Conversion of Pyridine *N*-Oxides to Tetrazolopyridines and Palladium-Catalyzed Regiocontrolled C–H/C–H Cross Coupling of Pyridine *N*-Oxides and Pyrroles

Inaugural-Dissertation

to obtain the academic degree

Doctor rerum naturalium (Dr. rer. nat.)

submitted to the Department of Biology, Chemistry and Pharmacy of

Freie Universität Berlin

by

M.Sc. Shanshan Liu

from Henan, PR China

Berlin, 2016

Supervisor: Prof. Dr. C. C. Tzschucke

Second examiner: Prof. Dr. C. A. Schalley

Defense on the 16th February 2016

Contents

Acknowledgements

I would like to express my greatest appreciation to my PhD supervisor, Prof. Dr. C. Christoph Tzschucke for offering me a valuable opportunity to study in Berlin and his patient guidance during my PhD research period. My thanks go to my second reviewer Prof. Dr. Christoph A. Schalley for his efforts on my thesis. I would like to thank the China Scholarship Council (CSC) for giving me the financial support to finish my PhD project.

My thanks goes to the entire AG Tzschucke group for the help and the fun in and outside of the lab, Dr. Ralf Albrecht, Dr. Michal Andrä, Dr. Sasa Duric, Dr. Swantje Wiebalck, Dr. Fanni Sypaseuth, Emma Svensson, Anja Sokolowski, Sina Zucker, and Stefan Hentschel. Thanks to Fanni for the help in the initial phase of my PhD. I am very grateful to Ralf for his patient sharing his idears, useful suggestions and supports during the work in the lab. My thanks go to Emma and Stefan for their proofreading and help to improve the quality of my thesis.

I wold like to thank Dr. Andreas Springer and Thomas Kolrep for sharing their ideas on the MS analysis. I thank Dr. Andreas Schäfer for the NMR measurement. My thanks go to the whole NMR and MS department for their excellent work and ever ready support. I thank Prof. Dr. Lentz and Dr. Manuela Weber for the crystal structure analysis.

Thanks to Mazdak Asadian Birjand for the collaboration work in the OC lab course, thanks for the nice atmosphere. I also thank Dr. Lehmann, I learned a lot from the OC lab course.

I thank my Chinese friends in Berlin for the great time being together and the mutual support during the last years. Changzhu Wu, Xuejiao Zhang, Fang Du, Yiming Cao, Shengyi Dong, Wei Chen, Zhenhui Qi, Ning Liu, Nan Zhang, Chunhui Li, Yanyan Shen, Bo Zheng, and Lingyan Gao: we exchange idears both in life and research, you made my life in Berlin more colorful.

My deppest gratitude to my family, especially to my parents for their endless love and understanding. Thanks for coming to visite me last summer and always preparing different delicious foods. That is the most exciting time when I look back.

My most gratitude goes to my husband Lin-Yu, we shared the good time and went through bad moment together. I hope we can have a reunion soon.

Abbreviations

δ	Chemical Shift
Δ	Reflux Temperature
Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
BOM	Benzyloxymethyl
Bpy	Bipyridine
BQ	1,4-Benzoquinone
Br	Broad
br s	Broad Singlet
Bu	Butyl
n-Bu	*n*-Butyl
t-Bu	*t*-Butyl
Bz	Benzoyl
calcd.	Calculated
cat	Catylst
CDC	Cross Dehydrogenative-Coupling
CMD	Concerted Metallation/Deprotonation
CO	Carbon Monoxide
COD	1,5-Cyclooctadien

conc.	Concentrated
Cy	Cyclohexane
d	Doublet
dd	Double Doublet
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DFT	Density Functional Theory
DG	Directing Group
DIPEA	Diisopropylethylamine
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DMSO-d_6	Deuterated Dimethylsulfoxide
DPPA	Diphenylphosphoryl Azide
DPPB	1,4-Bis(diphenylphosphino)butane
DPPf	1,1'-Bis(diphenylphosphino)ferrocene
DPPP	1,3-Bis(diphenylphosphino)propane
EI	Electron Ionization
equiv	Equivalent
ESI	Electrospray Ionisation

GC-MS	Gas Chromatography-Mass Spectrometry
Het	Heteroatom
HFIP	Hexafluorisopropanol
HR	High Resolution
IR	Infrared Spectroscopy
J	NMR-Coupling Constant
KIE	Kinetic Isotope Effect
Lit.	Literature
LiTMP	Lithium Tetramethylpiperidide
m	Molar, Multiplet, or Medium
M	mol/L
m-	*meta*-
Me	Methyl
m.p.	Melting Point
MS	Mass Spectrometry
MW	Microwave
m/z	Mass/Charge
Nf-F	Nonafluorobutanesulfonyl Fluoride
NIS	*N*-Iodosuccinimide
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
o-	*ortho*-

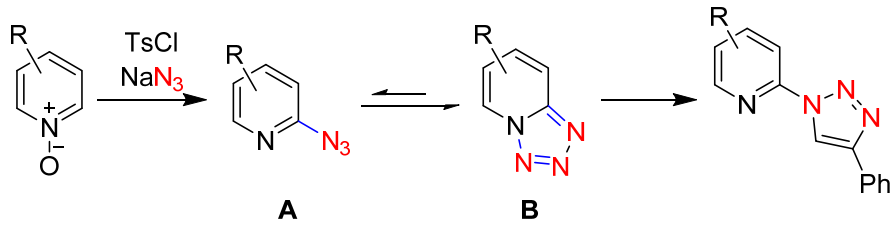
p-	*para*-
[Pd]	Palladium Complex
PG	Protecting Group
Ph	Phenyl
PhDave-Phos	2-Diphenylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl
Phen	Phenanthroline
pKa	Acid Dissociation Constant
PMB	4-Methoxybenzyl
ppm	Parts Per Million
i-Pr	*iso*-Oropyl
Py	Pyridine
q	Quartet
R	Organic Substituent
RT	Room Temperature
s	Singlet or Strong
t	Time or Triplet
TBAB	Tetra-*n*-Butylammonium Bromide
TBAF	Tetra-*n*-Butylammonium Fluoride
TBHP	*tert*-Butylhydroperoxid
TBTA	Tris(benzyltriazolylmethyl)amine
Temp	Temperature
tert-	Tertiary

Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TOF	Time-of-flight
TOSMIC	Toluenesulfonylmethyl Isocyanide
Ts	4-Toluenesulfonyl
UV	Ultraviolet
vw	Very Weak
w	Weak
X	Halogen or Triflate or Boron
XPhos	2-Dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl

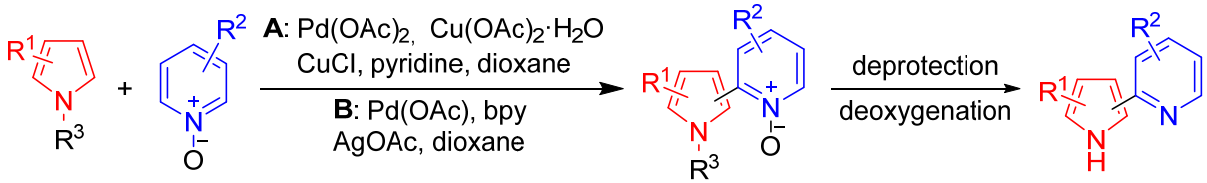
Abstract in English

This thesis describes two methodologies for the C–H bond functionalization of pyridine *N*-oxides. Deoxygenative nucleophilic substitution of the azide to pyridine *N*-oxides construct the corresponding tetrazolopyridines with a new C–N bond. Palladium-catalyzed oxidative cross coupling of pyridine *N*-oxides with pyrroles to accomplish a C–C bond formation.

The azides was introduced to the pyridine ring starting from pyridine *N*-oxides by one step through treatment with tosyl chloride and sodium azide in toluene at 120 °C, the resulting tetrazolopyridines were obtained in 17–99% yields with a variety of functional group tolerance. The tetrazole and azide equilibrium was observed in NMR spectrum and the ratio of this equilibrium changed in different deuterated solvents. The tosyl chloride and sodium azide are stable, inexpensive and widely commercialy available. Moreover, the terazolopyridines were used as synthetic intermediates to convert into pyridyl triazoles by copper-catalyzed click reaction.



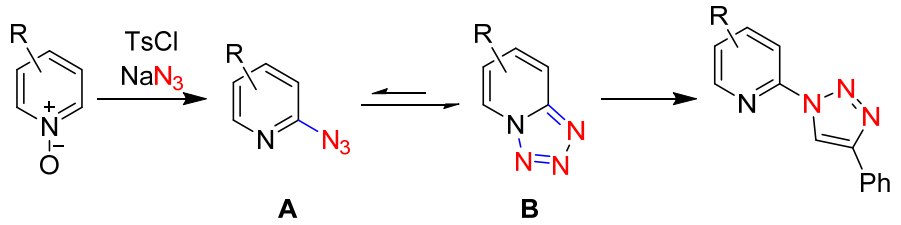
Palladium-catalyzed two fold C–H bonds cross coupling of pyrrole derivatives with a variety of pyridine oxides was demonstrated to prepare pyridylpyrroles. The method was feasable for sensitive pyrroles. The regioselectivity was controlled by the variation of different reaction conditions. The catalytic amount of oxidant and co-catalyst copper salt in the aerobic condition gave the desired C3 selective product in good to excellent yield, whereas the C2 selectivity was controlled by using bipyridine and silver salt. A broad substrate scope was tolerated by this methodology. The reported method combined the subsequent hydrogenation to realize deprotection and deoxygenation in one step and thereby efficiently construct pyridylpyrrol compounds.



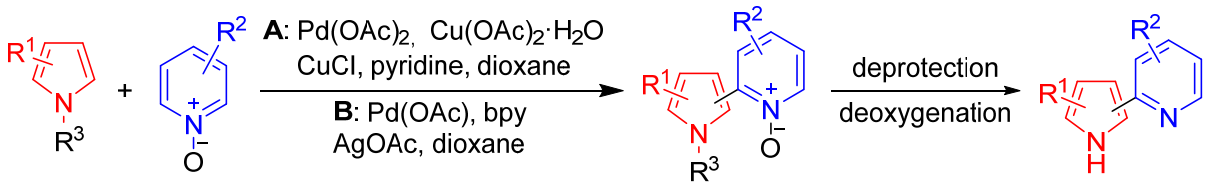
Abstract in German

In der vorliegenden Arbeit werden zwei Methoden der C–H-Funktionalisierung von Pyridin-*N*-oxiden beschrieben. Synthese von Tetrazolpyridinen, mit neuer C–N-Bindung, mittels desoxygentiver nukleophiler Addition eines Azids an Pyridin-*N*-oxide sowie palladium-katalysierte oxidative Kreuzkupplung von Pyridin-*N*-oxiden mit Pyrrolen unter Bildung einer neuen C–C-Bindung.

Die Einführung des Azids in die Pyridin-*N*-oxide erfolgte mittels einer einstufigen Reaktion mit Tosylchlorid und Natriumazid in Toluol bei 120 °C, die gebildeten Tetrazolpyridine mit verschiedenen funktionellen Gruppen wurden in 17–99% Ausbeute erhalten. Das Tetrazol-Azid-Gleichgewicht wurde mit NMR-Spektroskopie beobachtet, die Lage des Gleichgewichts war abhängig vom verwendeten deuterierten Lösemittel. Tosylchlorid und Natriumazid sind stabile, kostengünstige und kommerziell verfügbare Chemikalien. Darüber hinaus wurden die Tetrazolpyridine als Ausgangsmaterialien für die Synthese von Triazolpyridinen mittels kupfer-katalysierter Click-Reaktion eingesetzt.



Es konnte gezeigt werden, dass Pyridylpyrrole mittels palladiumkatalysierter oxidativer Kreuzkupplung von Pyrrolderivaten mit verschiedenen Pyridin-*N*-oxiden synthetisiert werden können. Diese Methode eignet sich auch für empfindliche Pyrrole. Die Regioselektivität wurde durch die Variation der Reaktionsbedingungen kontrolliert. Katalytische Mengen Oxidationsmittel und Kupfersalz als Kokatalysator unter aeroben Bedingungen ergaben gute bis ausgezeichnete Ausbeuten an C3-Produkt, während das C2-Produkt durch Beigabe von Bipyridin und Silbersalz erhalten wurde. Eine Vielzahl verschiedener Substrate konnte mit dieser Methode umgesetzt werden. Die beschriebene Methode vereint die anschließende Entschützung mittels Hydrierung und die Desoxygenierung in einem Schritt und stellt eine effektive Methode für die Synthese von pyridylpyrrolen dar.



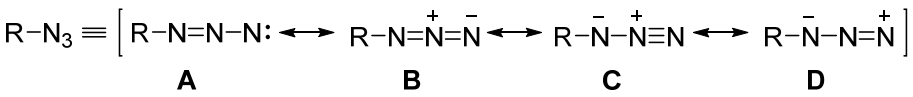
1 Chapter I:

Conversion of Pyridine *N*-Oxides to Tetrazolopyridines

1.1 Introduction

1.1.1 Aromatic Azides

Since the discovery of phenyl azide by Peter Grieß in 1864, these energy-rich and flexible intermediates have enjoyed a lot of interest.[1] The azide functional group can be described by several mesomeric structures. Aromatic azides are stabilized by conjugation with the aromatic system. The dipolar structures **C** and **D** (Scheme 1) account for the facile decomposition into the corresponding nitrene and dinitrogen as well as the reactivity as a 1,3-dipole. The mesomeric structure **D** explains the regioselectivity of their reactions with electrophiles and nucleophiles. Because of their relatively high stability, aryl azides have been used as biological and industrial photoaffinity labels,[2] as cross-linkers in photoresistors.[3] They can be used for conducting polymers[4] and light-induced activation of polymersurfaces.[5] They are valuable intermediates in organic chemistry for their participation in the "click reaction" and in Staudinger ligation, as well as precursors for nitrenes.

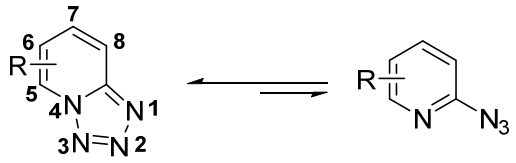


Scheme 1: The mesomeric structure of azides.

1.1.2 Tetrazolopyridines

1.1.2.1 Equilibrium of Tetrazole-Azide Systems

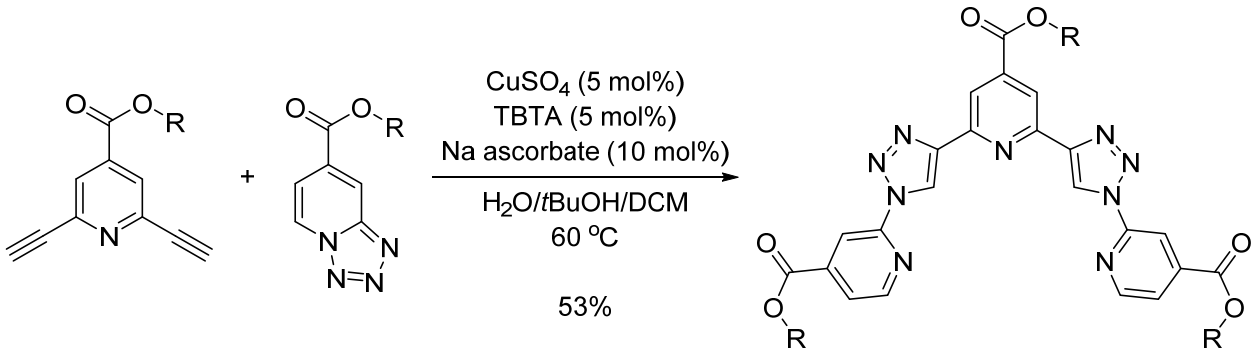
Nitrogen containing heterocyclic azides such as pyrido- and quinolino azides exist in equilibrium with the corresponding tetrazole. In most instances, the tetrazole is the predominant species present (Scheme 2). Wang compared the stability of the azide and its isomeric tetrazole by using the density functional theory (DFT) method.[6] They found the tetrazole ring has high aromaticity which implies an increase in the stability by the isomerization from an azide to a tetrazole. The effect of substituents, solvent and temperature on the equilibrium was investigated. The result showed (i) the electron-donating methyl group enhances the stability of the tetrazole form, but the electron-withdrawing bromo substituent favors the azido isomer.[7] (ii) The tetrazole form is favored in DMSO rather than in $CDCl_3$.[7-8] (iii) The azide-to-tetrazole isomerizations are exothermic. Simple sublimation usually causes significant ring opening of tetrazoles to azides.[9]



Scheme 2: Equilibrium of tetrazolopyridine and pyridoazide.

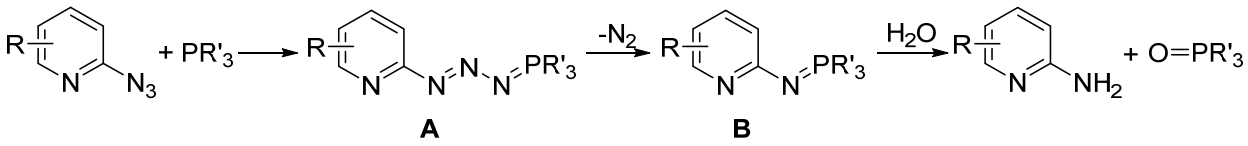
1.1.2.2 The Reaction of Tetrazolopyridines

Tetrazolopyridines are important synthetic intermediates. They can be converted into triazoles *via* copper-catalyzed azide–alkyne cycloaddition (CuAAC, Scheme 3).



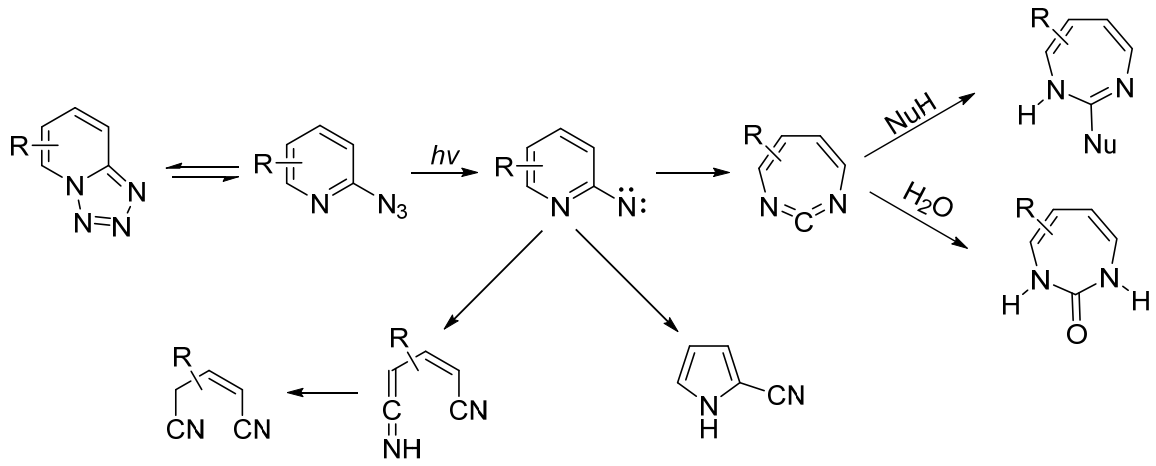
Scheme 3: Azides–alkyne-cycloaddition reaction.[10]

Azides can be reduced to amines by the Staudinger reaction (Scheme 4).[11] This reaction involves the formation of a phosphazide intermediate **A** by nucleophilic attack of the phosphorus atom at the terminal nitrogen atom of the organoazide, which immediately loses a nitrogen to form an iminophosphorane **B**, in the end, **B** is hydrolyzed to form a primary amine.



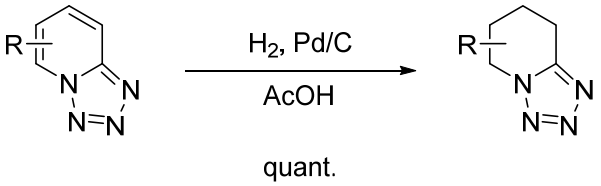
Scheme 4: The Staudinger reduction.

