (w), 950 (m), 906 (m), 827 (m), 789 (m), 741 (s), 686 (s), 592 (m), 574 (s).

1-(4-Methylbenzyl)-7,8-dimethoxy-1*H*-pyrazolo[4,3-*c*]isoquinoline (5.3.3c).



Starting from 4,5-dimethoxy-2-(1-(4-methylbenzyl)-4-nitro-1*H*-pyrazol-5-yl)benzaldehyde **5.2.1t** (0.381 g, 1 mmol), Pd/C (0.030 g, 0.10 mmol) and H_2 balloon in 25 mL MeOH, the product **5.3.3c** was isolated as a gray solid (0.300 g, 90%). Mp: 168-170°C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.27 (s, 3H, Me), 3.77 (s, 3H, OMe), 4.00 (s, 3H, OMe), 5.96 (s, 2H, CH_2), 6.97 (d, 2H, ^3J = 8.1 Hz, CH_{Ar}), 7.08 (d, 2H, ^3J = 8.1 Hz, CH_{Ar}), 7.28 (s, 1H, CH_{Ar}), 7.38 (s, 1H, CH_{Ar}), 8.34 (s, 1H, pyrazole), 8.87 (s, 1H, Py).

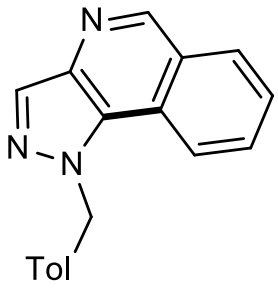
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.0 (Me), 56.0 (OMe), 56.1 (CH_2), 56.3 (OMe), 101.9, 108.2 (CH), 118.8, 122.7 (C), 125.7, 128.4 (CH), 128.5 (C), 129.8, 132.0 (CH), 132.1 (C), 133.8 (CH), 133.9, 135.9, 137.7 (C), 147.4 (CH), 149.4, 152.8 (C).

MS (GC, 70 eV): *m/z* (%) = 333 (M^+, 100), 105 (72).

HRMS (EI): calcd for $C_{20}H_{19}N_3O_2$ (M^+) 333.14718, found 333.14682.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2920 (w), 1622 (w), 1582 (w), 1495 (m), 1436 (m), 1405 (m), 1265 (m), 1191 (m), 1154 (s), 1117 (s), 1072 (m), 1016 (m), 926 (m), 850 (m), 803 (m), 783 (m), 753 (m), 719 (s), 693 (s), 575 (m), 538 (s).

1-(4-Methylbenzyl)-1*H*-pyrazolo[4,3-*c*]isoquinoline (5.3.3d).



Starting from 2-(1-(4-methylbenzyl)-4-nitro-1*H*-pyrazol-5-yl)benzaldehyde **5.2.1s** (0.321 g, 1 mmol), Pd/C (0.030 g, 0.10 mmol) and H_2 balloon in 25 mL MeOH, the product **5.3.3d** was isolated as a yellow solid (0.256 g, 94%). Mp: 163-164°C.

^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 2.18 (s, 3H, Me), 6.06 (s, 2H, CH_2), 6.98 (d, 2H, ^3J = 8.4 Hz, CH_{Ar}), 7.07 (d, 2H, ^3J = 8.4 Hz, CH_{Ar}), 7.69-7.75 (m, 1H, CH_{Ar}), 7.80-7.86 (m, 1H, CH_{Ar}), 8.25-8.32 (m, 2H, CH_{Ar}), 8.43 (s, 1H, pyrazole), 9.08 (s, 1H, Py).

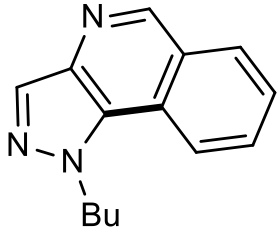
^{13}C NMR (62.9 MHz, DMSO-*d*$_6$): δ = 20.5 (Me), 55.1 (CH_2), 121.5 (CH), 122.2 (C), 126.1 (CH), 126.7 (C), 127.2, 129.3, 131.1, 134.0 (CH), 134.1, 136.6, 136.7 (C), 149.5 (CH).

MS (GC, 70 eV): *m/z* (%) = 273 (M^+, 75), 105 (100).

HRMS (ESI): calcd for $C_{18}H_{16}N_3$ (M+H) 274.13387, found 274.13397.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3129 (w), 1621 (w), 1531 (w), 1512 (w), 1474 (w), 1415 (m), 1349 (m), 1309 (m), 1179 (w), 11052 (w), 1063 (m), 1019 (w), 994 (w), 952 (w), 927 (w), 889 (m), 836 (m), 793 (s), 759 (s), 734 (m), 698 (m), 615 (w), 578 (s).

1-Butyl-1*H*-pyrazolo[4,3-*c*]isoquinoline (5.3.3e).



Starting from 2-(1-butyl-4-nitro-1*H*-pyrazol-5-yl)benzaldehyde **5.2.1q** (0.273 g, 1 mmol), Pd/C (0.030 g, 0.10 mmol) and H_2 balloon in 25 mL MeOH, the product **5.3.3e** was isolated as a yellow solid (0.209 g, 93%). Mp: 137-139°C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.98 (t, 3H, ^3J = 7.5 Hz, $CH_2CH_2CH_2\mathit{CH_3}$), 1.39-1.54 (m, 2H, $CH_2CH_2\mathit{CH_2}CH_3$), 1.93-2.05 (m, 2H, $CH_2\mathit{CH_2}CH_2CH_3$), 4.80 (t, 2H, ^3J = 7.5 Hz, $\mathit{CH_2}CH_2CH_2CH_3$), 7.69-7.76 (m, 1H, CH_{Ar}), 7.87-7.93 (m, 1H, CH_{Ar}), 8.15-8.18 (m, 1H, CH_{Ar}), 8.26-8.30 (m, 2H, pyrazole, CH_{Ar}), 9.03 (s, 1H, Py).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.7 (Me), 19.9, 31.9, 52.8 (CH_2), 121.1 (CH), 123.5 (C), 127.1, 129.8, 131.3, 133.6 (CH), 136.1, 147.6, 149.0 (C).

MS (GC, 70 eV): *m/z* (%) = 225 (M^+, 20), 182 (100), 169 (35), 128 (28).

HRMS (EI): calcd for $C_{14}H_{15}N_3$ (M^+) 225.12605, found 225.12597.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2955 (w), 2930 (w), 2205 (w), 2063 (m), 1958 (m), 1463 (m), 1412 (m), 1346 (m), 1313 (w), 1275 (m), 1232 (w), 1086 (w), 1053 (m), 978 (m), 930 (m), 875 (m), 859 (m), 781 (s), 743 (s), 700 (s), 596 (w), 569 (s).

General Procedure for the Synthesis of Fused 3-Nitropyridines by Cyclocondensation.

Synthesis of Compounds 6.1.3a-m: Corresponding aminoheterocycle or aniline **6.1.2** (1 equiv.) and nitromalonaldehyde **6.1.1** (1.5 equiv.) were placed in a pressure tube under the flow of dry argon and dissolved in dry DMF (10 mL for 10 mmol of aminoheterocycle or aniline) containing TMSCl (10 equiv.). The mixture was heated at 100°C for 12h. Then the solution was evaporated under reduced pressure. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired fused 3-nitropyridines.

General Procedure for Preparation of Starting Fused 3-Nitropyridines from 3-Nitrochromone. Synthesis of compounds 6.1.5a-d,f and 6.1.7a-c: The corresponding 3-nitrochromone **6.1.4** (1 equiv.) and the nucleophile **6.1.2**, **6.1.6** (appropriate amino heterocyclic, 3-aminocrotononitrile, corresponding substituted hydrazine, hydroxylamine hydrochloride) (1.2 equiv.) were dissolved in acetic acid (20 mL for 10 mmol of 3-nitrochromone). The mixture was heated under reflux under an inert atmosphere for 8h. Then the solution was evaporated under reduced pressure. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired product.

General Procedure for the Synthesis of Compound 6.1.5e: Corresponding aniline **6.1.2** (1.2 equiv.) and 3-nitrochromone **6.1.4** (1 equiv.) were placed in a pressure tube under the flow of dry argon and dissolved in dry DMF (10 mL for 10 mmol of 3-nitrochromone) containing TMSCl (10 equiv.). The mixture was heated at 100°C for 12h. Then the solution was evaporated under reduced pressure. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired product.

General Procedure for TM-catalyzed γ-C-H Arylation of Fused 3-Nitropyridines. Synthesis of Compounds 6.2.1a-o and 6.2.2a-g: The corresponding fused 3-nitropyridine **6.1.3** (1 equiv.), CuI (1.2 equiv.), K_2CO_3 (1.3 equiv.), $(CH_3)_3CCO_2H$ (0.3 equiv.) and $PdCl_2(PPh_3)_2$ (or $NiCl_2(PPh_3)_2$) (0.05 equiv.) were weighed in air and placed successively in a Schlenk flask equipped with a magnetic stir bar, which was capped with a rubber septum. The reaction vessel was evacuated and back-filled with argon (three times). Dry DMF (8 mL for 1 mmol of fused 3-nitropyridine) and aryl bromide (4 equiv.) were added with a syringe (in case of solid aryl bromide, first it was dissolved in dry DMF under inert atmosphere), and the reaction mixture was heated to 130ºC for 16h. Afterwards, the reaction mixture was cooled to room temperature and concentrated under vacuum. The residue was purified by column

chromatography typically using heptane/ethyl acetate mixtures to provide the desired arylated product.

General Procedure for Pd-catalyzed C-H Arylation of Pyrrolo[2,3-*b*]pyridine Derivative. Synthesis of Compounds 6.2.3a-h: The corresponding pyrrolo[2,3-*b*]pyridine derivative **6.1.3h** (1 equiv.), CuI (1.2 equiv.), K_2CO_3 (1.3 equiv.), $(CH_3)_3CCO_2H$ (0.3 equiv.) and $PdCl_2(PPh_3)_2$ (0.05 equiv.) were weighed in air and placed successively into a Schlenk flask equipped with a magnetic stir bar, which was capped with a rubber septum. The reaction vessel was evacuated and back-filled with argon (three times). Dry DMF (8 mL for 1 mmol of pyrrolo[2,3-*b*]pyridine derivative) and aryl bromide (2 equiv.) were added with a syringe (in case of solid aryl bromide, first it was dissolved in dry DMF under inert atmosphere), and the reaction was heated to 130ºC for 16h. Upon completion, the reaction was cooled to room temperature and concentrated under vacuum. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired arylated product.

General Procedure for Intramolecular Aromatic Nucleophilic Substitution of Nitro Group by Hydroxy Group. Synthesis of Compounds 6.2.4a-f: The corresponding fused 3-nitropyridine **6.1.5** (1 equiv.) and K_2CO_3 (1.3 equiv.) were weighed in air and placed successively into a Schlenk flask equipped with a magnetic stir bar, which was capped with a rubber septum. The reaction vessel was evacuated and back-filled with argon. Dry DMF (8 mL for 1 mmol of fused 3-nitropyridine) was added with a syringe, and the reaction mixture was heated to 130ºC for 16h. Upon completion, the reaction was cooled to room temperature and concentrated under vacuum. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired product.

General Procedure for One-Pot Pd-catalyzed Domino Nitro Group Substitution-C-H Arylation Reaction. Synthesis of Compounds 6.2.5a-c: The corresponding fused 3-nitropyridine **6.1.5** (1 equiv.), CuI (1.2 equiv.), K_2CO_3 (2.3 equiv.) and $(CH_3)_3CCO_2H$ (0.3 equiv.) were weighed in air and placed successively into a Schlenk flask equipped with a magnetic stir bar, which was capped with a rubber septum. The reaction vessel was evacuated and back-filled with argon (three times). Dry DMF (8 mL for 1 mmol of fused 3-nitropyridine) was added with a syringe, and the reaction mixture was heated to 130ºC for 6h. Afterwards, the reaction was cooled to room temperature. Successively, $PdCl_2(PPh_3)_2$ (0.05

equiv.) and aryl bromide (4 equiv.) were weighed in air, dissolved in dry DMF under inert atmosphere and added with a syringe to the reaction mixture. The reaction vessel was evacuated and back-filled with argon, and the reaction mixture was heated to 130^{o}C for 10h. Upon completion, the reaction was cooled to room temperature and concentrated under vacuum. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired arylated product.

General Procedure for Pd-catalyzed C-H Arylation of Furo[3,2-*b*]pyridine Derivatives. Synthesis of Compounds 6.2.5a-d: The corresponding fused furo[3,2-*b*]pyridine derivative **6.2.4** (1 equiv.), CuI (1.2 equiv.), K_2CO_3 (1.3 equiv.), $(CH_3)_3CCO_2H$ (0.3 equiv.) and $PdCl_2(PPh_3)_2$ (0.05 equiv.) were weighed in air and placed successively into a Schlenk flask equipped with a magnetic stir bar, which was capped with a rubber septum. The reaction vessel was evacuated and back-filled with argon (three times). Dry DMF (8 mL for 1 mmol of furo[3,2-*b*]pyridine derivative) and aryl bromide (4 equiv.) were added with a syringe (in case of solid aryl bromide, first it was dissolved in dry DMF under inert atmosphere), and the reaction was heated to 130^{o}C for 16h. Upon completion, the reaction was cooled to room temperature and concentrated under vacuum. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired arylated product.

General Procedure for Reduction of Arylated Fused 3-Nitropyridines. Synthesis of Compounds 6.3.1a-c and 6.3.3a: To a Schlenk flask equipped with a magnetic stir bar and filled with the corresponding arylated fused 3-nitropyridine **6.2.1b**,**l**,**i** or **6.2.2c** (1 equiv.) was added 10% Pd/C (0.1 equiv.). The flask was fitted with a rubber septum and then held under vacuum for 3min before it was filled with MeOH (25 mL for 1 mmol of arylated fused 3-nitropyridine) and H_2. Holding under vacuum was repeated one more time, and after sequential filling with H_2, the reaction mixture was stirred for 5h under a H_2 atmosphere (H_2 balloon). Afterwards, the reaction mixture was filtered through a Celite pad, and the filtrate was evaporated to dryness or (if necessary) purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired product.

General Procedure for Reduction of Arylated Fused 3-Nitropyridine 6.2.1e with Formaldehyde. Synthesis of Compound 6.3.2a: To a Schlenk flask equipped with a magnetic stir bar and filled with the arylated fused 3-nitropyridine **6.2.1e** (1 equiv.) was added

10% Pd/C (0.1 equiv.). The flask was fitted with a rubber septum and held under vacuum for 3min before it was filled with MeOH (25 mL for 1 mmol of arylated fused 3-nitropyridine), formaldehyde solution (6 equiv., 37 wt% in H_2O, contains 10-15% methanol as stabiliser), and H_2. Holding under vacuum was repeated one more time, and after sequential filling with H_2, the reaction mixture was stirred for 5h under a H_2 atmosphere (H_2 balloon). Afterwards, the reaction mixture was filtered through a Celite pad, and the filtrate was evaporated to dryness. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired product.

General Procedure for the Synthesis of Compound 6.3.3a from Arylated Fused 3-Nitropyridine 6.2.1a and Formaldehyde: To a Schlenk flask equipped with a magnetic stir bar and filled with the arylated fused 3-nitropyridine **6.2.1a** (1 equiv.) was added 10% Pd/C (0.1 equiv.). The flask was fitted with a rubber septum and held under vacuum for 3min before it was filled with MeOH (25 mL for 1 mmol of arylated fused 3-nitropyridine), formaldehyde solution (1.5 equiv., 37 wt% in H_2O, contains 10-15% methanol as stabiliser), and H_2. Holding under vacuum was repeated one more time, and after sequential filling with H_2, the reaction mixture was stirred for 5h under a H_2 atmosphere (H_2 balloon). Afterwards, the reaction mixture was filtered through Celite pad, and filtrate was evaporated to dryness. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired product.

General Procedure for Semi-One-Pot Transfer of Nitro Group to Bromo Substituent. Synthesis of Compound 6.3.4: To a Schlenk flask equipped with a magnetic stir bar and filled with pyrazolo[3,4-*b*]pyridine derivative **6.1.3a** (1 equiv.) was added 10% Pd/C (0.1 equiv.). The flask was fitted with a rubber septum and then held under vacuum for 3min before it was filled with MeOH (25 mL for 1 mmol of pyrazolo[3,4-*b*]pyridine derivative) and H_2. Holding under vacuum was repeated one more time, and after sequential filling with H_2, the reaction mixture was stirred for 5h under a H_2 atmosphere (H_2 balloon). Afterwards, the reaction mixture was filtered through a Celite pad, and the filtrate was evaporated to dryness. The crude mass was dissolved in dry acetonitrile (5 mL for 1 mmol of corresponding amine) under inert atmosphere. The resulting solution was slowly added over a period of 5min to the three necked round bottom flask containing dry $CuBr_2$ (1.2 equiv.), solution of *tert*-butyl nitrite (1.5 equiv.) in dry acetonitrile (40 mL), and equipped with a reflux condenser, addition funnel or solid inlet tube, and a gas outlet tube. After complete gas evolution, the reaction

mixture was poured into 200 mL of 20% aqueous hydrochloric acid and extracted with ether. The organic layer was washed with 20% aqueous hydrochloric acid. The resulting ether solution was dried over anhydrous $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired product.

General Procedure for Suzuki-Miyaura Reaction of Fused 3-Bromopyridine. Synthesis of Compounds 6.3.5a-f: Corresponding fused 3-bromopyridine **6.3.4** (1 equiv.), appropriate boronic acid (1.5 equiv.), K_2CO_3 (2 equiv.) and $PdCl_2(PPh_3)_2$ (0.02 equiv.) were weighed in air and placed successively into a pressure tube under the flow of argon and dissolved in dry 1,4-dioxane (4 mL for 1 mmol of fused 3-bromopyridine). The mixture was heated at 90°C for 8h. Then the solution was evaporated under reduced pressure. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired product.

General Procedure for Sonogashira Reaction of Fused 3-Bromopyridine. Synthesis of Compound 6.3.6a: Corresponding fused 3-bromopyridine **6.3.4** (1 equiv.), appropriate acetylene (2 equiv.), TEA (1.3 equiv.) and $PdCl_2(PPh_3)_2$ (0.02 equiv.) were weighed in air and placed successively into a pressure tube under the flow of argon and dissolved in dry DMF (4 mL for 1 mmol of fused 3-bromopyridine). The mixture was heated at 120°C for 8h. Then the solution was evaporated under reduced pressure. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired product.

General Procedure for Mizoroki-Heck Reaction of Fused 3-Bromopyridine. Synthesis of Compounds 6.3.7a-c: Corresponding fused 3-bromopyridine **6.3.4** (1 equiv.), appropriate alkene (3 equiv.), TEA (4 equiv.) and $PdCl_2(PPh_3)_2$ (0.04 equiv.) were weighed in air and placed successively into a pressure tube under the flow of argon and dissolved in dry DMF (4 mL for 1 mmol of fused 3-bromopyridine). The mixture was heated at 140°C for 14h. Then the solution was evaporated under reduced pressure. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired product.

Competitive Experiment Between Two Various Fused 3-Nitropyridines. The corresponding fused 3-nitropyridines **6.1.3a** and **6.1.3b** (from each 1 equiv.), CuI (1.2 equiv.), K_2CO_3 (1.3 equiv.), $(CH_3)_3CCO_2H$ (0.3 equiv.), and $PdCl_2(PPh_3)_2$ (0.05 equiv.) successively

were weighed in air and placed in a Schlenk flask, equipped with a magnetic stir bar, which then was capped with a rubber septum. The reaction vessel was evacuated and back filled with argon (three times). The dry DMF (8 mL for 2 mmol of fused 3-nitropyridines) and aryl bromide (1.1 equiv.) were added *via* syringe (in the case of solid aryl bromide, first it was dissolved in dry DMF under inert atmosphere), and the reaction was heated to 130°C for 16h. After the reaction was stopped, the mixture was filtered through Celite pad and the filtrate was submitted to GC/MS analysis.

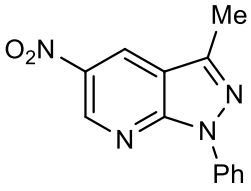
Competitive Experiment Between Fused 3-Nitropyridine and 4-Nitropyrazole. The corresponding fused 3-nitropyridine **6.1.3a** and 4-nitropyrazole **5.1.3c** (from each 1 equiv.), CuI (1.2 equiv.), K_2CO_3 (1.3 equiv.), $(CH_3)_3CCO_2H$ (0.3 equiv.), and $PdCl_2(PPh_3)_2$ (0.05 equiv.) successively were weighed in air and placed in a Schlenk flask, equipped with a magnetic stir bar, which then was capped with a rubber septum. The reaction vessel was evacuated and back filled with argon (three times). The dry DMF (8 mL for 2 mmol of starting heterocycles) and aryl bromide (1.1 equiv.) were added *via* syringe (in the case of solid aryl bromide, first it was dissolved in dry DMF under inert atmosphere), and the reaction was heated to 130°C for 16h. After the reaction was stopped, the mixture was filtered through Celite pad and the filtrate was submitted to GC/MS analysis.

Competitive Experiment Between Fused 3-Nitropyridine and 4-Nitroimidazole. The corresponding fused 3-nitropyridine **6.1.3a** and 4-nitroimidazole **4.1.3f** (from each 1 equiv.), CuI (1.2 equiv.), K_2CO_3 (1.3 equiv.), $(CH_3)_3CCO_2H$ (0.3 equiv.), and $PdCl_2(PPh_3)_2$ (0.05 equiv.) successively were weighed in air and placed in a Schlenk flask, equipped with a magnetic stir bar, which then was capped with a rubber septum. The reaction vessel was evacuated and back filled with argon (three times). The dry DMF (8 mL for 2 mmol of starting heterocycles) and aryl bromide (1.1 equiv.) were added *via* syringe (in the case of solid aryl bromide, first it was dissolved in dry DMF under inert atmosphere), and the reaction was heated to 130°C for 16h. After the reaction was stopped, the mixture was filtered through Celite pad and the filtrate was submitted to GC/MS analysis.

Competitive Experiment Between 4-Nitropyrazole and 4-Nitroimidazole. The corresponding 4-nitropyrazole **5.1.3c** and 4-nitroimidazole **4.1.3f** (from each 1 equiv.), CuI (1.2 equiv.), K_2CO_3 (1.3 equiv.), $(CH_3)_3CCO_2H$ (0.3 equiv.), and $PdCl_2(PPh_3)_2$ (0.05 equiv.) successively were weighed in air and placed in a Schlenk flask, equipped with a magnetic stir

bar, which then was capped with a rubber septum. The reaction vessel was evacuated and back filled with argon (three times). The dry DMF (8 mL for 2 mmol of starting heterocycles) and aryl bromide (1.1 equiv.) were added *via* syringe (in the case of solid aryl bromide, first it was dissolved in dry DMF under inert atmosphere), and the reaction was heated to 130°C for 16h. After the reaction was stopped, the mixture was filtered through Celite pad and the filtrate was submitted to GC/MS analysis.

3-Methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (6.1.3a).



Starting from 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (1.73 g, 10 mmol), enolate of nitromalonaldehyde (2.08 g, 15 mmol) and TMSCl (10.86 g, 100 mmol) in 10 mL DMF, the product **6.1.3a** was isolated as a yellow solid (2.24 g, 88%). Mp: 130-132ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.71 (s, 3H, Me), 7.32-7.38 (m, 1H, CH_{Ar}), 7.51-7.56 (m, 2H, CH_{Ar}), 8.18-8.21 (m, 2H, CH_{Ar}), 8.90 (d, 1H, ^4J = 2.5 Hz, Py), 9.43 (d, 1H, ^4J = 2.5 Hz, Py).

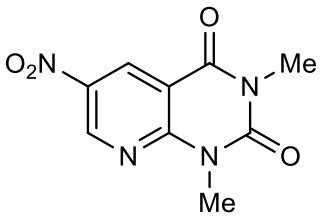
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 12.5 (Me), 116.0 (C), 121.3, 126.3, 126.9, 129.2 (CH), 138.4, 139.2 (C), 145.0 (CH), 145.2, 151.2 (C).

MS (GC, 70 eV): *m/z* (%) = 254 (M^+, 100), 208 (14), 167 (12), 140 (12), 77 (15).

HRMS (ESI): calcd for $C_{13}H_{10}N_4O_2$ (M+H) 255.08765, found 255.08749.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3078 (w), 1593 (m), 1522 (m), 1504 (m), 1476 (m), 1437 (m), 1383 (w), 1350 (m), 1328 (s), 1265 (m), 1160 (w), 1123 (m), 1030 (w), 1011 (w), 962 (w), 933 (w), 914 (w), 790 (m), 772 (s), 752 (s), 689 (s), 671 (m), 656 (m), 595 (s).

1,3-Dimethyl-6-nitropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (6.1.3b).



Starting from 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (1.55 g, 10 mmol), enolate of nitromalonaldehyde (2.08 g, 15 mmol) and TMSCl (10.86 g, 100 mmol) in 10 mL DMF, the product **6.1.3b** was isolated as a white solid (2.15 g, 91%). Mp: 202-204ºC.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.51 (s, 3H, Me), 3.78 (s, 3H, Me), 9.20 (d, 1H, ^4J = 2.7 Hz, Py), 9.46 (d, 1H, ^4J = 2.7 Hz, Py).

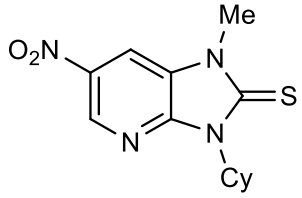
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 28.9, 30.4 (Me), 110.0 (C), 133.5 (CH), 140.0 (C), 149.7 (CH), 150.7, 153.7, 159.7 (C).

MS (GC, 70 eV): *m/z* (%) = 236 (M^+, 100), 208 (11), 124 (53), 78 (11).

HRMS (ESI): calcd for $C_9H_8N_4O_4$ (M+H) 237.0618, found 237.0622.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3059 (w), 2923 (w), 2853 (w), 1722 (w), 1666 (m), 1591 (s), 1536 (m), 1471 (m), 1412 (m), 1376 (m), 1334 (s), 1280 (s), 1163 (m), 1097 (s), 1005 (m), 981 (m), 949 (m), 910 (w), 829 (m), 796 (s), 751 (s), 733 (s), 711 (m), 675 (m), 580 (m).

3-Cyclohexyl-1-methyl-6-nitro-1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-thione (6.1.3d).



Starting from 4-amino-3-cyclohexyl-1-methyl-1*H*-imidazole-2(3*H*)-thione (2.11 g, 10 mmol), enolate of nitromalonaldehyde (2.08 g, 15 mmol) and TMSCl (10.86 g, 100 mmol) in 10 mL DMF, the product **6.1.3d** was isolated as a yellow solid (2.31 g, 79%). Mp: 198-200°C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.24-1.50 (m, 6H, CH_{2Cy}), 1.63-1.66 (m, 2H, CH_{2Cy}), 1.77-1.80 (m, 2H, CH_{2Cy}), 2.89-2.96 (m, 1H, CH_{Cy}), 3.45 (s, 3H, Me), 7.62 (d, 1H, ^4J = 2.11 Hz, Py), 8.86 (d, 1H, ^4J = 2.11 Hz, Py).

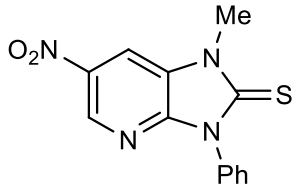
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 24.7, 25.5 (CH_2), 31.4 (Me), 33.4 (CH_2), 64.7 (CH), 106.7 (CH), 125.8 (C), 136.7 (CH), 137.3, 143.1, 155.1 (C).

MS (GC, 70 eV): *m/z* (%) = 292 (M^+, 43), 263 (16), 249 (100), 237 (13), 203 (20).

HRMS (EI): calcd for $C_{13}H_{16}O_2N_4S$ (M^+) 292.09885, found 292.099655.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3097 (w), 2922 (s), 2852 (s), 1732 (w),1647 (s),1583 (m),1519 (s),1448 (s),1430 (s),1395 (m),1336 (s), 1285 (s), 1261 (s), 1218 (m), 1147 (s), 1106 (s), 1076 (s), 1013 (m), 970 (s), 916 (s), 892 (m), 871 (m), 822 (s), 795 (m), 743 (s), 600 (s).

1-Methyl-6-nitro-3-phenyl-1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-thione (6.1.3e).



Starting from 4-amino-1-methyl-3-phenyl-1*H*-imidazole-2(3*H*)-thione (2.05 g, 10 mmol), enolate of nitromalonaldehyde (2.08 g, 15 mmol) and TMSCl (10.86 g, 100 mmol) in 10 mL DMF, the product **6.1.3e** was isolated as a red solid (2.38 g, 83%). Mp: 260-262°C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.86 (s, 3H, Me), 7.51-7.65 (m, 5H, CH_{Ar}), 8.78 (d, 1H, ^4J = 2.3 Hz, Py), 9.05 (d, 1H, ^4J = 2.3 Hz, Py).

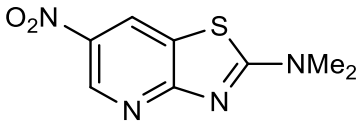
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 31.6 (Me), 111.9 (CH), 126.2 (C), 128.5, 129.2, 129.3 (CH), 134.0 (C), 137.0 (CH), 141.0, 148.7, 173.8 (C).

MS (GC, 70 eV): *m/z* (%) = 286 (M^+, 100), 239 (45), 224 (12), 77 (12).

HRMS (EI): calcd for $C_{13}H_{10}N_2O_2S$ (M^+) 286.05190, found 286.051426.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3021 (w), 1597 (w), 1567 (w), 1536 (m), 1486 (w), 1444 (w),1414 (w),1393 (w), 1322 (m),1283 (s), 1248 (m), 1127 (m), 1061 (m), 950 (m), 938 (m), 900 (m), 771 (s), 744 (m), 719 (m), 657 (m), 631 (m), 564 (m).

_N_,_N_-Dimethyl-6-nitrothiazolo[4,5-_b_]pyridin-2-amine (6.1.3f).



Starting from N^2,N^2-dimethylthiazole-2,4-diamine hydrochloride (1.79 g, 10 mmol), enolate of nitromalonaldehyde (2.08 g, 15 mmol) and TMSCl (10.86 g, 100 mmol) in 10 mL DMF, the product **6.1.3f** was isolated as a yellow viscous oil (1.70 g, 76%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.27 (s, 6H, 2xMe), 9.05 (d, 1H, ^4J = 2.6 Hz, Py), 9.12 (d, 1H, ^4J = 2.6 Hz, Py).

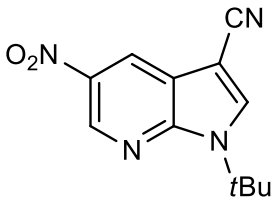
^{13}C NMR: due to bed solubility it was not possible to measure.

MS (EI, 70 eV): *m/z* (%) = 224 (M^+, 67), 209 (100), 181 (35), 163 (21), 108 (14).

HRMS (EI): calcd for $C_8H_8O_2N_4S$ (M^+) 224.03680, found 224.03686.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3048 (w), 2967 (w), 1582 (w), 1563 (m), 1484 (m), 1438 (m), 1384 (m), 1309 (m), 1290 (m), 1239 (s), 1107 (s), 1066 (m), 1054 (m), 1028 (m), 937 (m), 801 (w), 769 (s), 744 (m), 707 (w), 636 (m).

1-(*Tert*-butyl)-5-nitro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (6.1.3h).



Starting from 5-amino-1-(*tert*-butyl)-1*H*-pyrrole-3-carbonitrile (1.63 g, 10 mmol), enolate of nitromalonaldehyde (2.08 g, 15 mmol) and TMSCl (10.86 g, 100 mmol) in 10 mL DMF, the product **6.1.3h** was isolated as an orange solid (2.27 g, 93%). Mp: 218-220ºC.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.79 (s, 9H, *t*Bu), 8.00 (s, 1H, pyrrole), 8.82 (d, 1H, ^4J = 2.6 Hz, Py), 9.24 (d, 1H, ^4J = 2.5 Hz, Py).

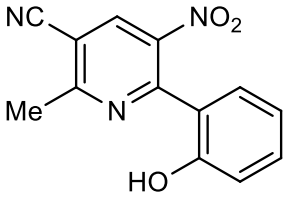
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 29.1 (*t*Bu), 59.9, 86.0, 113.7, 120.3 (C), 124.1, 136.6 (CH), 140.0 (C), 140.1 (CH), 148.7 (C).

MS (GC, 70 eV): *m/z* (%) = 244 (M^+, 24), 188 (100), 142 (28).

HRMS (ESI): calcd for $C_{12}H_{13}N_4O_2$ (M+H) 245.1033, found 245.1032.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3167 (w), 2974 (w), 2222 (s), 1604 (m), 1575 (m), 1515 (s), 1414 (m), 1333 (s), 1292 (s), 1196 (s), 1119 (m), 912 (m), 776 (m), 744 (m), 660 (m), 619 (m).

6-(2-Hydroxyphenyl)-2-methyl-5-nitropyridine-3-carbonitrile (6.1.5f).



Starting from 3-nitro-4*H*-chromen-4-one **6.1.4** (1.91 g, 10 mmol) and 3-aminobut-2-enenitrile (0.985 g, 12 mmol) in 20 mL AcOH, the product **6.1.5f** was isolated as a yellow solid (2.12 g, 83%). Mp: 182-183°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.90 (s, 3H, Me), 6.92-6.98 (m, 1H, CH_{Ar}), 7.02 (dd, 1H, ^3J = 8.4 Hz, ^4J = 0.9 Hz, CH_{Ar}), 7.29 (dd, 1H, ^3J = 8.0 Hz, ^4J = 1.5 Hz, CH_{Ar}), 7.38-7.44 (m, 1H, CH_{Ar}), 8.34 (s, 1H, Py), 9.77 (s, 1H, OH).

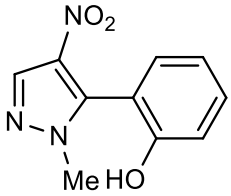
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 23.7 (Me), 107.1 (CN), 114.6, 117.8 (C), 118.4, 120.7, 129.4, 134.0, 136.9 (CH), 142.8, 153.4, 157.0, 163.0 (C).

MS (GC, 70eV): *m/z* (%) = 255 (M^+, 45), 209 (100).

HRMS (EI): calcd for $C_{13}H_9N_3O_3$ (M^+) 255.06384, found 255.06358.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3330 (m), 2246 (m), 1596 (m), 1549 (m), 1522 (s), 1456 (m), 1348 (m), 1301 (m), 1241 (m), 1119 (m), 1094 (m), 1026 (w), 936 (m), 846 (m), 819 (m), 758 (s), 620 (m).

2-(1-Methyl-4-nitro-1*H*-pyrazol-5-yl)phenol (6.1.7a).



Starting from 3-nitro-4*H*-chromen-4-one **6.1.4** (1.91 g, 10 mmol) and methylhydrazine (0.553 g, 12 mmol) in 20 mL AcOH, the product **6.1.7a** was isolated as a yellow viscous oil (1.55 g, 71%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.92 (s, 3H, Me), 6.83-6.90 (m, 2H, CH_{Ar}), 7.23-7.29 (m, 2H, CH_{Ar}), 8.81 (s, 1H, pyrazole), 9.69 (s, 1H, OH).

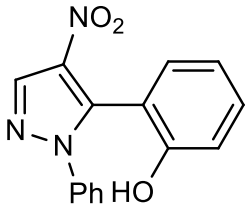
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 37.6 (Me), 115.4, 118.2, 118.6, 130.1, 130.3, 131.8 (CH), 133.1, 144.1, 155.8 (C).

MS (EI, 70eV): *m/z* (%) = 219 (M^+, 86), 173 (100), 145 (44).

HRMS (ESI): calcd for $C_{10}H_{10}N_3O_3$ (M+H) 220.07167, found 220.07180.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3129 (m), 1616 (w), 1491 (s), 1391 (m), 1325 (s), 1256 (s), 1194 (m), 1111 (m), 821 (s), 752 (s), 692 (m).

2-(4-Nitro-1-phenyl-1*H*-pyrazol-5-yl)phenol (6.1.7b).



Starting from 3-nitro-4*H*-chromen-4-one **6.1.4** (1.91 g, 10 mmol) and phenylhydrazine (1.28 g, 12 mmol) in 20 mL AcOH, the product **6.1.7b** was isolated as a brown solid (2.59 g, 92%). Mp: 165-167°C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.80 (dt, 1H, ^3J = 7.5 Hz, ^4J = 0.9 Hz, CH_{Ar}), 6.87 (dd, 1H, ^3J = 8.3 Hz, ^4J = 0.7 Hz, CH_{Ar}), 7.16 (dd, 1H,

^{3}J = 7.7 Hz, ^{4}J = 1.7 Hz, CH_{Ar}), 7.24-7.31 (m, 3H, CH_{Ar}), 7.36-7.41 (m, 3H, CH_{Ar}), 8.61 (s, 1H, pyrazole), 10.02 (s, 1H, OH).

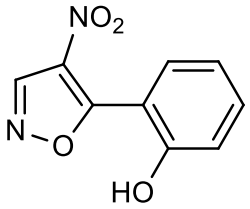
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 113.8 (C), 115.7, 119.0, 124.9, 128.8, 129.0, 131.1, 131.8 (CH), 134.1 (C), 137.1 (CH), 138.5, 139.1, 155.6 (C).

MS (GC, 70eV): *m/z* (%) = 281 (M^+, 45), 235 (100), 77 (49).

HRMS (EI): calcd for $C_{15}H_{11}N_3O_3$ (M^+) 281.07949, found 281.07944.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3134 (m), 1724 (w), 1614 (w), 1558 (w), 1516 (s), 1496 (m), 1452 (m), 1328 (s), 1153(m), 1110 (m), 1038 (w), 965 (m), 910 (w), 867 (w), 824 (s), 758 (s), 686 (s), 626 (m).

2-(4-Nitroisoxazol-5-yl)phenol (6.1.7c).



Starting from 3-nitro-4*H*-chromen-4-one **6.1.4** (1.91 g, 10 mmol) and hydroxylamine hydrochloride (0.834 g, 12 mmol) in 20 mL AcOH, the product **6.1.7c** was isolated as a brown solid (1.19 g, 58%). Mp: 119-120ºC.

^{1}H NMR (300 MHz, DMSO): δ = 7.38-7.46 (m, 2H, CH_{Ar}), 7.69-7.75 (m, 1H, CH_{Ar}), 7.99-8.02 (m, 1H, CH_{Ar}), 9.61 (br. s, 2H, CH oxazole, OH).

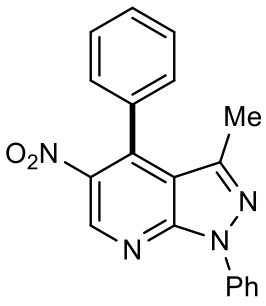
^{13}C NMR (62.9 MHz, DMSO): δ = 116.5 (CH), 116.8, 122.0 (C), 125.4, 125.9, 134.1 (CH), 151.2, 162.7, 167.3 (C).

MS (EI, 70eV): *m/z* (%) = 206 (M^+, 100), 159 (58), 148 (17), 120 (75), 104 (20), 92 (33).

HRMS (EI): calcd for $C_9H_6N_2O_4$ (M^+) 206.03221, found 206.03178.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3376 (m), 3094 (m), 1623 (m), 1607 (m), 1533 (w), 1465 (m), 1282 (s), 1221 (s), 1037 (m), 918 (w), 866 (w), 749 (s), 639 (s).

3-Methyl-5-nitro-1,4-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine (6.2.1a).



Starting from 3-methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.1.3a** (0.254 g, 1 mmol), bromobenzene (0.628 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), $(NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.1a** was isolated as a yellow solid (0.254 g, 77%^{Pd}), (0.142 g, 43%^{Ni}). Mp: 135-137ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.90 (s, 3H, Me), 7.38-7.43 (m, 1H, CH_{Ar}), 7.47-7.51 (m, 2H, CH_{Ar}), 7.55-7.62 (m, 5H, CH_{Ar}), 8.14-8.17 (m, 2H, CH_{Ar}), 9.29 (s, 1H, Py).

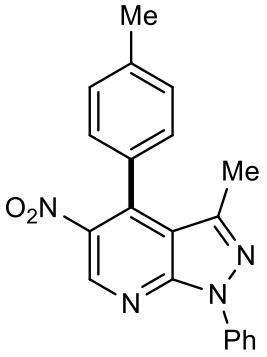
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 13.9 (Me), 114.8 (C), 121.1, 126.8, 128.0, 128.3, 129.2, 129.3, 132.0 (CH), 138.0, 139.8, 141.5, 145.2 (C), 149.8 (CH).

MS (GC, 70eV): *m/z* (%) = 330 (M^+, 100), 283 (17), 243 (10), 77 (21).

HRMS (EI): calcd for $C_{19}H_{14}N_4O_2$ (M^+) 330.11113, found 330.111158.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2925 (w), 1579 (m), 1562 (m), 1521 (s), 1438 (m), 1337 (s), 1300 (s), 1153 (m), 1115 (m), 1028 (m), 928 (w), 901 (w), 796 (m), 758 (S), 701 (s), 988 (s), 629 (m), 555 (m).

3-Methyl-5-nitro-1-phenyl-4-*p*-tolyl-1*H*-pyrazolo[3,4-*b*]pyridine (6.2.1b).



Starting from 3-methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.1.3a** (0.254 g, 1 mmol), 1-bromo-4-methylbenzene (0.684 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), ($NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.1b** was isolated as a brown solid (0.186 g, 54%^{Pd}), (0,120 g, 35%^{Ni}). Mp: 170-172ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.94 (s, 3H, Me), 2.43 (s, 3H, Me), 7.38-7.43 (m, 5H, CH_{Ar}), 7.56-7.63 (m, 2H, CH_{Ar}), 8.14-8.17 (m, 2H, CH_{Ar}), 9.26 (s, 1H, Py).

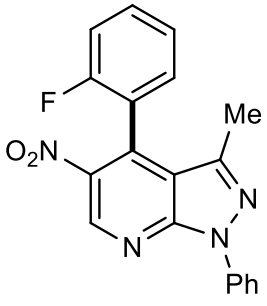
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 14.2, 20.9 (Me), 114.9 (C), 121.2, 126.7, 128.0, 129.3 (CH), 138.0, 138.8, 140.1, 141.5, 145.2 (C), 145.7 (CH), 149.8 (C).

MS (GC, 70eV): *m/z* (%) = 344 (M^+, 100), 77 (18).

HRMS (EI): calcd for $C_{20}H_{16}N_4O_2$ (M^+) 344.12678, found 344.126555.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1575 (m), 1556 (m), 1506 (s), 1439 (m), 1299 (m), 1153 (w), 1114 (m), 1023 (w), 976 (w), 933 (w), 906 (w), 846 (w), 820 (m), 784 (m), 762 (s), 688 (s), 667 (s), 619 (m), 604 (m).

4-(2-Fluorophenyl)-3-methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (6.2.1c).



Starting from 3-methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.1.3a** (0.254 g, 1 mmol), 1-bromo-2-fluorobenzene (0.700 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.1c** was isolated as a yellow solid (0.209 g, 60%^{Pd}). Mp: 187-189ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.99 (s, 3H, Me), 7.40-7.51 (m, 3H, CH_{Ar}), 7.56-7.71 (m, 4H, CH_{Ar}), 8.15 (d, 2H, ^{3}J = 7.7 Hz, CH_{Ar}), 9.38 (s, 1H, Py).

^{19}F NMR (282 MHz, DMSO-d_6): δ = -115.0 (CF).

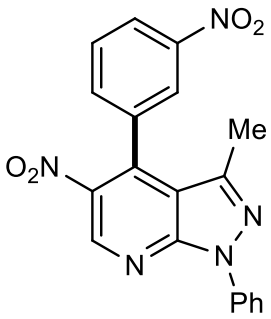
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 13.5 (Me), 114.7 (C), 115.6 (d, J = 20.6 Hz, CH), 119.7 (d, J = 16.4 Hz, C), 121.4, 124.7, 127.0, 129.3, 130.4 (CH), 132.1 (d, J = 7.0 Hz, CH), 135.3, 137.8, 139.6, 144.9 (C), 146.3 (CH), 150.0 (C), 158.4 (d, ^{1}J = 248.4 Hz, CF).

MS (GC, 70eV): *m/z* (%) = 348 (M^+, 100), 77 (22).

HRMS (EI): calcd for $C_{19}H_{13}N_4O_2F$ (M^+) 348.10171, found 348.101769.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1622 (w), 1581 (m), 1565 (s), 1500 (s), 1440 (s), 1385 (w), 1339 (s) 1307 (s), 1235 (m), 1215 (m), 1157 (m), 1111 (m), 1031 (m), 978 (w), 850 (m), 790 (m), 751 (s), 689 (s), 630 (s), 559 (m).

3-Methyl-5-nitro-4-(3-nitrophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (6.2.1d).



Starting from 3-methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.1.3a** (0.254 g, 1 mmol), 1-bromo-3-nitrobenzene (0.808 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.1d** was isolated as a yellow solid (0.233 g, 62%^{Pd}). Mp: 210-212°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.99 (s, 3H, Me), 7.36-7.43 (m, 1H, CH_{Ar}), 7.52-7.60 (m, 2H, CH_{Ar}), 7.69-7.80 (m, 2H, CH_{Ar}), 8.15-8.20 (m, 2H, CH_{Ar}), 8.28-8.29 (m, 1H, CH_{Ar}), 8.41-8.46 (m, 1H, CH_{Ar}), 9.34 (s, 1H, Py).

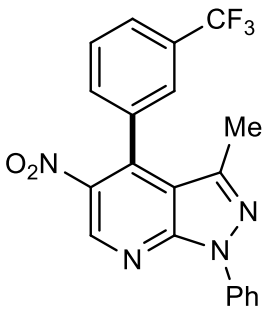
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.6 (Me), 121.7 (CH), 123.0 (C), 124.2, 127.2, 129.3, 129.7, 133.7 (CH), 134.4, 138.1, 144.7 (C), 146.1 (CH).

MS (GC, 70eV): *m/z* (%) = 375 (M^+, 100).

HRMS (EI): calcd for $C_{19}H_{13}N_5O_4$ (M^+) 375.09621, found 375.09617.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3077 (w), 1594 (m), 1564 (m), 1533 (s), 1505 (s), 1438 (m), 1390 (w), 1346 (s), 1330 (s), 1232 (w), 1154 (m), 1118 (m), 1104 (m), 1075 (w), 1032 (w), 991 (w), 927 (w), 897 (w), 883 (w), 832 (w), 810 (w), 788 (m), 753 (m), 731 (s), 688 (s), 667 (m), 657 (m), 632 (m), 566 (w).

4-(2-(Trifluoromethyl)phenyl)-3-methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (6.2.1e).



Starting from 3-methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.1.3a** (0.254 g, 1 mmol), 1-bromo-3-(trifluoromethyl)benzene (0.900 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), $(NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.1e** was isolated as a yellow solid (0.330 g, 83%^{Pd}), (0.247 g, 62%^{Ni}). Mp: 145-146ºC.

^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 1.87 (s, 3H, Me), 7.40-7.45 (m, 1H, CH_{Ar}), 7.59-7.64 (m, 2H, CH_{Ar}), 7.79-7.88 (m, 2H, CH_{Ar}), 7.95-8.01 (m, 2H, CH_{Ar}), 8.15-8.18 (m, 2H, CH_{Ar}), 9.40 (s, 1H, Py).

^{19}F NMR (282 MHz, DMSO-*d*$_6$): δ = -61.0 (CF_3).

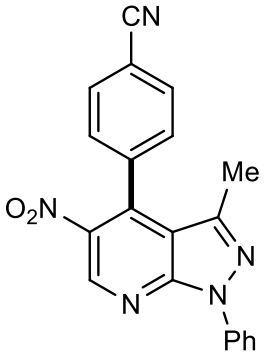
^{13}C NMR (62.9 MHz, DMSO-*d*$_6$): δ = 14.0 (Me), 115.0 (C), 121.2 (CH), 125.9 (C), 126.9 (q, ^1J = 240.0 Hz, CF_3), 127.0, 129.4, 129.5, 132.2 (CH), 133.6, 137.9, 139.2 (C), 139.4 (q, ^2J = 40.0 Hz, CCF_3), 140.1, 145.1 (C), 146.3 (CH), 150.0 (C).

MS (GC, 70eV): *m/z* (%) = 398 (M^+, 100), 77 (18).

HRMS (EI): calcd for $C_{20}H_{13}N_4O_2F_3$ (M^+) 398.09851, found 398.097866.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1595 (m), 1581 (m), 1563 (m), 1526 (m), 1506 (s), 1434 (m), 1324 (s), 1307 (s), 1260 (s), 1169 (m), 1153 (s), 1121 (s), 1074 (s), 985 (m), 909 (w), 862 (w), 789 (m), 780 (m), 752 (s), 714 (m), 703 (m), 687 (s), 654 (m), 608 (m).

4-(3-Methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl)benzonitrile (6.2.1f).



Starting from 3-methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.1.3a** (0.254 g, 1 mmol), 4-bromobenzonitrile (0.728 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), $(NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.1f** was isolated as a yellow solid (0.302 g, 85%^{Pd}), (0,188 g, 53%^{Ni}). Mp: 170-172ºC.

^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 1.89 (s, 3H, Me), 7.42 (tt, 1H, ^3J = 7.4 Hz, ^4J = 1.0 Hz, CH_{Ar}), 7.58-7.64 (m, 2H, CH_{Ar}), 7.75-7.79 (m, 2H, CH_{Ar}), 8.05-8.08 (m, 2H, CH_{Ar}), 8.14-8.18 (m, 2H, CH_{Ar}), 9.39 (s, 1H, Py).

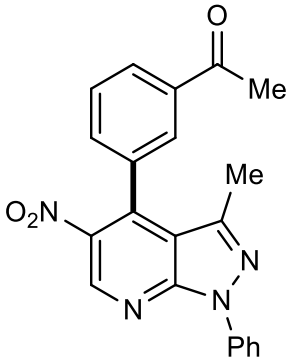
^{13}C NMR (62.9 MHz, DMSO-*d*$_6$): δ = 14.1 (Me), 112.0, 114.5, 118.4 (C), 121.2, 128.0, 129.1, 129.4, 132.2, 133.0 (CH), 137.6, 137.8, 138.8, 140.1, 145.1 (C), 146.3 (CH), 149.9 (C).

MS (GC, 70eV): *m/z* (%) = 355 (M^+, 100), 77 (21).

HRMS (EI): calcd for $C_{20}H_{13}N_5O_2$ (M^+) 355.10638, found 355.105826.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2228 (m), 1581 (m), 1556 (m), 1523 (m), 1504 (s), 1436 (m), 1336 (s), 1304 (s), 1152 (m), 1115 (m), 1084 (m), 1020 (w), 937 (w), 908 (w), 834 (m), 788 (s), 762 (s), 688 (s), 664 (m), 639 (m), 553 (m).