The thermal or photochemical decomposition of pyridine azides has well investigated by the Wentrup group to give pyridyl nitrenes, which undergo easily ring contraction to 2-cyanopyrrole and ring expansion to 1,3-diazepines in the presence of the appropriate nucleophile (Scheme 5).[12] In some cases, ketenimines and glutacononitriles are believed to be formed *via* the cleavage of the C–N bond in the 2-pyridylnitrenes to ring-opened, transient cyanovinylnitrenes, a H-shift then generates ketenimines, which tautomerize to the glutacononitriles at elevated temperature.[8a]



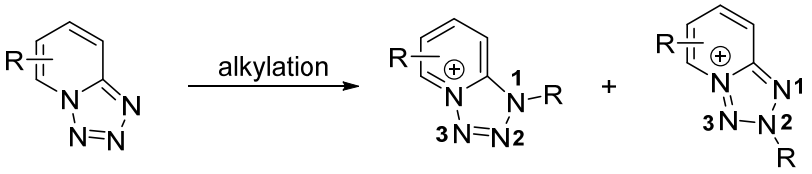
Scheme 5: Nitrene–nitrene rearrangement.[12],[8a]

One untypical reaction for tetrazolopyridines was catalytic hydrogenation to give aliphatic tetrazoles in nearly quantitative yield (Scheme 6).[13]

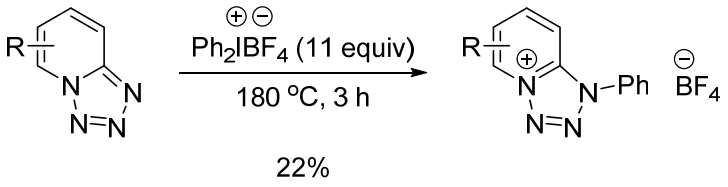


Scheme 6: Reduction of pyridotetrazole.

Alkylation[14] of tetrazolopyridine by methyl iodide, dimethyl sulfate, trimethyloxonium, and triethyloxonium salts give mixtures of 1- and 2-alkyl compounds in different ratios preferably to 1-methyl compound. While arylation[15] of the tetrazole affords only 1-aryltetrazolium salts in the presence of diphenyliodonium fluoroborate (Scheme 7).



Ratio (1-alkyl product/products)	Me_2SO_4	MeI	$Me_3O^+[BF_4]^-$	$Et_3O^+[BF_4]^-$
	85	96	86	75



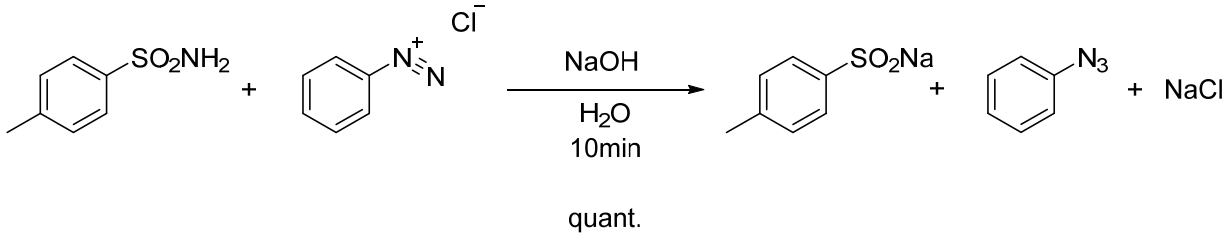
Scheme 7: Alkylation and arylation of tetrazolopyridines.

1.1.3 Synthetic Methods

1.1.3.1 Synthesis of Aryl Azides

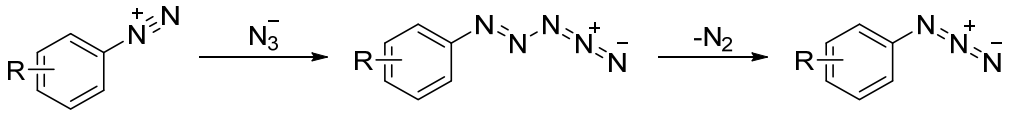
1.1.3.1.1 Synthesis of Aryl Azides from Diazonium Salts

Due to its importance, a variety of synthetic approaches have been developed for this transformation. Dutt and co-workers reported the synthesis of aryl azide by reaction of *p*-toluenesulphonamide and benzenediazonium chloride (Scheme 8).[16]



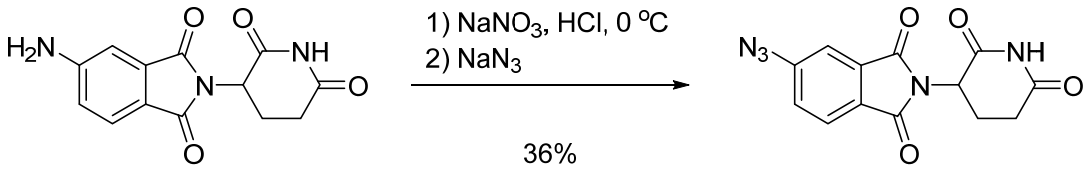
Scheme 8: Synthesis of aryl azide by diazonium salt and sulfonamide.[16]

A convenient method for synthesis of aryl azides is the reaction of diazonium salts with azide ions. Alkali azides or trimethylsilyl azide serves as azide source. Unlike the Sandmeyer reaction, this reaction does not take place with the cleavage of the C–heteroatom bond but occurs with the attack of the azide on the diazonium ion to the formation of aryl pentazene (Scheme 9). The corresponding azides are obtained at low reaction temperature with a loss of dinitrogen.



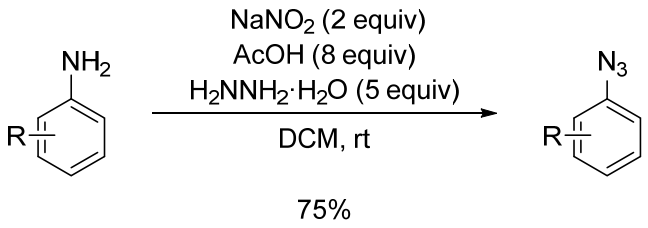
Scheme 9: Mechanism of the conversion of diazonium ions into azides.[17]

The Brown group illustrated the synthesis of azidothalidomide from diazonium salts (Scheme 10). Diazotization of the amino group and the subsequent reaction with sodium azide gave the final product.[18]



Scheme10: Synthesis of azido-thalidomide.[18]

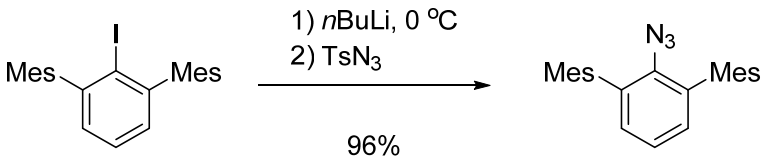
A modified method was reported using sodium nitrite and hydrazine hydrate to form azide ion in situ, then it reacted with diazonium salts which were generated from the sodium nitrite and aniline to give aryl azides (Scheme 11). Short reaction time and simple work-up procedure are advantages of this method.[19]



Scheme 11: Aniline converted into azide using sodium nitrite and hydrazine hydrate.[19]

1.1.3.1.2 Sythesis of Aryl Azides from Organometallic Compounds

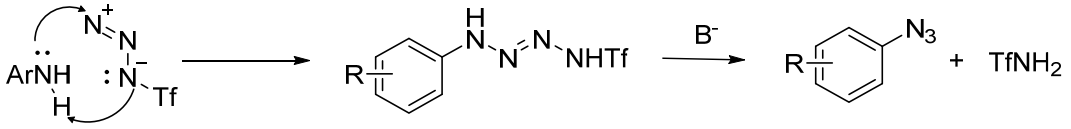
In the last decades, the preparation of aryl azides from organometallic reagents have been significantly developed. For example, tosyl azide reacts with Grignard or lithium reagent (Scheme 12). The limitations of this transformation are that many functional groups are incompatible with Grignard reagents or lithium reagent, such as acid, hydroxy, amino, carbonyl, carbamoyl, and ester group.[20]



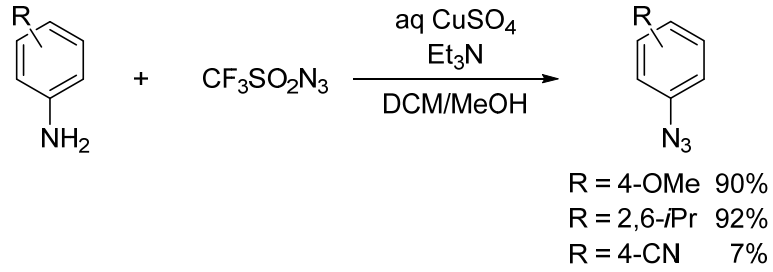
Scheme 12: Aryl azides from organometallic reagents.[20]

1.1.3.1.3 Synthesis of Aryl Azides by Azo-Transfer Reaction

Heteroaryl azides can also be prepared by the azo transfer reaction. The reaction may involve the formation of an intermediate triazene anion which may decompose to give the observed products (Scheme 13). Electron rich anilines gave very high yields in these transformations, electron poor anilines such as 4-cyano aniline are weakly nucleophilic and react sluggishly (Scheme 14).[21]



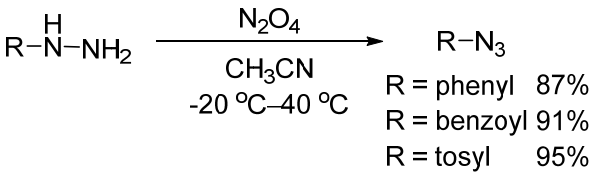
Scheme 13: The mechanism of the azo-transfer reaction.



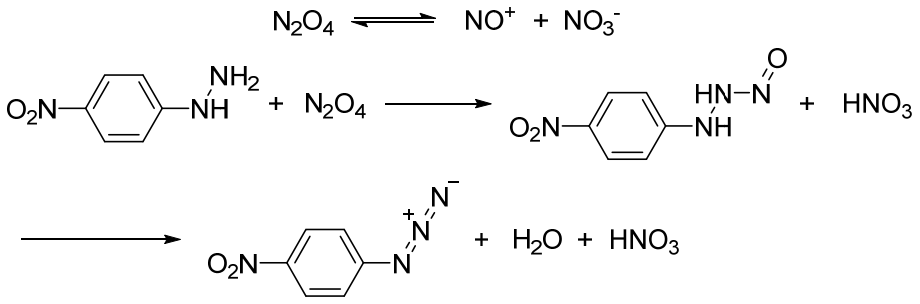
Scheme 14: Conversion of aromatic amine into aryl azide by azo-transfer reaction.[21]

1.1.3.1.4 Synthesis of Aryl Azides by Diazotization of Hydrazines

Dinitrogen tetroxide is a good nitrosation reagent for activating hydrazines convert into numerous azide compounds such as aromatic azides, acyl azides, and sulfonyl azides (Scheme 15).[22] The electrophilic attack of nitrosyl ions on the nitrogen atom of the amine affords the corresponding β-nitroso hydrazine intermediate which may finally convert into the azides. However, the higly toxic hydrazines and harsh reaction conditions limited the general use of this transformation (Scheme 16).



Scheme 15: Conversion of the aromatic hydrazine into aryl azide.[22]

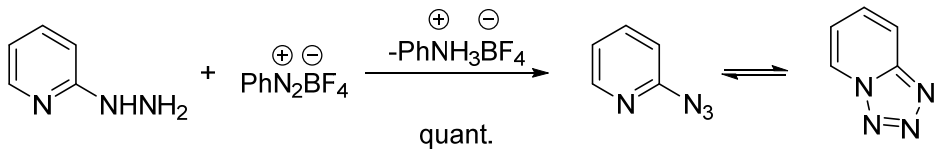


Scheme 16: Mechanism of the diazotization of hydrazines.

1.1.3.2 Synthesis of Tetrazolopyridine

1.1.3.2.1 Synthesis of Tetrazolopyridine by Aza-Transfer Reaction

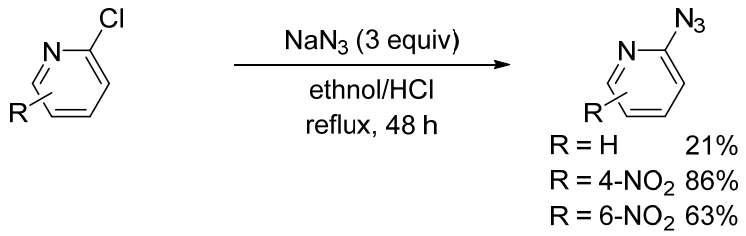
In 1976, Fipicer-Smolnika and co-workers first presented an aza transfer reaction between heterocyclic hydrazino compounds and benzenediazonium tetrafluoroborate. The reation proceeded in methanol at room temperature for 5–10 minutes and underwent a nitrogen atom transfer from benzenediazonium salt to the pyridine hydrazino compound to give either a pyridine azide compound or tetrazolopyridine in almost quantitative yield (Scheme 17).[23]



Scheme 17: Aza-transfer reaction.

1.1.3.2.2 Synthesis of Tetrazolopyridine by Nucleophilic Aromatic Substitution

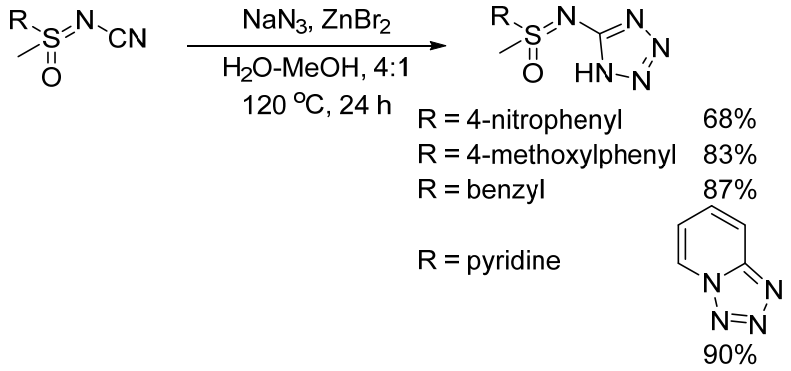
Although the conversion of diazonium salts into aryl azides represents one of the most efficient methods, the need of preparation of the diazonium salts is a limitation. Much effort has been focused on mild and efficient synthetic routes. For example, nucleophilic substitution of azide ions to the aryl halides generates the corresponding azides by NaN_3, $TMSN_3$, or hydrazoic acid (Scheme 18).[8b, 24] [25]. However, only electron deficient arenes are allowed in this mothod.[8b]



Scheme 18: Nucleophilic aromatic substitution to give aryl azide.[8b]

However, the preparation of the starting materials need additional synthetic steps, such as halogenation of the corresponding pyridone[26] or direct halogenation of the pyridine ring.[27] Preparation from pyridine *N*-oxide, however, often proceeds with poor 2-, or 4- regioselectivity and low yield.[28]

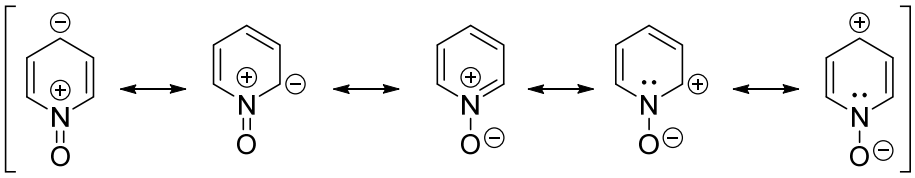
In 2007, Bolm et, al. reported a method for the synthesis of *N*-(1*H*)-tetrazole sulfoximines from sulfoximines in the presence of $ZnBr_2$ and NaN_3 (Scheme 19). Interestingly, only 2-pyridyl sulfoximine did not give the tetrazole sulfoximine, but tetrazolopyridine was obtained by the displacement of the sulfoximidoyl group at the pyridine core with NaN_3 in 90% yield.[29]



Scheme 19: Synthesis of tetrazolopyridine from sulfoximine.[29]

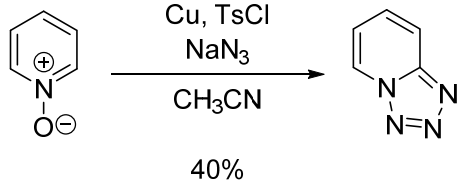
1.1.3.2.3 Synthesis of Tetrazolopyridine by Modified Reissert–Henze Method.

A more direct approach would start from pyridine *N*-oxides, by using pyridine *N*-oxides to activate the aromatic ring, thereby allowing both nucleophilic and electrophilic attack due to the σ-electron-withdrawing and π-back-donating character of the *N*-oxide moiety. Nucleophilic substitutions typically occur at the 2- or 4-positions of pyridine *N*-oxides based on the nature of the nucleophile (Scheme 20).



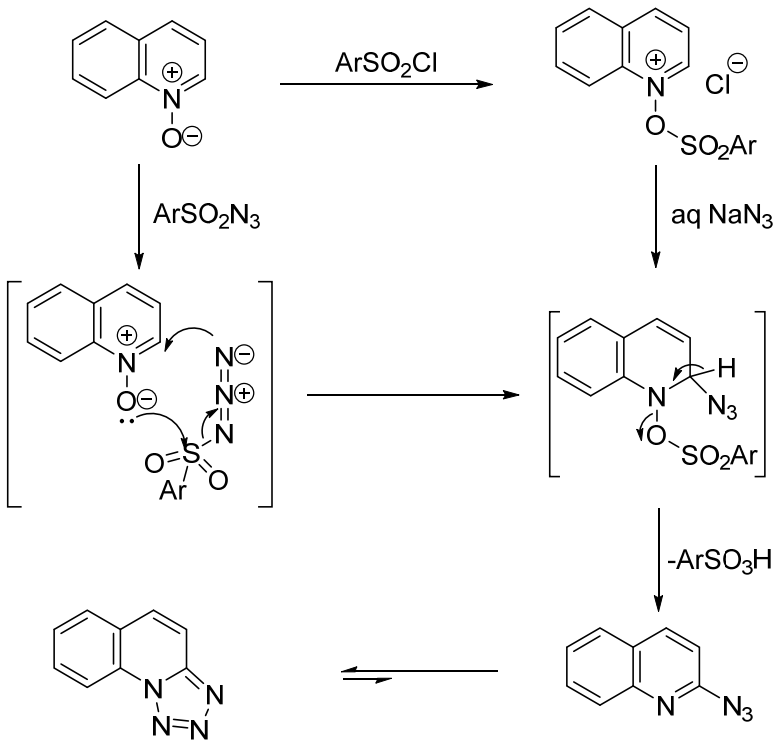
Scheme 20: Electronic properties of pyridine *N*-oxides.

Reddy and co-workers reported an addition of arylsulfonyl azides to pyridine *N*-oxides in the early 1980s (Scheme 21). The reaction proceeded smoothly by heating the reactants in acetonitrile with a catalytic amount of copper powder, gave the tetrazolopyridine as the major product (40%).[30]



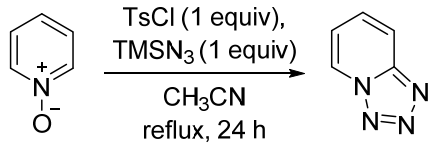
Scheme 21: Synthesis of tetrazolopyridines from pyridine *N*-oxide.[30]

Quinoline *N*-oxide was employed for mechanistic investigation, the oxygen atom of *N*-oxide attacked the tosyl azide with concomitant nucleophilic substitution of the azide on the α-position of the heterocycle to deliver a Reissert-type intermediate (Scheme 22). A spontaneously elimination of arylsulfonic acid resulted in the α-azido compound, which could isomerize readily to the tetrazole form. In order to clarify the mechanism, a quinolinium salt was allowed to react with sodium azide, the tetrazoloquinoline was afforded in moderate yields (45%), indicating that the Reissert-type intermediate was formed in the reaction.



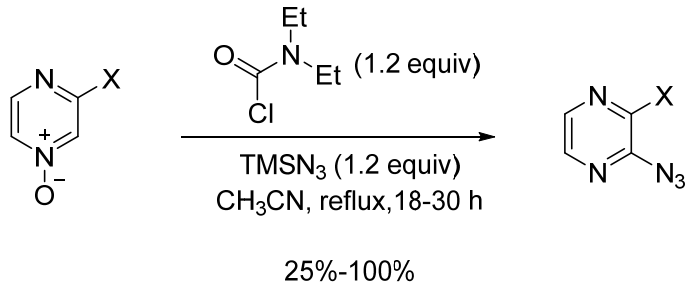
Scheme 22: The mechanism of synthesis of tetrazoloquinoline.[30]

A modified method was illustrated by the variation of the activating reagent or nucleophiles. The Nishiyama group[31] reported that the treatment of pyridine *N*-oxide with TsCl and $TMSN_3$, leading to the tetrazolopyridine in 29% yield (Scheme 23). $TMSN_3$ was proved to be a better choice than NaN_3, which only yielded target product in 5% yield.[30] Likewise, the general method for synthesis of azidopyrazine was presented by using trimethylsilyl azide in conjunction with diethylcarbamoyl chloride in refluxing acetonitrile (Scheme 24).[32]



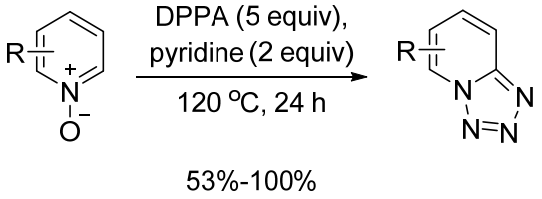
29%

Scheme 23: Synthesis of pyridine *N*-oxide.[31]



Scheme 24: Synthesis of pyrazine *N*-oxides.[32]

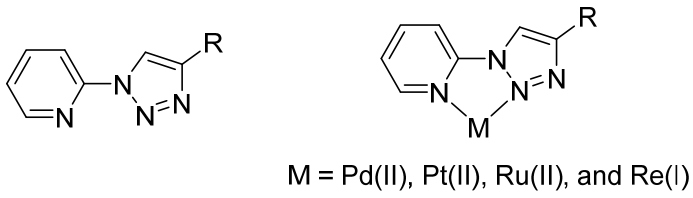
In 2006, Keith and co-workers revisited the scope of the reaction by exploring the efficiency of various activating groups (sulfonyl, sulfuryl, phosphonyl, and phosphoryl halides) (Scheme 25). They found that the use of diphenylphosphoryl azide (DPPA) as both activating agent and azide source gave a quantitative yield of the product. The reaction was easily scaled up without significant decreased in yield.[33]



Scheme 25: Deoxidative azidation of pyridine *N*-oxides by DPPA.