1-(3-(3-Methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl)phenyl)ethanone (6.2.1g).



Starting from 3-methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.1.3a** (0.254 g, 1 mmol), 1-(3-bromophenyl)ethanone (0.796 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), ($NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.1g** was isolated as a brown solid (0.242 g, 65%^{Pd}), (0.119 g, 32%^{Ni}). Mp: 172-174ºC.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.96 (s, 3H, Me), 2.66 (s, 3H, Me), 7.34-7.41 (m, 1H, CH_{Ar}), 7.52-7.70 (m, 4H, CH_{Ar}), 7.97-7.98 (m, 1H, CH_{Ar}), 8.11-8.20 (m, 3H, CH_{Ar}), 9.28 (s, 1H, Py).

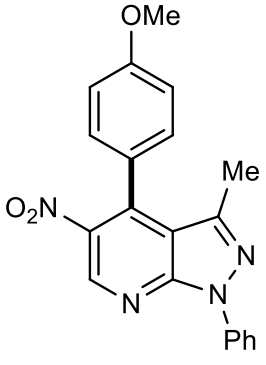
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.5, 26.7 (Me), 115.2 (C), 121.7, 127.0, 127.6, 128.9, 129.2, 129.3, 132.3 (CH), 133.1, 137.1, 138.3, 139.3, 140.8, 145.2 (C), 145.9 (CH), 150.5 (C), 197.0 (C=O).

MS (GC, 70eV): *m/z* (%) = 372 (M^+, 100), 313 (64), 241 (72), 209 (45), 113 (52), 77 (95).

HRMS (ESI): calcd for $C_{21}H_{17}N_4O_3$ (M+H) 373.12952, found 373.12909.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1682 (m), 1575 (m), 1559 (m), 1521 (m), 1488 (m), 1338 (s), 1309 (m), 1280 (m), 1247 (m), 1221 (m), 1155 (m), 1118 (m), 1083 (m), 1018 (w), 962 (m), 856 (w), 799 (m), 785 (m), 763 (s), 693 (m), 645 (m), 607 (m), 588 (m), 555 (m).

4-(4-Methoxyphenyl)-3-methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (6.2.1h).



Starting from 3-methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.1.3a** (0.254 g, 1 mmol), 1-bromo-4-methoxybenzene (0.748 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.1h** was isolated as a yellow solid (0.249 g, 68%^{Pd}). Mp: 168-170ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.00 (s, 3H, Me), 3.86 (s, 3H,

OMe), 7.11-7.14 (m, 2H, CH_{Ar}), 7.38-7.46 (m, 3H, CH_{Ar}), 7.57-7.62 (m, 2H, CH_{Ar}), 8.15-8.18 (m, 2H, CH_{Ar}), 9.25 (s, 1H, Py).

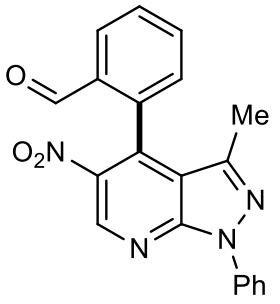
^{13}C NMR (62.9 MHz, DMSO-*d*$_6$): δ = 14.3 (Me), 55.2 (OMe), 113.8 (CH), 115.0 (C), 121.1 (CH), 123.5 (C), 126.7, 129.3, 129.6 (CH), 138.0, 140.4, 141.3, 145.2 (C), 145.7 (CH), 149.8, 160.0 (C).

MS (GC, 70eV): *m/z* (%) = 360 (M^+, 100).

HRMS (EI): calcd for $C_{20}H_{16}N_4O_3$ (M^+) 360.12169, found 360.12119.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1606 (m), 1576 (m), 1509 (m), 1440 (m), 1340 (m), 1303 (m), 1253 (m), 1177 (m), 1030 (m), 840 (m), 785 (m), 765 (m), 689 (m), 607 (m).

2-(3-Methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl)benzaldehyde (6.2.1i).



Starting from 3-methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.1.3a** (0.254 g, 1 mmol), 2-bromobenzaldehyde (0.740 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.1i** was isolated as a brown solid (0.215 g, 60%^{Pd}). Mp: 148-150ºC.

^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 1.73 (s, 3H, Me), 7.39-7.44 (m, 1H, CH_{Ar}), 7.53-7.63 (m, 3H, CH_{Ar}), 7.83-7.90 (m, 2H, CH_{Ar}), 8.17-8.21 (m, 3H, CH_{Ar}), 9.42 (s, 1H, Py), 9.94 (s, 1H, CHO).

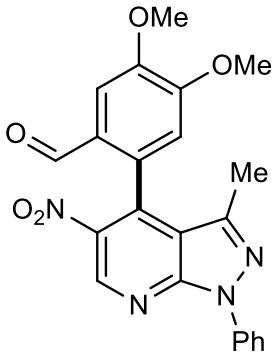
^{13}C NMR (62.9 MHz, DMSO-*d*$_6$): δ = 13.4 (Me), 115.0 (C), 121.1, 126.8, 129.2, 129.3, 130.0, 132.7 (CH), 133.0, 133.5, 134.0, 137.9, 138.9, 141.2, 145.1 (C), 146.3 (CH), 150.0 (C), 192.6 (CHO).

MS (GC, 70eV): *m/z* (%) = 358 (M^+, 27), 312 (100), 77 (24).

HRMS (EI): calcd for $C_{20}H_{14}N_4O_3$ (M^+) 358.10604, found 358.105910.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2857 (w), 2759 (w), 1699 (s), 1581 (m), 1560 (s), 1507 (s), 1492 (s), 1440 (m), 1339 (s), 1300 (s), 1264 (m), 1200 (m), 1155 (m), 1115 (m), 1012 (w), 929 (w), 862 (m), 818 (m), 792 (m), 762 (s), 705 (s), 695 (s), 668 (m), 625 (s), 555 (m).

4,5-Dimethoxy-2-(3-methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl)benzaldehyde (6.2.1j).



Starting from 3-methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.1.3a** (0.254 g, 1 mmol), 2-bromo-4,5-dimethoxybenzaldehyde (0.980 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.1j** was isolated as a brown solid (0.217 g, 52%^{Pd}). Mp: 80-82ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.86 (s, 3H, Me), 3.84 (s, 3H, OMe), 3.97 (s, 3H, OMe), 7.20 (s, 1H, CH_{Ar}), 7.40-7.45 (m, 1H, CH_{Ar}), 7.59-7.64 (m, 2H, CH_{Ar}), 7.70 (s, 1H, CH_{Ar}), 8.17-8.20 (m, 2H, CH_{Ar}), 9.41 (s, 1H, Py), 9.74 (s, 1H, CHO).

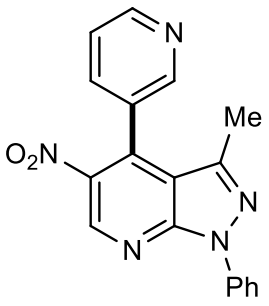
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 13.5 (Me), 55.8, 56.3 (OMe), 112.4, 113.1 (CH), 115.5 (C), 126.7, 126.8 (CH), 126.8, 127.7 (C), 129.3 (CH), 137.9, 139.5, 140.5, 145.4 (C), 146.2 (CH), 149.1, 149.9, 153.1 (C), 190.6 (CHO).

MS (GC, 70eV): *m/z* (%) = 418 (M^+, 14), 372 (100).

HRMS (ESI): calcd for $C_{22}H_{19}N_4O_5$ (M+H) 419.1350, found 419.1346.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1682 (m), 1594 (m), 1558 (m), 1505 (s), 1440 (m), 1337 (s), 1304 (m), 1277 (s), 1220 (m), 1163 (m), 1124 (s), 1075 (m), 1003 (m), 869 (w), 781 (m), 757 (s), 685 (m).

3-Methyl-5-nitro-1-phenyl-4-(pyridin-3-yl)-1*H*-pyrazolo[3,4-*b*]pyridine (6.2.1k).



Starting from 3-methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.1.3a** (0.254 g, 1 mmol), 3-bromopyridine (0.632 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), ($NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.1k** was isolated as a yellow solid (0.222 g, 67%^{Pd}), (0.119 g, 36%^{Ni}). Mp: 151-153ºC.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.00 (s, 3H, Me), 7.35-7.41 (m, 1H, CH_{Ar}), 7.52-7.58 (m, 3H, CH_{Ar}), 7.73-7.76 (m, 1H, CH_{Ar}), 8.16-8.20 (m, 2H, CH_{Ar}), 8.74-8.99 (br. m, 2H, Py), 9.31 (s, 1H, Py).

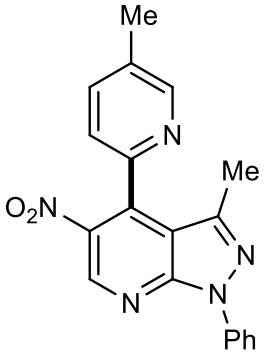
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.7 (Me), 115.4 (C), 121.7, 127.1, 129.3, 135.4 (CH), 138.2, 139.4 (C), 145.1 (CH), 145.9, 150.4 (C).

MS (GC, 70eV): *m/z* (%) = 331 (M^+, 100), 284 (21).

HRMS (EI): calcd for $C_{18}H_{13}N_5O_2$ (M^+) 331.10638, found 331.10624.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2921 (w), 1595 (m), 1574 (m), 1557 (s), 1506 (s), 1444 (s), 1333 (s), 1305 (s), 1234 (w), 1192 (w), 1152 (m), 1119 (m), 1088 (m), 1046 (w), 1023 (m), 978 (w), 942 (m), 913 (w), 845 (w), 808 (m), 785 (m), 765 (s), 716 (s), 693 (s), 655 (m), 638 (m), 616 (m), 554 (m).

3-Methyl-4-(5-methylpyridin-2-yl)-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (6.2.1l).



Starting from 3-methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.1.3a** (0.254 g, 1 mmol), 2-bromo-5-methylpyridine (0.688 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), ($NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.1l** was isolated as a brown solid (0.276 g, 80%^{Pd}), (0.166 g, 48%^{Ni}). Mp: 153-155ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.96 (s, 3H, Me), 2.44 (s, 3H, Me), 7.38-7.43 (m, 1H, CH_{Ar}), 7.56-7.66 (m, 3H, CH_{Ar}), 7.84-7.87 (m, 1H, CH_{Ar}), 8.14-8.17 (m, 2H, CH_{Ar}), 8.60 (s, 1H, Py), 9.31 (s, 1H, CH_{Ar}).

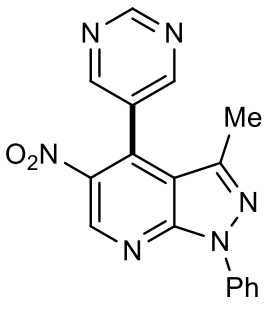
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 14.2, 17.8 (Me), 114.3 (C), 121.2, 123.7, 126.8, 129.3 (CH), 133.8 (C), 137.1 (CH), 137.9, 139.2, 139.9, 144.9 (C), 146.0 (CH), 148.0 (C), 149.7 (CH), 150.3 (C).

MS (GC, 70eV): *m/z* (%) = 345 (M^+, 49), 328 (61), 298 (100), 193 (11), 77 (26).

HRMS (EI): calcd for $C_{19}H_{15}N_5O_2$ (M^+) 345.12203, found 345.121980.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2922 (w), 1558 (m), 1525 (m), 1504 (s), 1436 (m), 1354 (m), 1303 (m), 1248 (m), 1166 (w), 1121 (m), 1084 (m), 1028 (m), 987 (w), 926 (m), 800 (m), 767 (m), 759 (s), 697 (m), 687 (m), 667 (s), 640 (m), 604 (m).

3-Methyl-5-nitro-1-phenyl-4-(pyrimidin-5-yl)-1*H*-pyrazolo[3,4-*b*]pyridine (6.2.1m).



Starting from 3-methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.1.3a** (0.254 g, 1 mmol), 5-bromopyrimidine (0.636 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.1m** was isolated as a brown solid (0.226 g, 68%^{Pd}). Mp: 149-151ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.98 (s, 3H, Me), 7.41-7.47 (m, 1H, CH_{Ar}), 7.47-7.66 (m, 2H, CH_{Ar}), 8.15-8.18 (m, 2H, CH_{Ar}), 9.09 (s, 2H, Py, CH_{Ar}), 9.43 (s, 1H, CH_{Ar}), 9.48 (s, 1H, CH_{Ar}).

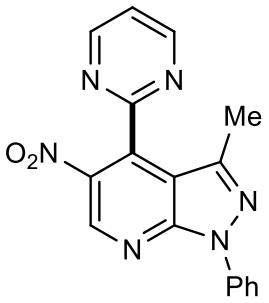
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 14.7 (Me), 115.1 (C), 121.3, 127.1 (CH), 127.7 (C), 129.4, 135.6, 137.7, 139.1, 145.2 (CH), 146.6 (C), 149.9 (CH), 155.5, 158.7 (C).

MS (GC, 70eV): *m/z* (%) = 332 (M^+, 100), 285 (10), 77 (22).

HRMS (EI): calcd for $C_{17}H_{12}N_6O_2$ (M^+) 332.10163, found 332.10176.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2923 (w), 1594 (w), 1561 (w), 1547 (m), 1505 (s), 1483 (m), 1422 (m), 1387 (m), 1330 (s), 1303 (s), 1236 (w), 1159 (w), 1118 (m), 1082 (w), 1044 (w), 970 (w), 918 (w), 843 (w), 789(m), 764 (s), 725 (m), 694 (s), 682 (m), 623 (s), 571 (w), 550 (m).

3-Methyl-5-nitro-1-phenyl-4-(pyrimidin-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridine (6.2.1n).



Starting from 3-methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.1.3a** (0.254 g, 1 mmol), 2-chloropyrimidine (0.458 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.1n** was isolated as a yellow solid (0.156 g, 47%^{Pd}). Mp: 183-185ºC.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.01 (s, 3H, Me), 7.39-7.45 (m, 1H, CH_{Ar}), 7.57-7.63 (m, 2H, CH_{Ar}), 7.77 (t, 1H, ^{3}J = 5.5 Hz, CH_{Ar}), 8.14-8.18 (m, 2H, CH_{Ar}), 9.08 (d, 2H, ^{3}J = 5.0 Hz, CH_{Ar}), 9.40 (s, 1H, Py).

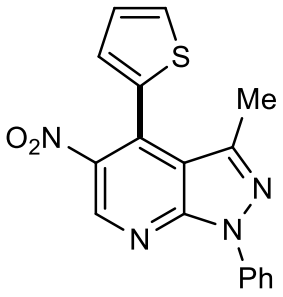
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 13.9 (Me), 113.4 (C), 121.4, 121.7, 127.0, 129.3 (CH), 137.7, 138.2, 144.5 (C), 146.3 (CH), 150.7 (C), 157.9 (CH), 160.2 (C).

MS (GC, 70eV): *m/z* (%) = 332 (M^+, 100), 285 (10), 77 (22).

HRMS (ESI): calcd for $C_{17}H_{13}N_6O_2$ (M+H) 333.10945, found 333.10947.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3306 (w), 2920 (w), 1596 (w), 1558 (s), 1505 (s), 1487 (s), 1436 (s), 1412 (s), 1342 (s), 1311 (m), 1261 (m), 1244 (m), 1172 (m), 1093 (m), 1020 (m), 940 (w), 913 (w), 816 (m), 784 (s), 765 (s), 728 (m), 694 (s), 635 (s), 620 (s).

3-Methyl-5-nitro-1-phenyl-4-(thiophen-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridine (6.2.1o).



Starting from 3-methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.1.3a** (0.254 g, 1 mmol), 5-bromothiophene-2-carboxylic acid (0.828 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.1o** was isolated as a yellow solid (0.094 g, 28%^{Pd}). Mp: 197-199ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.09 (s, 3H, Me), 7.27-7.30 (m, 1H, CH_{Ar}), 7.39-7.45 (m, 2H, CH_{Ar}), 7.57-7.64 (m, 2H, CH_{Ar}), 7.94 (dd, 1H, ^3J = 5.5 Hz, ^4J = 1.3 Hz, CH_{Ar}), 8.12-8.16 (m, 2H, CH_{Ar}), 9.27 (s, 1H, Py).

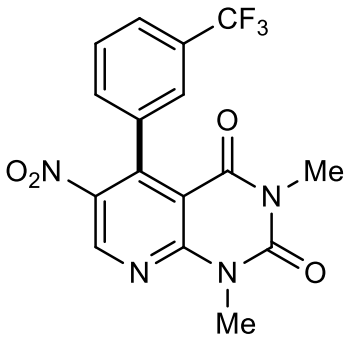
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 13.6 (Me), 115.4 (C), 121.3, 126.7, 127.4, 129.3, 129.4 (CH), 129.9 (C), 130.2 (CH), 134.4, 137.9, 141.0, 145.0 (C), 145.6 (CH), 149.6 (C).

MS (GC, 70eV): *m/z* (%) = 336 (M^+, 100), 318 (45), 275 (22), 247 (19), 207 (26), 77 (75).

HRMS (ESI): calcd for $C_{17}H_{12}N_4O_2S$ (M^+) 336.06755, found 336.06777.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1594 (m), 1563 (m), 1505 (s), 1435 (m), 1382 (w), 1335 (s), 1301 (s), 1260 (m), 1145 (m), 1114 (m), 1028 (w), 952 (w), 899 (w), 854 (w), 811 (w), 787 (m), 759 (s), 710 (s), 688 (s).

5-(3-(Trifluoromethyl)phenyl)-1,3-dimethyl-6-nitropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (6.2.2a).



Starting from 1,3-dimethyl-6-nitropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **6.1.3b** (0.236 g, 1 mmol), 1-bromo-3-(trifluoromethyl)benzene (0.900 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), ($NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.2a** was isolated as a yellow solid (0.243 g, 64%^{Pd}), (0.103 g, 27%^{Ni}). Mp: 204-206ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.15 (s, 3H, Me), 3.67 (s, 3H, Me), 7.52-7.55 (m, 1H, CH_{Ar}), 7.64-7.69 (m, 2H, CH_{Ar}), 7.78-7.81 (m, 1H, CH_{Ar}), 9.37 (s, 1H, Py).

^{19}F NMR (282 MHz, DMSO-d_6): δ = -61.0 (CF_3).

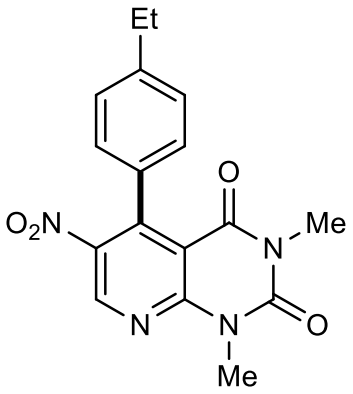
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 28.3, 30.3 (Me), 108.3, 121.1 (C), 124.0 (CH), 124.1 (q, ^1J = 274 Hz, CF_3), 124.8 (CH), 128.5 (q, ^2J = 32 Hz, CCF_3), 128.8, 131.1 (CH), 132.0, 134.8, 141.8, 145.0 (C), 148.7 (CH), 150.3, 153.1, 159.0 (C).

MS (GC, 70eV): *m/z* (%) = 380 (M^+, 100), 311 (21), 265 (14).

HRMS (ESI): calcd for $C_{16}H_{12}N_4O_4F_3$ (M+H) 381.0805, found 381.0808.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1720 (m), 1681 (s), 1558 (m), 1534 (s), 1469 (m), 1365 (m), 1325 (s), 12844 (m), 1204 (w), 1164 (m), 1129 (s), 1070 (s), 1016 (w), 925 (w), 831 (w), 806 (m), 752 (m), 705 (m), 661 (w), 597 (w).

5-(4-Ethylphenyl)-1,3-dimethyl-6-nitropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (6.2.2b).



Starting from 1,3-dimethyl-6-nitropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **6.1.3b** (0.236 g, 1 mmol), 1-bromo-4-ethylbenzene (0.740 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.2b** was isolated as an orange solid (0.156 g, 46%^{Pd}). Mp: 146-147ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.24 (t, 3H, ^3J = 7.7 Hz, Me), 2.68 (q, 2H, ^3J = 7.7 Hz, CH_2), 3.15 (s, 3H, Me), 3.64 (s, 3H, Me), 7.11 (d, 2H, ^3J = 8.03 Hz, CH_{Ar}), 7.25 (d, 2H, ^3J = 8.03 Hz, CH_{Ar}), 9.25 (s, 1H, Py).

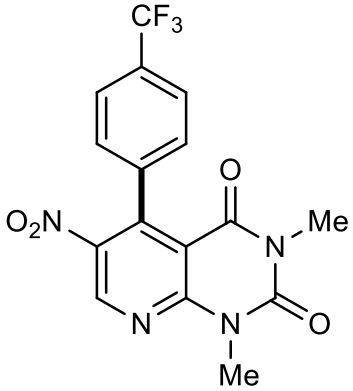
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 15.2 (Me), 27.9 (CH_2), 28.2, 30.2 (Me), 108.3 (C), 127.1 (CH), 130.3, 143.1, 143.7, 146.5 (C), 147.6 (CH), 150.4, 152.9, 158.9 (C).

MS (GC, 70eV): *m/z* (%) = 340 (M^+, 100), 323 (35), 295 (32), 269 (19), 140 (23).

HRMS (ESI): calcd for $C_{17}H_{17}N_4O_4$ (M+H) 341.12443, found 341.12451.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2973 (w), 1716 (s), 1673 (s), 1585 (m), 1553 (s), 1531 (s), 1471 (s), 1360 (s), 1331 (s), 1201 (w), 1060 (w), 1005 (w), 957 (m), 834 (m), 731 (m), 751 (s), 718 (m), 664 (w), 636 (w), 610 (m).

5-(4-(Trifluoromethyl)phenyl)-1,3-dimethyl-6-nitropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (6.2.2c).



Starting from 1,3-dimethyl-6-nitropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **6.1.3b** (0.236 g, 1 mmol), 1-bromo-4-(trifluoromethyl)benzene (0.900 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), ($NiCl_2(PPh_3)_2$ (0.033 g, 0.05 mmol)), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.2c** was isolated as a yellow solid (0.213 g, 56%^{Pd}), (0.095 g,

25%^{Ni}). Mp: 197-199ºC.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.33 (s, 3H, Me), 3.81 (s, 3H, Me), 7.30 (d, 2H, ^{3}J = 8.0 Hz, CH_{Ar}), 7.71 (d, 2H, ^{3}J = 8.0 Hz, CH_{Ar}), 9.16 (s, 1H, Py).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -62.6 (CF_3).

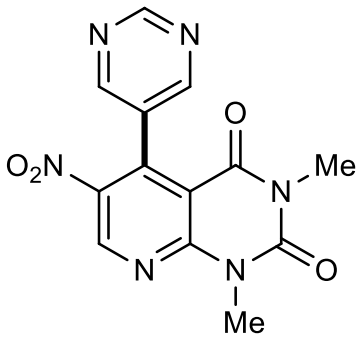
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 28.9, 30.8 (Me), 115.6 (C), 107.9 (CH), 123.9 (q, ^{1}J = 270 Hz, CF_3), 125.1, 125.2, 125.3 (CH), 127.3 (C), 131.0 (q, ^{2}J = 35 Hz, CCF_3), 136.7, 142.3, 147.0 (C), 148.7 (CH), 150.4, 153.4, 159.1 (C).

MS (GC, 70eV): *m/z* (%) = 380 (M^+, 100), 363 (33), 306 (19), 236 (16).

HRMS (EI): calcd for $C_{16}H_{11}N_4O_4F_3$ (M^+) 380.07269, found 380.07227.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2925 (w), 1722 (m), 1672 (s), 1593 (m), 1562 (s), 1520 (m), 1470 (m), 1411 (w), 1348 (m), 1323 (s), 1164 (m), 1106 (s), 1062 (s), 1005 (m), 943 (w), 843 (m), 814 (m), 751 (m), 725 (m), 661 (w), 618 (m).

1,3-Dimethyl-6-nitro-5-(pyrimidin-5-yl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (6.2.2d).



Starting from 1,3-dimethyl-6-nitropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **6.1.3b** (0.236 g, 1 mmol), 5-bromopyrimidine (0.636 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.2d** was isolated as a yellow solid (0.173 g, 55%^{Pd}). Mp: 113-115ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.16 (s, 3H, Me), 3.68 (s, 3H, Me), 8.73 (s, 2H, CH_{Ar}), 9.25 (s, 1H, Py), 9.49 (s, 1H, CH_{Ar}).

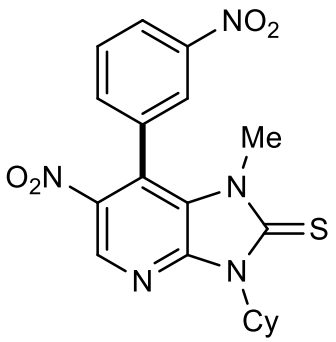
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 28.4, 30.4 (Me), 108.6 (C), 128.7 (CH), 129.4 (C), 131.4 (CH), 140.9 (C), 149.6 (CH), 150.3, 153.4 (C), 154.3, 157.5 (CH), 159.5 (C).

MS (GC, 70eV): *m/z* (%) = 314 (M^+, 66), 297 (13), 284 (100), 267 (17), 147 (21).

HRMS (EI): calcd for $C_{13}H_{10}N_6O_4$ (M^+) 314.07580, found 314.07520.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2952 (w), 1716 (m), 1660 (s), 1592 (m), 1557 (s), 1471 (m), 1428 (m), 1352 (m), 1328 (s), 1187 (m), 1118 (m), 1072 (m), 1002 (m), 963 (m), 912 (w), 813 (m), 753 (m), 720 (s), 694 (m), 629 (m), 615 (m), 538 (s).