1.1.4 1-(2-Pyridyl)-1,2,3-triazoles

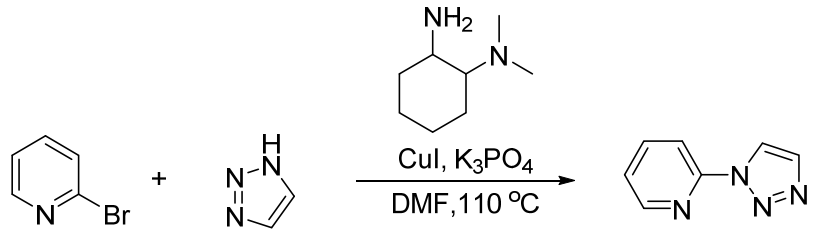
As an isomer of the 4-(2-pyridyl)-1,2,3-triazole moiety, 1-(2-pyridyl)-1,2,3-triazole is much less common due to its complicated synthesis procedure, there are only few related reports about its application in coordination complexes (Scheme 26).[34] [34a] [34b] [35]



Scheme 26: 1-(2-Pyridyl)-1,2,3-triazoles and their metal complexes.

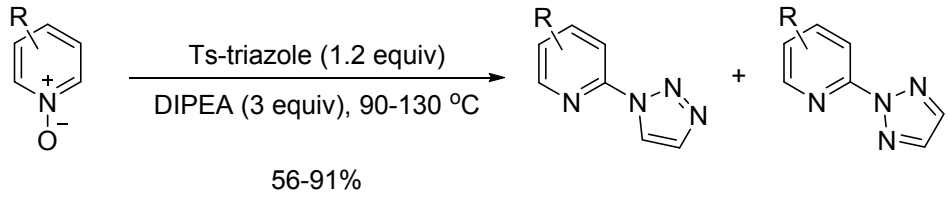
1.1.4.1 Synthesis of 1-(2-Pyridyl)-1,2,3-triazoles

Because of the high biological importance of pyridyl- and quinolinyl-containing triazoles, there are some synthetic reports about 1-(2-pyridyl)-1,2,3-triazoles, they can be prepared by base-promoted substitution between 1,2,3-triazole and 2-halopyridine (Scheme 27).[36]



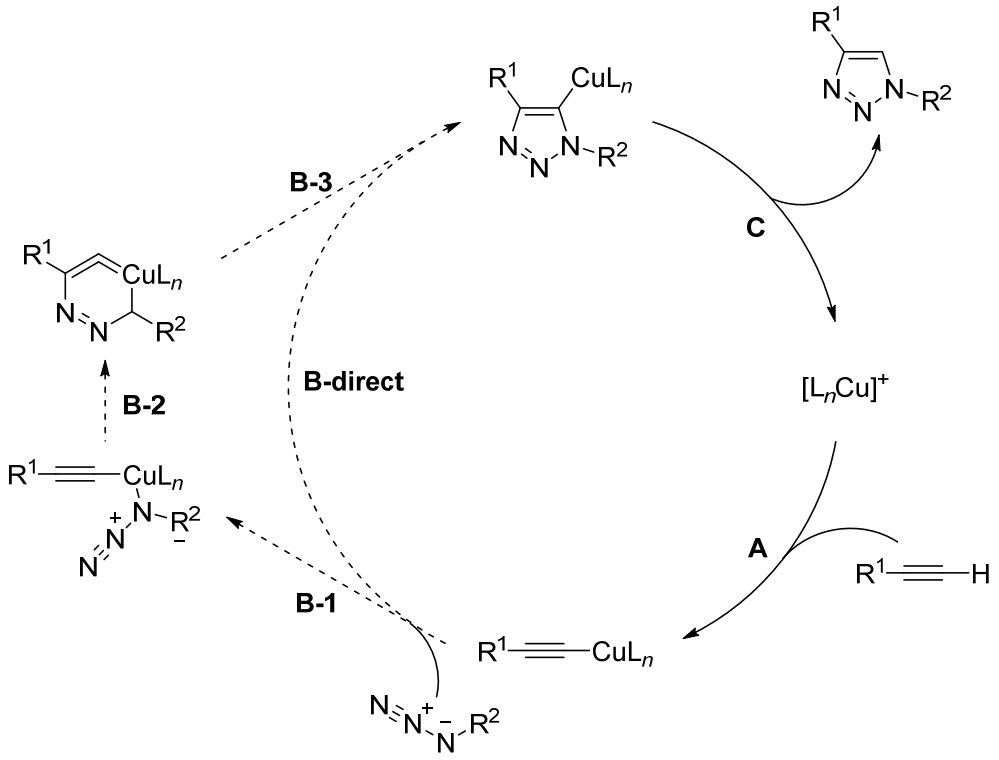
Scheme 27: Base-promoted substitution between 1,2,3-triazole and 2-halopyridine.

In 2010, the Keith group described a method for the conversion of pyridine *N*-oxides into the α-triazole by treatment with the corresponding *p*-toluenesulfonylazoles and Hunig's base at elevated temperature (Scheme 28). The desired 1-arylated product was obtained in good yield with small amount of 2-arylated byproduct.[37]



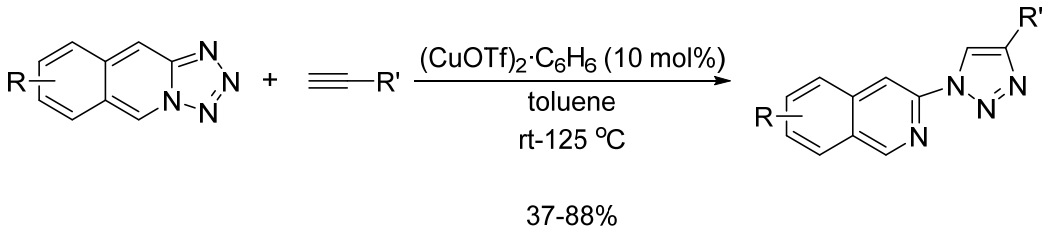
Scheme 28: Synthsis triazoles from pyridine *N*-oxides.[37]

A breakthrough in triazole chemistry was made by the groups of Meldal[38] and Sharpless[39] that the reaction of copper(I)-catalyzed 1,3-dipolar cycloaddition of azides and terminal alkynes (Scheme 29).[40] These reactions are considered as a contribution to the current "click chemistry" because they are biocompatible[41] and performing particularly well in aqueous media and carried out very efficiently with high regioselectivity. However, only a few examples for successful click reaction of pyridyl azides were reported. There are some reasons for this phenomenon: (a) the predominant tetrazole form would be unreactive; (b) the pyridine in the key intermediate may coordinate with Cu(I) to form a complex, which will lead to difficult reduction elimination (step **C**); (c) the product may also coordinate with Cu(I) to shut down the catalytic cycle.



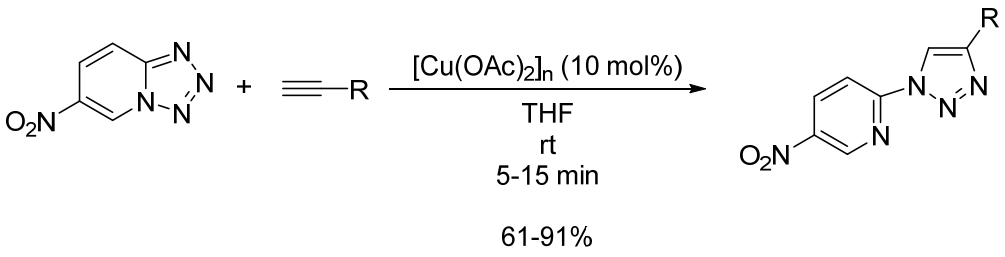
Scheme 29: Proposed catalytic cycle for the copper(I)-catalyzed cycloaddition of azides and terminal alkynes.[40]

Gevorgyan et, al. developed a method which allows for the efficient synthesis of 1,2,3-triazoles from fused tetrazoles through $(CuOTf)_2 \cdot C_6H_6$-catalyzed click reaction with alkynes (Scheme 30).[24]



Scheme 30: Click reaction for the synthesis of triazoles catalyzed by $(CuOTf)_2 \cdot C_6H_6$.[24]

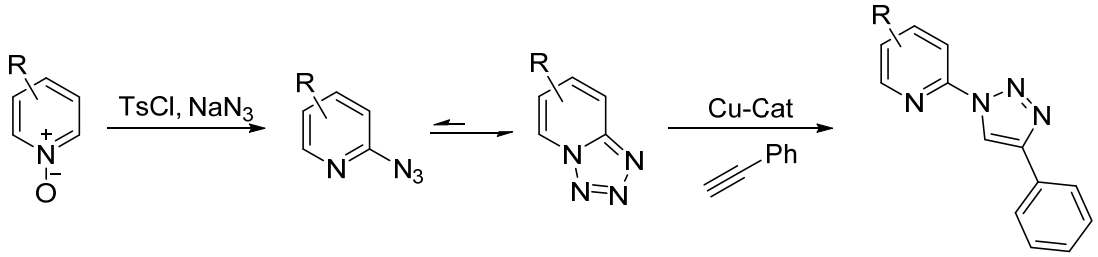
Based on this, Hu and Wang reported another efficient azide–alkyne cycloaddition to prepare 1-(pyridin-2-yl)-1,2,3-triazoles by using simply copper(II) acetate as catalyst (Scheme 31). The in situ formed HOAc played important dual roles for efficient protonation of the key intermediate 5-cupuric 1,2,3-triazole and prevention of the product coordination to copper(I).[42]



Scheme 31: Copper(II) acetate-catalyzed azide–alkyne cycloaddition.[42]

1.2 Motivation

Tetrazolopyridines are versatile synthetic intermediates of high interest. Based on the previous synthetic methods, synthesis of tetrazolopyridines from diazonium compounds need additional synthetic steps to prepare diazonium salts. Only electron deficient arenes are allowed to access tetrazolopyridines by nucleophilic aromatic substitution. Conversion of pyridine *N*-oxides into tetrazolopyridines suffers from either low yields or expensive activating reagent. It is nessary to reexamine the reaction and optimize the conditions. The aim of this work is effective conversion of pyridine *N*-oxides to tetrazolopyridines by treatment with a combination of sodium azides as a stable, nonvolatile source of azide and tosyl chloride as a cost-efficient activating agent. Organic azides are important components in click chemistry, we are wondering if we could employ relative inert tetrazole as an intermediate to synthesis triazoles by copper-catalyzed alkyne–azide cycloaddition (Scheme 32).



Scheme 32: Preparation of tetrazolopyridine and 1-(pyridin-2-yl)-1,2,3-triazoles.

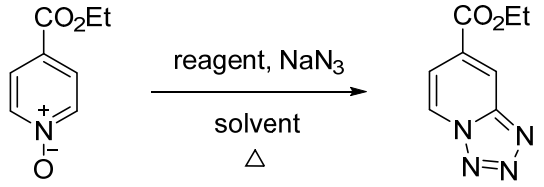
1.3 Results and Discussion

1.3.1 Synthesis of Tetrazolopyridines

1.3.1.1 Optimization of the Reaction Conditions

The initial attempt of treatment 4-ethoxycarbonyl pyridine *N*-oxide with 2 equivalents of sodium azide and tosyl chloride in MeCN at 120 °C for 24 h gave the desired product in 53% yield (Table 1, entry 1). The yield could be slightly increased by extending the reaction time to 48 h (entry 3) and elevating the reaction temperature (entry 4), whereas increasing the amount of sodium azide and tosyl chloride to 5 equivalents had much more pronounced effect (entry 5). This observation led us to believe that the decomposition of the reagents might be the reason for the incomplete conversion of starting material. However, heating tosylchloride with sodium azide afforded TsN_3 prior to the addition of *N*-oxide decreased the product yield (entry 6) as did batchwise addition of the reagents (entry 8). Heating tosylchloride with the *N*-oxide prior to the addition of sodium azide activated the pyridine *N*-oxides by increase the electrophility (entry 7), which decreased the product yield as well. Lowering the concentration did not affect the result (entry 9). We briefly compared other activators of the reaction. Thus, methanesulfonyl chloride and propyl phosphonic anhydride (T_3P) gave the product albeit in lower yield while Nf-F (nonafluorobutanesulfonyl fluoride) and P_2O_5 (phosphorus pentoxide) were ineffective (entries 13–19). The influence of solvent was investigated as well. Since acetonitrile had to be heated significantly above its atmospheric boiling point in a closed vessel in order to reach the reaction temperature of 120 °C, we switched to toluene as a higher boiling point solvent. Indeed, this change improved the yield markedly (entry 11). Among the other solvents investigated, pyridine gave only low yields (entries 22 and 23), whereas no product was formed in polar solvent such as DMSO or DMF (entries 20 and 21). The yield was not impoved in the presence of phase transfer catalyst such as TBAB (tetrabutylammonium bromide) (entry 23).

Table 1: Screening of reaction conditions.[a]



1a **2a**

Entry	Reagent	Additive	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	TsCl	–	MeCN	120	24	53
2	TsCl	TBAB, DIPEA	MeCN	120	24	–
3	TsCl	–	MeCN	120	48	64
4	TsCl	–	MeCN	80	48	55
5	TsCl	–	MeCN	120	48	82[c]
6	TsCl	–	MeCN	120	48	42[d]
7	TsCl	–	MeCN	120	48	51[e]
8	TsCl	–	MeCN	120	48	61[f]
9	TsCl	–	MeCN	120	48	65[g]
10	TsCl	–	toluene	120	48	80
11	**TsCl**	**–**	**toluene**	**120**	**48**	**96[c]**
12	TsCl	–	toluene	120	48	50[h]
13	MsCl	–	toluene	120	48	55
14	T_3P	–	toluene	120	48	16
15	P_2O_5	–	toluene	120	48	–
16	Nf-F	–	toluene	80	48	–
17	Nf-F	–	toluene	120	48	–
18	Nf-F	–	DCE	80	48	–
19	Nf-F	–	DCE	120	48	–
20	TsCl	–	DMSO	120	24	–
21	TsCl	–	DMF	120	48	–
22	TsCl	–	pyridine	120	24	39
23	TsCl	TBAB	pyridine	120	24	27

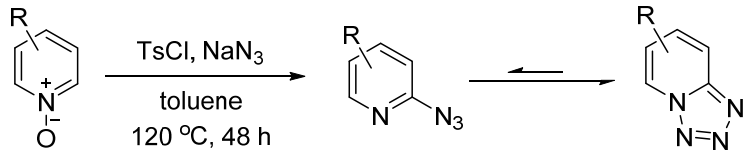
[a] All reactions ran on a 0.60 mmol scale relative to *N*-oxides, 3.0 equiv TsCl, and 3.0 equiv NaN_3 in solvent (0.30 M in substrate). [b] Isolated yield were reported. [c] 5.0 Equiv TsCl and 5.0 equiv NaN_3 were used. [d] Heating *N*-oxide and TsCl to 80 °C for 1 h followed by the addition of NaN_3 and heating to 120 °C for 48 h. [e] Heating NaN_3 and TsCl to 80 °C for 1 h followed by the addition of *N*-oxide and heating to120 °C for 48 h. [f] 5.0 Equiv TsCl and 5.0 equiv NaN_3 were added in batches. [g] Reaction ran in 5.0 mL MeCN (0.12 M in *N*-oxide). [h] 2.0 Equiv TsCl and 2.0 equiv NaN_3 were used.

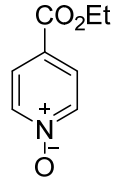
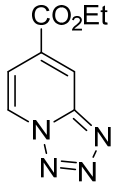
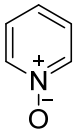
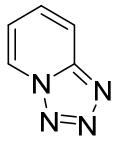
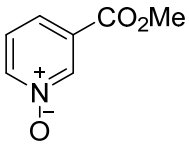
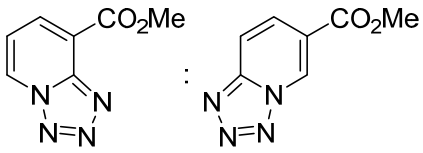
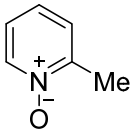
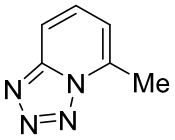
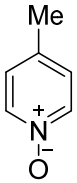
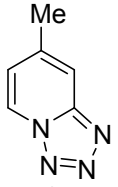
1.3.2 Substrate Scope

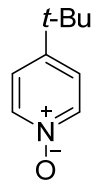
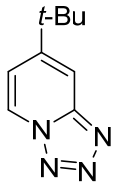
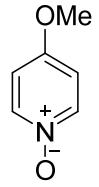
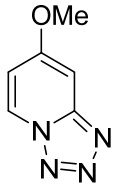
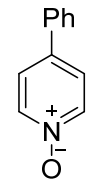
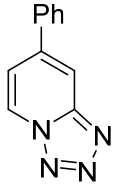
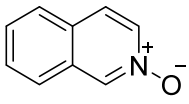
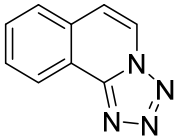
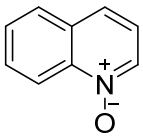
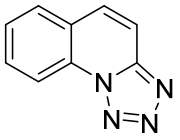
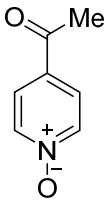
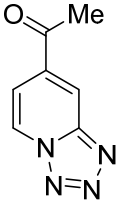
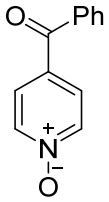
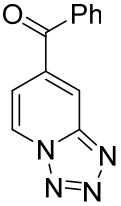
To probe the scope of the reaction, we applied the optimized conditions to a variety of pyridine *N*-oxides (Table 2). Pyridine *N*-oxides with no substituent, electron-withdrawing carbonyl substitutents or with a more electron-donating *tert*-butyl or phenyl substituent all gave very good yields of the corresponding tetrazolo[1,5-*a*]-pyridines (entries 1, 3, 4, 7, 9, 12, and 13). When the reaction was scaled up to 6 mmol of *N*-oxide **1a**, product **2a** was obtained in 91% yield, demonstrating its utility on a preparative scale. Functional groups like cyano or fluoride were tolerated under the standard reaction conditions. Cyano substituted *N*-oxides as well as quinoline *N*-oxide or isoquinoline *N*-oxide gave the product in moderate yields (entries 10, 11, 15, and 17).. In the case of isoquinoline *N*-oxide as expected only the regioisomer functionalized in the 1-position was formed as this did not disrupt the aromaticity of the annelated benzene ring (entry 10). Methyl or methoxy substituted pyridine *N*-oxides gave only relatively low yields, which might be related to the very hygroskopic nature of these compounds, they only led to a large extend decomposition of activating reagent (entries 5, 6, and 8). Bipyridine *N*-oxides, which are easily obtained by palladium-catalyzed direct arylation of pyridine *N*-oxides, were converted into the corresponding tetrazolopyridines in moderate yield, and small amounts of chlorinated side products were observed (entries 19–23). For these starting materials acetonitrile was the solvent of choice, whereas toluene led to lower yields or no reaction at all, possibly due to the limited solubility of the starting material in the latter solvent (entries 19, 20). When bipyridine *N*,*N*'-dioxide **1t** was used, the desired tetrazole product could not be obtained and only a small amount of product arising from nucleophilic attack of chloride was isolated (entry 24). The reaction proceeded with complete regioselectivity for the 2- and 6-positions adjacent to the pyridine-nitrogen. Thus, no reaction at the 4-position of the pyridine *N*-oxide was observed and 2,6-dimethylpyridine-*N*-oxide was unreactive as expected (entry 18). When 3-substituted pyridine *N*-oxides were used, both possible regioisomeric products were formed. In the case of the sterically less demanding cyano, methyl and fluoro substituent, the new C–N bond was formed preferentially in the 2-position, probably because the inductive effect of the substituent increased the electrophilicity and accelerated nucleophilic addition of the azide ion in this position (entries 14–16). In the case of the 3-methoxycarbonyl substituent, formation of the C–N bond in the

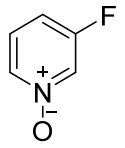
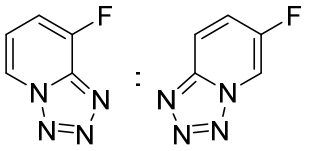
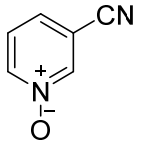
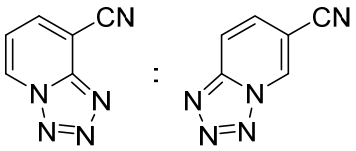
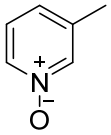
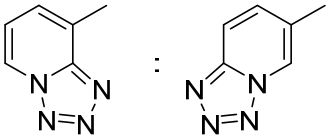
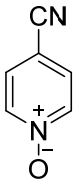
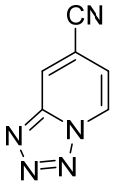
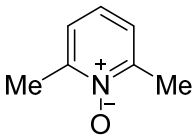
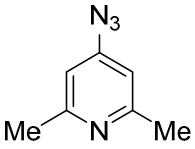
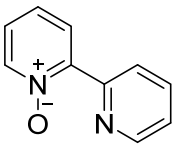
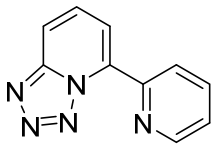
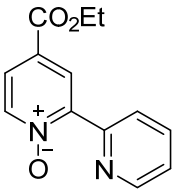
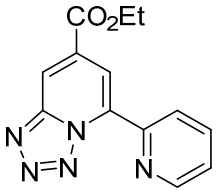
6-position was slightly favored, possibly as a result of the steric demand of the ester group competing with the electronic effect (entry 4).

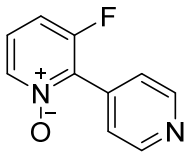
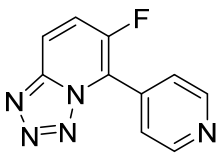
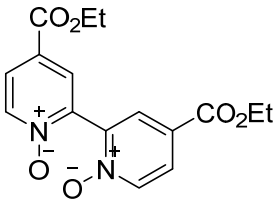
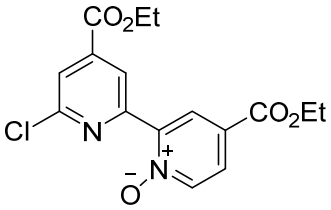
Table 2: Reaction scope with regard to pyridine *N*-oxides.[a]



Entry	*N*-Oxide	Product	Yield (%)[b]
1	 **1a**	 **2a**	96
2	**1a**	**2a**	91[c]
3	 **1b**	 **2b**	99 80[e]
4	 **1c**	 **2c** : **2c'** 39 : 52	91
5	 **1d**	 **2d**	42
6	 **1e**	 **2e**	21

7	 **1f**	 **2f**	87
8	 **1g**	 **2g**	17
9	 **1h**	 **2h**	92
10	 **1i**	 **2i**	65 (21)[f]
11	 **1j**	 **2j**	64
12	 **1k**	 **2k**	89
13	 **1l**	 **2l**	99

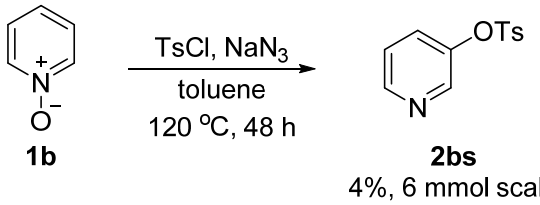
14	 **1m**	 **2m** : **2m'** 77 : 15	92[d]
15	 **1n**	 **2n** : **2n'** 37 : 13	50 (7)[f]
16	 **1u**	 **2u** : **2u'** 63 : 18	81
17	 **1o**	 **2o**	68
18	 **1p**	 **2p**	–
19	 **1q**	 **2q**	56
20	**1q**	**2q**	62 (in MeCN)
21	 **1r**	 **2r**	0

22	**1r**	**2r**	52 (in MeCN)
23	 **1s**	 **2s**	49 (in MeCN)
24	 **1t**	 **3t**	16

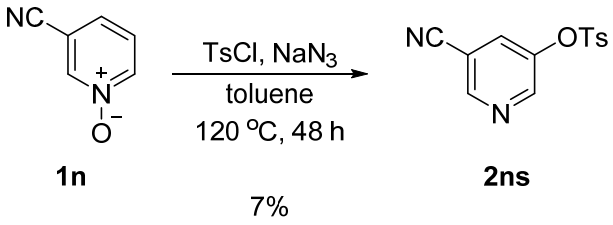
[a] Reaction conditions: TsCl (5.0 equiv), and NaN_3 (5.0 equiv) were added to a solution of 0.60 mmol of pyridine *N*-oxide in toluene (0.30 M in substrate) and heated to 120 °C for 48 h. [b] Isolated yields. [c] Isolated yield on 6.0 mmol scale. [d] Combined yield of inseparable isomers. [e] The reaction was conducted in 6 mmol scale. [f] 3-Tosylated side product.

Undesired tosylated byproducts were isolated in the reaction with unsubstitued pyridine *N*-oxide **1b**, 2-ethoxycarbonyl pyridine *N*-oxide **1x** and 3-cyano pyridine *N*-oxide **1n**. 3-Tosylated pyridine **2bs** was obtained in 4% yield when pyridine *N*-oxide **1b** was used as substrate (Scheme 33). 3-Cyano pyridine *N*-oxide **1n** gave 7% of 5-tosylated side product **2ns** (Scheme 34). The 2-Ethoxycarbonyl pyridine *N*-oxide **1x** afforded 8% of the isolated 6-toslyated product **2xs** and 11% of a mixture of 5-tosylated product and 2-ethoxycarbnoyl tetrazolopyridine with a ratio of 4:3. (Scheme 35). To investigate the formation of side product, a control experiment was conducted by using 2-ethoxycarbonyl pyridine *N*-oxide **1x** and tosyl chloride under the reaction conditions. However, no tosylated product was observed. Instead, 37% of 6-chlorinated product **2xp** was obtained, which might indicate that the need of NaN_3 for formation of the tosylated product (Scheme 35). The 2-tosylated product may be formed by nucleophilic attack of the tosylate anion at the C2 position of chloropyridine. The formation of 3-tosylate product is surprising. One possibility may involve an aryne intermediate, and subsequent the nucleophilic attack of the tosylate at the C3 position of pyridine to place the carboncation close to electronegative nitrogen. However, a strong base is needed to form the aryne, which makes this pathway unlikely (Scheme 36, top). The other possibility may involve tosyl group attacking at the oxygen atom of the pyridine

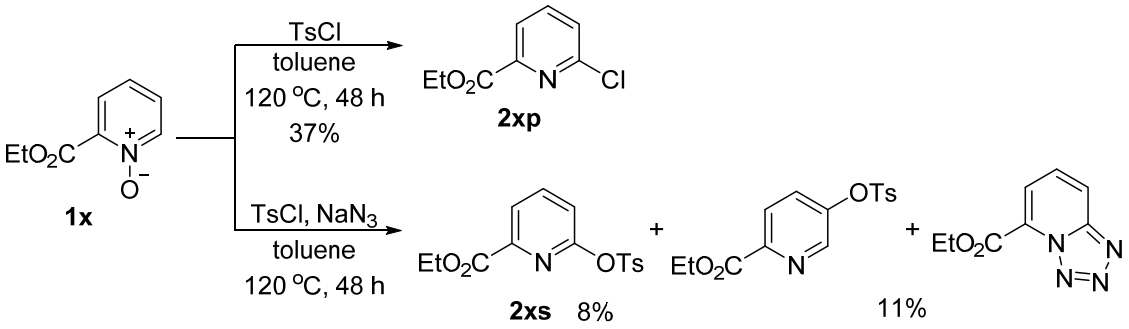
N-oxide to form a pyridinium, which undergoes electrophilic substitution at the C3 position of pyridine (Scheme 36, lower). However, the feasibility of this pathway is unknown.



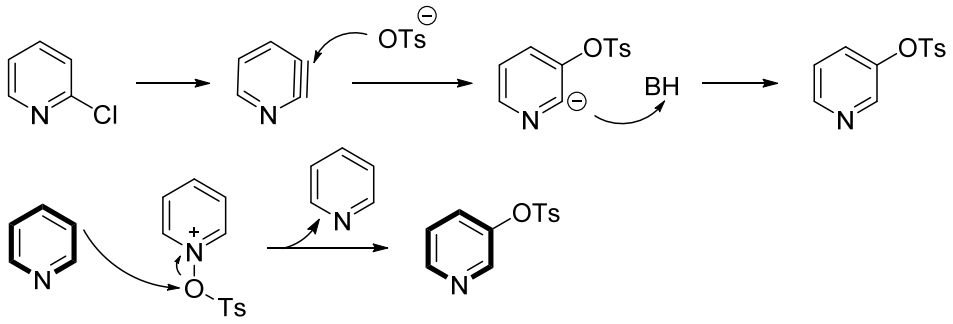
Scheme 33: Reaction of **1b** to form the corresponding side product **2bs**.



Scheme 34: Reaction of **1n** to the corresponding side product **2ns**.



Scheme 35: Control experiments for the formation of tosylated product.



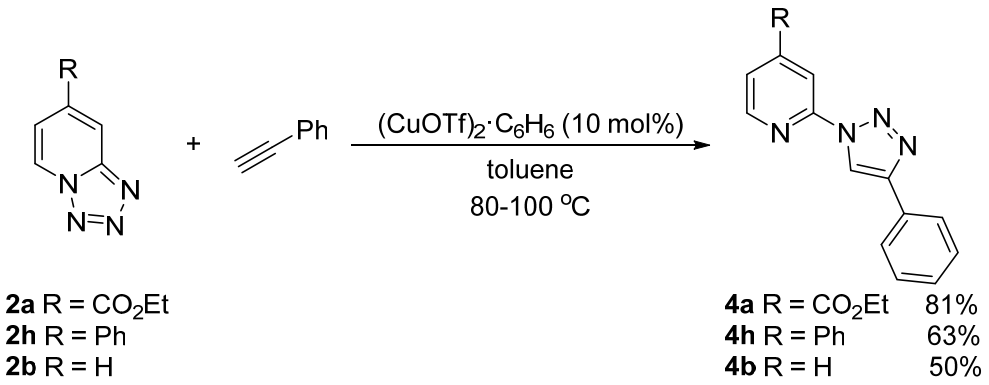
Scheme 36: Possible explanation for the formation of side products.

An equilibrium between the tetrazole and the azide form was observed only in the case of the nitrile **2n'**, **2n**, and the pyridyl substituted product **2r**. In $CDCl_3$ solution a ratio of tetrazole to azide

of 2:1 for **2n'** and of 6.2:1 for **2r**, respectively, was detected by ^{1}H NMR spectroscopy. Compound **2n** was measured in methylene-d_2 solution due to the solubility, a ratio of 17:1 of tetrazole and azide for **2n** was observed. In DMSO-d_6 only the tetrazole form was found for the above cases, which is in accordance with earlier observations by Wilson for similar compounds.[8b] These observations indicate that a polar solvent sometimes increases the stability of the condensed tetrazole or even promotes the cyclisation of the azide.

The structural of compound **2n** was determined by X-ray diffraction analysis (Figure S1 in experimental part). All atoms are essentially coplanar and the alternating bond lengths are in accordance with localized single or double bonds depicted by the Lewis-structure.

1.3.3 Synthesis of 1-(Pyridin-2-yl)-1,2,3-triazoles



Scheme 37: Synthesis of 1,2,3- pyridotriazoles from pyridotetrazoles.

We employed the tetrazolopyridine as click component in copper(II)-catalyzed 1,3-dipolar cycloaddition reaction to prepare 1,2,3-triazoles. However, the tetrazolopyridine did not undergo cycloaddition in the presence of 10 mol% CuI, 2 equiv Et_3N, and THF. Trace amounts of desired pyridotriazole were formed by using 5 mol% $CuSO_4 \cdot 5H_2O$, 5 mol% TBTA, 10 mol% NaAsc in H_2O/*t*BuOH/DCM at 60 °C. The tetrazolopyridine is inert under the typical conditions such as CuI/Et_3N and $CuSO_4 \cdot 5H_2O$/NaAsc due to the predominance of the unreactive closed pyridotetrazole form. In our hands, only $Cu(OTf)_2 \cdot C_6H_6$ as described by Gevorgyan and co-workers was a suitable catalyst for the cycloaddition reaction and we obtained the resulting pyridyltriazoles **4a**, **4b**, and **4h** in yields comparable to those reported for similar compounds. **4a**

exhibited high reactivity probably because the electron-withdrawing ester group favors the azide form more than other substrates (Scheme 37).[24]

1.4 Conclusion

Pyridine *N*-oxides were converted into the corresponding tetrazolopyridines in good yields by treatment with tosylchloride and sodium azide in toluene at elevated temperature. Both reagents used are stable, inexpensive, and widely available. No protective atmosphere or rigorously dried solvent was necessary, which adds to the convenience of the procedure. A draw-back common to our procedure and the published one is the use of a large excess of reagents, which necessitates column chromatography to purify the product. The utility of the tetrazole products as synthetic intermediates was demonstrated for the conversion to triazoles by copper-catalyzed alkyne–azide cycloaddition.

2 Palladium-Catalyzed Regiocontrolled C–H/C–H Cross Coupling of Pyrroles and Pyridine *N*-Oxides

2.1 Introduction

2.1.1 Palladium-Catalyzed oxidative Cross Coupling and C–H Bond Activation

2.1.1.1 Palladium-Catalyzed Dehydrogenative Cross Coupling Reactions

Dehydrogenative cross coupling of two unfunctionalized substrates is the most straightforward method for the C–C bond formation, which is not only the academic interest but also draws a lot of attention from industry due to the possibility of reducing the number of synthetic steps and the waste of reactions. This transformation requires a terminal oxidant and even can be performed under aerobic conditions. Various transition metals (Pd, Rh, Ru, Cu, and Fe) have shown to be effective for oxidative cross-coupling reactions. This chapter maily focuses on the palladium-catalyzed dehydrogenative cross coupling reactions (Scheme 38).

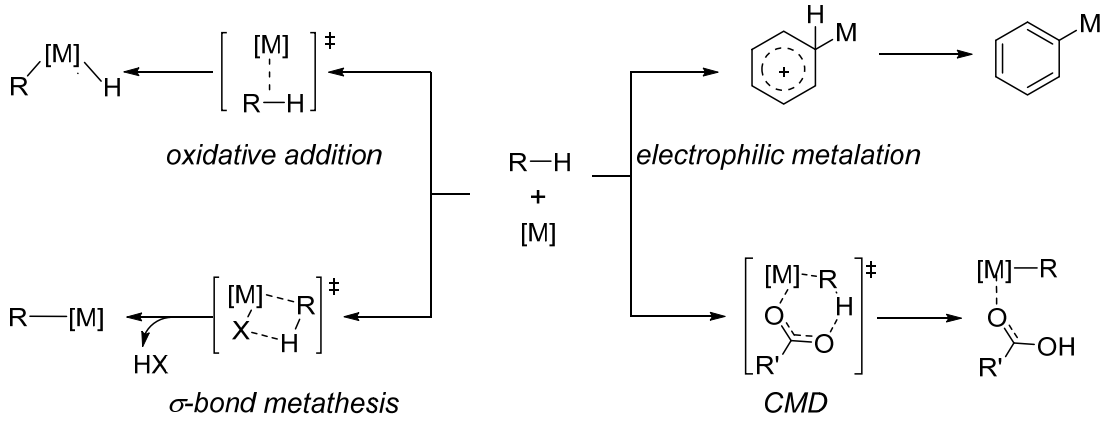
$$R^1\text{—}H + R^2\text{—}H \xrightarrow{[Pd]} R^1\text{—}R^2$$

Scheme 38: Palladium-catalyzed dehydrogenative cross coupling reactions.

2.1.1.2 Palladium-Catalyzed C–H Bond Activation

Different mechanisms are considered associated with C–H bond metalations,[43] such as oxidative addition, σ-bond metathesis, electrophilic activation, and concerted metalation/deprotonation (CMD) (Scheme 39). The oxidative addition pathway is always considered for electron-rich, low-valent, late transition metals such as Re, Fe, Ru, Os, Rh, Ir, and Pt. Oxidative addition of hydrocarbons proceeds *via* concerted pathways (Scheme 39, top left). Hydrocarbons direct coordinate to a metal ion to form a three-centered σ complex, followed by the C–H bond cleavage to form an oxidized complex. The resulting ligands will be mutually *cis*, although subsequent isomerization may occur. *σ*-Bond metathesis (Scheme 39. Left lower) is a

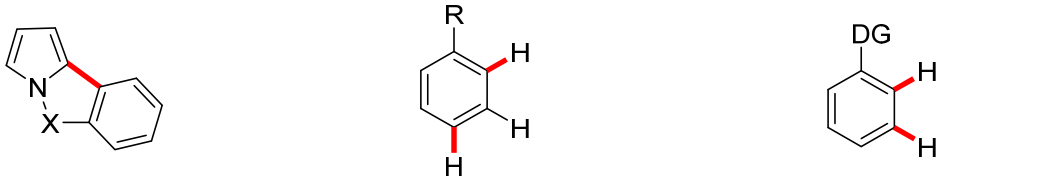
common reaction mechanism with early transition metals which have d^0 configuration, it involves a *σ*-complex intermediate and a four centered transition state, then the hydrogen atom is displayed by the metal. Electrophilic metalation occurs for late transition metals such as Pd^{2+}, Pt^{2+}/Pt^{4+}, Hg^{2+}, and Tl^{3+}, it involves a slow electrophilic attack of metal to arenes and a fast deprotonation to give a C–M bond (Scheme 39, upuer right). The CMD mechanism is proposed *via* a metalation and a concerted deprotonation promoted by the base such as carboxylates or carbonates (Scheme 39, lower right). Experimental and computational studies have provided strong evidence for various C–H bond metalations to proceed by concerted metalation deprotonation. For instance, palladium, iridium, ruthenium, or rhodium complexes are found to follow this reaction pathway. The regioselectivity depends on the acidity of the C–H bond that being cleaved. The reactivity shows complete reversion relative to the electrophilic metalation pathway with electron deficient arenes reacting preferentially.



Scheme 39: General mechanisms for the C–H bond metalation.

Regarding the palladium-catalyzed C–H bond activation in dehydrogenative cross coupling reactions, electrophilic metalation and concerted metalation deprotonation pathways have been most commonly proposed. Achieving regioselective activation of a certain C–H bond out of multiple C–H bonds remains a challenge. There are some factors used to control the regioselectivity (Figure 1). (a) Intramolecular reactions control the regioselectivity through tethering the reacting groups to limit the degrees of freedom in the system.[44] (b) The electronic and steric properties of substrates have dramatic influence on the position of electrophilic metalation. (c) Directing groups play important roles in regioselective activation the C–H bond.

The directing groups containing lewis basic heteroatoms such as nitrogen, oxygen, phosphorus, silicon, as well as sulfur usually coordinate to the metal center and bring the metal into close proximity to a specific C–H bond allowing the formation of metallacycles.[45] While the unusual remote directing group allowed the C–H bond activation occurs at remote site.[46]



(a) intromolecular controlled regioselectivity

(b) substituents controlled *ortho*-*meta*- and *para*-selectivity

(c) directing group direct *ortho*- or *meta*-selectivity

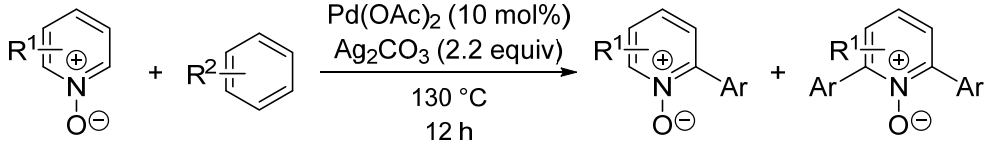
Figure1: Regioselective C–H bond activation.