3-Cyclohexyl-1-methyl-6-nitro-7-(3-nitrophenyl)-1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-thione (6.2.2e).



Starting from 3-cyclohexyl-1-methyl-6-nitro-1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-thione **6.1.3d** (0.292 g, 1 mmol), 1-bromo-3-nitrobenzene (0.808 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.2e** was isolated as a yellow viscous oil (0.268 g, 65%^{Pd}).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.24-1.78 (m, 10H, CH_{2Cy}), 2.82 (s, 3H, Me), 2.90-2.94 (m, 1H, CH_{Cy}), 7.66-7.69 (m, 2H, CH_{Ar}), 8.22-8.23 (m, 1H, CH_{Ar}), 8.34-8.39 (m, 1H, CH_{Ar}), 8.58 (s, 1H, Py).

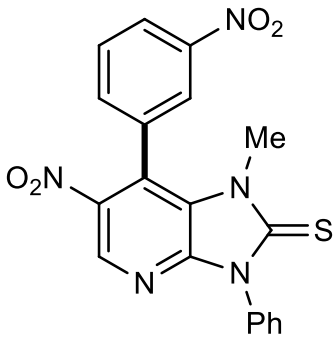
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 24.6, 25.6 (CH_{2Cy}), 29.8 (Me), 33.3, 34.5 (CH_{2Cy}), 64.6 (CH_{Cy}), 122.1, 123.3, 124.5, 124.6, 129.5, 130.3, 133.0, 135.5 (CH), 136.2, 145.0, 147.8 (C).

MS (GC, 70eV): *m/z* (%) = 413 (M^+, 47), 370 (100).

HRMS (EI): calcd for $C_{19}H_{19}N_5O_4S$ (M^+) 413.11523, found 413.11493.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2925 (w), 2851 (w), 1633 (m), 1582 (w), 1519 (s), 1462 (m), 1435 (m), 1342 (s), 1280 (m), 1206 (m), 1129 (m), 1021 (w), 969 (w), 891 (w), 829 (m), 817 (m), 77 (w), 32 (m), 704 (m), 688 (m), 630 (m), 599 (m).

1-Methyl-6-nitro-7-(3-nitrophenyl)-3-phenyl-1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-thione (6.2.2f).



Starting from 1-methyl-6-nitro-3-phenyl-1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-thione **6.1.3e** (0.286 g, 1 mmol), 1-bromo-3-nitrobenzene (0.808 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.2f** was isolated as a yellow viscous oil (0.301 g, 74%^{Pd}).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.89 (s, 3H, Me), 7.47-7.51 (m, 1H, CH_{Ar}), 7.54-7.66 (m, 4H, CH_{Ar}), 7.73-7.75 (m, 2H, CH_{Ar}), 8.30-8.42 (m, 2H, CH_{Ar}), 8.86 (s, 1H, Py).

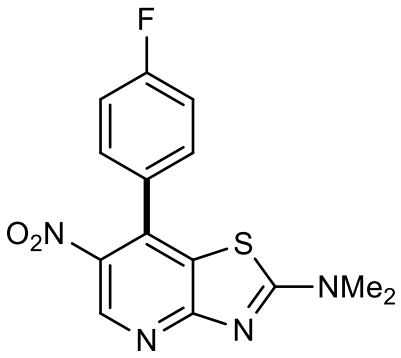
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 29.8 (Me), 122.3 (C), 124.2, 124.4, 126.8, 129.5, 129.6 (CH), 132.0, 132.7 (C), 135.1, 138.8 (CH), 141.0, 146.0, 147.9, 153.3 (C).

MS (GC, 70eV): *m/z* (%) = 407 (M^+, 100).

HRMS (EI): calcd for $C_{19}H_{13}N_5O_5$ (M+H) 392.09895, found 392.09894. Resubmission of compound **6.2.2f** showed that after first synthesis of the substance (approximately 1 year ago) the C=S bond was hydrolysed to C=O.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1723 (m) 1622 (w), 1528 (m), 1497 (m), 1469 (m), 1453 (s), 1389 (w), 1348 (m), 1326 (s), 1289 (m), 1255 (m), 1149 (m), 1128 (m), 1073 (m), 1029 (w), 906 (w), 882 (w), 783 (w), 808 (m), 760 (m), 738 (m), 710 (m), 686 (s), 632 (m), 536 (m).

7-(4-Fluorophenyl)-*N*,*N*-dimethyl-6-nitrothiazolo[4,5-*b*]pyridin-2-amine (6.2.2g).



Starting from *N*,*N*-dimethyl-6-nitrothiazolo[4,5-*b*]pyridin-2-amine **6.1.3f** (0.224 g, 1 mmol), 1-bromo-4-fluorobenzene (0.700 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.2g** was isolated as a yellow viscous oil (0.204 g, 64%^{Pd}).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.21 (br. s, 6H, 2xMe), 7.36-7.42 (m, 2H, CH_{Ar}), 7.53-7.58 (m, 2H, CH_{Ar}), 9.06 (s, 1H, Py).

^{19}F NMR (282 MHz, DMSO-d_6): δ = -111.9 (CF).

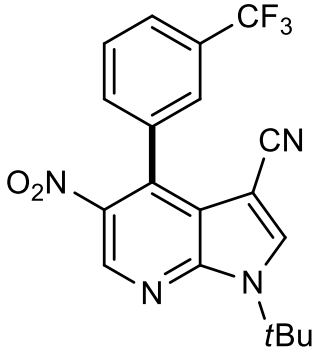
^{13}C NMR: Due to bed solubility it was not possible to measure.

MS (GC, 70eV): *m/z* (%) = 318 (M^+, 100), 289 (62), 202 (32), 158 (35).

HRMS (ESI): calcd for $C_{14}H_{12}FN_4O_2S$ (M+H) 319.06595, found 319.06607.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2927 (w), 1719 (w), 1593 (m), 1532 (m), 1489 (m), 1410 (m), 1378 (m), 1323 (s), 1219 (m), 1067 (m), 906 (m), 829 (m), 734 (m), 587 (m).

1-*Tert*-butyl-4-(3-(trifluoromethyl)phenyl)-5-nitro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (6.2.3a).



Starting from 1-(*tert*-butyl)-5-nitro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile **6.1.3h** (0.244 g, 1 mmol), 1-bromo-3-(trifluoromethyl)benzene (0.450 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.3a** was isolated as a yellow solid (0.144 g, 37%^{Pd}). Mp: 133-134ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.81 (s, 9H, *t*Bu), 7.72-7.90 (m, 4H, CH_{Ar}), 8.78 (s, 1H, pyrrole), 9.22 (s, 1H, Py).

^{19}F NMR (282 MHz, DMSO-d_6): δ = -61.2 (CF_3).

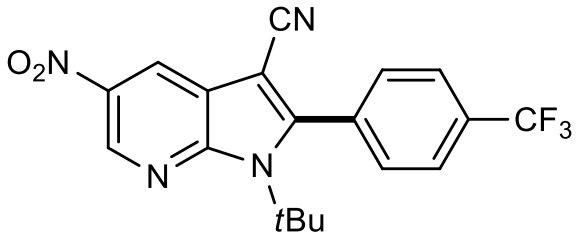
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 28.5 (*t*Bu), 59.7, 84.2, 113.3, 119.4 (C), 120.4 (q, ^{1}J = 273 Hz, CF_3), 125.3, 125.4, 125.8 (CH), 128.9 (q, ^{2}J = 32 Hz, CCF_3), 129.3, 132.5 (CH), 133.2, 136.5, 139.5 (C), 140.4, 140.8 (CH), 147.1 (C).

MS (GC, 70eV): *m/z* (%) = 388 (M^+, 24), 332 (100), 57 (29).

HRMS (EI): calcd for $C_{19}H_{15}N_4F_3O_2$ (M^+) 388.11416, found 388.11386.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3156 (w), 2985 (w), 2225 (m), 1615 (w), 1574 (m), 1520 (s), 1435 (w), 1399 (m), 1326 (s), 1292 (s), 1229 (w), 1170 (s), 1120 (s), 1075 (s), 1013 (m), 929 (m), 862)w), 812 (m), 797 (m), 782 (m), 707 (m), 661 (m), 620 (m).

1-*Tert*-butyl-2-(4-(trifluoromethyl)phenyl)-5-nitro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (6.2.3b).



Starting from 1-(*tert*-butyl)-5-nitro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile **6.1.3h** (0.244 g, 1 mmol), 1-bromo-4-(trifluoromethyl)benzene (0.450 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.3b** was isolated as a brown solid (0.144 g, 37%^{Pd}). Mp: 175-177°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72 (s, 9H, *t*Bu), 7.61 (d, 2H, ^{3}J = 8.1 Hz, CH_{Ar}), 7.80 (d, 2H, ^{3}J = 8.1 Hz, CH_{Ar}), 8.85 (d, 1H, ^{4}J = 2.6 Hz, Py), 9.33 (d, 1H, ^{4}J = 2.6 Hz, Py).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -62.9 (CF_3).

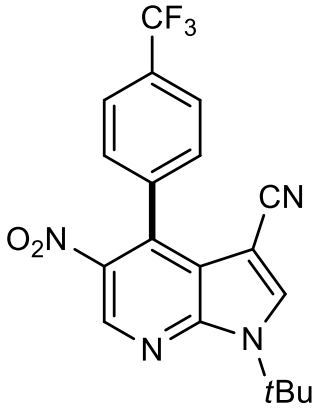
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 30.4 (*t*Bu), 63.1 (C*t*Bu), 89.4, 112.3, 118.3 (C), 122.4 (CH), 122.8 (q, ^{1}J = 280 Hz, CF_3), 124.6 (q, ^{3}J = 4 Hz, CH), 126.2, 126.4 (CH), 127.2 (C), 129.2, 130.2 (CH), 131.5 (q, ^{2}J = 33 Hz, CCF_3), 134.5 (C), 138.9 (CH), 138.9, 139.2, 145.9, 149.3, 150.1 (C).

MS (GC, 70eV): *m/z* (%) = 388 (M^+, 2), 332 (100).

HRMS (EI): calcd for $C_{19}H_{15}N_4O_2F_3$ (M^+) 388.11416, found 388.11409.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3167 (w), 2975 (w), 2223 (m), 1861 (w), 1744 (w), 1605 (m), 1576 (m), 1516 (s), 1471 (w), 1415 (m), 1402 (m), 1337 (s), 1292 (s), 1250 (m), 1198 (s), 1119 (s), 1067 (m), 1020 (m), 934 (m), 913 (m), 875 (m), 815 (m), 786 (m), 762 (m), 745 (m), 702 (w), 661 (m), 618 (s), 569 (m).

1-*Tert*-butyl-4-(4-(trifluoromethyl)phenyl)-5-nitro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (6.2.3c).



Starting from 1-(*tert*-butyl)-5-nitro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile **6.1.3h** (0.244 g, 1 mmol), 1-bromo-4-(trifluoromethyl)benzene (0.450 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.3c** was isolated as a yellow viscous oil (0.167 g, 43%^{Pd}).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.86 (s, 9H, *t*Bu), 7.48-7.53 (m, 2H, CH_{Ar}), 7.78-7.81 (m, 2H, CH_{Ar}), 8.02 (s, 1H, pyrrole), 9.11 (s, 1H, Py).

^{19}F NMR (282 MHz, DMSO-d_6): δ = -62.7 (CF_3).

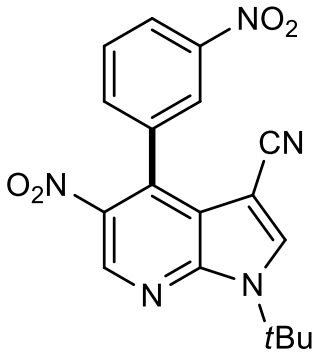
^{13}C NMR: Due to bed solubility it was not possible to measure.

MS (GC, 70eV): *m/z* (%) = 388 (M^+, 24), 332 (100).

HRMS (EI): calcd for $C_{19}H_{15}N_4O_2F_3$ (M^+) 388.11416, found 388.11383.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2928 (w), 2226 (m), 1426 (w), 1583 (m), 1521 (m), 1468 (w), 1405 (m), 1345 (m), 1322 (s), 1286 (s), 1204 (m), 1168 (s), 1121 (s), 1108 (s), 1066 (s), 1020 (m), 863 (m), 833 (m), 769 (m), 669 (m), 631 (m), 609 (m), 544 (w).

1-*Tert*-butyl-5-nitro-4-(3-nitrophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (6.2.3d).



Starting from 1-(*tert*-butyl)-5-nitro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile **6.1.3h** (0.244 g, 1 mmol), 1-bromo-3-nitrobenzene (0.404 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.3d** was isolated as a yellow solid (0.157 g, 43%^{Pd}). Mp: 166-168ºC.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.87 (s, 9H, *t*Bu), 7.71-7.74 (m, 2H, CH_{Ar}), 8.03 (s, 1H, pyrrole), 8.24-8.26 (m, 1H, CH_{Ar}), 8.39-8.43 (m, 1H, CH_{Ar}), 9.19 (s, 1H, Py).

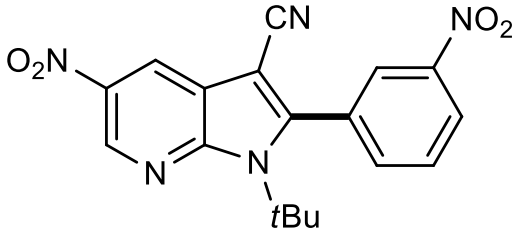
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 29.1 (*t*Bu), 60.2 (C*t*Bu), 85.7 (CN), 113.0, 119.7 (C), 123.7, 124.5, 129.7 (CH), 133.4 (C), 134.4 (CH), 136.2 (C), 137.8 (CH), 139.6 (C), 140.9 (CH), 147.7, 148.0 (C).

MS (GC, 70eV): *m/z* (%) = 365 (M^+, 20), 309 (100).

HRMS (EI): calcd for $C_{18}H_{15}N_5O_4$ (M^+) 365.11186, found 365.11148.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3082 (w), 2977 (w), 2225 (m), 1575 (m), 1522 (s), 1398 (m), 1338 (s), 1232 (m), 1192 (s), 1150 (m), 1105 (m), 926 (m), 864 (w), 842 (m), 809 (s), 773 (m), 739 (m), 727 (s), 699 (m), 670 (m), 651 (m), 623 (m), 595 (w).

1-*Tert*-butyl-5-nitro-2-(3-nitrophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (6.2.3e).



Starting from 1-(*tert*-butyl)-5-nitro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile **6.1.3h** (0.244 g, 1 mmol), 1-bromo-3-nitrobenzene (0.404 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.3e** was isolated as a brown solid (0.142 g, 39%^{Pd}). Mp: 213-215ºC.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.72 (s, 9H, *t*Bu), 7.72-7.84 (m, 2H, CH_{Ar}), 8.34-8.35 (m, 1H, CH_{Ar}), 8.42-8.46 (m, 1H, CH_{Ar}), 8.87 (d, 1H, ^4J = 2.5 Hz, Py), 9.36 (d, 1H, ^4J = 2.5 Hz, Py).

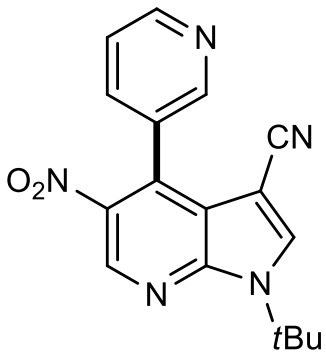
^{13}C NMR: Due to bed solubility it was not possible to measure.

MS (GC, 70eV): *m/z* (%) = 365 (M^+, 4), 309 (100), 263 (15), 217 (12), 78 (29).

HRMS (ESI): calcd for $C_{18}H_{15}N_5NaO_4$ (M+Na) 388.10163, found 388.10171.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2920 (m), 1713 (w), 1579 (w), 1515 (s), 1456 (w), 1407 (m), 1345 (s), 1293 (m), 1242 (m), 1200 (m), 1165 (m), 1095 (m), 915 (m), 26 (m), 813 (m), 781 (m), 717 (s), 579 (m).

1-*Tert*-butyl-5-nitro-4-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (6.2.3f).



Starting from 1-(*tert*-butyl)-5-nitro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile **6.1.3h** (0.244 g, 1 mmol), 3-bromopyridine (0.316 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.3f** was isolated as a yellow solid (0.144 g, 44%^{Pd}). Mp: 160-162ºC.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.81 (s, 9H, *t*Bu), 7.54-7.66 (m, 2H, CH_{Ar}), 7.93-7.97 (m, 1H, CH_{Ar}), 8.66-8.73 (m, 1H, CH_{Ar}), 8.80 (s, 1H, pyrrole), 9.23 (s, 1H, Py).

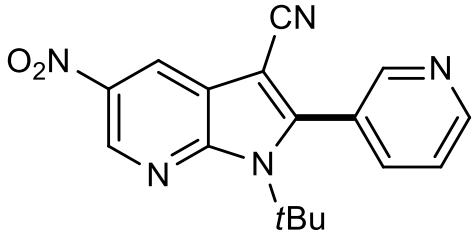
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 28.5 (*t*Bu), 59.8 (C*t*Bu), 84.2 (CN), 113.6, 119.6 (C), 123.0 (CH), 128.7 (C), 131.4 (CH), 135.0 (C), 136.3 (CH), 139.8 (C), 140.4, 140.9 (CH), 147.0 (C), 148.1, 150.0 (CH).

MS (GC, 70eV): *m/z* (%) = 321 (M^+, 33), 265 (100), 235 (17), 192 (18).

HRMS (EI): calcd for $C_{17}H_{15}N_5O_2$ (M^+) 321.12203, found 321.12202.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3060 (w), 2924 (w), 2226 (w), 1731 (w), 1575 (m), 1516 (s), 1483 (m), 1398 (m), 1370 (m), 1329 (s), 1287 (s), 1189 (s), 1144 (m), 1105 (m), 1025 (m), 997 (w), 937 (w), 853 (w), 806 (m), 771 (m), 749 (m), 718 (s), 672 (m), 642 (m), 621 (s), 566 (w), 540 (s).

1-*Tert*-butyl-5-nitro-2-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (6.2.3g).



Starting from 1-(*tert*-butyl)-5-nitro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile **6.1.3h** (0.244 g, 1 mmol), 3-bromopyridine (0.316 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.3g** was isolated as a brown solid (0.123 g, 38%^{Pd}). Mp: 137-139ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.67 (s, 9H, *t*Bu), 7.61-7.66 (m, 1H, CH_{Ar}), 8.14-8.18 (m, 1H, CH_{Ar}), 8.80-8.86 (m, 2H, CH_{Ar}), 8.94 (d, 1H, ^4J = 2.5 Hz, Py), 9.36 (d, 1H, ^4J = 2.5 Hz, Py).

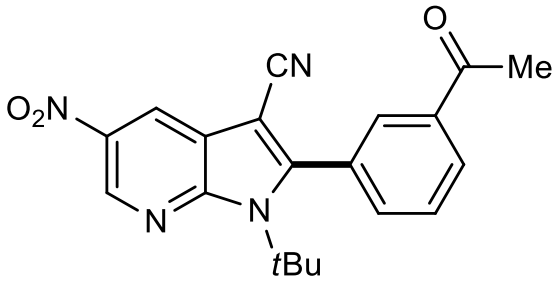
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 30.6 (*t*Bu), 63.7 (C*t*Bu), 89.7 (CN), 113.6, 118.6 (C), 123.2, 123.5, (CH), 128.3 (C), 137.5, 139.7 (CH), 140.0, 149.5 (C), 149.6 (CH), 150.2 (C), 151.1 (CH).

MS (GC, 70eV): *m/z* (%) = 321 (M^+, 1), 265 (100), 219 (25).

HRMS (EI): calcd for $C_{17}H_{15}N_5O_2$ (M^+) 321.12203, found 321.12190.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3044 (w), 2928 (w), 2227 (w), 1731 (w), 1598 (m), 1577 (m), 1514 (s), 1471 (m), 1404 (s), 1350 (s), 1293 (s), 1229 (m), 1194 (s), 1170 (s), 1113 (m), 1024 (m), 986 (w), 942 (w), 833 (m), 779 (m), 748 (m), 722 (s), 708 (m), 613 (w), 582 (s).

1-*Tert*-butyl-2-(3-acetylphenyl)-5-nitro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (6.2.3h).



Starting from 1-(*tert*-butyl)-5-nitro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile **6.1.3h** (0.244 g, 1 mmol), 1-(3-bromophenyl)ethanone (0.398 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.3h** was isolated as a brown solid (0.141 g, 39%[Pd]). Mp: 137-139ºC.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.70 (s, 9H, *t*Bu), 2.67 (s, 3H, Me), 7.64-7.66 (m, 2H, CH_{Ar}), 8.05 (br. s, 1H, CH_{Ar}), 8.11-8.13 (m, 1H, CH_{Ar}), 8.84 (d, 1H, ^4J = 2.4 Hz, Py), 9.33 (d, 1H, ^4J = 2.4 Hz, Py).

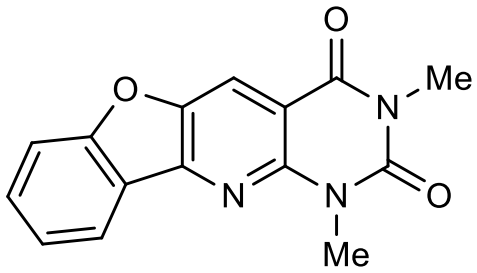
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 26.7 (Me), 31.4 (*t*Bu), 64.0 (C*t*Bu), 90.3 (CN), 113.5, 119.3 (C), 123.3, 129.0, 129.3, 130.2 (CH), 132.4 (C), 133.8 (CH), 137.1 (C), 139.8 (CH), 140.1, 150.3, 151.8 (C), 196.8 (C=O).

MS (GC, 70eV): *m/z* (%) = 362 (M^+, 100).

HRMS (ESI): calcd for $C_{20}H_{19}N_4O_3$ (M+H) 363.14517, found 363.14609.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3040 (w), 2930 (w), 2226 (w), 1745 (w), 1580 (m), 1530 (s), 1470 (m), 1404 (s), 1370 (s), 1293 (s), 1230 (m), 1180 (s), 1153 (s), 1110 (m), 1025 (m), 987 (w), 945 (w), 831 (m), 780 (m), 752 (s), 702 (s), 626 (w), 580 (s).

1,3-Dimethylbenzofuro[2',3':5,6]pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (6.2.4a).



Starting from 7-(2-hydroxyphenyl)-1,3-dimethyl-6-nitropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **6.1.5b** (0.328 g, 1 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.4a** was isolated as a white solid (0.228 g, 81%). Mp: 265-267ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.37 (s, 3H, Me), 3.74 (s, 3H, Me), 7.57 (t, 1H, ^3J = 7.2 Hz, CH_{Ar}), 7.76-7.81 (m, 1H, CH_{Ar}), 7.86-7.89 (m, 1H, CH_{Ar}), 8.24-8.27 (m, 1H, CH_{Ar}), 8.68 (s, 1H, Py).

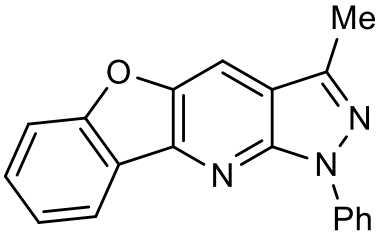
^{13}C NMR: Due to bed solubility it was not possible to measure.

MS (GC, 70eV): *m/z* (%) = 281 (M^+, 100), 253 (33), 169 (62).

HRMS (EI): calcd for $C_{15}H_{11}N_3O_3$ (M^+) 281.07949, found 281.07931.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3082 (w), 1705 (m), 1667 (s), 1627 (s), 1583 (m), 1516 (m), 1447 (s), 1407 (s), 1379 (s), 1314 (s), 1384 (s), 1193 (m), 1099 (m), 968 (m), 922 (m), 842 (m), 772 (s), 751 (s), 703 (m), 671 (m), 611 (m).

3-Methyl-1-phenyl-1*H*-benzofuro[3,2-*b*]pyrazolo[4,3-*e*]pyridine (6.2.4b).



Starting from 2-(3-methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl)phenol **6.1.5a** (0.346 g, 1 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.4b** was isolated as a yellow viscous oil (0.278 g, 93%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.69 (s, 3H, Me), 7.26-7.32 (m, 1H, CH_{Ar}), 7.40-7.45 (m, 1H, CH_{Ar}), 7.52-7.60 (m, 4H, CH_{Ar}), 7.99 (s, 1H, Py), 8.28-8.31 (m, 1H, CH_{Ar}), 8.41-8.45 (m, 2H, CH_{Ar}).

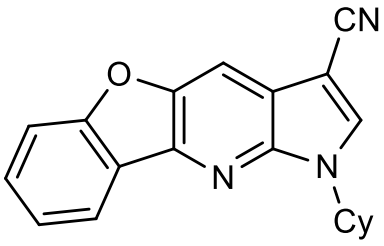
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 12.6 (Me), 109.6, 112.1 (CH), 116.0 (C), 120.5, 122.1, 123.1 (CH), 123.3 (C), 125.2, 129.0, 130.2 (CH), 139.9, 142.5, 145.3, 146.3, 148.9, 159.4 (C).

MS (GC, 70eV): *m/z* (%) = 299 (M^+, 100), 284 (16).