2.1.2 Palladium-Catalyzed Oxidative C–C Bond Formation of Pyridine *N*-Oxides

Pyridine derivatives represent important fragements in natural products and pharmaceuticals.[47] However, the pyridine ring has low reactivity and low energy of the π-system, leading to the difficulties for the direct C–H bond functionalization. The *N*-functionalized pyridinium reagents are more reactive and more acidic in the α-position compared with the parent pyridine ring. Pyridine *N*-oxides have been widely used in functionalization of pyridine due to their ease of synthesis and commercial availability. In recent years, with the development of transition metal-catalyzed oxidative coupling reactions, a lot of efforts have been focused on the arylation,[48] alkenylation,[49] and alkylation[50] of pyridine *N*-oxides. Among the transition metals suitable for this purpose, palladium plays an important role due to its versatility in different synthetic protocols and tolerance towards many functional groups.

2.1.2.1 Palladium-Catalyzed Oxidative Coupling between Pyridine *N*-Oxides and (Hetero)arenes

In 2008, the Chang group devolped a palladium-catalyzed oxidative coupling of pyridine *N*-oxides with simple arenes (Scheme 40).[51] This reaction exhibits good reactivity and moderate to excellent selectivity for monoarylation products.

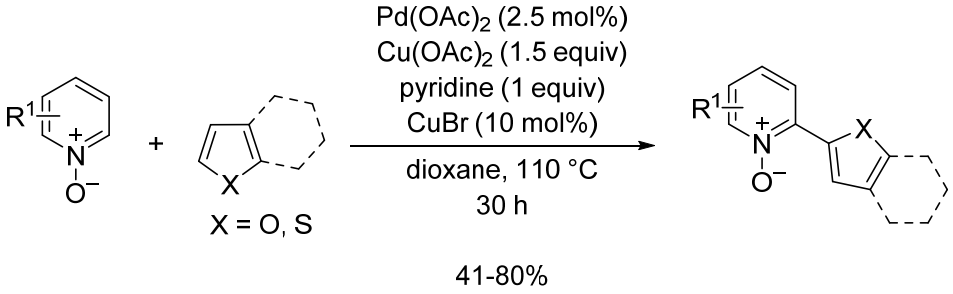


R^1 = H; R^2 = H 56% **A**/**B** = 3:1
R^1 = H; R^2 = 1,2-dimethyl 79% **A**/**B** = 15:1
R^1 = H; R^2 = 1,2-dichloro 68% **A**/**B** = 2.5:1

Scheme 40: Palladium-catalyzed oxidative coupling of pyridine *N*-oxides with simple arenes.[51]

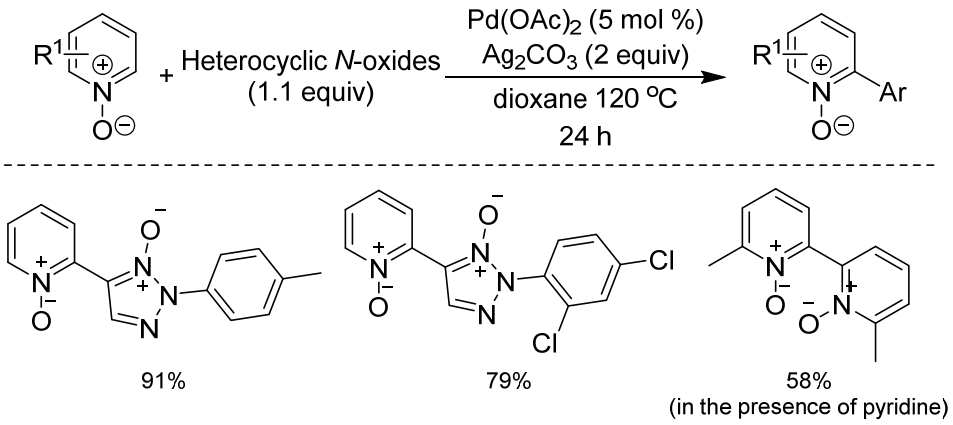
You and co-workers reported a regioselective dehydrogenative cross-coupling of pyridine *N*-oxides with various electron-rich heterocycles, such as furans and thiophenes, under palladium catalysis (Scheme 41).[52] A catalytic amount of CuBr was used to enhance the reactivity of pyridine *N*-oxides. The reaction exhibits excellent reactivity with a large range of electron-rich

heteroarenes such as 2-methylthiophene, 2,3-dimethylfuran, and benzothiophene. Quinoline and pyridine *N*-oxides afford the corresponding heteroarylation products in moderate to good yields.

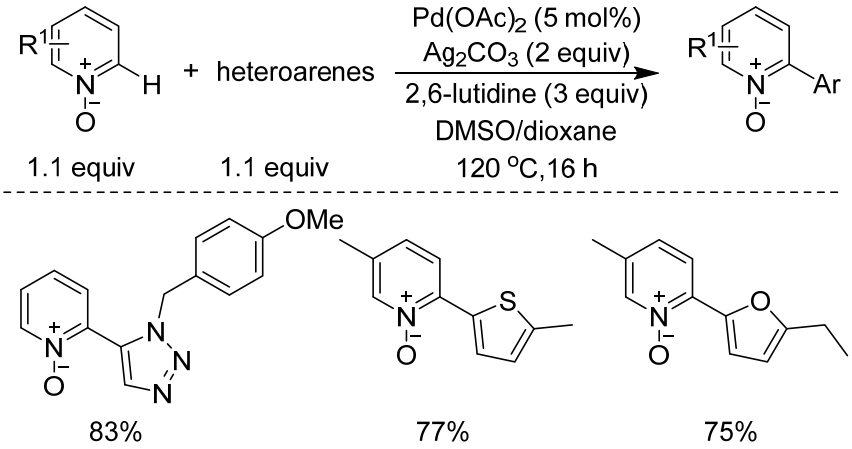


Scheme 41: Palladium-catalyzed oxidative coupling of pyridine *N*-oxides with heterocycles.[52]

Kuang and co-workers reported a protocol for C–H/C–H bonds cross-coupling between pyridine *N*-oxide derivatives and 2-aryl-1,2,3-triazole *N*-oxides. The method was suitable for various pyridine *N*-oxides and azole *N*-oxides. It was notable that the homocoupling of some pyridine *N*-oxide derivatives were developed in the presence of pyridine (Scheme 42).[53] Later on, the same group further investigated the palladium-catalyzed oxidative cross-coupling of pyridine *N*-oxides with five membered heterocycles such as 1-benzyl-1,2,3-triazoles, thiophenes, and furans in the presence of 2,6-lutidine (Scheme 43).[54]

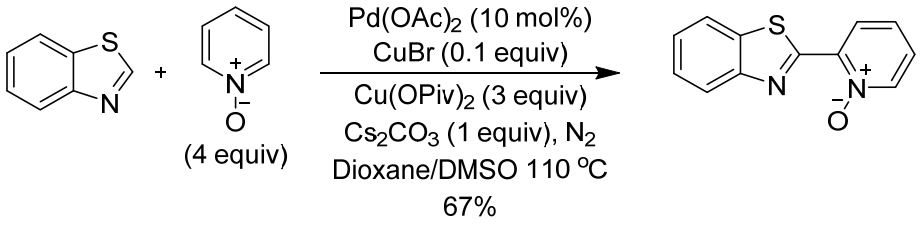


Scheme 42: Palladium-catalyzed oxidative coupling between 2-aryl-1,2,3-triazole *N*-oxides and pyridine *N*-oxide.[53]

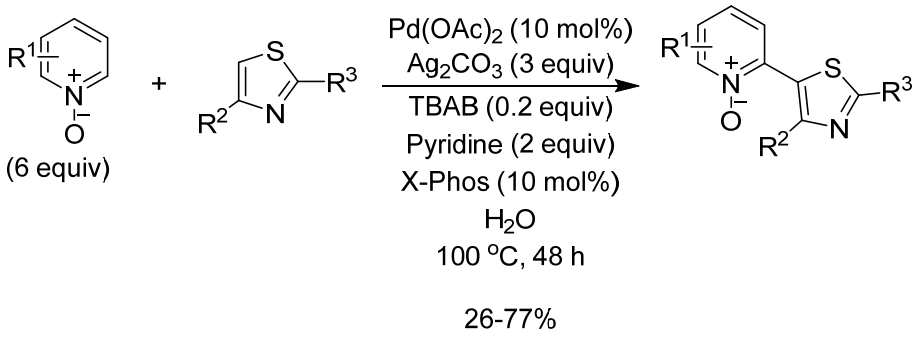


Scheme 43: Palladium catalyzed C–H/C–H cross-coupling of pyridine *N*-oxides with five membered heterocycles.[54]

The cross-dehydrogenative coupling (CDC) of benzothiazoles with pyridine *N*-oxides was demonstrated by the Li group. Copper(II) pivalate was an efficient dual-function reagent serving as both oxidant and pivalate anion probably involving in the C–H bond cleavage (Scheme 44).[55] Further studies disclosed the dehydrogenative cross-coupling reaction of pyridine *N*-oxides and thiazoles in an aqueous media. This protocol is regioselective, operationally simple, and doesn't require an inert atmosphere (Scheme 45).[56]

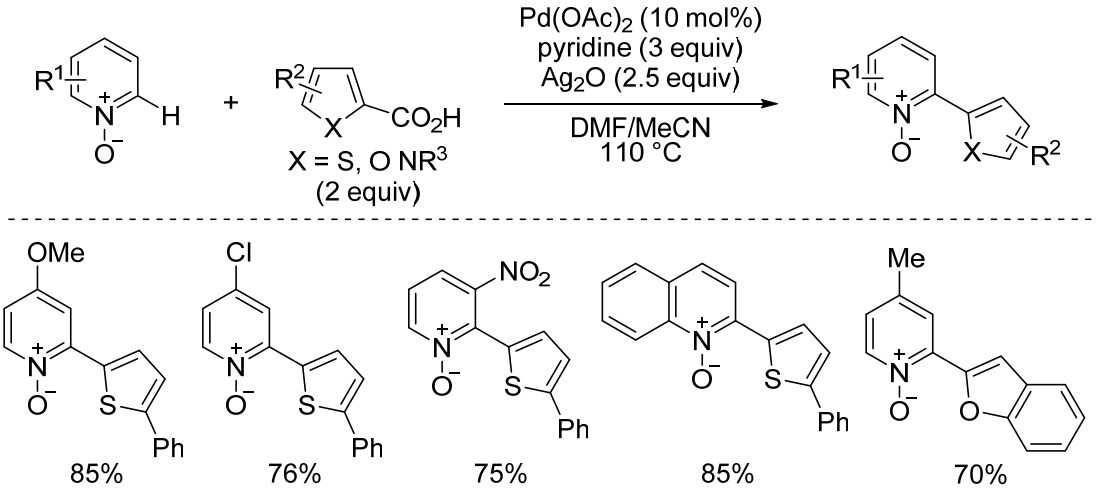


Scheme 44: The CDC reaction between benzothiazole and pyridine *N*-oxide.[55]



Scheme 45: The CDC reaction of pyridine *N*-oxides and thiazoles in aqueous media.[56]

The palladium-catalyzed oxidative cross coupling of substituted pyridine *N*-oxides with heteroarylcarboxylic acids afforded the C2 heteroarylated pyridine *N*-oxides *via* decarboxylation (Scheme 46).[48b] The decarboxylation step was proposed by silver salt through transmetalation to the palladium species. Importantly, pyridine *N*-oxides with metal-susceptible substituents such as bromo and iodo groups were tolerated under the coupling conditions. Interestingly, the reaction of 3-nitropyridine *N*-oxide led to a sterically hindered 2-thionylation as the sole product. The origin of this selectivity is not clear, it is probably due to the stabilization of the palladium species by the nitro group.

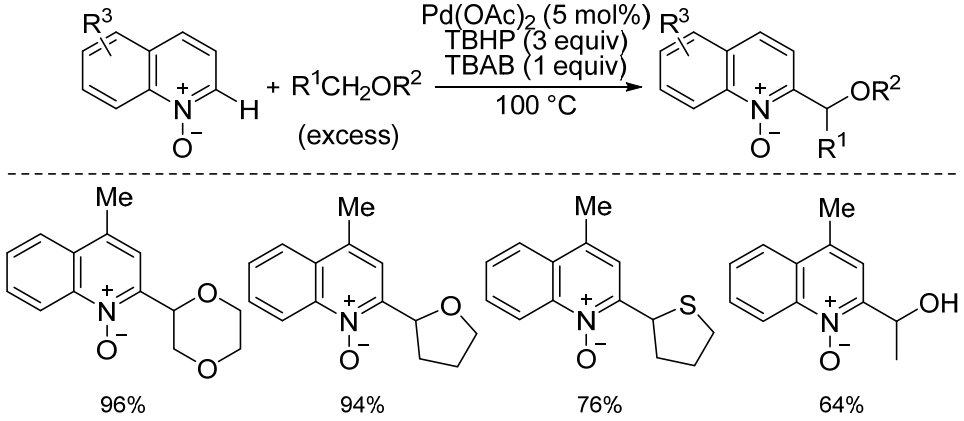


Scheme 46: Palladium-catalyzed arylation of substituted pyridine *N*-oxides with heteroarylcarboxylic acids.[48b]

2.1.2.2 Palladium-Catalyzed Oxidative Coupling of Pyridine *N*-Oxides with Alkanes

A palladium-catalyzed direct C2 alkylation of quinoline *N*-oxides with ethers was developed by

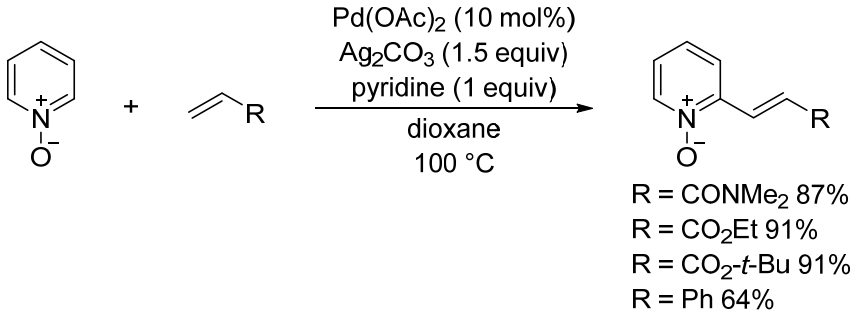
Cui and Wu.[50] The reactions of 4-methylquinoline *N*-oxide with cyclic ethers, sulfide, and simple aliphatic alcohols produced the corresponding dehydrogenative cross-coupling products in good to excellent yields (Scheme 47). The number of oxygen atoms and the size of the cyclic ether did not obviously influence the transformation.



Scheme 47: Dehydrogenative cross coupling of quinoline *N*-oxides with ethers under palladium catalysis.[50]

2.1.2.3 Palladium-Catalyzed Oxidative Coupling of Pyridine *N*-Oxides with Alkenes

Chang and co-workers addressed a palladium-catalyzed oxidative alkenylation of pyridine *N*-oxides in the presence of silver salt as external oxidant to provide highly chemo- and stereoselective (*E*)-products.[57] A variety of alkenes conjugated with electron-deficient group such as ester, amide, ketone, and phosphonate groups were well tolerant to give monoalkenylated products (Scheme 48). Numerous types of *N*-oxides derived from pyrazine, quinoxaline, and pyridazine also reacted smoothly in this transformation.



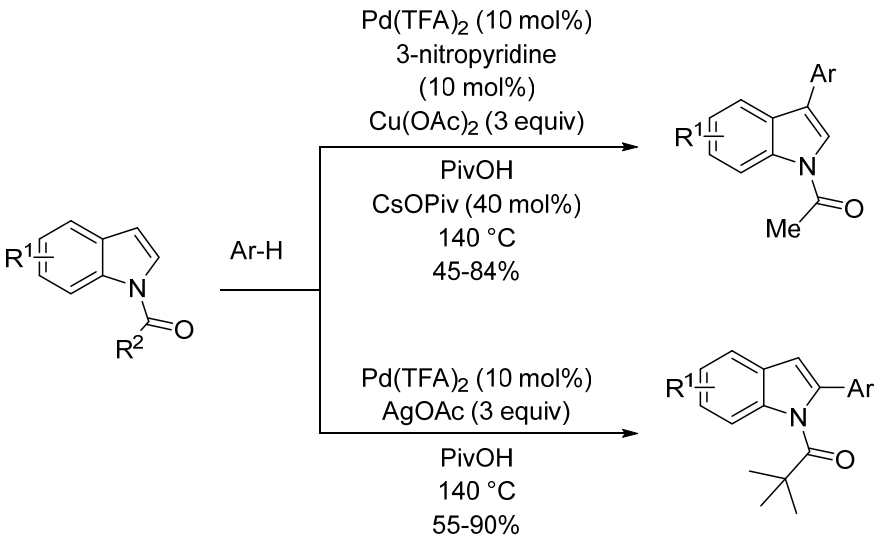
Scheme 48: Palladium-catalyzed oxidative alkenylation of pyridine *N*-oxides with alkenes.[57]

2.1.3 Palladium-Catalyzed Regioselective C–C Bond Formation of Indoles *via* Double C–H Bond Activation

The development of methodologies concerning indole functionalization has attracted a lot of attention in organic chemistry.[58] The transition metal catalytic systems were proven to be fruitful tools for these transformations, while the C–H bond functionalization of indoles were always triggered the issue of regioselectivity. In terms of palladium-catalyzed oxidative C–C bond formation, the electronic properties of indoles prefer reacting at the C3 position. Intermolecular C2 regioselective coupling was achieved with the aid of chelation strategy[55a, 59] or appropriate reaction conditions.[60]

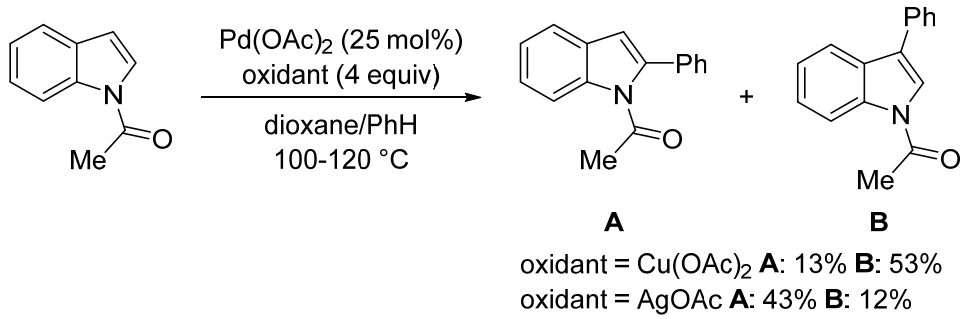
2.1.3.1 The Regiocontrolled Oxidative Arylation of Indoles

In 2007, Fagnou and co-workers developed an oxidative arylation both at C-2 and C-3 positions of indoles with a high degree of regioselectivity (Scheme 49).[59b, 60b] The choice of the *N*-protecting group and oxidant were found to be crucial to control the regioselectivity. 3-Arylindoles were selectively achieved by using a stoichiometric amount of $Cu(OAc)_2$, while the 2-arylindoles were accessed on *N*-pivalyl-substituted indole by the use of AgOAc as terminal oxidant. Their studies indicated that the acetate base imparted the increased C2 selectivity to the palladium catalyst, mixed Pd–Cu complexes may behave similarly to the analogous trinuclear palladium carboxylate clusters which favored high C3 selectivity.



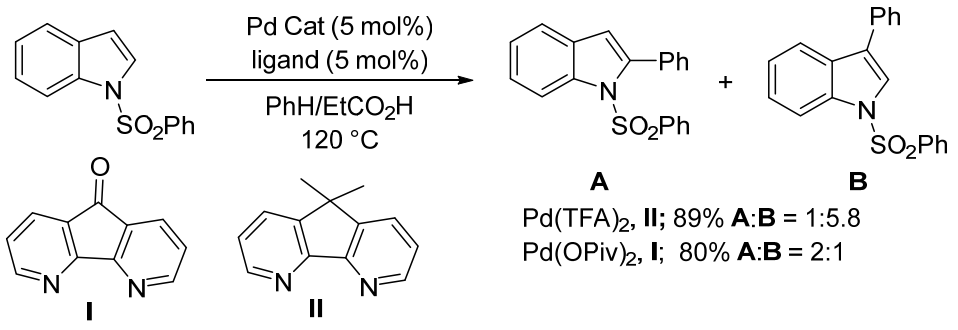
Scheme 49: Palladium-catalyzed regioselective oxidative arylation of indoles.[58b]

The DeBoef group investigated an oxidative coupling of arenes and *N*-acetyl indoles as well, the use of $Cu(OAc)_2$ as the stoichiometric oxidant afforded selective C3 arylation product while AgOAc produced selective C2 arylation product (Scheme 50).[61] They proposed that the formation of polymetallic, catalytically active clusters were involved in the C–H bond activation and C–C bond formation step. The $Cu(OAc)_2$ oxidant formed a polymetallic cluster with $Pd(OAc)_2$ that selectively arylates at the C3 position of *N*-acetylindole, while the AgOAc oxidant formed either a different polymetallic cluster or 'naked' $Pd(OAc)_2$ that migration from the indole's 3- to the 2-position occurs, followed by deprotonation of the indole's C2-position.



Scheme 50: Oxidant controlled regioselective C–C coupling of arenes and indoles.[61]

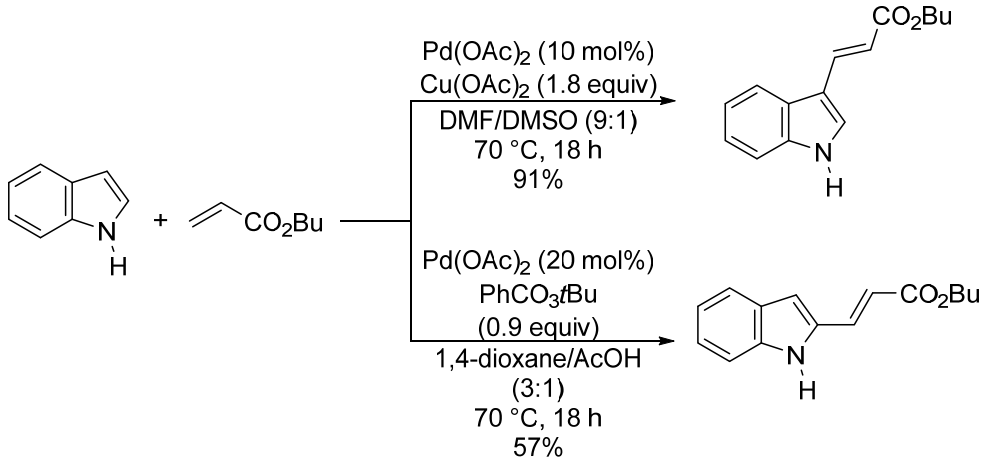
Stahl et, al. demonstrated that a similar reaction using O_2 as oxidant, the regioselectivity was controlled by the catalyst system (Scheme 51). The high level of C3 selectivity was achieved by using of ligand **II** and $Pd(TFA)_2$, while the C2 selectivity was improved by the presence of combination of ligand **I** and $Pd(OPiv)_2$.[62]



Scheme 51: Catalyst controlled regioselective arylation of indoles.[62]

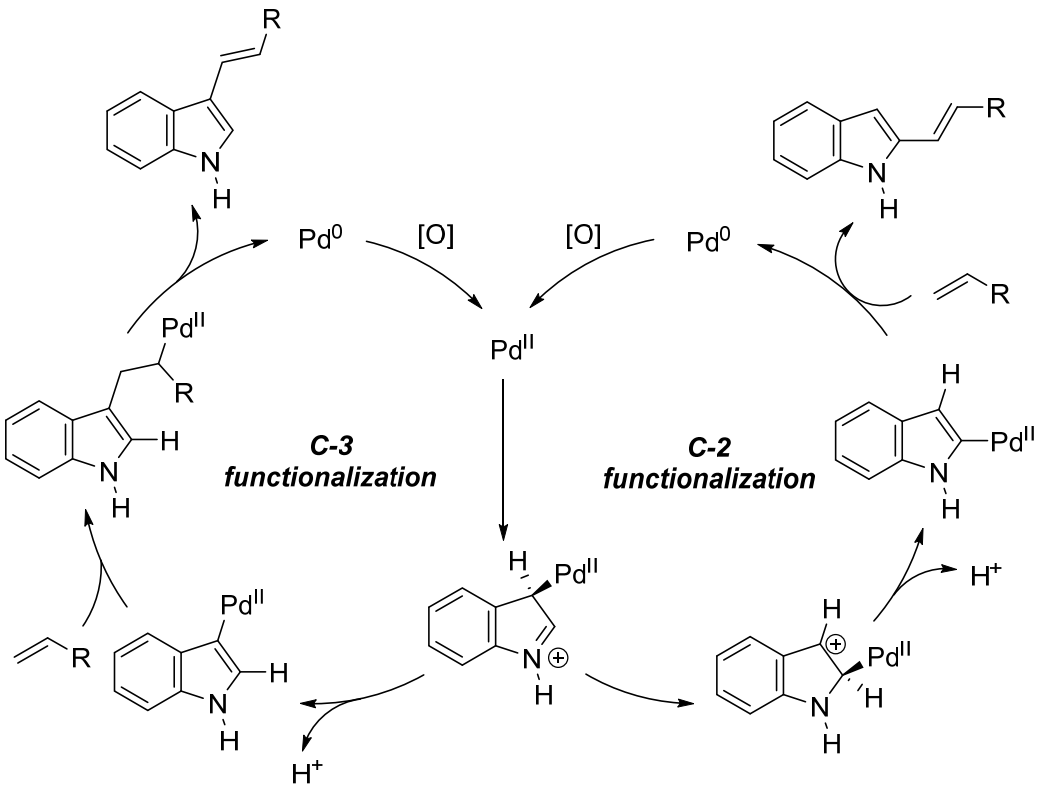
2.1.3.2 The Regiocontrolled Oxidative Alkenylation of Indoles

The oxidative C–H bond alkenylation of the C2 and C3 positions of the unprotected indole nucleus was realized under different conditions published by Gaunt and co-workers (Scheme 52). When the reaction was carried out in aprotic polar solvents, such as DMSO and DMF, with $Cu(OAc)_2$ as oxidant, the alkenylation occured at the C3 position of indole selectively. Conversely, the use of dioxane with the addition of acetic acid as a polar coordinating co-solvent and in the presence of *tert*-butyl benzoyl peroxide, changed the selectivity to C2 substituted indoles.[63]



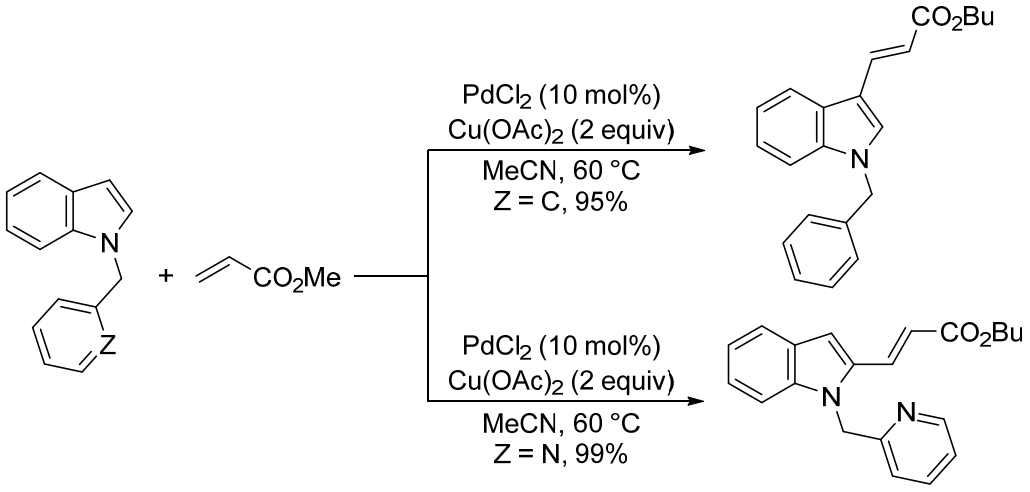
Scheme 52: Regioselective alkenylation of the unprotected indole.[63]

The mechanistic explanation for this outcome involves first direct palladation at the C3 position. Under neutral conditions, a proton can be easily removed to generate a 3-indolyl-palladium complex (Scheme 53, left). Conversely, acidic conditions make the deprotonation step slow enough to allow a palladium migration to C2 position, which leads to the aryl palladium intermediate (Scheme 53, right). Subsequently, both intermediates undergo Heck type reaction to give the final products.



Scheme 53: Plausible mechanism of the selective alkenylation of indole.[63]

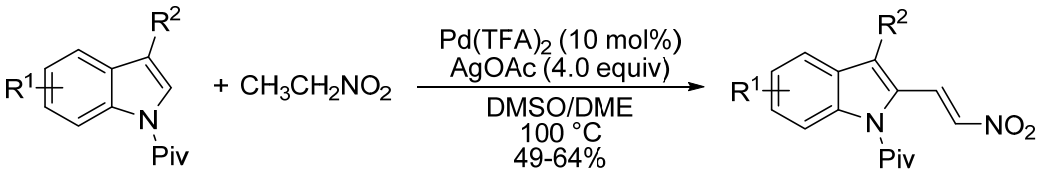
An alternative approach to address the C2 alkenylation of the indole is based on the directing group strategy. Alkenylation of *N*-benzyl-protected indole took place selectively at the C3 position in the presence of $PdCl_2$ as catalyst and $Cu(OAc)_2$ as oxidant, while the reaction of the *N*-(2-pyridylmethyl)-substituted indole led to the C-2 substituted indole (Scheme 54).[59c]



Scheme 54: Directing group controlled selective alkenylation of indoles.[59c]

The Su group developed a dehydrogenative cross-coupling between indoles and nitroethane to

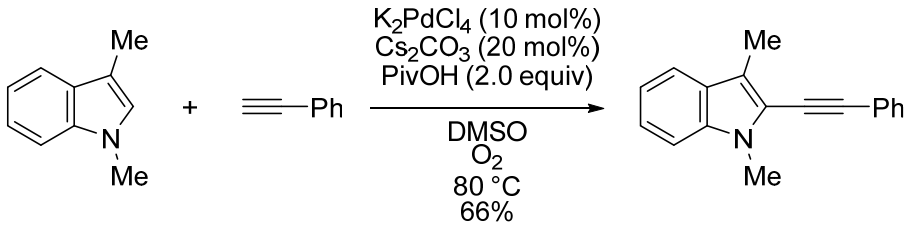
construct β-indolenitroethylenes under palladium catalysis (Scheme 55). Mechanistic experiments showed the reaction of mesitylene as well as benzene with freshly prepared nitroethylene under standard conditions. However, neither gave the olefination product, respectively. β-Nitroethylbenzene afforded β-nitrostyrene in 73% yield under standard conditions. These observations demonstrated the possibility that β-nitroethylbenzene rather than nitroethylene might be the intermediate in the transformation. [64]



Scheme 55: Multi-dehydrogenative cross-coupling between indoles and nitroethane.[64]

2.1.3.3 The Regiocontrolled Oxidative Alkynylation of Indoles

In 2010, palladium-catalyzed direct oxidative Heck–Cassar–Sonogashira (HCS) type alkynylation of indoles with terminal alkynes was carried out by Li and co-workers under an atmosphere of O_2 (Scheme 56).[65] Only a catalytic amount of base was required and dioxygen (O_2) was used as the terminal oxidant to generate H_2O as a side product.



Scheme 56: Palladium-catalyzed direct oxidative HCS-type alkynylation of indoles.[65]

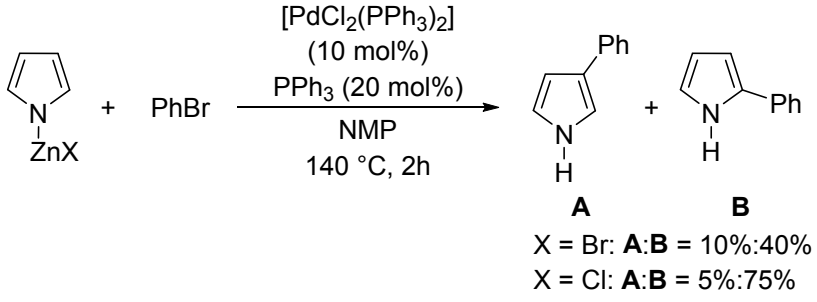
2.1.4 Regioselective C–H Bond Activation and C–C Bond Formation of Pyrroles

Despite the successful C–H bond activation of indoles, pyrroles have been rarely used due to their instability under acidic and oxidative conditions. The cross coupling of pyrroles suffers from low selectivity, reactivity as well as polymerization.[63] The inherent electronic property of pyrroles prefers the C2 selectivity towards electrophilic aromatic substitution, however, electron rich pyrrole rings allow to access both the C2 and the C3 positions. The typical way to induce regioselective C–H bond functionalization is to use substituents to block one reactive position of pyrrole. It is still a challenge to control regioselectivity of unsubstituted pyrroles.

2.1.4.1 Intermolecular C–H Bond Arylation of Unsubstituted Pyrroles

2.1.4.1.1 Palladium-Catalyzed Cross Coupling of Pyrrole Anions with Aryl Halides

In 1992, Filippini and co-workers reported a palladium catalyzed arylation of pyrrol-1-ylzinc halides with bromobenzene[66] to give a mixture of 2- and 3-phenylpyrrole (Scheme 57). The nature of the zinc halides on the pyrrole influenced the reactivity of the transformation. Zinc chloride is harder lewis acid than zinc bromide, which promotes the electrophilic substitution on pyrrole ring.

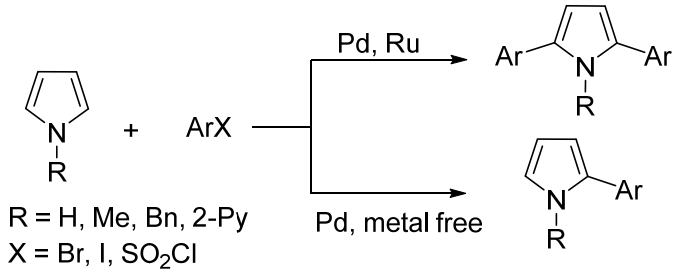


Scheme 57: Palladium-catalyzed arylation of pyrrol-1-ylzinc halides with bromobenzene.[66]

2.1.4.1.2 Direct (Hetero)arylation of Unsubstituted Pyrroles

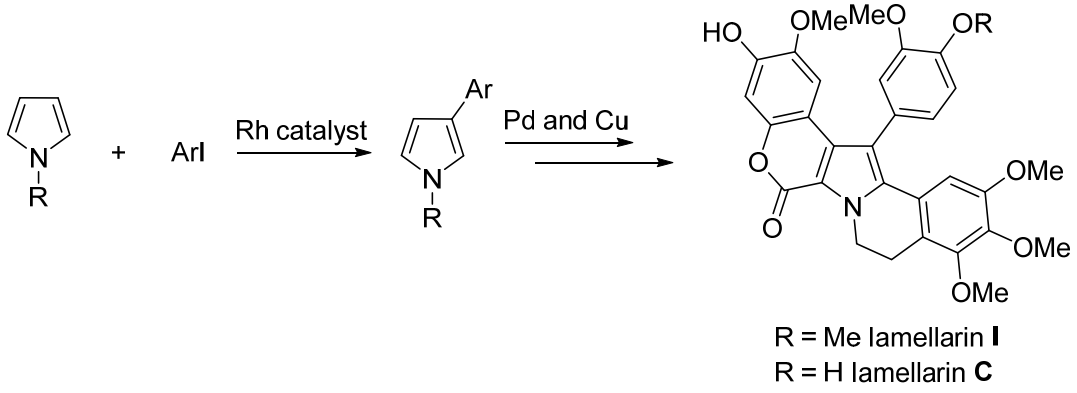
The palladium-catalyzed direct arylation of *N*-protecting pyrrole is well studied. The reactions usually proceed at the more reactive C2 or C5 position of pyrroles rather than the C3 or C4

position. The Langer group reported a diarylation of *N*-methyl pyrrole by using tetrabutylammonium acetate as an ionic solvent, and simple palladium salts or polyvinylpyrrolidone-stabilized palladium nanoparticles as a catalyst.[67] Doucet and co-workers reported a C2 arylation of *N*-methyl pyrrole using only 0.01–0.5 mol% of $Pd(OAc)_2$ as the catalyst.[68] Ackermann et. al. reported a base-assisted ruthenium-catalyzed direct arylation of 2-pyridyl- or 2-pyrimidyl-substituted pyrroles to afford 2,5-diarylated pyrroles.[43] Direct C2 arylation of unsubstituted pyrroles with diaryliodonium demonstrated by the Yu group (Scheme 58).[69] Palladium-catalyzed direct desulfinative heteroarylation of pyrroles using heterosulfonyl chlorides as coupling partners was reported. These C–H bond functionalizations occurred at the C2 or/and C5 position of pyrrole.[70]



Scheme 58: Direct α-selective (hetero)arylation of pyrroles.[70]

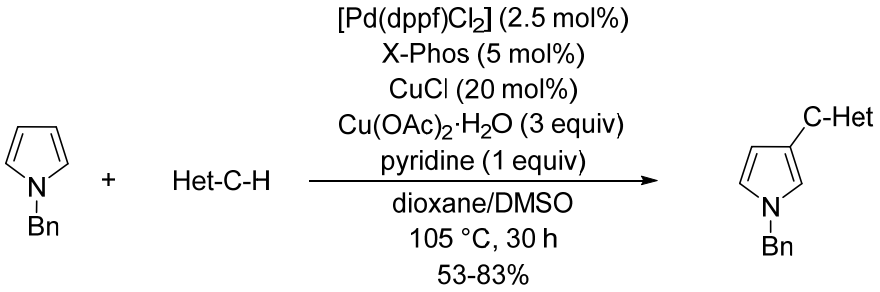
The unusual C3 or C4 selective C−H bond arylation of pyrroles using a rhodium catalyst has been reported, this strategy was employed in de novo synthesis of pyrrole alkaloids, lamellarins **C** and **I** (Scheme 59).**[71]**



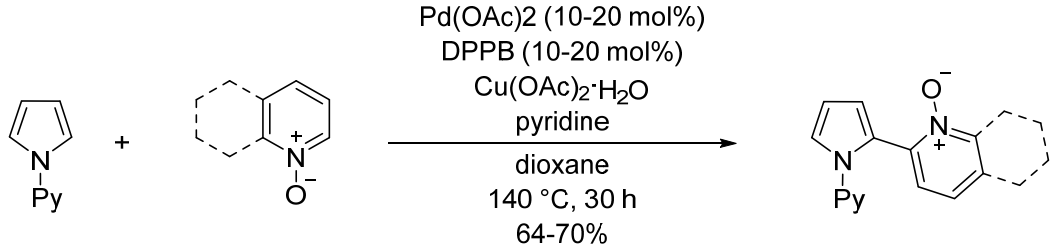
Scheme 59: Rhodium-catalyzed β-selective arylation of pyrroles.**[71]**

2.1.4.1.3 Oxidative Heteroarylation of Unsubstituted Pyrroles

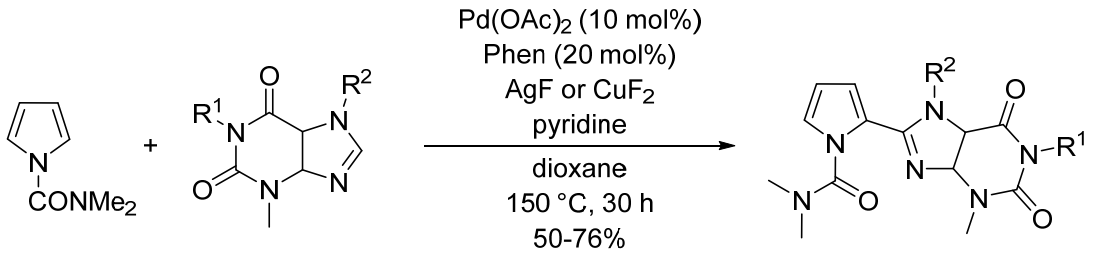
You and co-workers reported a palladium-catalyzed oxidative cross-coupling of indoles and pyrroles with heteroarenes. Some examples of coupling of pyrroles with xanthines, purines, benzothiazoles, benzoxazoles, and quinoxaline *N*-oxide were described to form 3-heteroarylated pyrroles in synthetically useful yields (Scheme 60).[72] Later on, the directing group assisted C2 selective oxidative coupling of *N*-pyridyl pyrroles with quinoline and pyridine *N*-oxides were reported by the same group (Scheme 61). With a *N*,*N*-dimethylcarbamoyl group as directing group, pyrrole could also be coupled with xanthines at the C2 position. The oxidant containing a F^- counterion proved crucial for achieving the switch of regioselectivity and the addition of 1,10-phenanthroline further improved the C2/C3 ratio (Scheme 62).[72]



Scheme 60: Palladium-catalyzed C3 hetroarylation of pyrroles.[72]

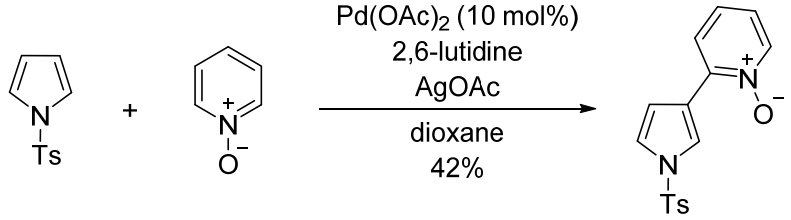


Scheme 61: Palladium-catalyzed C2 heteroarylation of pyrroles by using pyridyl directing group.[72]