HRMS (ESI): calcd for $C_{19}H_{14}N_3O$ (M+H) 300.11314, found 300.11335.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1628 (w), 1588 (m), 1506 (m), 1416 (m), 1374 (m), 1328 (m), 1250 (m), 1168 (m), 1122 (m), 1074 (m), 987 (m), 893 (m), 854 (m), 803 (m), 747 (s), 686 (m), 650 (m).

1-Cyclohexyl-1*H*-benzofuro[3,2-*b*]pyrrolo[3,2-*e*]pyridine-3-carbonitrile (6.2.4c).



Starting from 1-cyclohexyl-6-(2-hydroxyphenyl)-5-nitro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile **6.1.5c** (0.362 g, 1 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.4c** was isolated as a yellow solid (0.280 g, 89%). Mp: 258-260ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.21-1.36 (m, 1H, Cy), 1.49-1.62 (m, 2H, Cy), 1.74-1.94 (m, 5H, Cy), 2.06-2.08 (m, 2H, Cy), 4.87-4.96 (m, 1H, CH_{Cy}), 7.47-7.52 (m, 1H, CH_{Ar}), 7.64-7.69 (m, 1H, CH_{Ar}), 7.78-7.81 (m, 1H, CH_{Ar}), 8.22-8.24 (m, 1H, CH_{Ar}), 8.48 (s, 1H, Py), 8.78 (s, 1H, pyrrole).

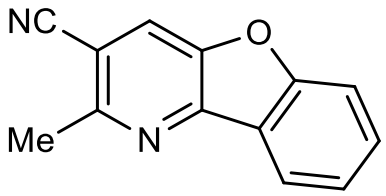
^{13}C NMR: Due to bed solubility it was not possible to measure.

MS (GC, 70eV): *m/z* (%) = 315 (M^+, 26), 233 (100).

HRMS (EI): calcd for $C_{20}H_{17}N_3O$ (M^+) 315.13661, found 315.13650.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3121 (w), 3931 (m), 2221 (s), 1719 (w), 1568 (w), 1531 (m), 1446 (m), 1421 (m), 1379 (m), 1328 (m), 1262 (m), 1185 (s), 1142 (m), 1097 (m), 997 (m), 932 (m), 861 (s), 742 (s), 614 (s).

2-Methylbenzofuro[3,2-*b*]pyridine-3-carbonitrile (6.2.4d).



Starting from 6-(2-hydroxyphenyl)-2-methyl-5-nitronicotinonitrile **6.1.5f** (0.255 g, 1 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.4d** was isolated as a white solid (0.177 g, 85%). Mp: 206-208ºC.

^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 2.91 (s, 3H, Me), 7.44-7.49 (m, 1H, CH_{Ar}), 7.59-7.64 (m, 2H, CH_{Ar}), 7.98 (s, 1H, Py), 8.20-8.23 (m, 1H, CH_{Ar}).

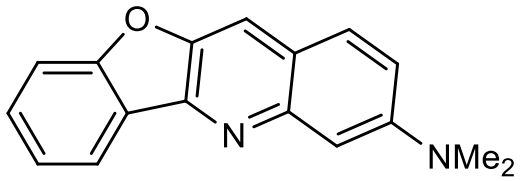
^{13}C NMR (62.9 MHz, DMSO-*d*$_6$): δ = 23.5 (Me), 105.5 (C), 112.5 (CH), 117.4 (C), 121.9, 122.0 (CH), 122.1 (C), 124.3, 131.1 (CH), 146.4, 147.1, 157.2, 159.0.

MS (GC, 70eV): *m/z* (%) = 208 (M^+, 100).

HRMS (EI): calcd for $C_{13}H_8N_2O$ (M^+) 208.06311, found 208.06311.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2219 (w), 1633 (w), 1590 (w), 1553 (w), 1446 (m), 1402 (m), 1345 (m), 1250 (w), 1104 (m), 1019 (w), 948 (w), 906 (s), 855 (m), 755 (s), 734 (s), 648 (m), 607 (m).

***N*,*N*-dimethylbenzofuro[3,2-*b*]quinolin-3-amine (6.2.4e).**



Starting from 2-(7-(dimethylamino)-3-nitroquinolin-2-yl)phenol **6.1.5e** (0.309 g, 1 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.4e** was isolated as a red solid (0.189 g, 72%). Mp: 184-186ºC.

^{1}H NMR (250 MHz, DMSO-*d*$_6$): δ = 3.08 (s, 6H, 2xMe), 7.20 (d, 1H, ^4J = 2.5 Hz, CH_{Ar}), 7.38 (dd, 1H, ^3J = 9.2 Hz, ^4J = 2.6 Hz, CH_{Ar}), 7.46-7.52 (m, 1H, CH_{Ar}), 7.66-7.78 (m, 2H, CH_{Ar}), 7.92 (d, 1H, ^3J = 9.2 Hz, CH_{Ar}), 8.21-8.25 (m, 1H, CH_{Ar}), 8.38 (s, 1H, Py).

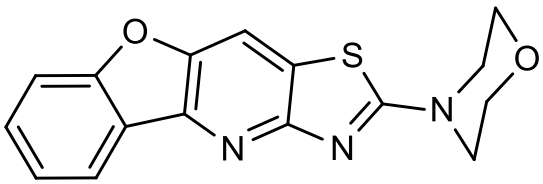
^{13}C NMR (62.9 MHz, DMSO-*d*$_6$): δ = 40.0 (Me), 105.8, 112.3, 114.9, 116.9 (CH), 119.6 (C), 121.5 (CH), 122.6 (C), 123.6, 128.4, 130.6 (CH), 145.3, 145.8, 147.7, 150.2, 158.4 (C).

MS (EI, 70eV): *m/z* (%) = 262 (M^+, 100), 219 (20).

HRMS (EI): calcd for $C_{17}H_{14}N_2O$ (M^+) 262.11006, found 262.10936.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2798 (w), 1618 (m), 1515 (m), 1545 (s), 1376 (m), 1305 (m), 1180 (m), 1124 (m), 1099 (m), 973 (w), 891 (m), 844 (m), 798 (s), 735 (s), 703 (s), 636 (m).

2-Morpholinobenzofuro[3,2-*b*]thiazolo[5,4-*e*]pyridine (6.2.4f).



Starting from 2-(2-morpholino-6-nitrothiazolo[4,5-*b*]pyridin-5-yl)phenol **6.1.5d** (0.358 g, 1 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.4f** was isolated as a green solid (0.202 g, 65%). Mp: 251-252ºC.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.62-3.67 (m, 4H, Morpholine), 3.74-3.79 (m, 4H, Morpholine), 7.44-7.7.50 (m, 1H, CH_{Ar}), 7.57-7.64 (m, 1H, CH_{Ar}), 7.75 (d, 1H, ^3J = 8.2 Hz, CH_{Ar}), 8.10-8.13 (m, 1H, CH_{Ar}), 8.64 (s, 1H, Py).

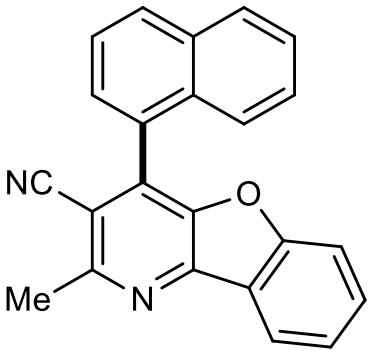
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 47.7, 65.4 (Morpholine), 112.3, 113.4, 120.5 (CH), 123.0 (C), 123.6 (CH), 123.7 (C), 128.8 (CH), 140.3, 144.9, 156.8, 160.8, 169.4 (C).

MS (EI, 70eV): *m/z* (%) = 311 (M^+, 100), 254 (80), 226 (25).

HRMS (EI): calcd for $C_{16}H_{13}N_3O_2S$ (M^+) 311.07230, found 311.07209.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2860 (w), 1589 (w), 1540 (m), 1446 (m), 1379 (m), 1286 (m), 1264 (m), 1174 (m), 1113 (s), 1033 (m), 972 (m), 898 (w), 867 (s), 752 (s), 632 (m).

2-Methyl-4-(naphthalen-1-yl)benzofuro[3,2-*b*]pyridine-3-carbonitrile (6.2.5a).



Starting from 6-(2-hydroxyphenyl)-2-methyl-5-nitronicotinonitrile **6.1.5f** (0.255 g, 1 mmol)$^{\text{one-pot}}$, (2-methylbenzofuro[3,2-b]pyridine-3-carbonitrile **6.2.4d** (0.208 g, 1 mmol))$^{\text{consecutive}}$, 1-bromonaphthalene (0.828 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.320 g, 2.3 mmol)$^{\text{one-pot}}$, (K_2CO_3 (0.179 g, 1.3 mmol))$^{\text{consecutive}}$, in 8 mL DMF, the product **6.2.5a** was isolated as a yellow solid (0.210 g, 63%$^{\text{consecutive}}$), (0.157 g, 47%$^{\text{one-pot}}$). Mp: 237-238ºC.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.94 (s, 3H, Me), 7.44-7.49 (m, 2H, CH_{Ar}), 7.53-7.67 (m, 2H, CH_{Ar}), 7.69-7.71 (m, 2H, CH_{Ar}), 7.75-7.80 (m, 2H, CH_{Ar}), 8.13 (d, 1H, ^3J = 8.2 Hz, CH_{Ar}), 8.22 (dd, 1H, ^3J = 7.6 Hz, ^4J = 2.4 Hz, CH_{Ar}), 8.27-8.31 (m, 1H, CH_{Ar}).

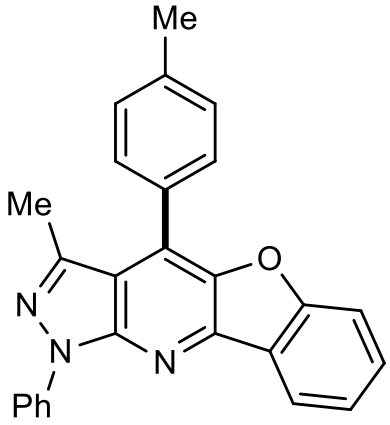
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 23.7 (Me), 106.7 (C), 112.8 (CH), 116.6 (C), 121.8 (CH), 121.9 (C), 124.6, 124.8, 125.5, 126.7, 127.3, 128.2 (CH), 128.3 (C), 128.6 (CH), 130.2 (C), 130.4, 131.4 (CH), 130.1, 134.9, 145.5, 157.7, 158.3 (C).

MS (GC, 70eV): *m/z* (%) = 334 (M^+, 100).

HRMS (EI): calcd for $C_{23}H_{14}N_2O$ (M^+) 334.11006, found 334.10935.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2222 (w), 1713 (w), 1627 (m), 1586 (m), 1547 (m), 1444 (w), 1375 (s), 1243 (m), 1196 (s), 1100 (m), 982 (w), 887 (w), 805 (s), 777 (s), 746 (s), 670 (m), 611 (m).

3-Methyl-1-phenyl-4-(*p*-tolyl)-1*H*-benzofuro[3,2-*b*]pyrazolo[4,3-*e*]pyridine (6.2.5b).



Starting from 2-(3-methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl)phenol **6.1.5a** (0.346 g, 1 mmol)$^{\text{one-pot}}$, (3-methyl-1-phenyl-1*H*-benzofuro[3,2-*b*]pyrazolo[4,3-*e*]pyridine **6.2.4b** (0.299 g, 1 mmol))$^{\text{consecutive}}$, 1-bromo-4-methylbenzene (0.684 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.320 g, 2.3 mmol)$^{\text{one-pot}}$, (K_2CO_3 (0.179 g, 1.3 mmol))$^{\text{consecutive}}$, in 8 mL DMF, the product **6.2.5b** was isolated as a yellow solid (0.303 g, 78%$^{\text{consecutive}}$), (0.163 g, 42%$^{\text{one-pot}}$). Mp: 169-170ºC.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.47 (s, 3H, Me), 3.32 (s, 3H, Me), 7.31-7.37 (m, 4H, CH_{Ar}), 7.43-7.51 (m, 3H, CH_{Ar}), 7.57-7.73 (m, 2H, CH_{Ar}), 8.24 (d, 1H, ^3J = 7.5 Hz, CH_{Ar}), 8.38-8.42 (m, 2H, CH_{Ar}).

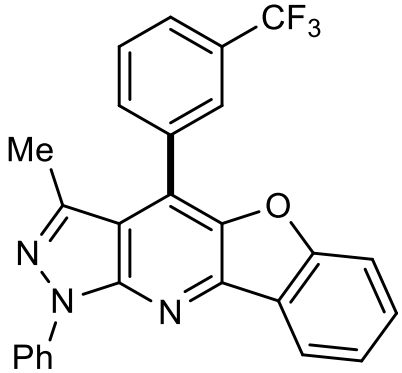
^{13}C NMR: Due to bed solubility it was not possible to measure.

MS (GC, 70eV): *m/z* (%) = 389 (M^+, 100).

HRMS (EI): calcd for $C_{26}H_{19}N_3O$ (M^+) 389.15226, found 389.15200.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1628 (w), 1596 (w), 1504 (m), 1438 (w), 1354 (m), 1211 (m), 1350 (m), 1017 (m), 930 (m), 874 (w), 743 (s), 690 (s), 606 (m).

3-Methyl-1-phenyl-4-(3-(trifluoromethyl)phenyl)-1*H*-benzofuro[3,2-*b*]pyrazolo[4,3-*e*]pyridine (6.2.5c).



Starting from 2-(3-methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl)phenol **6.1.5a** (0.346 g, 1 mmol)$^{\text{one-pot}}$, (3-methyl-1-phenyl-1*H*-benzofuro[3,2-*b*]pyrazolo[4,3-*e*]pyridine **6.2.4b** (0.299 g, 1 mmol))$^{\text{consecutive}}$, 1-bromo-3-(trifluoromethyl)benzene (0.900 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.320 g, 2.3 mmol)$^{\text{one-pot}}$, (K_2CO_3 (0.179 g, 1.3

mmol))^{consecutive}, in 8 mL DMF, the product **6.2.5c** was isolated as a yellow viscous oil (0.363 g, 82%^{consecutive}), (0.248 g, 56%$^{one\text{-}pot}$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.61 (s, 3H, Me), 7.21-7.39 (m, 4H, CH_{Ar}), 7.41-7.56 (m, 4H, CH_{Ar}), 7.66-7.92 (m, 2H, CH_{Ar}), 8.19-8.23 (m, 1H, CH_{Ar}), 8.36-8.41 (m, 2H, CH_{Ar}).

^{19}F NMR (282 MHz, DMSO-*d*$_6$): δ = -62.5 (CF_3).

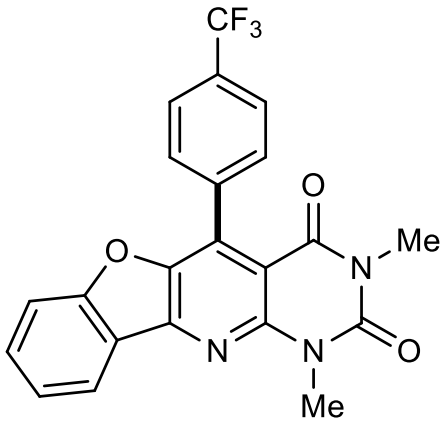
^{13}C NMR: Due to bed solubility it was not possible to measure.

MS (GC, 70eV): *m/z* (%) = 443 (M^+, 100).

HRMS (EI): calcd for $C_{26}H_{16}N_3F_3O$ (M^+) 443.12400, found 443.12378.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2921 (w), 1327 (w), 1598 (m), 1573 (w), 1505 (m), 1460 (m), 1416 (m), 1373 (m), 1327 (m), 1265 (m), 1250 (m), 1212 (m), 1167 (m), 1121 (s), 1072 (m), 1012 (m), 987 (m), 892 (m), 854 (m), 803 (m), 745 (s), 686 (s), 650 (s), 616 (m), 559 (m).

1,3-Dimethyl-5-(4-(trifluoromethyl)phenyl)benzofuro[2',3':5,6]pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (6.2.5d).



Starting from 1,3-dimethylbenzofuro[2',3':5,6]pyrido [2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **6.2.4a** (0.281 g, 1 mmol), 1-bromo-4-(trifluoromethyl)benzene (0.900 g, 4 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **6.2.5d** was isolated as an orange viscous oil (0.247 g, 58%^{consecutive}).

^{1}H NMR (250 MHz, DMSO-*d*$_6$): δ = 3.19 (s, 3H, Me), 3.76 (s, 3H, Me), 7.49-7.56 (m, 1H, CH_{Ar}), 7.69-7.91 (m, 6H, CH_{Ar}), 8.18-8.24 (m, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, DMSO-*d*$_6$): δ = -60.9 (CF_3).

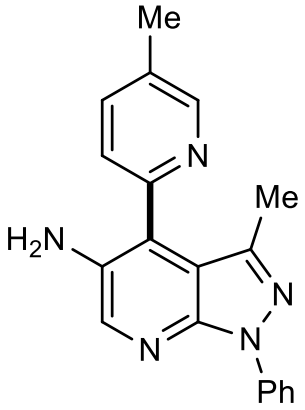
^{13}C NMR: Due to bed solubility it was not possible to measure.

MS (GC, 70eV): *m/z* (%) = 425 (M^+, 100), 313 (33).

HRMS (EI): calcd for $C_{22}H_{14}N_3O_3F_3$ (M^+) 425.09818, found 425.09691.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1703 (m), 1658 (s), 1582 (m), 1514 (m), 1448 (m), 1408 (m), 1367 (m), 1314 (m), 1282 (m), 1193 (m), 1064 (m), 968 (w), 842 (m), 772 (m), 749 (s), 672 (w), 611 (w).

3-Methyl-4-(5-methylpyridin-2-yl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-amine (6.3.1a).



Starting from 3-methyl-4-(5-methylpyridin-2-yl)-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.2.1l** (0.345 g, 1 mmol), Pd/C (0.030 g, 0.10 mmol) and H_2 balloon in 25 mL MeOH, the product **6.3.1a** was isolated as a brown solid (0.265 g, 84%). Mp: 163-165ºC.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.16 (s, 3H, Me), 2.45 (s, 3H, Me), 4.31 (br s, 2H, NH_2), 7.21-7.27 (m, 1H, CH_{Ar}), 7.38-7.51 (m, 3H, CH_{Ar}), 7.69-7.72 (m, 1H, CH_{Ar}), 8.17-8.24 (m, 3H, CH_{Ar}), 8.63 (s, 1H, Py).

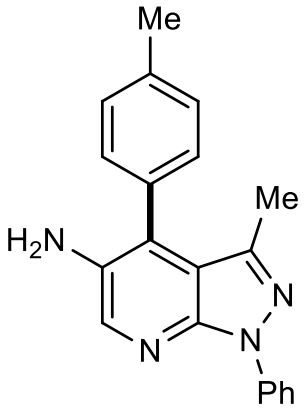
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.3, 18.4 (Me), 114.5 (C), 120.7 (CH), 121.1, 124.0 (C), 125.2, 125.6, 129.0 (CH), 133.1, 135.5 (C), 137.5 (CH), 139.6, 140.7 (C), 141.2 (CH), 147.0 (C), 149.9 (CH), 150.6 (C).

MS (GC, 70eV): *m/z* (%) = 315 (M^+, 100), 77 (23).

HRMS (EI): calcd for $C_{19}H_{18}N_5$ (M+H) 316.15567, found 316.15578.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3442 (w), 3341 (w), 1713 (w), 1592 (m), 1504 (s), 1434 (m), 1404 (s), 1355 (m), 1324 (m) 1309 (m), 1290 (m), 1129 (m), 1109 (m), 1084 (m), 1030 (m), 986 (m), 946 (m), 904 (m), 836 (m), 799 (m), 755 (s), 692 (s), 625 (m), 610 (m), 555 (m).

3-Methyl-5-amino-1-phenyl-4-*p*-tolyl-1*H*-pyrazolo[3,4-*b*]pyridine (6.3.1b).



Starting from 3-methyl-5-nitro-1-phenyl-4-(*p*-tolyl)-1*H*-pyrazolo[3,4-*b*]pyridine **6.2.1b** (0.344 g, 1 mmol), Pd/C (0.030 g, 0.10 mmol) and H_2 balloon in 25 mL MeOH, the product **6.3.1b** was isolated as a brown viscous oil (0.245 g, 78%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.04 (s, 3H, Me), 2.45 (s, 3H, Me), 4.20 (br s, 2H, NH_2), 7.20-7.36 (m, 5H, CH_{Ar}), 7.45-7.50 (m, 2H, CH_{Ar}), 8.19-8.22 (m, 2H, CH_{Ar}), 8.23 (s, 1H, Py).

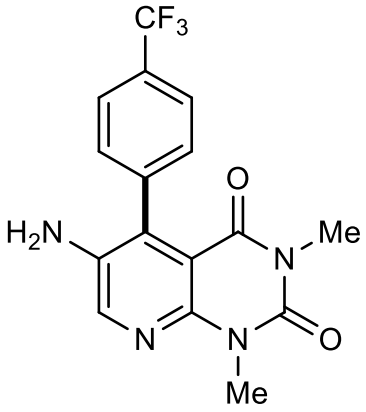
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.5, 21.4 (Me), 115.7 (C), 120.6, 120.9, 125.2 (CH), 128.6 (C), 129.0, 129.3, 129.7 (CH), 130.2, 138.8, 139.7 (C), 140.5 (CH), 141.8, 147.1 (C).

MS (GC, 70eV): *m/z* (%) = 314 (M^+, 100), 77 (14).

HRMS (EI): calcd for $C_{20}H_{18}N_4$ (M^+) 314.15260, found 314.15199.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3336 (w), 1594 (m), 1504 (s), 1435 (m), 1409 (m), 1385 (m), 1356 (m), 1288 (m), 1182 (w), 1134 (m), 1100 (m), 1079 (m), 1021 (m), 981 (m), 933 (m), 902 (m), 816 (m), 787 (m), 753 (s), 677 (s), 626 (m), 552 (s).

6-Amino-5-(4-(trifluoromethyl)phenyl)-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (6.3.1c).



Starting from 1,3-dimethyl-6-nitro-5-(4-(trifluoromethyl) phenyl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **6.2.2c** (0.380 g, 1 mmol), Pd/C (0.030 g, 0.10 mmol) and H_2 balloon in 25 mL MeOH, the product **6.3.1c** was isolated as a yellow solid (0.263 g, 75%). Mp: 229-230ºC.

^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 3.11 (s, 3H, Me), 3.55 (s, 3H, Me), 4.58 (br s, 2H, NH_2), 7.35 (d, 2H, ^3J = 7.9 Hz, CH_{Ar}), 7.71 (d, 2H, ^3J = 7.8 Hz, CH_{Ar}), 8.33 (s, 1H, Py).

^{19}F NMR (235 MHz, DMSO-*d*$_6$): δ = -62.8 (CF_3).

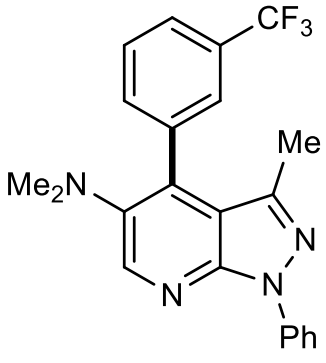
^{13}C NMR (62.9 MHz, DMSO-*d*$_6$): δ = 27.9, 29.3 (Me), 107.3 (C), 125.3 (q, ^3J = 3.6 Hz, *C*HCCF$_3$), 127.8 (q, ^3J = 3.1 Hz, *C*HCCF$_3$), 128.8 (q, ^1J = 271.3 Hz, CF_3), 129.1 (CH), 131.6 (q, ^2J = 33 Hz, CCF_3), 139.2, 140.6 (C), 136.7, 142.3, 147.0 (C), 141.1 (CH), 150.2, 160.4 (C).

MS (GC, 70eV): *m/z* (%) = 350 (M^+, 100), 364 (39), 196 (17).

HRMS (EI): calcd for $C_{16}H_{13}N_4O_2F_3$ (M^+) 350.09851, found 350.09780.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3428 (w), 3339 (w), 1702 (m), 1653 (s), 1469 (m), 1409 (m), 1349 (m), 1316 (s), 1286 (s), 1161 (m), 1103 (s), 1061 (m), 984 (m), 942 (m), 791 (m), 750 (s), 654 (m).

4-(3-(Trifluoromethyl)phenyl)-*N*,*N*,3-trimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-amine (6.3.2a).



Starting from 3-methyl-5-nitro-1-phenyl-4-(3-(trifluoromethyl) phenyl)-1*H*-pyrazolo[3,4-*b*]pyridine **6.2.1e** (0.398 g, 1 mmol), CH_2O (0.180 g, 6 mmol (37 wt % in H_2O)), Pd/C (0.030 g, 0.10 mmol) and H_2 balloon in 25 mL MeOH, the product **6.3.2a** was isolated as a yellow solid (0.230 g, 58%). Mp: 87-88ºC.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.63 (s, 3H, Me), 2.22 (s, 6H, NMe_2), 6.85 (m, 1H, CH_{Ar}), 7.08-7.14 (m, 2H, CH_{Ar}), 7.23-7.25 (m, 2H, CH_{Ar}), 7.33-7.34 (m, 2H, CH_{Ar}), 7.83-7.87 (m, 2H, CH_{Ar}), 8.17 (s, 1H, Py).

^{19}F NMR (282 MHz, DMSO-*d*$_6$): δ = -62.6 (CF_3).