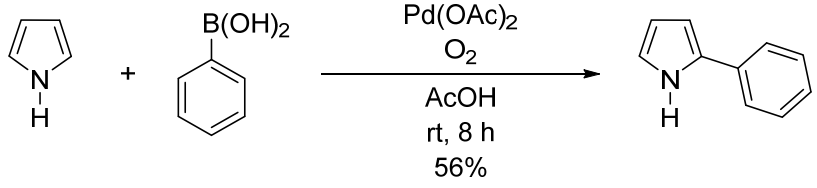
Scheme 62: Palladium-catalyzed C2 heteroarylation of pyrroles by using *N,N*-dimethylcarbamoyl group.[72]

The Itami group illustrated an oxidative coupling of azine and indoles/pyrroles nuclei to synthesis Eudistomin U, a single example was described for the reaction of *N*-Ts pyrrole with pyridine oxide, proceeding at the C3 position (Scheme 63).[73]



Scheme 63: Palladium-catalyzed cross coupling of *N*-Ts pyrroles with pyridine *N*-oxide.[73]

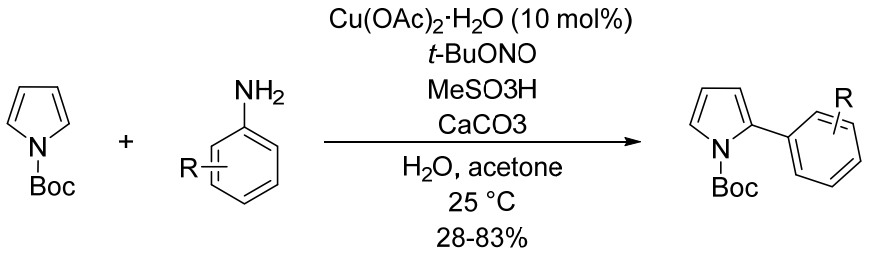
Shi and co-workers developed a palladium-catalyzed arylation of heteroarenes with arylbronic acids using O_2 as terminal oxidant. The N–H pyrrole was described coupling with arylbronic acid to afford the C2 product in moderate yield (Scheme 64).[74]



Scheme 64: Palladium-catalyzed oxidative arylation of unsubstituted pyrrole.[74]

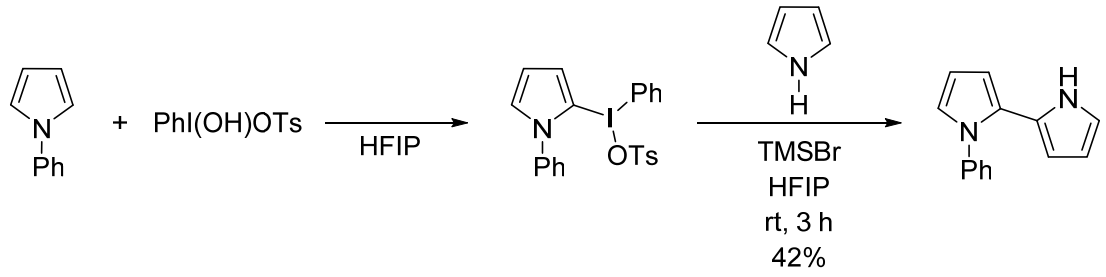
Copper-catalyzed radical arylation of pyrroles with aryldiazonium salts generated from aniline in situ under neutral conditions was reported (Scheme 65). The methodology featured aqueous solvents, room temperature, and inexpensive reagents. $CaCO_3$ was crucial for the reaction probably because it facilitated the deprotonation of the pyrrolo cation.[75] Seayad and co-workers reported a similar process including arylation of heteroarenes with *N*-methyl pyrrole by an in situ

diazotization in the presence of silver nitrate as an unusual nitrosating reagent.[76]



Scheme 65: Copper-catalyzed radical arylation of pyrroles.[76]

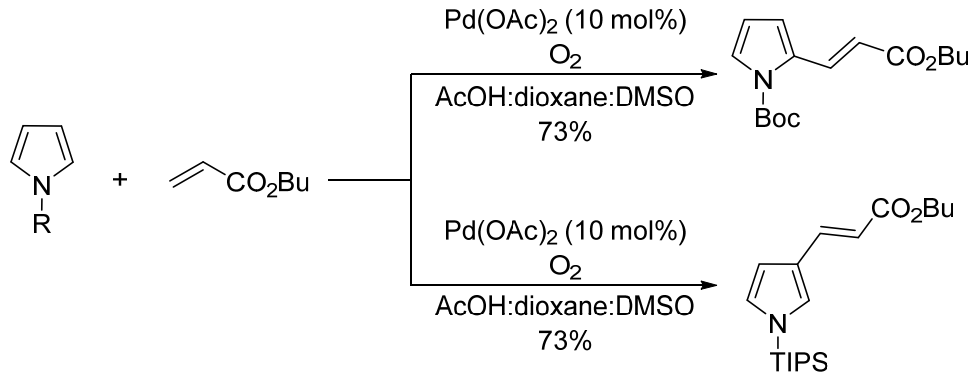
Oxidative coupling of two pyrroles promoted by hypervalent iodine(III) reagents was described, the method exhibited very high regioselectivity (Scheme 66).[77]



Scheme 66: Oxidative coupling of pyrroles promoted by hypervalent iodine(III) reagents.

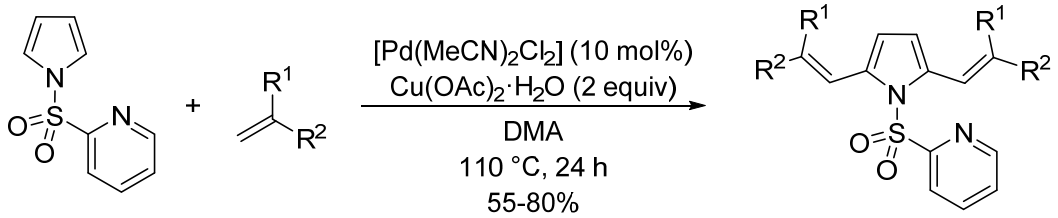
2.1.4.2 Transition Metal-Catalyzed Intermolecular C–H Bond Alkenylation of Unsubstituted Pyrroles

Gaunt and co-workers have developed an efficient palladium(II) oxidation system for C–H bond alkenylation of pyrroles under aerobic conditions (Scheme 67).[63] The regioselectivity was controlled by switching *N*-protecting groups to form products with either C2 or C3 functionalization. *N*-Boc pyrroles coupled at the C2 position, exploiting the inherent reactivity of this heteroarene. In contrast, *N*-TIPS pyrrole underwent the C–H bond alkenylation at the C3 position because of the steric demand of the silyl group. This method could be used to generate a range of alkenylated products. In terms of the *N*-Boc pyrrole, the natural C2 selectivity controlled the electrophilic palladation. The *N*-TIPS is extremely bulky and slightly electron donating. The steric bulk group inhibited reaction at the adjacent C2 position, while the highly activated nature of the pyrrole allowed palladation at the less nucleophilic C3 position even under mild catalytic conditions.

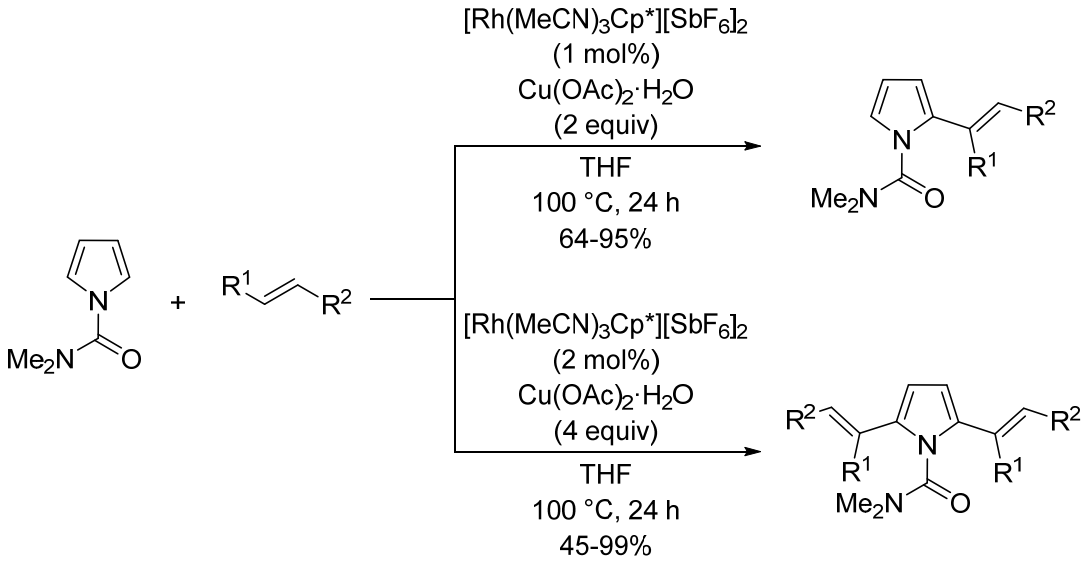


Scheme 67: Regioselective alkenylation of pyrroles.[63]

Transition metal-catalyzed direct C2 alkenylation of indoles and pyrroles assisted by the *N*-directing group was addressed by the Carretero[78] (Scheme 68) and Wang groups (Scheme 69).[79]



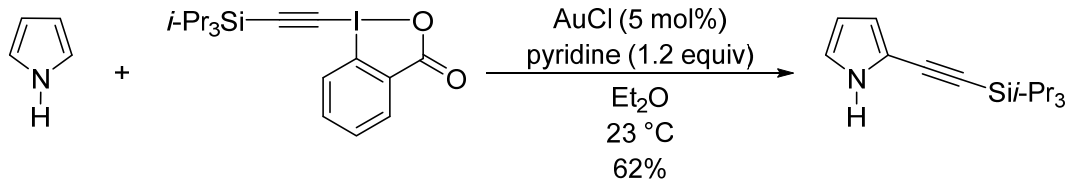
Scheme 68: Direct C–H bond alkenylation of *N*-(2-pyridyl)sulfonyl pyrroles.[78]



Scheme 69: Rhodium-catalyzed oxidative C2 alkenylation of pyrroles.[79]

2.1.4.3 Intermolecular Cross Coupling of Unsubstituted Pyrrole with Alkynes.

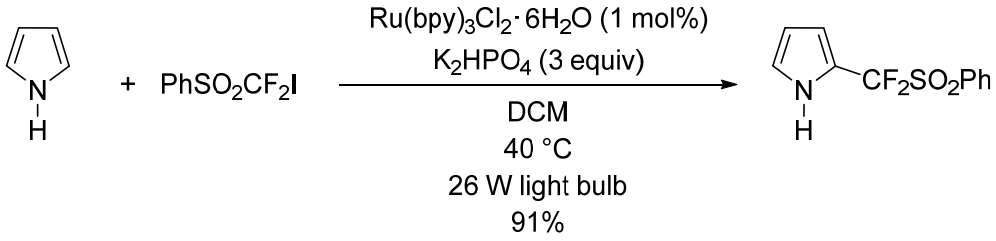
The C2 alkynylation of pyrroles was achieved by gold catalyst using alkynyl hypervalent iodine reagents (Scheme 70). High yields were obtained in the presense of pyridine. The alkynylation method showed a regioselectivity consistent with an electrophilic aromatic substitution to give C2 alkynylation product.[80]



Scheme 70: Gold-catalyzed alkynylation of pyrroles.[80]

2.1.4.4 Intermolecular C–H Bond Alkylation of Unsubstituted Pyrroles

Visible-light photoredox-catalyzed difluoromethylation of pyrrole was explored to afford the difluoromethylated pyrroles (Scheme 71).[81] Mechanistic study indicated that the reaction went through a radical pathway. The visible light promoted the Ru(II) to the excited state to initiate the radical chain.



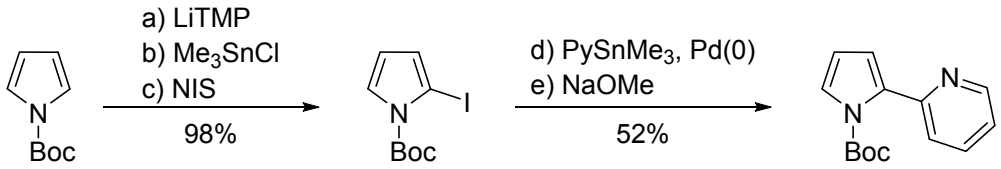
Scheme 71: Phtoredox-catalyzed difluromethylation of pyrroles.[81]

2.1.5 Previous Methods for Synthesis of Pyridopyrroles

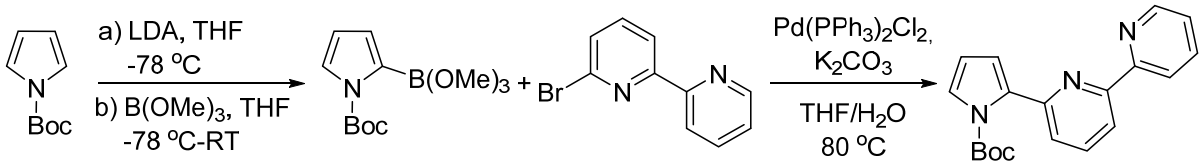
Two general approaches concerning the synthesis of pyridopyrrole either at C2 or C3 position of pyrrole were reported, the palladium-catalyzed cross coupling reaction and the pyrrole synthesis.

Sammelhack and co-workers reported the synthesis of 2-pyridopyrrole through the Stille reaction,

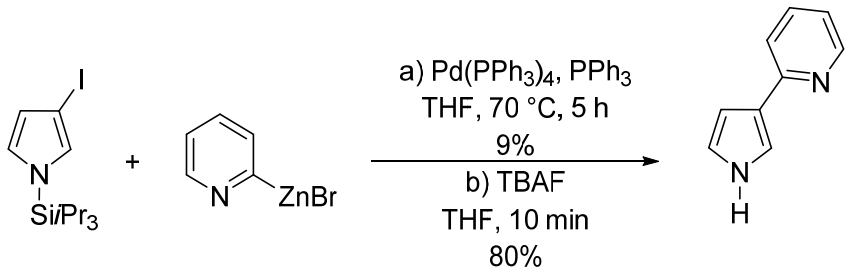
N-Boc pyrrole was converted into 2-iodopyrrole *via* lithiation and iodination, which coupled with 2-trimethylstannylpyridine under palladium catalyst to afford 2-pyridopyrrole in 52% yield (Scheme 72).[82] The Johannes group illustrated preparation of 2-bipyridopyrrole by in situ Suzuki coupling of the C2 substituted boronic acid of Boc-protected pyrrole with the bipyridyl bromides (Scheme 73).[83] The Negishi coupling reaction was employed to access the 3-pyridopyrrole. Howerer, 3-iodopyrrole reacted with pyridylzinc bromide to give the corresponding product in only 9% yield, subsequently deprotection afford the desired product (Scheme 74).[84]



Scheme 72: Synthesis of 2-pyridopyrrole *via* Stille reaction.[82]

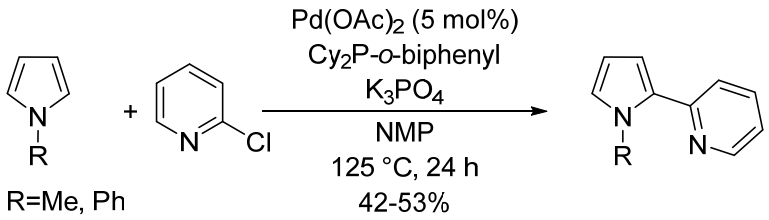


Scheme 73: Synthesis of 2-pyridopyrrole *via* Suzuki reaction.[83]



Scheme 74: Synthesis of 2-pyridopyrrole *via* Negishi reaction.[84]

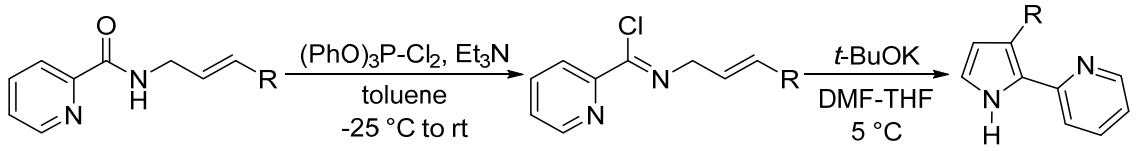
The direct arylation is a more economic approach to construct the target molecular, Daugulis and co-workers described the preparation of 2-pyridopyrroles from *N*-protecting pyrrole (Scheme 75).[85]



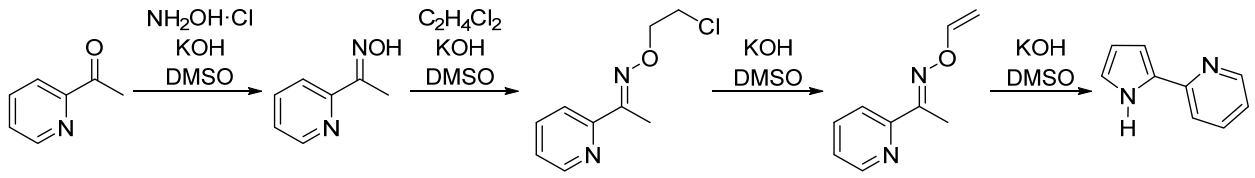
Scheme 75: Direct arylation of *N*-protected pyrrole for the preparation of 2-pyridopyrroles.[85]

One single oxidative coupling reaction to access 3-pyridopyrrole was described by the Itami group, the pyridine *N*-oxide coupled with *N*-Ts pyrrole at the C3 position in 42% yield (refer to Scheme 63).

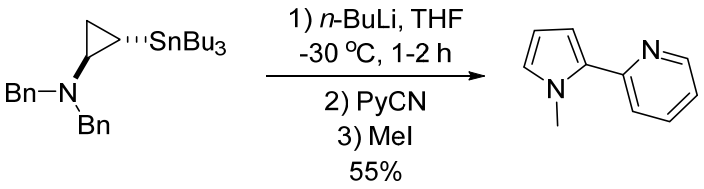
A varity of synthetic routes for substituted pyrrole were reported. The 2-pyridopyrroles could be prepared by intramolecular cyclization of imino chlorides which were prepared from allyl amides using the triphenylphosphite dichloride as chlorinating reagent (Scheme 76).[86] The 2-pyridopyrroles can be formed by a one pot strategy from ketones, hydroxylamine, and 1,2-dichloroethane through the rearrangement of *O*-vinyl ketoximes under (super)basic conditions (Scheme 77).[87] Synthesis of 2-pyridopyrrole started from 2-(tributylstannyl) *N*,*N*-dibenzylcyclopropylamines, which underwent tin-lithium exchange and treatment with nitrile to give aminocyclopropyl ketimine, followed by ring opening upon addition of water, cyclization, and elimination to afford the desired product in 55% yield (Scheme 78).[88] The preparation of 2-pyridopyrrole can be realized by multistep strategy from *N*-Boc lactam through addition to the organolithium reagents, and hydrolysis to afford *r*-ketoaldehyde, which underwent Paal–Knorr pyrrole synthesis to give the desired product (Scheme 79).[89] The 3-pyridopyrrole could be accessed from vinyl arenes and tosylmethyl isocyanide (TOSMIC) in one step (Scheme 80).[90]



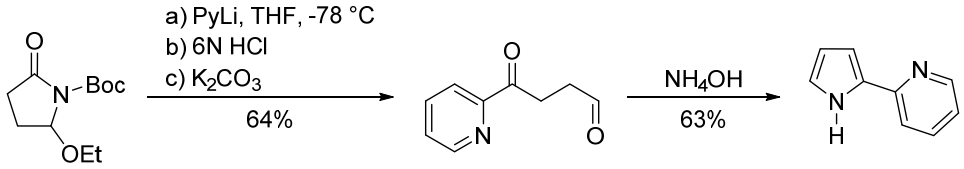
Scheme 76: Generel route from *N*-allyamides to pyrroles.[86]



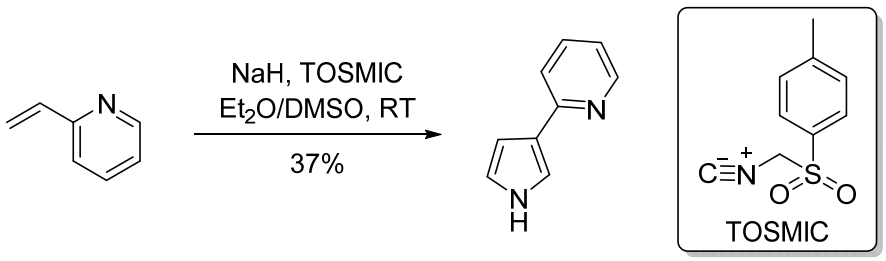
Scheme 77: The formation of pyrroles from ketones and dichloroethane.[87]



Scheme 78: Synthesis of 2-pyridopyrrole from 2-lithiated *N*,*N*-dibenzylcyclopropylamines with nitriles.[88]



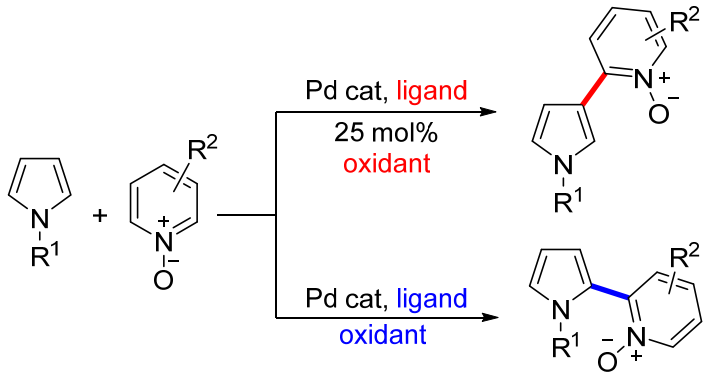
Scheme 79: Multistep strategy for the synthesis of 2-pyridopyrrole.[89]



Scheme 80: Synthesis of 3-pyridopyrrole from vinyl arenes and tosylmethyl isocyanide.[90]

2.2 Motivation

Based on the previous methods for the synthesis of pyridopyrroles, there are still some drawbacks. The additional synthetic steps are needed to prepare the starting materials, multistep reaction was required to complish the synthesis and the methods suffering from low yields. It is highly desired to devolp an economic method for the synthesis of pyridopyrroles from unfunctionalized starting materials. Dehydrogenative C–H/C–H cross coupling between *N*-protecting pyrroles and pyridine *N*-oxides under palladium catalysis is the method of choice to realize the desired target (Scheme 81). We try to achieve regioselective control as well by the variation of reaction conditions.