^{13}C NMR (62.9 MHz, DMSO-*d*$_6$): δ = 14.9 (Me), 44.8 (NMe_2), 115.6 (C), 120.7 (CH), 124.0 (q, ^1J = 272.0 Hz, CF_3), 124.7 (q, ^4J = 4.1 Hz, *C*HCCF$_3$), 125.4 (CH), 126.6 (q, ^4J = 4.1 Hz,

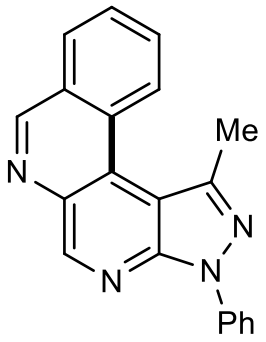
*C*HCCF$_3$), 128.5, 129.0 (CH), 130.5 (q, ^2J = 33.2 Hz, CCF$_3$), 133.0 (CH), 136.3, 136.5, 139.4, 141.6, 141.8 (C), 144.0 (CH), 148.1 (C).

MS (GC, 70eV): *m/z* (%) = 396 (M^+, 100), 379 (11).

HRMS (ESI): calcd for $C_{22}H_{20}N_4F_3$ (M+H) 397.15618, found 397.1620.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2927 (w), 2784 (w), 1598 (m), 1504 (s), 1435 (m), 1411 (m), 1354 (m), 1325 (s), 1262 (s), 1164 (s), 1121 (s), 1071 (s), 1018 (m), 971 (m), 904 (m), 845 (w), 781 (m), 754 (s), 724 (m), 676 (s), 614 (w), 562 (s).

1-Methyl-3-phenyl-3*H*-benzo[*c*]pyrazolo[4,3-*f*][1,7]naphthyridine (6.3.3a).



Starting from 2-(3-methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl)benzaldehyde **6.2.1i** (0.358 g, 1 mmol), (3-methyl-5-nitro-1,4-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.2.1a** (0.330 g, 1 mmol)), (CH_2O (0.180 g, 6 mmol (37 wt % in H_2O))), Pd/C (0.030 g, 0.10 mmol) and H_2 balloon in 25 mL MeOH, the product **6.3.3a** was isolated as a yellow solid (0.202 g, 65%$^{\text{from 6.2.1i}}$), (0.143 g, 46%$^{\text{from 6.2.1a}}$). Mp: 143-145^{o}C.

^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 2.64 (s, 3H, Me), 7.28-7.33 (m, 1H, CH$_{Ar}$), 7.51-7.57 (m, 2H, CH$_{Ar}$), 7.85 (d, 2H, ^3J = 8.3 Hz, CH$_{Ar}$), 8.02 (d, 2H, ^3J = 8.3 Hz, CH$_{Ar}$), 8.26-8.29 (m, 2H, CH$_{Ar}$), 8.67 (d, 1H, ^4J = 2.2 Hz, CH$_{Ar}$), 8.98 (d, 1H, ^4J = 2.2 Hz, CH$_{Ar}$).

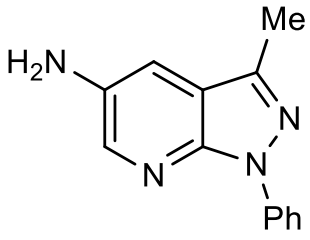
^{13}C NMR (62.9 MHz, DMSO-*d*$_6$): δ = 12.1 (Me), 116.8 (C), 119.7 (CH), 122.1 (C), 125.4, 125.7, 125.8, 127.7 (CH), 128.2 (C), 128.8, 129.1 (CH), 139.0, 141.4, 143.5 (C), 148.4 (CH), 149.8 (C).

MS (GC, 70eV): *m/z* (%) = 310 (M^+, 1), 252 (100).

HRMS (ESI): calcd for $C_{20}H_{15}N_4$ (M+H) 311.1291, found 311.1294.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2920 (s), 2851 (s), 1595 (m), 1505 (s), 1444 (s), 1411 (s), 1381 (s), 1285 (m), 1217 (m), 1168 (w), 1125 (m), 1068 (s), 973 (w), 906 (w), 835 (w), 756 (s), 689 (s), 669 (s), 601 (m), 584 (m).

3-Methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-amine (6.3.1d).



Starting from 3-methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.1.3a** (0.254 g, 1 mmol), Pd/C (0.030 g, 0.10 mmol) and H_2 balloon in 25 mL MeOH, the product **6.3.1d** was isolated as a grey solid (0.191 g, 85%). Mp: 102-104^{o}C.

^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 2.49 (s, 3H, Me), 5.27 (br s,

2H, NH_2), 7.18-7.23 (m, 1H, CH_{Ar}), 7.26 (d, 1H, ^4J = 2.5 Hz, CH_{Ar}), 7.46-7.51 (m, 2H, CH_{Ar}), 8.16 (d, 1H, ^4J = 2.5 Hz, CH_{Ar}), 8.24-8.28 (m, 2H, CH_{Ar}).

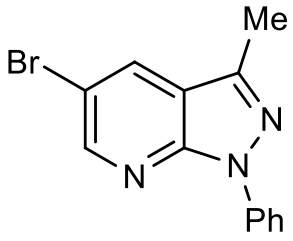
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 12.1 (Me), 109.8 (CH), 117.2 (C), 118.7, 124.2, 129.0, 139.6 (CH), 139.7, 140.4, 140.8, 144.8 (C).

MS (GC, 70 eV): *m/z* (%) = 224 (M^+, 100).

HRMS (ESI): calcd for $C_{13}H_{12}N_4$ (M+H) 225.11232, found 225.11233.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3346 (w), 1632 (w), 1591 (m), 1503 (s), 1441 (w), 1410 (m), 1385 (m), 1268 (m), 1201 (w), 1128 (m), 1066 (m), 966 (m), 906 (m), 862 (m), 754 (s), 717 (m), 691 (s), 671 (s).

5-Bromo-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (6.3.4).



Starting from 3-methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.1.3a** (0.254 g, 1 mmol), Pd/C (0.030 g, 0.10 mmol), H_2 balloon in 25 mL MeOH, *tert*-butyl nitrite (0.131 g, 1.5 mmol) and $CuBr_2$ (0.268 g, 1.2 mmol) in 40 mL MeCN, the product **6.3.4** was isolated as a white solid (0.245 g, 85%). Mp: 110-112ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.56 (s, 3H, Me), 7.28-7.34 (m, 1H, CH_{Ar}), 7.50-7.56 (m, 2H, CH_{Ar}), 8.15-8.19 (m, 2H, CH_{Ar}), 8.66 (dd, 2H, ^3J = 9.1 Hz, ^4J = 2.2 Hz, Py).

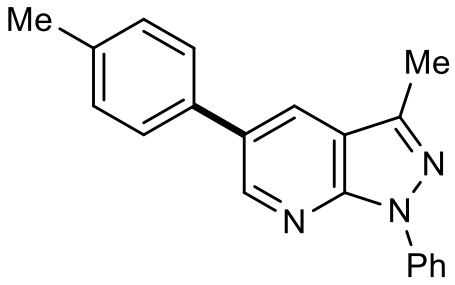
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 12.0 (Me), 112.2, 118.3 (C), 119.9, 125.6, 129.1, 132.6 (CH), 138.7, 142.4, 148.4 (C), 149.5 (CH).

MS (GC, 70 eV): *m/z* (%) = 287 (M^+, 100), 272 (13), 207 (18), 167 (12), 140 (130), 77 (40).

HRMS (ESI): calcd for $C_{13}H_{10}N_3Br$ (M^+) 287.00526, found 287.004794.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1592 (m), 1564 (w), 1504 (s), 1438 (m), 1414 (s), 1380 (m), 1321 (m), 1266 (s), 1209 (w), 117 (w), 1114 (m), 1070 (m), 1010 (w), 949 (m), 904 (w), 883 (m), 820 (m), 766 (s), 744 (s), 688 (s), 668 (s), 651 (m).

3-Methyl-1-phenyl-5-(*p*-tolyl)-1*H*-pyrazolo[3,4-*b*]pyridine (6.3.5a).



Starting from 5-bromo-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.3.4** (0.288 g, 1 mmol), *p*-tolylboronic acid (0.204 g, 1.5 mmol), $PdCl_2(PPh_3)_2$ (0.014 g, 0.02 mmol) and K_2CO_3 (0.276 g, 2 mmol) in 4 mL dioxane, the product **6.3.5a** was isolated as a yellow solid (0.260 g, 87%). Mp: 130-132ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.36 (s, 3H, Me), 2.63 (s, 3H, Me), 7.27-7.32 (m, 3H,

CH_{Ar}), 7.54 (t, 2H, ^{3}J = 8.2 Hz, CH_{Ar}), 7.68 (d, 2H, ^{3}J = 7.8 Hz, CH_{Ar}), 8.30 (d, 2H, ^{3}J = 8.2 Hz, CH_{Ar}), 8.53 (s, 1H, Py), 8.90 (s,1H, Py).

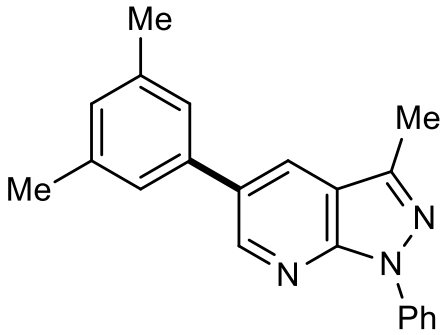
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 12.1, 20.6 (Me), 116.9 (C), 125.2, 126.8, 127.6, 129.1, 129.6, 129.7 (CH), 134.4, 137.0, 139.2, 143.2 (C), 148.1 (CH), 149.5 (C).

MS (GC, 70 eV): *m/z* (%) = 299 (M^+, 100).

HRMS (EI): calcd for $C_{20}H_{17}N_3$ (M^+) 299.14170, found 299.141349.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3023 (w),1612 (w), 1594 (s), 1504 (s), 1416 (s), 1381 (m), 1344 (m), 1279 (m), 1256 (m), 1212 (w), 1118 (m), 1078 (m), 1011 (w), 957 (w), 903 (m), 852 (w), 816 (s), 760 (s), 695 (s), 665 (s), 589 (m), 569 (m).

5-(3,5-Dimethylphenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (6.3.5b).



Starting from 5-bromo-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.3.4** (0.288 g, 1 mmol), (3,5-dimethylphenyl)boronic acid (0.225 g, 1.5 mmol), $PdCl_2(PPh_3)_2$ (0.014 g, 0.02 mmol) and K_2CO_3 (0.276 g, 2 mmol) in 4 mL dioxane, the product **6.3.5b** was isolated as an orange solid (0.298 g, 95%). Mp: 96-98ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.36 (s, 6H, 2xMe), 2.65 (s, 3H, Me), 7.05 (s, 1H, CH_{Ar}), 7.30 (t, 1H, ^{3}J = 7.2 Hz, CH_{Ar}), 7.41 (s, 2H, CH_{Ar}), 7.52-7.58 (m, 2H, CH_{Ar}), 8.30 (d, 2H, ^{3}J = 7.9 Hz, CH_{Ar}), 8.57 (d, 1H, ^{4}J = 2.0 Hz, Py), 8.91 (d, 1H, ^{4}J = 2.0 Hz, Py).

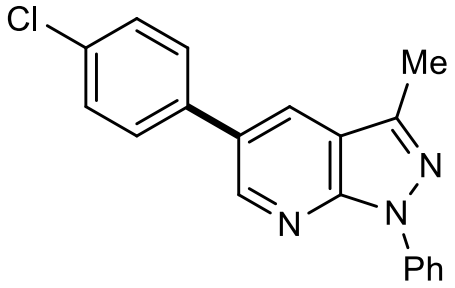
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 12.2, 21.0 (Me), 116.9 (C), 119.7, 124.8, 125.2, 128.0, 129.0, 129.1 (CH), 130.0, 137.2, 138.1, 139.2, 143.3 (C), 148.3 (CH), 149.6 (C).

MS (GC, 70 eV): *m/z* (%) = 313 (M^+, 100).

HRMS (EI): calcd for $C_{21}H_{19}N_3$ (M^+) 313.15735, found 313.156954.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2914 (w), 1589 (m), 1504 (m), 1430 (m), 1411 (m), 1365 (w), 1272 (m), 1219 (m), 1181 (w), 1118 (m), 1030 (w), 960 (w), 898 (m), 880 (w), 836 (s), 757 (s), 683 (s), 669 (s), 603 (m), 589 (m).

5-(4-Chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (6.3.5c).



Starting from 5-bromo-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.3.4** (0.288 g, 1 mmol), (4-chlorophenyl)boronic acid (0.234 g, 1.5 mmol), $PdCl_2(PPh_3)_2$ (0.014 g, 0.02 mmol) and K_2CO_3 (0.276 g, 2 mmol) in 4 mL dioxane, the product **6.3.5c** was isolated as a yellow solid (0.288 g, 90%). Mp: 157-159ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.64 (s, 3H, Me), 7.30 (t, 1H, ^3J = 7.6 Hz, CH_{Ar}), 7.52-7.59 (m, 4H, CH_{Ar}), 7.84 (d, 2H, ^3J = 8.4 Hz, CH_{Ar}), 8.29 (d, 2H, ^3J = 8.4 Hz, CH_{Ar}), 8.63 (d, 1H, ^4J = 1.8 Hz, Py), 8.95 (d, 1H, ^4J = 1.8 Hz, Py).

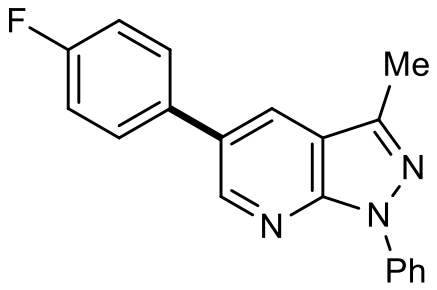
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 12.2 (Me), 116.8 (C), 119.7, 125.3, 128.2, 128.5, 128.7, 129.0, 129.1 (CH), 132.6, 136.2, 139.1, 143.4 (C), 148.2 (CH), 149.7 (C).

MS (GC, 70 eV): *m/z* (%) = 319 (M^+, 100).

HRMS (EI): calcd for $C_{19}H_{14}N_3Cl$ (M^+) 319.08708, found 319.086462.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3037 (w), 1611 (w), 1593 (m), 1558 (w), 1500 (s), 1440 (m), 1414 (s), 1343 (m), 1277 (m), 1255 (m), 1210 (w), 1118 (m), 1093 (m), 1076 (m), 1010 (m), 956 (w), 902 (m), 849 (m), 827 (s), 762 (s), 695 (s), 647 (m), 586 (m).

5-(4-Fluorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (6.3.5d).



Starting from 5-bromo-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.3.4** (0.288 g, 1 mmol), (4-fluorophenyl)boronic acid (0.210 g, 1.5 mmol), $PdCl_2(PPh_3)_2$ (0.014 g, 0.02 mmol) and K_2CO_3 (0.276 g, 2 mmol) in 4 mL dioxane, the product **6.3.5d** was isolated as a yellow solid (0.267 g, 88%). Mp: 168-169ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.63 (s, 3H, Me), 7.27-7.38 (m, 3H, CH_{Ar}), 7.50-7.56 (m, 2H, CH_{Ar}), 7.81-7.86 (m, 2H, CH_{Ar}), 8.27-8.30 (m, 2H, CH_{Ar}), 8.57 (d, 1H, ^4J = 2.2 Hz, Py), 8.91 (d, 1H, ^4J = 2.2 Hz, Py).

^{19}F NMR (282 MHz, DMSO-d_6): δ = -115.1 (CF).

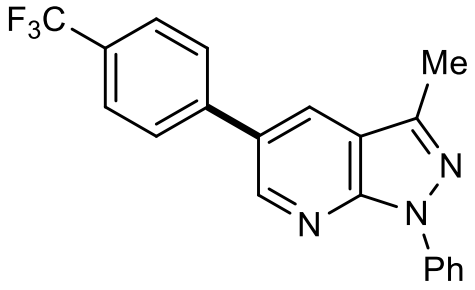
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 12.1 (Me), 115.7, 116.0 (CH), 116.8 (C), 119.7, 125.2, 128.1, 128.8, 129.0, 129.1, 129.2 (CH), 133.8 (d, J = 3.0 Hz, C), 139.1, 143.3 (C), 148.2 (CH), 149.5, 162.0 (d, J = 245 Hz, C).

MS (GC, 70 eV): *m/z* (%) = 303 (M^+, 100).

HRMS (EI): calcd for $C_{19}H_{14}N_3F$ (M^+) 303.11663, found 303.116054.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1610 (w), 1594 (s), 1563 (w), 1504 (s), 1490 (s), 1416 (s), 1346 (w), 1259 (m), 1224 (s), 1163 (m), 1117 (m), 1076 (m), 1012 (w), 957 (w), 901 (m), 855 (m), 834 (s), 804 (m), 762 (s), 969 (s), 665 (s), 588 (m).

3-Methyl-1-phenyl-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazolo[3,4-*b*]pyridine (6.3.5e).



Starting from 5-bromo-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.3.4** (0.288 g, 1 mmol), (4-(trifluoromethyl)phenyl)boronic acid (0.285 g, 1.5 mmol), $PdCl_2(PPh_3)_2$ (0.014 g, 0.02 mmol) and K_2CO_3 (0.276 g, 2 mmol) in 4 mL dioxane, the product **6.3.5e** was isolated as a yellow solid (0.322 g, 91%). Mp: 144-145ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.65 (s, 3H, Me), 7.29-7.33 (m, 1H, CH_{Ar}), 7.55 (t, 2H, ^3J = 8.0 Hz, CH_{Ar}), 7.86 (d, 2H, ^3J = 8.0 Hz, CH_{Ar}), 8.04 (d, 2H, ^3J = 8.0 Hz, CH_{Ar}), 8.29 (d, 2H, ^3J = 7.8 Hz, CH_{Ar}), 8.71 (d, 1H, ^4J = 2.1 Hz, Py), 9.00 (d, 1H, ^4J = 2.1 Hz, Py).

^{19}F NMR (282 MHz, DMSO-d_6): δ = -60.9 (CF_3).

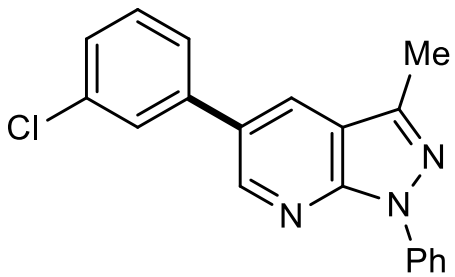
^{13}C NMR: due to bed solubility it was not possible to measure.

MS (GC, 70 eV): *m/z* (%) = 353 (M^+, 100), 338 (14).

HRMS (EI): calcd for $C_{20}H_{14}N_3F_3$ (M^+) 353.11343, found 353.113271.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1612 (m), 1598 (m), 1505 (m), 1408 (w), 1441 (w), 1418 (m), 1384 (w), 1324 (s), 1283 (m), 1258 (m), 1163 (s), 1104 (s), 1067 (s), 1012 (m), 955 (m), 904 (m), 849 (m), 837 (s), 773 (m), 752 (s), 702 (m), 689 (s), 668 (m), 635 (w), 594 (s), 552 (w).

5-(3-Chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (6.3.5f).



Starting from 5-bromo-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.3.4** (0.288 g, 1 mmol), (3-chlorophenyl)boronic acid (0.234 g, 1.5 mmol), $PdCl_2(PPh_3)_2$ (0.014 g, 0.02 mmol) and K_2CO_3 (0.276 g, 2 mmol) in 4 mL dioxane, the product **6.3.5f** was isolated as an orange solid (0.278 g, 87%). Mp: 140-142ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.64 (s, 3H, Me), 7.30 (t, 1H, ^3J = 7.2 Hz, CH_{Ar}), 7.46-7.57 (m, 4H, CH_{Ar}), 7.79 (d, 1H, ^3J = 7.5 Hz, CH_{Ar}), 7.91 (s, 1H, CH_{Ar}), 8.29 (d, 2H, ^3J = 7.5

Hz, CH_{Ar}), 8.68 (d, 1H, ^4J = 2.0 Hz, Py), 8.97 (d, 1H, ^4J = 2.0 Hz, Py).

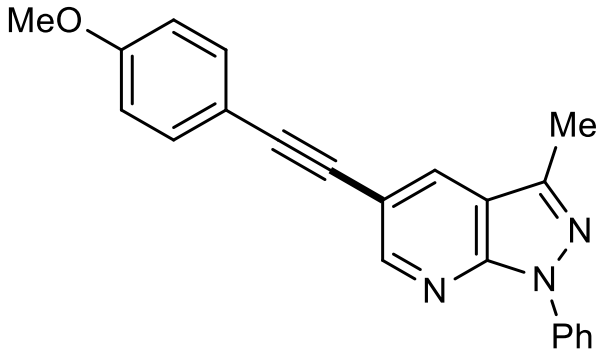
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 12.7 (Me), 116.9 (C), 119.8, 125.4, 125.7, 126.8, 127.4 (CH), 128.3 (C), 128.6, 129.1, 130.8 (CH), 133.9, 139.1, 139.5, 143.5 (C), 148.3 (CH), 149.8 (C).

MS (GC, 70 eV): *m/z* (%) = 319 (M^+, 100).

HRMS (EI): calcd for $C_{19}H_{14}N_3Cl$ (M^+) 319.08708, found 319.087283.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3031 (w), 1594 (m), 1569 (m), 1497 (m), 1460 (m), 1436 (m), 1412 (m), 1383 (m), 1273 (m), 1251 (m), 1176 (w), 1097 (m), 1075 (m), 1045 (m), 957 (w), 896 (m), 878 (m), 787 (s), 775 (m), 742 (s), 697 (s), 683 (s), 607 (m), 589 (s).

5-((4-Methoxyphenyl)ethynyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (6.3.6a).



Starting from 5-bromo-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.3.4** (0.288 g, 1 mmol), 1-ethynyl-4-methoxybenzene (0.264 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.014 g, 0.02 mmol), CuI (0.010 g, 0.05 mmol) and TEA (0.131 g, 1.3 mmol) in 4 mL DMF, the product **6.3.6a** was isolated as a yellow solid (0.288 g, 85%). Mp: 92-94ºC.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.62 (s, 3H, Me), 3.81 (s, 3H, OMe), 7.01 (d, 2H, ^3J = 8.9 Hz, CH_{Ar}), 7.29-7.35 (m, 1H, CH_{Ar}), 7.53-7.59 (m, 4H, CH_{Ar}), 8.52 (d, 2H, ^3J = 8.3 Hz, CH_{Ar}), 8.56-8.57 (m, 1H, Py), 8.76-8.77 (m, 1H, Py).

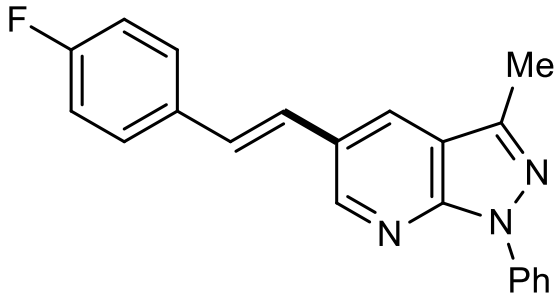
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 12.0 (Me), 55.2 (OMe), 85.3, 90.9, 113.0, 113.9 (C), 114.4 (CH), 116.3 (C), 120.0, 125.6, 129.1, 132.9 (CH), 138.8, 143.3, 148.5 (C), 151.3 (CH), 159.6 (C).

MS (GC, 70 eV): *m/z* (%) = 339 (M^+, 100), 324 (31).

HRMS (EI): calcd for $C_{22}H_{17}N_3O$ (M^+) 339.13661, found 339.136346.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2916 (w), 1595 (s), 1556 (m), 1504 (s), 1455 (m), 1438 (s), 1413 (s), 1382 (s), 1351 (m), 1299 (s), 1265 (m), 1242 (s), 1206 (m), 1173 (s), 1117 (s), 1066 (m), 1031 (s), 970 (m), 911 (m), 896 (m), 824 (s), 772 (s), 746 (s), 671 (s), 649 (m), 593 (s), 563 (m), 531 (s).

(*E*)-5-(4-fluorostyryl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (6.3.7a).



Starting from 5-bromo-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.3.4** (0.288 g, 1 mmol), 1-fluoro-4-vinylbenzene (0.366 g, 3 mmol), $PdCl_2(PPh_3)_2$ (0.028 g, 0.04 mmol) and TEA (0.408 g, 4 mmol) in 4 mL DMF, the product **6.3.7a** was isolated as a yellow solid (0.214 g, 65%). Mp: 115-117ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.60 (s, 3H, Me), 7.19-7.30 (m, 3H, CH_{Ar}, C=CH), 7.37-7.39 (m, 2H, CH_{Ar}), 7.50-7.55 (m, 2H, CH_{Ar}), 7.62-7.67 (m, 2H, CH_{Ar}), 8.26 (d, 2H, ^3J = 7.6 Hz, CH_{Ar}), 8.50 (d, 1H, ^4J = 1.9 Hz, Py), 8.81 (d, 1H, ^4J = 1.9 Hz, Py).

^{19}F NMR (62.9 MHz, DMSO-d_6): δ = -114.1 (CF).

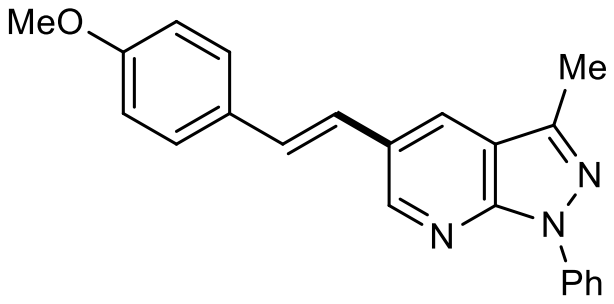
^{13}C NMR: due to bed solubility it was not possible to measure.

MS (GC, 70 eV): *m/z* (%) = 329 (M^+, 100).

HRMS (EI): calcd for $C_{21}H_{16}N_3F$ (M^+) 329.13228, found 329.131861.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3035 (w), 1593 (s), 1505 (s), 1440 (m), 1413 (s), 1384 (m), 1280 (m), 1228 (s), 1158 (m), 1118 (m), 1069 (w), 1030 (w), 1012 (w), 950 (m), 900 (m), 853 (m), 771 (m), 750 (s), 687 (m), 668 (m), 588 (m).

(*E*)-5-(4-methoxystyryl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (6.3.7b).



Starting from 5-bromo-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.3.4** (0.288 g, 1 mmol), 1-methoxy-4-vinylbenzene (0.402 g, 3 mmol), $PdCl_2(PPh_3)_2$ (0.028 g, 0.04 mmol) and TEA (0.408 g, 4 mmol) in 4 mL DMF, the product **6.3.7b** was isolated as a yellow solid (0.240 g, 70%). Mp: 131-133ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.61 (s, 3H, Me), 3.78 (s, 3H, OMe), 6.97 (d, 2H, ^3J = 8.5 Hz, CH_{Ar}), 7.22-7.40 (m, 3H, CH_{Ar}, C=CH), 7.51-7.57 (m, 4H, CH_{Ar}), 8.27 (dd, 2H, ^3J = 8.6 Hz, ^4J = 1.1 Hz, CH_{Ar}), 8.49 (d, 1H, ^4J = 2.0 Hz, Py), 8.81 (d, 1H, ^4J = 2.0 Hz, Py).

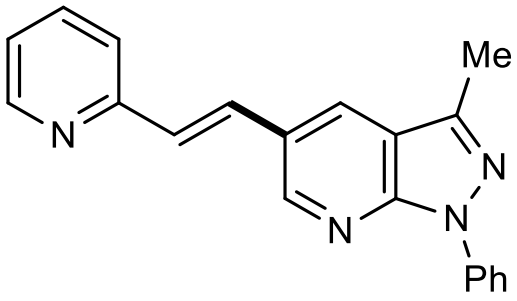
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 12.2 (Me), 55.1 (OMe), 114.2 (CH), 117.0 (C), 119.6, 122.7, 125.2, 125.9 (CH), 127.4 (C), 127.7, 128.6, 129.1 (CH), 129.5, 139.2, 143.1 (C), 148.8 (CH), 149.4, 159.0 (C).

MS (GC, 70 eV): *m/z* (%) = 341 (M^+, 100).

HRMS (EI): calcd for $C_{22}H_{19}N_3O$ (M^+) 341.15226, found 341.152368.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1593 (m), 1559 (w), 1504 (s), 1436 (m), 1414 (m), 1385 (m), 1281 (m), 1250 (m), 1213 (m), 1176 (m), 1119 (m), 1068 (w), 1019 (m), 964 (m), 951 (s), 902 (m), 581 (s), 810 (m), 773 (s), 747 (s), 688 (s), 671 (m), 588 (s).

(*E*)-3-methyl-1-phenyl-5-(2-(pyridin-2-yl)vinyl)-1*H*-pyrazolo[3,4-*b*]pyridine (6.3.7c).



Starting from 5-bromo-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **6.3.4** (0.288 g, 1 mmol), 2-vinylpyridine (0.315 g, 3 mmol), $PdCl_2(PPh_3)_2$ (0.028 g, 0.04 mmol) and TEA (0.408 g, 4 mmol) in 4 mL DMF, the product **6.3.7c** was isolated as a yellow viscous oil (0.222 g, 71%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.63 (s, 3H, Me), 7.25-7.32 (m, 2H, C=CH), 7.47-7.56 (m, 4H, CH_{Ar}), 7.78-7.89 (m, 2H, CH_{Ar}), 8.27 (d, 2H, ^3J = 7.6 Hz, CH_{Ar}), 8.59-8.65 (m, 2H, CH_{Ar}, Py), 8.92 (d, 1H, ^4J = 1.7 Hz, Py).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 12.2 (Me), 117.0 (C), 119.7, 122.3, 122.4, 125.3 (CH), 126.4 (C), 127.3, 128.4, 128.8, 129.1, 136.9 (CH), 139.1, 149.5, 149.7, 154.7 (C).

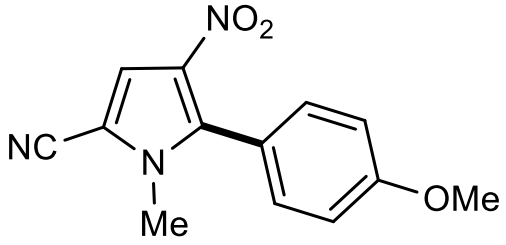
MS (GC, 70 eV): *m/z* (%) = 312 (M^+, 29), 311 (100).

HRMS (ESI): calcd for $C_{20}H_{17}N_4$ (M+H) 313.14477, found 313.14502.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2919 (w), 1595 (w), 1582 (s), 1561 (m), 1504 (s), 1467 (s), 1430 (s), 1413 (s), 1384 (m), 1259 (m), 1218 (m), 1148 (m), 1115 (m), 1069 (m), 1011 (w), 964 (s), 604 (m), 849 (w), 752 (s), 739 (s), 689 (s), 670 (s), 588 (s), 568 (m).

General Procedure for Pd-catalyzed C-H Arylation of 3-Nitropyrrole Derivative and 2-Nitrothiophene. Synthesis of Compounds 7.2a-c: The corresponding 3-nitropyrrole derivative or 2-nitrothiophene **7.1h**,**i** (1 equiv.), CuI (1.2 equiv.), K_2CO_3 (1.3 equiv.), $(CH_3)_3CCO_2H$ (0.3 equiv.) and $PdCl_2(PPh_3)_2$ (0.05 equiv.) were weighed in air and placed successively into a Schlenk flask equipped with a magnetic stir bar, which was capped with a rubber septum. The reaction vessel was evacuated and back-filled with argon (three times). Dry DMF (8 mL for 1 mmol of starting nitroarene) and aryl bromide (2 equiv.) were added with a syringe (in case of solid aryl bromide, first it was dissolved in dry DMF under inert atmosphere), and the reaction was heated to 130ºC for 16h. Upon completion, the reaction was cooled to room temperature and concentrated under vacuum. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired arylated product.

5-(4-Methoxyphenyl)-1-methyl-4-nitro-1*H*-pyrrole-2-carbonitrile (7.2a).



Starting from 1-methyl-4-nitro-1*H*-pyrrole-2-carbonitrile **7.1h** (0.151 g, 1 mmol), 1-bromo-4-methoxybenzene (0.374 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **7.2a** was isolated as a brown solid (0.123 g, 48%^{Pd}). Mp: 150-152°C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.52 (s, 3H, NMe), 3.84 (s, 3H, OMe), 7.10 (d, 2H, ^3J = 8.5 Hz, CH_{Ar}), 7.45 (d, 2H, ^3J = 9.0 Hz, CH_{Ar}), 7.85 (s, 1H, pyrrole).

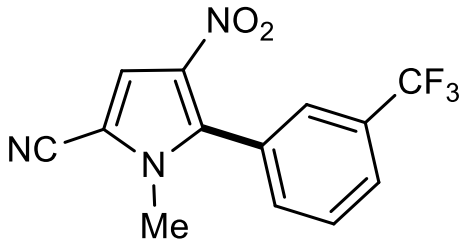
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 34.2 (Me), 55.3 (OMe), 104.0 (CN), 112.1 (C), 114.0, 116.1 (CH), 119.1 (C), 131.8 (CH), 132.7, 138.1, 160.4 (C).

MS (GC, 70eV): *m/z* (%) = 257 (M^+, 100), 195 (16).

HRMS (EI): calcd for $C_{13}H_{11}N_3O_3$ (M^+) 257.07949, found 257.07949.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3149 (w), 2224 (m), 1611 (w), 1502 (m), 1454 (m), 1404 (m), 1322 (s), 1239 (m), 1174 (m), 1108 (m), 1026 (s), 851 (s), 796 (m), 760 (s), 655 (m), 570 (m).

1-Methyl-4-nitro-5-(3-(trifluoromethyl)phenyl)-1*H*-pyrrole-2-carbonitrile (7.2b).



Starting from 1-methyl-4-nitro-1*H*-pyrrole-2-carbonitrile **7.1h** (0.151 g, 1 mmol), 1-bromo-3-(trifluoromethyl)benzene (0.450 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **7.2b** was isolated as a brown solid (0.174 g, 59%^{Pd}). Mp: 118-119°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.59 (s, 3H, NMe), 7.47 (s, 1H, pyrrole), 7.55-7.58 (m, 1H, CH_{Ar}), 7.63-7.71 (m, 2H, CH_{Ar}), 7.80-7.83 (m, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -62.7 (CF_3).

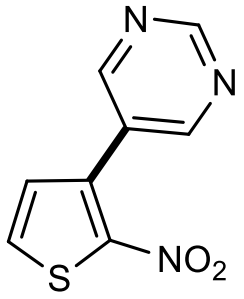
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 34.3 (Me), 105.4 (CN), 111.2 (C), 115.7 (CH), 123.4 (q, ^1J = 273.4 Hz, CF_3), 127.0 (q, ^3J = 3.7 Hz, CF_3CCH_{Ar}), 127.3 (q, ^3J = 3.7 Hz, CF_3CCH_{Ar}), 128.2, 129.6 (C), 131.6 (q, ^2J = 31.2 Hz, CCF_3), 133.5 (CH), 134.0, 135.9 (C).

MS (GC, 70eV): *m/z* (%) = 295 (M^+, 100), 179 (27).

HRMS (EI): calcd for $C_{13}H_8N_3O_2F_3$ (M^+) 295.05631, found 295.05619.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3159 (w), 2922 (w), 2229 (w), 1558 (w), 1498 (m), 1458 (m), 1425 (m), 1320 (s), 1227 (m), 1114 (s), 1074 (s), 1021 (m), 905 (m), 835 (m), 815 (m), 759 (m), 700 (m), 651 (m).

5-(2-Nitrothiophen-3-yl)pyrimidine (7.2c).



Starting from 2-nitrothiophene **7.1i** (0.129 g, 1 mmol), 5-bromopyrimidine (0.318 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), CuI (0.228 g, 1.2 mmol), PivOH (0.030 g, 0.3 mmol) and K_2CO_3 (0.179 g, 1.3 mmol) in 8 mL DMF, the product **7.2c** was isolated as a brown viscous oil (0.108 g, 52%^{Pd}).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 7.35 (d, 1H, ^3J = 4.1 Hz, thiophene), 7.97 (d, 1H, ^3J = 4.1 Hz, thiophene), 9.04-9.29 (br m, 3H, pyrimidine).

^{13}C NMR: Due to bed solubility it was not possible to measure.

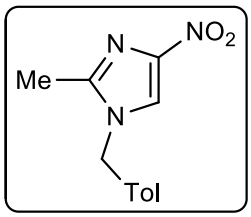
MS (GC, 70eV): *m/z* (%) = 207 (M^+, 100), 177 (19), 117 (39), 63 (41).

HRMS (EI): calcd for $C_8H_5N_3O_2S$ (M^+) 207.00970, found 207.01000.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3112 (w), 1579 (w), 1551 (m), 1492 (s), 1438 (m), 1406 (m), 1336 (s), 1265 (m), 1181 (m), 1114 (m), 1050 (m), 911 (m), 826 (m), 814 (m), 732 (s), 631 (s).

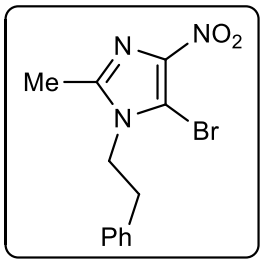
A.1.3. Crystallographic data

Crystal data and structure refinement for ***4.1.3g***



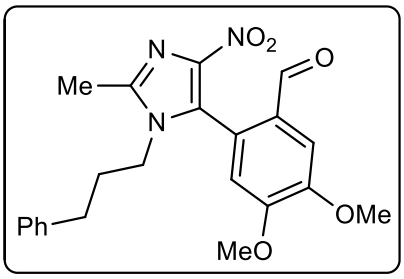
Identification code	ag95	
Empirical formula	$C_{12}H_{13}N_3O_2$	
Formula weight	231.25	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/c$	
Unit cell dimensions	a = 13.2661 (8) Å	α = 90°
	b = 8.4355 (4) Å	β = 110.075 (3)°
	c = 11.2895 (6) Å	γ = 90°
Volume	1186.61 (11) Å^3	
Z	4	
Calculated density	1.294 mg/m^3	
Absorption coefficient	0.09 mm^{-1}	
F(000)	488	
Crystal size	0.31 x 0.18 x 0.09 mm	
Θ range for data collection	3.1 to 23.3°	
Limiting indices:	-18≤h≤18, -6≤k≤11, -15≤l≤15	
Reflections collected / unique	15718 / 3151 [R(Int) = 0.0445]	
Completeness to Θ	26.07°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3151 / 0 / 157	
Goodness-of-fit on F^2	1.033	
Final R indices [I>2σ(I)]	R1 = 0.0901, wR2 = 0.1274	
R indices (all data)	R1 = 0.0507, wR2 = 0.1062	
Largest diff. peak and hole	0.228 and -0.269 e. Å^{-3}	

Crystal data and structure refinement for ***4.1.6a***



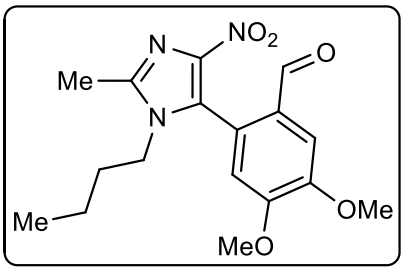
Identification code	sm6002	
Empirical formula	$C_{12}H_{12}BrN_3O_2$	
Formula weight	310.16	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Orthorhombic $P2_12_12_1$	
Unit cell dimensions	a = 7.0209 (2) Å	α = 90°
	b = 7.6049 (2) Å	β = 90°
	c = 23.4143 (5) Å	γ = 90°
Volume	1250.17 (6) Å^3	
Z	4	
Calculated density	1.2648 mg/m^3	
Absorption coefficient	3.29 mm^{-1}	
F(000)	624	
Crystal size	0.19 x 0.15 x 0.08 mm	
Θ range for data collection	5.6 to 55.1°	
Limiting indices:	-6≤h≤10, -11≤k≤10, -33≤l≤34	
Reflections collected / unique	16351 / 4127 [R(Int) = 0.0326]	
Completeness to Θ	28.68°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4127 / 0 / 164	
Goodness-of-fit on F^2	1.028	
Final R indices [I>2σ(I)]	R1 = 0.0450, wR2 = 0.0645	
R indices (all data)	R1 = 0.0322, wR2 = 0.0613	
Largest diff. peak and hole	0.517 and -0.984 e. Å^{-3}	

Crystal data and structure refinement for ***4.2.1d***



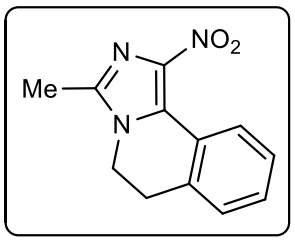
Identification code	ib13	
Empirical formula	$C_{22}H_{23}N_3O_5$	
Formula weight	409.43	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/n$	
Unit cell dimensions	a = 8.5834 (3) Å	α = 90°
	b = 14.8435 (5) Å	β = 99.823 (1)°
	c = 16.2877 (6) Å	γ = 90°
Volume	2044.76 (12) $Å^3$	
Z	4	
Calculated density	1.330 mg/m^3	
Absorption coefficient	0.10 mm^{-1}	
F(000)	864	
Crystal size	0.52 x 0.12 x 0.12 mm	
Θ range for data collection	5.5 to 66.1°	
Limiting indices:	$-12\leq h\leq 8$, $-21\leq k\leq 21$, $-23\leq l\leq 23$	
Reflections collected / unique	28259 / 5047 [R(Int) = 0.0274]	
Completeness to Θ	28.46°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6497 / 0 / 274	
Goodness-of-fit on F^2	1.031	
Final R indices [I>2σ(I)]	R1 = 0.0616, wR2 = 0.1242	
R indices (all data)	R1 = 0.0445, wR2 = 0.1121	
Largest diff. peak and hole	0.319 and -0.285 e. $Å^{-3}$	

Crystal data and structure refinement for ***4.2.1t***



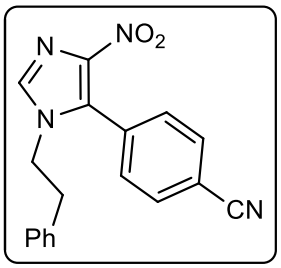
Identification code	sm680	
Empirical formula	$C_{17}H_{21}N_3O_5$	
Formula weight	347.37	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Orthorhombic *Pbca*	
Unit cell dimensions	*a* = 14.4847 (4) Å	α = 90°
	b = 14.2985 (4) Å	β = 90°
	c = 16.2284 (5) Å	γ = 90°
Volume	3361.06 (17) $Å^3$	
Z	8	
Calculated density	1.373 mg/m^3	
Absorption coefficient	0.10 mm^{-1}	
F(000)	1472	
Crystal size	0.85 x 0.14 x 0.06 mm	
Θ range for data collection	4.7 to 60.4°	
Limiting indices:	-21≤h≤21, -21≤k≤21, -24≤l≤24	
Reflections collected / unique	46084 / 6085 [R(Int) = 0.0676]	
Completeness to Θ	29.69°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6085 / 0 / 230	
Goodness-of-fit on F^2	1.018	
Final R indices [I>2σ(I)]	R1 = 0.0974, wR2 = 0.1337	
R indices (all data)	R1 = 0.0485, wR2 = 0.1073	
Largest diff. peak and hole	0.344 and -0.300 e. $Å^{-3}$	

Crystal data and structure refinement for ***4.2.2b***



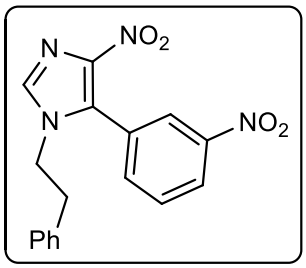
Identification code	t29	
Empirical formula	$C_{12}H_{11}N_3O_2$	
Formula weight	229.24	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Orthorhombic, *Pna*2$_1$	
Unit cell dimensions	*a* = 15.7337 (7) Å	α = 90°
	b = 7.0498 (4) Å	β = 90°
	c = 9.9110 (10) Å	γ = 90°
Volume	1099.32 (10) Å^3	
Z	4	
Calculated density	1.385 mg/m^3	
Absorption coefficient	0.10 mm^{-1}	
F(000)	480	
Crystal size	0.27 x 0.19 x 0.05 mm	
Θ range for data collection	2.6 to 24.1°	
Limiting indices:	-20≤h≤21, -6≤k≤9, -12≤l≤13	
Reflections collected / unique	11098 / 4956 [R(Int) = 0.0277]	
Completeness to Θ	31.07°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4956 / 2 / 226	
Goodness-of-fit on F^2	1.017	
Final R indices [I>2σ(I)]	R1 = 0.0822, wR2 = 0.0974	
R indices (all data)	R1 = 0.0439, wR2 = 0.0819	
Largest diff. peak and hole	0.118 and -0.175 e. Å^{-3}	

Crystal data and structure refinement for ***4.2.4a***



Identification code	sm652_1	
Empirical formula	$C_{18}H_{14}N_4O_2$	
Formula weight	318.33	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, *Cc*	
Unit cell dimensions	*a* = 10.4755 (4) Å	α = 90°
	b = 14.1633 (6) Å	β = 100.198 (2)°
	c = 10.9706 (6) Å	γ = 90°
Volume	1601.97 (11) $Å^3$	
Z	4	
Calculated density	1.320 mg/m^3	
Absorption coefficient	0.09 mm^{-1}	
F(000)	664	
Crystal size	0.25 x 0.18 x 0.18 mm	
Θ range for data collection	4.9 to 60.3°	
Limiting indices:	-15≤h≤15, -21≤k≤21, -16≤l≤7	
Reflections collected / unique	10868 / 3671 [R(Int) = 0.0255]	
Completeness to Θ	29.12°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3671 / 0 / 217	
Goodness-of-fit on F^2	1.031	
Final R indices [I>2σ(I)]	R1 = 0.0475, wR2 = 0.0886	
R indices (all data)	R1 = 0.0363, wR2 = 0.0826	
Largest diff. peak and hole	0.299 and -0.235 e. $Å^{-3}$	

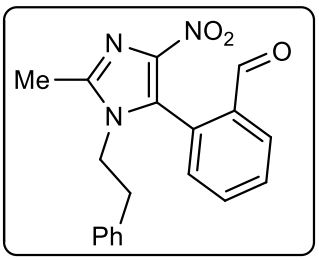
Crystal data and structure refinement for ***4.2.4c***



Identification code	sm786	
Empirical formula	$C_{17}H_{14}N_4O_4$	
Formula weight	338.32	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, *Pn*	
Unit cell dimensions	*a* = 7.5869 (4) Å	α = 90°
	b = 14.3161 (8) Å	β = 117.226 (2)°
	c = 7.9651 (4) Å	γ = 90°
Volume	762.28 (7) $Å^3$	
Z	2	
Calculated density	1.461 mg/m^3	
Absorption coefficient	0.11 mm^{-1}	
F(000)	352	
Crystal size	0.38 x 0.18 x 0.13 mm	
Θ range for data collection	3.1 to 31.3°	
Limiting indices:	$-11 \leq h \leq 10$, $-21 \leq k \leq 18$, $-12 \leq l \leq 11$	
Reflections collected / unique	11098 / 4956 [R(Int) = 0.0277]	
Completeness to Θ	31.07°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4956 / 2 / 226	
Goodness-of-fit on F^2	1.037	
Final R indices [I>2σ(I)]	R1 = 0.0669, wR2 = 0.1051	
R indices (all data)	R1 = 0.0454, wR2 = 0.0919	
Largest diff. peak and hole	0.263 and -0.276 e. $Å^{-3}$	

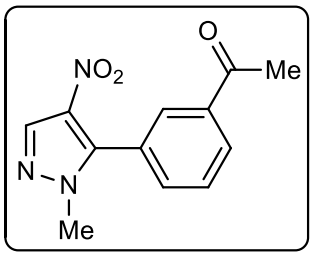
Crystal data and structure refinement for ***4.3.1a***

(4.2.1g)



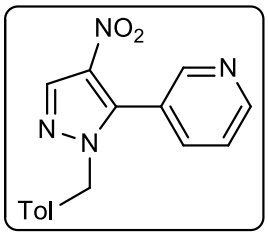
Identification code	sm644	
Empirical formula	$C_{19}H_{17}N_3O_3$	
Formula weight	335.36	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/c$	
Unit cell dimensions	a = 13.9795 (4) Å	α = 90°
	b = 8.4328 (2) Å	β = 91.868 (2)°
	c = 14.2374 (4) Å	γ = 90°
Volume	1677.50 (8) $Å^3$	
Z	4	
Calculated density	1.328 mg/m^3	
Absorption coefficient	0.09 mm^{-1}	
F(000)	704	
Crystal size	0.26 x 0.19 x 0.13 mm	
Θ range for data collection	5.7 to 54.4°	
Limiting indices:	-19≤h≤19, -10≤k≤11, -20≤l≤20	
Reflections collected / unique	18626 / 4868 [R(Int) = 0.0384]	
Completeness to Θ	27.14°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4868 / 0 / 227	
Goodness-of-fit on F^2	1.021	
Final R indices [I>2σ(I)]	R1 = 0.0838, wR2 = 0.1234	
R indices (all data)	R1 = 0.0484, wR2 = 0.1062	
Largest diff. peak and hole	0.258 and -0.196 e. $Å^{-3}$	

Crystal data and structure refinement for ***5.2.1n***



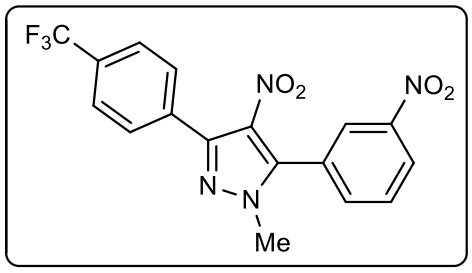
Identification code	ag407	
Empirical formula	$C_{12}H_{11}N_3O_3$	
Formula weight	245.24	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/c$	
Unit cell dimensions	a = 7.2879 (12) Å	α = 90°
	b = 18.828 (3) Å	β = 93.045 (6)°
	c = 8.5038 (14) Å	γ = 90°
Volume	1165.3 (3) $Å^3$	
Z	4	
Calculated density	1.398 mg/m^3	
Absorption coefficient	0.10 mm^{-1}	
F(000)	512	
Crystal size	0.27 x 0.15 x 0.05 mm	
Θ range for data collection	5.3 to 49.3°	
Limiting indices:	$-7\leq h\leq 10$, $-26\leq k\leq 25$, $-11\leq l\leq 11$	
Reflections collected / unique	16039 / 3387 [R(Int) = 0.0486]	
Completeness to Θ	27.0°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3387 / 0 / 165	
Goodness-of-fit on F^2	1.018	
Final R indices [I>2σ(I)]	R1 = 0.1153, wR2 = 0.1387	
R indices (all data)	R1 = 0.0564, wR2 = 0.1127	
Largest diff. peak and hole	0.310 and -0.297 e. $Å^{-3}$	

Crystal data and structure refinement for ***5.2.1v***



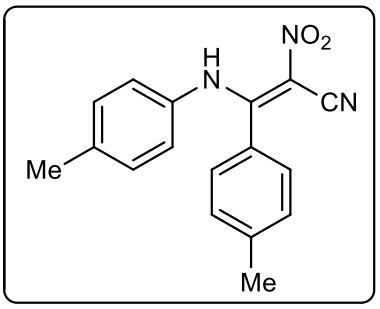
Identification code	ag421	
Empirical formula	$C_{16}H_{14}N_4O_2$	
Formula weight	294.31	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/n$	
Unit cell dimensions	a = 11.8416 (4) Å	α = 90°
	b = 6.0888 (2) Å	β = 105.700 (2)°
	c = 21.1714 (7) Å	γ = 90°
Volume	1469.53 (8) $Å^3$	
Z	4	
Calculated density	1.330 mg/m^3	
Absorption coefficient	0.09 mm^{-1}	
F(000)	616	
Crystal size	0.70 x 0.46 x 0.32 mm	
Θ range for data collection	4.5 to 65.2°	
Limiting indices:	$-17\leq h\leq 17$, $-8\leq k\leq 7$, $-30\leq l\leq 26$	
Reflections collected / unique	19154 / 4681 [R(Int) = 0.0369]	
Completeness to Θ	29.2°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4681 / 0 / 200	
Goodness-of-fit on F^2	1.038	
Final R indices [I>2σ(I)]	R1 = 0.0575, wR2 = 0.1310	
R indices (all data)	R1 = 0.0460, wR2 = 0.1218	
Largest diff. peak and hole	0.350 and -0.223 e. $Å^{-3}$	

Crystal data and structure refinement for ***5.2.2c***



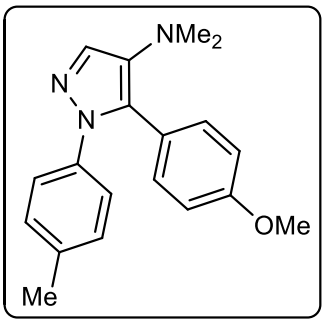
Identification code	ag506ff	
Empirical formula	$C_{17}H_{11}F_3N_4O_4$	
Formula weight	392.30	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Triclinic, *P*	
Unit cell dimensions	*a* = 7.7337 (2) Å	α = 99.709 (1)°
	b = 9.7692 (2) Å	β = 95.981 (1)°
	c = 11.6204 (3) Å	γ = 106.250 (1)°
Volume	820.10 (3) $Å^3$	
Z	2	
Calculated density	1.589 mg/m^3	
Absorption coefficient	0.14 mm^{-1}	
F(000)	400	
Crystal size	0.54 x 0.15 x 0.10 mm	
Θ range for data collection	4.4 to 63.9°	
Limiting indices:	$-11 \leq h \leq 11$, $-14 \leq k \leq 14$, $-17 \leq l \leq 17$	
Reflections collected / unique	27547 / 5917 [R(Int) = 0.0207]	
Completeness to Θ	29.72°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5917 /0 / 254	
Goodness-of-fit on F^2	1.026	
Final R indices [I>2σ(I)]	R1 = 0.0698, wR2 = 0.1305	
R indices (all data)	R1 = 0.0459, wR2 = 0.1128	
Largest diff. peak and hole	0.394 and -0.291 e. $Å^{-3}$	

*Crystal data and structure refinement for **5.2.1"***



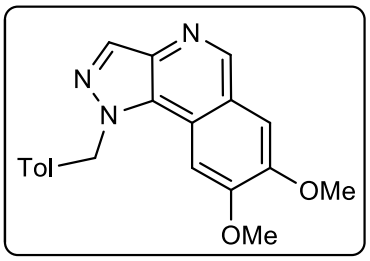
Identification code	Ag636lf	
Empirical formula	$C_{17}H_{15}N_3O_2$	
Formula weight	293.32	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, *Cc*	
Unit cell dimensions	*a* = 12.4481 (14) Å	α = 90°
	b = 14.0884 (16) Å	β = 121.412 (3)°
	c = 9.7990 (11) Å	γ = 90°
Volume	1466.6 (3) $Å^3$	
Z	4	
Calculated density	1.328 mg/m^3	
Absorption coefficient	0.09 mm^{-1}	
F(000)	616	
Crystal size	0.40 x 0.12 x 0.08 mm	
Θ range for data collection	4.8 to 49.6°	
Limiting indices:	-16≤h≤16, -19≤k≤19, -13≤l≤12	
Reflections collected / unique	8140 / 3675 [R(Int) = 0.0327]	
Completeness to Θ	26.39°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3675 / 2 / 205	
Goodness-of-fit on F^2	1.041	
Final R indices [I>2σ(I)]	R1 = 0.0801, wR2 = 0.1312	
R indices (all data)	R1 = 0.0523, wR2 = 0.1155	
Largest diff. peak and hole	0.223 and -0.293 e. $Å^{-3}$	

Crystal data and structure refinement for ***5.3.1c***



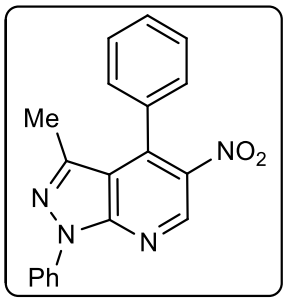
Identification code	Od010	
Empirical formula	$C_{19}H_{21}N_3O$	
Formula weight	307.39	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/n$	
Unit cell dimensions	a = 5.7024 (11) Å	α = 90°
	b = 18.533 (3) Å	β = 92.984 (5)°
	c = 15.727 (3) Å	γ = 90°
Volume	1659.8 (5) $Å^3$	
Z	4	
Calculated density	1.230 mg/m^3	
Absorption coefficient	0.08 mm^{-1}	
F(000)	656	
Crystal size	0.22 x 0.20 x 0.12 mm	
Θ range for data collection	5.6 to 51.2°	
Limiting indices:	$-7\leq h\leq 7$, $-24\leq k\leq 23$, $-20\leq l\leq 20$	
Reflections collected / unique	19009 / 3975 [R(Int) = 0.0604]	
Completeness to Θ	26.22°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3975 / 0 / 212	
Goodness-of-fit on F^2	1.018	
Final R indices [I>2σ(I)]	R1 = 0.0808, wR2 = 0.1165	
R indices (all data)	R1 = 0.0464, wR2 = 0.1000	
Largest diff. peak and hole	0.169 and -0.205 e. $Å^{-3}$	

Crystal data and structure refinement for ***5.3.2c***



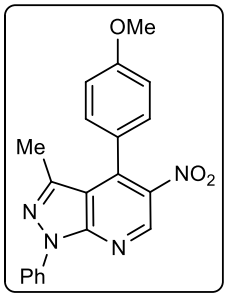
Identification code	Ag459	
Empirical formula	$C_{20}H_{19}N_3O_2$	
Formula weight	333.38	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/c$	
Unit cell dimensions	a = 9.6100 (3) Å	α = 90°
	b = 26.7655 (8) Å	β = 105.485 (1)°
	c = 6.8056 (2) Å	γ = 90°
Volume	1686.97 (9) $Å^3$	
Z	4	
Calculated density	1.313 mg/m^3	
Absorption coefficient	0.09 mm^{-1}	
F(000)	704	
Crystal size	0.55 x 0.44 x 0.21 mm	
Θ range for data collection	5.4 to 65.2°	
Limiting indices:	-12≤h≤14, -40≤k≤30, -10≤l≤10	
Reflections collected / unique	30515 / 6109 [R(Int) = 0.0244]	
Completeness to Θ	29.80°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6109 / 0 / 229	
Goodness-of-fit on F^2	1.071	
Final R indices [I>2σ(I)]	R1 = 0.0591, wR2 = 0.1390	
R indices (all data)	R1 = 0.0498, wR2 = 0.1314	
Largest diff. peak and hole	0.406 and -0.291 e. $Å^{-3}$	

Crystal data and structure refinement for ***6.2.1a***



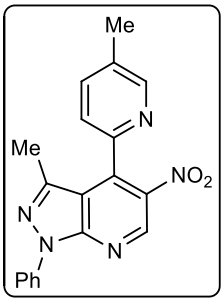
Identification code	ag229	
Empirical formula	$C_{19}H_{14}N_4O_2$	
Formula weight	330.34	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Orthorhombic, *Pbca*	
Unit cell dimensions	*a* = 6.8138 (3) Å	α = 90°
	b = 18.164 (9) Å	β = 90°
	c = 25.7766 (2) Å	γ = 90°
Volume	3191.0 (3) $Å^3$	
Z	8	
Calculated density	1.375 mg/m^3	
Absorption coefficient	0.09 mm^{-1}	
F(000)	1376	
Crystal size	0.36 x 0.16 x 0.06 mm	
Θ range for data collection	4.8 to 49.4°	
Limiting indices:	-8≤h≤9, -23≤k≤24, -30≤l≤35	
Reflections collected / unique	20505/ 4235 [R(Int) = 0.0515]	
Completeness to Θ	25.8°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4235 / 0 / 227	
Goodness-of-fit on F^2	1.016	
Final R indices [I>2σ(I)]	R1 = 0.0844, wR2 = 0.1205	
R indices (all data)	R1 = 0.0466, wR2 = 0.1007	
Largest diff. peak and hole	0.229 and -0.201 e. $Å^{-3}$	

Crystal data and structure refinement for ***6.2.1h***



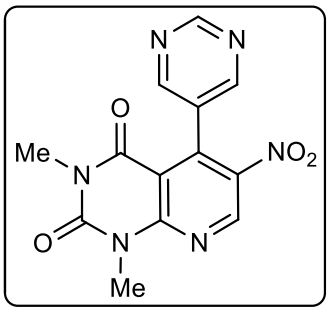
Identification code	ag336	
Empirical formula	$C_{20}H_{16}N_4O_3$	
Formula weight	360.37	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Triclinic, P^1	
Unit cell dimensions	a = 5.8619 (2) Å	α = 73.883 (2)°
	b = 11.6586 (3) Å	β = 83.073 (1)°
	c = 12.9563 (4) Å	γ = 89.011 (1)°
Volume	844.32 (4) $Å^3$	
Z	2	
Calculated density	1.417 mg/m^3	
Absorption coefficient	0.10 mm^{-1}	
F(000)	376	
Crystal size	0.33 x 0.21 x 0.11 mm	
Θ range for data collection	5.6 to 64.9°	
Limiting indices:	-8≤h≤8, -17≤k≤17, -19≤l≤19	
Reflections collected / unique	28963/ 6092 [R(Int) = 0.0233]	
Completeness to Θ	29.7°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6092 / 0 / 246	
Goodness-of-fit on F^2	1.037	
Final R indices [I>2σ(I)]	R1 = 0.0573, wR2 = 0.1213	
R indices (all data)	R1 = 0.0424, wR2 = 0.1088	
Largest diff. peak and hole	0.452 and -0.277 e. $Å^{-3}$	

Crystal data and structure refinement for ***6.2.1l***



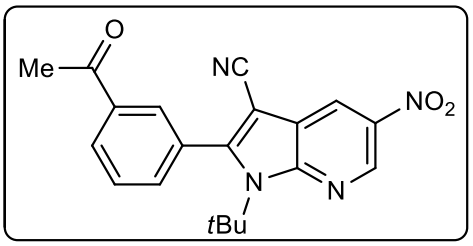
Identification code	ag242	
Empirical formula	$C_{19}H_{15}N_5O_2$	
Formula weight	345.36	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Triclinic, P^1	
Unit cell dimensions	a = 7.2260 (3) Å	α = 114.869 (2)°
	b = 10.7957 (5) Å	β = 104.592 (2)°
	c = 11.9938 (5) Å	γ = 90.707 (2)°
Volume	814.00 (6) $Å^3$	
Z	2	
Calculated density	1.409 mg/m^3	
Absorption coefficient	0.10 mm^{-1}	
F(000)	480	
Crystal size	0.38 x 0.15 x 0.10 mm	
Θ range for data collection	5.9 to 60.1°	
Limiting indices:	$-10\leq h\leq 10$, $-14\leq k\leq 15$, $-16\leq l\leq 16$	
Reflections collected / unique	4697 / 3808 [R(Int) = 0.0234]	
Completeness to Θ	27.10°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4697 / 0 / 237	
Goodness-of-fit on F^2	1.032	
Final R indices [I>2σ(I)]	R1 = 0.0556, wR2 = 0.1183	
R indices (all data)	R1 = 0.0428, wR2 = 0.1079	
Largest diff. peak and hole	0.367 and -0.238 e. $Å^{-3}$	

Crystal data and structure refinement for ***6.2.2d***



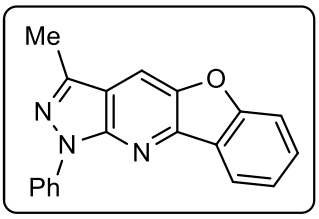
Identification code	ag345lf	
Empirical formula	$C_{13}H_{10}N_6O_4$	
Formula weight	314.27	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/c$	
Unit cell dimensions	a = 8.9906 (5) Å	α = 90°
	b = 9.5173 (5) Å	β = 99.095 (3)°
	c = 15.7437 (7) Å	γ = 90°
Volume	1330.19 (12) $Å^3$	
Z	4	
Calculated density	1.569 mg/m^3	
Absorption coefficient	0.12 mm^{-1}	
F(000)	648	
Crystal size	0.99 x 0.09 x 0.06 mm	
Θ range for data collection	4.6 to 49.4°	
Limiting indices:	$-11\leq h\leq 12$, $-12\leq k\leq 12$, $-21\leq l\leq 21$	
Reflections collected / unique	17814 / 3527 [R(Int) = 0.0555]	
Completeness to Θ	26.71°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3527 / 0 / 210	
Goodness-of-fit on F^2	1.061	
Final R indices [I>2σ(I)]	R1 = 0.0783, wR2 = 0.1273	
R indices (all data)	R1 = 0.0479, wR2 = 0.1106	
Largest diff. peak and hole	0.305 and -0.278 e. $Å^{-3}$	

Crystal data and structure refinement for ***6.2.3h***



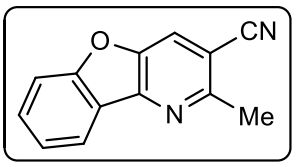
Identification code	Tg47	
Empirical formula	$C_{20}H_{18}N_4O_3$	
Formula weight	362.38	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/n$	
Unit cell dimensions	a = 8.3921 (5) Å	α = 90°
	b = 10.6133 (7) Å	β = 91.414 (3)°
	c = 19.9941 (13) Å	γ = 90°
Volume	1780.3 (2) $Å^3$	
Z	4	
Calculated density	1.352 mg/m^3	
Absorption coefficient	0.09 mm^{-1}	
F(000)	760	
Crystal size	0.34 x 0.24 x 0.10 mm	
Θ range for data collection	4.9 to 59.9°	
Limiting indices:	$-11 \leq h \leq 11$, $-14 \leq k \leq 14$, $-28 \leq l \leq 28$	
Reflections collected / unique	25064 / 5171 [R(Int) = 0.0533]	
Completeness to Θ	27.96°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5171 / 0 / 248	
Goodness-of-fit on F^2	1.040	
Final R indices [I>2σ(I)]	R1 = 0.0861, wR2 = 0.1251	
R indices (all data)	R1 = 0.0487, wR2 = 0.1083	
Largest diff. peak and hole	0.291 and -0.213 e. $Å^{-3}$	

Crystal data and structure refinement for ***6.2.4b***



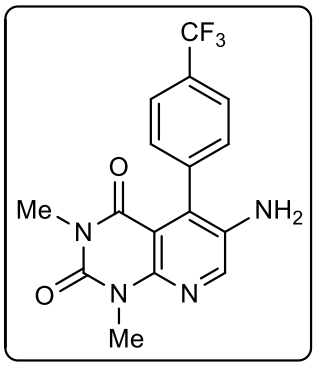
Identification code	ag596	
Empirical formula	$C_{19}H_{13}N_3O$	
Formula weight	299.32	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/c$	
Unit cell dimensions	a = 5.1753 (3) Å	α = 90°
	b = 22.4997 (15) Å	β = 99.267 (4)°
	c = 12.3015 (8) Å	γ = 90°
Volume	1413.72 (16) $Å^3$	
Z	4	
Calculated density	1.406 mg/m^3	
Absorption coefficient	0.09 mm^{-1}	
F(000)	624	
Crystal size	0.28 x 0.21 x 0.03 mm	
Θ range for data collection	2.5 to 23.7°	
Limiting indices:	-6≤h≤6, -30≤k≤29, -16≤l≤16	
Reflections collected / unique	17157 / 3558 [R(Int) = 0.0486]	
Completeness to Θ	26.59°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3558 / 0 / 209	
Goodness-of-fit on F^2	1.061	
Final R indices [I>2σ(I)]	R1 = 0.0896, wR2 = 0.1296	
R indices (all data)	R1 = 0.0494, wR2 = 0.1115	
Largest diff. peak and hole	0.222 and -0.329 e. $Å^{-3}$	

Crystal data and structure refinement for ***6.2.4d***



Identification code	Ag614ff	
Empirical formula	$C_{13}H_8N_2O$	
Formula weight	208.21	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/c$	
Unit cell dimensions	a = 12.4241 (4) Å	α = 90°
	b = 6.5008 (2) Å	β = 115.559 (2)°
	c = 13.3572 (4) Å	γ = 90°
Volume	973.24 (5) $Å^3$	
Z	4	
Calculated density	1.421 mg/m^3	
Absorption coefficient	0.09 mm^{-1}	
F(000)	432	
Crystal size	0.71 x 0.35 x 0.09 mm	
Θ range for data collection	6.3 to 62.0°	
Limiting indices:	-18≤h≤15, -9≤k≤9, -19≤l≤16	
Reflections collected / unique	14843 / 3084 [R(Int) = 0.0393]	
Completeness to Θ	29.17°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3084 / 0 / 146	
Goodness-of-fit on F^2	1.025	
Final R indices [I>2σ(I)]	R1 = 0.0520, wR2 = 0.1206	
R indices (all data)	R1 = 0.0424, wR2 = 0.1125	
Largest diff. peak and hole	0.442 and -0.242 e. $Å^{-3}$	

Crystal data and structure refinement for ***6.3.1c***



Identification code	Ag581lf	
Empirical formula	$C_{16}H_{13}F_3N_4O_2.C_2H_6OS$	
Formula weight	428.43	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Triclinic, P_1	
Unit cell dimensions	a = 8.7505 (3) Å	α = 68.601 (2)°
	b = 10.1118 (4) Å	β = 81.680 (2)°
	c = 12.5661 (5) Å	γ = 67.008 (2)°
Volume	953.00 (6) $Å^3$	
Z	2	
Calculated density	1.493 mg/m^3	
Absorption coefficient	0.23 mm^{-1}	
F(000)	444	
Crystal size	0.29 x 0.23 x 0.12 mm	
Θ range for data collection	4.7 to 63.0°	
Limiting indices:	-10≤h≤11, -13≤k≤13, -16≤l≤17	
Reflections collected / unique	27069 / 5046 [R(Int) = 0.0509]	
Completeness to Θ	27.26°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5046 / 22 / 357	
Goodness-of-fit on F^2	1.034	
Final R indices [I>2σ(I)]	R1 = 0.0734, wR2 = 0.1445	
R indices (all data)	R1 = 0.0513, wR2 = 0.1277	
Largest diff. peak and hole	0.515 and -0.496 e. $Å^{-3}$	

List of Abbreviations

Ar, Ar^1, Ar^2 etc - Aryl group

ArH - Arene

AIBN - Azobisisobutyronitrile

Ac - Acetyl group

aq. - Aqueous

acac - Acetylacetonate

Alk - Alkyl group

ATR - Attenuated total reflection (IR)

BINOL - 1,1'-Bi-2-naphthol

BINAP - 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl

BINEPINE - 4,5-Dihydro-3*H*-dinaphtho[2,1-*c*;1',2'-*e*]phosphepine

BINAM - 1,1′-Binaphthyl-2,2′-diamine

BQ - 1,4-Benzoquinone

Bz - Benzoyl group

Bpin - Pinacol boronic ester

br - Broad (NMR)

Cy - Cyclohexyl group

cod - 1,5-Cyclooctadiene

CMD - Concerted metalation-deprotonation

$CDCl_3$ - Deuterated chloroform

calcd - Calculated (HRMS)

CI - Chemical ionization (MS)

DavePhos - 2-Dicyclohexylphosphino-2′-(N,N-dimethylamino)biphenyl

DCM - Dichloromethane

DMF - N,N-Dimethylformamide

DME - 1,2-Dimethoxyethane

DMA - N,N-Dimethylacetamide

DMSO - Dimethyl sulfoxide

DMSO-d_6 - Deuterated dimethyl sulfoxide

dppp - 1,3-Bis(diphenylphosphino)propane

dppf - 1,1′-Bis(diphenylphosphino)ferrocene

dppe - 1,2-Bis(diphenylphosphino)ethane

dppm - 1,1-Bis(diphenylphosphino)methane

DIOP - 2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane

DPEPhos - Bis[(2-diphenylphosphino)phenyl]ether

DG - Directing group

DFT - Density functional theory

d - Doublet (NMR)

dd - Doublet of doublets (NMR)

dt - Double of triplet (NMR)

EWG - Electron withdrawing group

EDG - Electron donating group

Et - Ethyl group

Et_2O - Diethyl ether

equiv. - Equivalent

EI - Electron ionization (HRMS)

ESI - Electrospray ionization (HRMS)

eV - Electron-volt

FG - Functional group

GBH reaction - Gomberg-Bachmann-Hey reaction

GC - Gas chromatography

GC-MS - Gas chromatography-mass spectrometry

g - gram

Hal - Halogen

h - Hours

hν - Light irradiation (photon energy)

HFIP - Hexafluoroisopropanol

HRMS - High resolution mass spectrometry

Hz - Hertz

(Het)Ar - (Hetero)arene

***i*Pr** - Isopropyl group

IR - Infrared spectroscopy

J - Coupling constant

LG - Leaving group

L_n - Ligand

MOP - 2-(Diphenylphosphino)-2′-methoxy-1,1′-binaphthyl

MePhos - 2-Methyl-2′-dicyclohexylphosphinobiphenyl

M - Metal or metalorganic functionality

M - Molar solution

MTES - N-Methyl-N,N,N-triethylammonium methylsulfate

min - Minutes

Me - Methyl group

MX_n - Salt of metal

Ms (OMs) - Methanesulfonyl group (mesylate)

MS - Mass spectrometry

m - *Meta* position

m - Multiplet (NMR)

m - Medium intensity (IR)

MeOH - Methanol

MeCN - Acetonitrile

Mp - Melting point

MHz - Megaherz

m/z - Mass to charge ratio

mL - Milliliter

NOBIN - 2-Amino-2'-hydroxy-1,1'-binaphthyl

***n*Bu or Bu** - Butyl group

NMP - N-Methyl-2-pyrrolidone

NMR - Nuclear magnetic resonance

Nu - Nucleophile

o - *Ortho* position

Pr - Propyl group

Py - Pyridine

Ph - Phenyl group

PivOH - Pivalic acid (dimethylpropanoic acid)

Piv - Pivaloyl group

p - *Para* position

ppm - Parts per million (NMR)

q - Quartet (NMR)

R, R^1, R^2 etc - Functional group

SPhos - 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl

s - Strong intensity (IR)

s - Singlet (NMR)

TM - Transition metal

TFA - Trifluoroacetic acid

T - Temperature

THF - Tetrahydrofuran

TMS - Trimethylsilyl group

TMSCl - Trimethylsilyl chloride

TCP - 1,2,3-Trichloropropane

Tf (OTf) - Trifluoromethanesulfonyl group (triflate)

Ts (OTs) - *p*-Toluenesulfonyl group (tosylate)

TEA - Triethylamine

***t*Bu** - *Tert*-butyl group

TBAF - Tetra-*n*-butylammonium fluoride

Tol - *p*-Tolyl group

TLC - Thin layer chromatography

t - Triplet (NMR)

td - Triple doublet (NMR)

tt - Triple triplet (NMR)

ttt - Triple triple triplet (NMR)

XPhos - 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

w - Week intensity (IR)

XantPhos - 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

δ - Chemical shift (NMR)

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Curriculum Vitae

Personal data

	Ashot Gevorgyan.
Address	Albert-Einstein-Str. 29, Zi. 2.02.05.1, 18059, Rostock.
Nationality	Armenian.
Date and place of birth	11.10.1989, Nor Yerznka, Armenia.
Gender	Male.
Marital status	Married.
Email	ashotchem@gmail.com, ashotpharm@gmail.com.

Education

10.2012-up today	PhD in Organic Chemistry, Institute of Chemistry, University of Rostock, Germany (supported by DAAD).
09.2006-06.2011	Diploma in Pharmaceutical Chemistry, Yerevan State University, Armenia. Thesis: "*Chromones and Substituted Enaminones as Versatile Precursors for the Regioselective Synthesis of Purin-like Compounds*". **Grade Point: 5 (excellent)**. Qualified as Chemist-Pharmaceutist, Provisor's in the Field of "Pharmaceutical Chemistry".
01.10.2009-31.03.2010 01.10.2010-31.03.2011	Research Work at University of Rostock, Germany (supported by DAAD).
09.1996-07.2006	Secondary School of Nor Yerznka, Armenia. **Grade Point: 5 (excellent)**.
Language skills	Armenian (mother tongue), Russian (good), English (good), German (basic knowledge).

List of publication

13. "*Synthesis of 4-quinolones, benzopyran derivatives and other fused systems based on the domino ANRORC reactions of (ortho-fluoro)-3-benzoylchromones*", V. O. Iaroshenko,* S. Mkrtchyan, **A. Gevorgyan**, T. Grigoryan, A. Villinger, P. Langer,* *RSC Adv.* **2015**, *5*, 28717-28724.

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