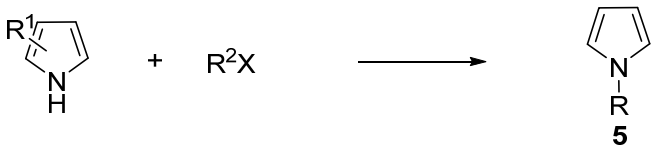
Scheme 81: Regiocontrolled oxidative coupling of pyrroles and pyridine *N*-oxides under different conditions.

2.3 Results and Discussion

2.3.1 Synthesis of *N*-Protecting Pyrrole Derivatives

The substituents on the nitrogen atom of pyrrole were introduced to eliminate side reactions of C–N bond cross coupling between free N–H pyrrole and pyridine *N*-oxides. Several *N*-protecting pyrroles were prepared from simple pyrrole through nucleophilic substitution under different reaction conditions (Table 3). *N*-Bn pyrrole and *N*-Ts pyrrole were obtained from pyrrole and benzyl chloride or tosyl chloride, respectively in the presence of KOH in excellent yield without further purification. *N*-Boc pyrrole and *N*-Bz pyrrole were prepared using DMAP as catalyst. A stronger base was required to synthesize *N*-BOM, *N*-Methyl pivalate, *N*-pym pyrrole, and substituted *N*-Bn pyrroles. The resulting products were obtained in moderate yields, electron rich substituent exhibited better reactivity than electron poor substituents on pyrrole ring. The acylation of pyrrole with dimethylcarbamic chloride using *n*-BuLi as a base gave the desired product in good yield.

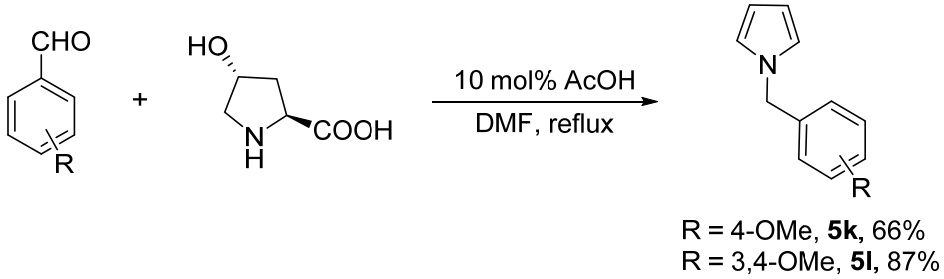
Table 3: Synthesis of *N*-protecting pyrroles.



Entry	R^1	R^2X	Conditions	Product, yield
1	H	BnCl	KOH, DMSO, 65 °C	**5b**, 99%
2	H	TsCl	KOH, DCE, rt	**5c**, 94%
3	H	acyl chloride	KOH, THF, reflux	**5q**, 72%
4	H	BocCl	DMAP, CH_3CN, rt	**5e**, 70%
5	H	BzCl	DMAP, Et_3N, DCM	**5m**, 71%
6	H	dimethylcarbamic chloride	*n*-BuLi, THF, -78-0 °C	**5d**, 80%
7	H	BOMCl	NaH, DMF, rt	**5j**, 40%
8	H	chloromethyl pivalate	NaH, DMF, rt	**5n**, 30%
9	H	2-pyrimidyl chloride	NaH, DMF, rt	**5o**, 42%
10	2-Et	BnBr	NaH, DMF, rt	**5g**, 60%
11	2-CO_2Et	BnBr	NaH, DMF, rt	**5h**, 41%

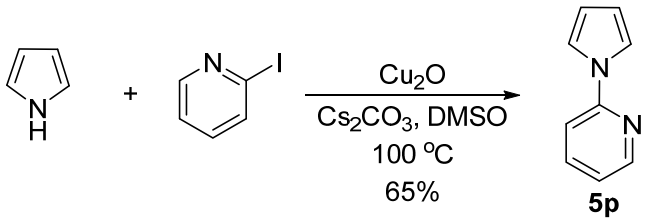
12	3-CO_2Et	BnBr	NaH, DMF, rt	**5i**, 24%

The reaction of aldehydes with *trans*-4-hydroxy-L-proline was employed to form the *N*-alkylpyrroles in good yields *via* decarboxylation followed by redox isomerization under neutral conditions (Scheme 82).



Scheme 82: Synthesis of *N*-alkylpyrroles from *trans*-4-hydroxy-L-proline.

Copper-catalyzed C–N bond cross coupling of pyrrole with iodo pyridine was an effective approach to prepare *N*-arylpyrroles (Scheme 83).



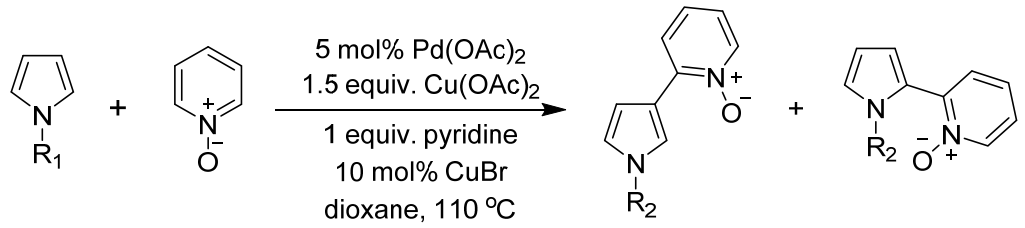
Scheme 83: Preparation of *N*-aryl pyrrole by copper-catalyzed C–N bond cross coupling.

2.3.2 Optimizition of the Reaction Conditions for the Oxidative C3 Heteroarylation of Pyrroles

2.3.2.1 The Effect of Different *N*-Substituents on Pyrroles

Initially, the effect of different *N*-substituents on the reactivity as well as selectivity was examined (Scheme 84). The results indicated that higher electron density of the pyrrole ring was necessary. The *N*-aryl and *N*-methyl substituents gave higher yields than *N*-urea, *N*-tosyl, and *N*-Boc substituents. The *N*-tosyl pyrrole led to the completely C3 selectivity. The *N*-Boc group was not compatible under these reaction conditions and resulted in deprotection products. However, the

N-urea gave a mixture of C2 and C3 products which could not be separated, the larger ratio of C2 product compared to other *N*-substituent due to the C2–H bond activation by forming cyclometalation assisted by the directing group. The *N*-benzyl group was chosen for reaction condition optimization.

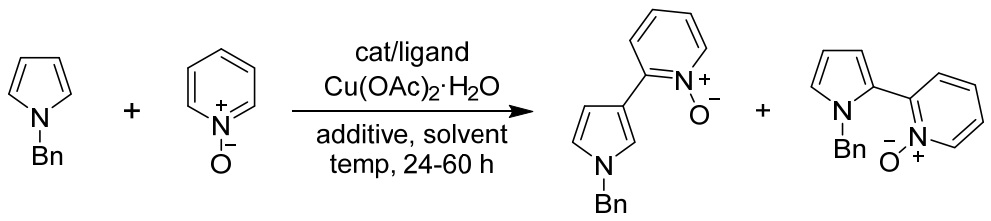


5a–f **1** **6ab–fb** **7ab-fb**

$R_1 = R_2$ = Me, 49%, **6ab**/**7ab** = 80:20
$R_1 = R_2$ = Bn, 55%, **6bb**/**7bb** = 87:13
$R_1 = R_2$ = Ts, 24%, **6cb**/**7cb** >99:1
$R_1 = R_2$ = C(O)NMe_2, 34%, **6db**/**7db** = 58:42
R_1 = Boc, R_2= H,13%, **6eb**/**7eb** >99:1
$R_1 = R_2$ = Ph, 43%, **6fb**/**7fb** = 67:33

Scheme 84: The influence of *N*-protecting group of pyrroles.

Table 4: Optimization of the C3 heteroarylation of pyrroles.[a]



5b **1b** **6bb** **7bb**

Entry	Catalyst	Ligand	$Cu(OAc)_2 \cdot H_2O$	Solvent	Additive	Yield[b] (%)	**6bb**/**7bb**
1	$Pd(OAc)_2$	–	1.5 equiv	dioxane	pyridine	48	83:17
2	–	–	1.5 equiv	dioxane	pyridine	–	–
3	$Pd(OAc)_2$	–	1.5 equiv	dioxane	–	36	50:50
4	$Pd(OAc)_2$	–	–	dioxane	pyridine	8	75:25
5	$Pd(NO_3)_2$	–	1.5 equiv	dioxane	pyridine	50	80:20
6	$Pd(TFA)_2$	–	1.5 equiv	dioxane	pyridine	42	87:13
7	$Pd(CH_3CN)_2Cl_2$	–	1.5 equiv	dioxane	pyridine	44	67:33
8	$Pd(OAc)_2$	dppp	1.5 equiv	dioxane	pyridine	52	92:8
9	$Pd(OAc)_2$	dppp	1.5 equiv	dioxane	pyridine	51[c]	89:11

10	$Pd(OAc)_2$	trianisylphosphine	1.5 equiv	dioxane	pyridine	46	90:10
11	$Pd(OAc)_2$	PhDave-Phos	1.5 equiv	dioxane	pyridine	52	93:7
12	$Pd(OAc)_2$	dppf	1.5 equiv	dioxane	pyridine	24.	75:25
13	$Pd(OAc)_2$	dppm	1.5 equiv	dioxane	pyridine	52	89:11
14	$Pd(OAc)_2$	dppp	1.5 equiv	DMSO	pyridine	trace	–
15	$Pd(OAc)_2$	dppp	1.5 equiv	dioxane/DMSO[d]	pyridine	36	>99:1
16	$Pd(OAc)_2$	dppp	1.5 equiv	dioxane/EtOH[d]	pyridine	40	>99:1
17	$Pd(OAc)_2$	dppp	1.5 equiv	dioxane/CH_3CN[d]	pyridine	45	90:10
18	$Pd(OAc)_2$	dppp	0.5 equiv	dioxane	pyridine	45	75:25
19	$Pd(OAc)_2$	dppp	0.5 equiv	dioxane	pyridine, K_2CO_3 (1equiv)	27	50:50
20	$Pd(OAc)_2$ CuCl	dppp	0.5 equiv	dioxane	pyridine	50	87:13
21	$Pd(OAc)_2$ CuCl	dppp	0.5 equiv	dioxane	pyridine, H_2O (1 equiv)	53	92:8
22	$Pd(OAc)_2$ CuBr	dppp	0.5 equiv	dioxane	pyridine, H_2O (1 equiv)	52	91:9
23	$Pd(OAc)_2$ CuCl	dppp	0.5 equiv	dioxane	pyridine, HOAc (1 equiv)	63	91:9
24	$Pd(OAc)_2$ CuCl	dppp	0.25 equiv	dioxane	pyridine, HOAc (2 equiv)	41	93:7[e]
25	$Pd(OAc)_2$ CuCl	dppp	0.25 equiv	dioxane	pyridine, HOAc (2 equiv)	59	92:8[f]
26	$Pd(OAc)_2$ CuCl	dppp	0.25 equiv	dioxane	pyridine, HOAc (2 equiv)	67	93:7[g]
27	$Pd(OAc)_2$ CuCl	dppp	0.25 equiv	AcOH	pyridine	–	–
28	$Pd(OAc)_2$	dppp	0.25 equiv	dioxane	pyridine, TBAC (10 mol%)	69	91:9
29	$Pd(OAc)_2$	dppp	0.25 equiv	dioxane	pyridine, NaCl (10 mol%)	66	92:8
30	$Pd(OAc)_2$	dppp	0.35 equiv	dioxane	pyridine	58	93:7

26	$Pd(OAc)_2$	CuCl	–	0.25 equiv	dioxane	pyridine, HOAc (2 equiv)	69	93:6

[a] Reaction conditions: **5b** (0.25 mmol), **6b** (1 mmol), catalyst (5 mol%), co-catalyst (10 mol%), ligand (5 mol%), pyridine (0.25 mmol) in solvent (1 mL) at 110 °C. [b] Isolated yield. [c] Reaction conducted at 130 °C. [d] The ratio of solvent (dioxane:co-solvent = 5:1). [e] Reaction conducted for 24 h. [f] Reaction conducted for 48 h. [g] Reaction conducted for 60 h. dppp = 1,3-bis(diphenylphosphino)propane; dppf = 1,1'-bis(diphenylphosphino)ferrocen; dppm = 1,1-bis(diphenylphosphino)methane.

Our reaction conditions screening started from the catalyst-ligand system. Palladium catalyst was essential to the transformation, only starting material was recovered in the absence of palladium catalyst (Table 4, entry 2). Other palladium sources gave slightly lower yields compared to $Pd(OAc)_2$ (entries 1, 5–7). Pyridine played a critical role in the reaction as it may stabilize the palladium(0) prior to re-oxidation[59b]. We found the absence of pyridine yielding unselective mixture of C2 and C3 products (entry 3). The presence of phosphine ligand favors the oxidative C3 arylation of indoles, as has been reported by You.[72, 91] After screening a variety of phosphine ligands, the best yield and selectivity were obtained with dppp or PhDave-Phos ligand. Dppp was chosen as model ligand for further screenings (entries 8–12). The phosphine oxide was observed after column chromatography. It is not clear at which stage of the reaction the oxidation of the phosphine occurred. However, the phosphines may serve as a ligand or additive to give slightly higher yield[92].

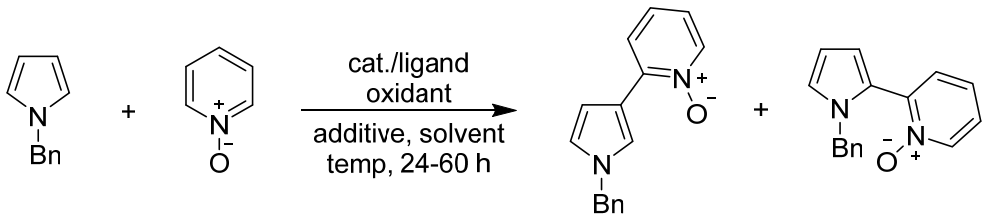
Different solvents were investigated, which indicated that the polarity of solvent highly influenced the regioselectivity. Polar solvents favored the C3 product perhaps by suppressing competitive C2 arylation, albeit reducing the yield (entries 13–16). Dioxane had very good performance in both yield and selectivity. Raising the temperature to 130 ^oC did not improve the yield (entry 9).

Subsequently, we examined the amount of oxidant used. The yield and selectivity dropped with the amount of oxidant decreased (entries 8 vs 17). The influence of additives was investigated, K_2CO_3 as basic additive did not improve the result (entry 18). The addition of Copper(I) chloride/bromide was found to increase the yields (entries 17 vs 19). To investigate the role of copper chloride, some control experiments were conducted. TBAC, NaCl, or additional $Cu(OAc)_2$ was added to the reaction mixture in the absence of CuCl. Adding TBAC or NaCl gave comparable yields to when CuCl was added. A lower yield was observed when $Cu(OAc)_2$ was

used, which indicates that the chloride anion rather than copper enhances the yield. To our delight, the addition of proton sources such as acetic acid or water had beneficial effects (entries 20–23). The addition of acetic acid dramatically improved the catalytic efficiency, perhaps because the acetate anion is involved in the C–H bond cleavage (entries 22 and 23). However, pyrroles were decomposed when acetic acid was used as solvent (entry 24). Finally, the desired product with good yield and selectivity preferring C3 position was achieved by using $Pd(OAc)_2$ (5 mol%), CuCl (10 mol%), DPPP (5 mol%), $Cu(OAc)_2 \cdot H_2O$ (25 mol%) as oxidant, both acetic acid and pyridine as additives. The reactions were proceeded under aerobic conditions in the presence of dioxane (entry 23).

2.3.3 Optimizition of the Reaction Conditions for the Oxidative C2 Heteroarylation of Pyrroles

Table 5: Optimization of the C2 heteroarylation of pyrroles.[a]



5b **1b** **6bb** **7bb**

Entry	Catalyst	Ligand	Oxidant	Solvent	Yield[b]	**6bb/7bb**
1	$Pd(OAc)_2$	pyridine	$Cu(OAc)_2 \cdot H_2O$	dioxane	48	83:17
	10 mol%	1 equiv	3 equiv			
2	$Pd(OAc)_2$	bipyridine	$Cu(OAc)_2 \cdot H_2O$	dioxane	43	50:50
	10 mol%	1 equiv	3 equiv			
3	$Pd(OAc)_2$	bipyridine	AgOAc	dioxane	44	20:80
	10 mol%	1 equiv	3 equiv			
4	$Pd(OAc)_2$	bipyridine	Ag_2CO_3	dioxane	33	25:75
	10 mol%	1 equiv	3 equiv			
5	$Pd(OAc)_2$	–	Ag_2CO_3	dioxane	19	33:67
	10 mol%		3 equiv			
6	–	bipyridine	AgOAc	dioxane	–	–
		40 mol%	2.3 equiv			

7	$Pd(TFA)_2$ 10 mol%	bipyridine 40 mol%	AgOAc 2.3 equiv	dioxane	36	83:17
8	$Pd(OAc)_2$ 5 mol%	bipyridine 20 mol%	AgOAc 2.3 equiv	dioxane	35	20:80
9	$Pd(OAc)_2$ 5 mol%	bipyridine 40 mol%	AgOAc 2.3 equiv	dioxane	42 37[c]	20:80 25:75
10	$Pd(OAc)_2$	terpyridine	AgOAc	dioxane	33	25:75
11	$Pd(OAc)_2$ 5 mol%	4,4'-dimethoxy-2,2'-bipyridine	AgOAc 2.3 equiv	dioxane	52	50:50
12	$Pd(OAc)_2$ 5 mol%	4,4'-dimethyl-2,2'-bipyridine	AgOAc 2.3 equiv	dioxane	38	25:75
13	$Pd(OAc)_2$ 5 mol%	6,6'-dimethyl-2,2'-bipyridine	AgOAc 2.3 equiv	dioxane	17	33:67
14	$Pd(OAc)_2$ 5 mol%	ethyl[2,2'-bipyridine]-4-carboxylate	AgOAc 2.3 equiv	dioxane	32	17:83
15	$Pd(OAc)_2$ 5 mol%	phenanthroline 40 mol%	AgOAc 2.3 equiv	dioxane	38	25:75
16	$Pd(OAc)_2$ 10 mol%	bipyridine 40 mol%	AgOAc 2.3 equiv	dioxane	26[d]	20:80[d]
17	$Pd(OAc)_2$ 10 mol%	bipyridine 40 mol%	AgOAc 2.3 equiv	dioxane	45[e] 40[f]	25:75[e] 25:75
18	$Pd(OAc)_2$ 10 mol%	bipyridine 40 mol%	AgOAc 2.3 equiv	PhCl	30	25:75
19	$Pd(OAc)_2$ 10 mol%	bipyridine 40 mol%	AgOAc 2.3 equiv	dioxane/PhCl[g]	40	14:86
20	$Pd(OAc)_2$ 10 mol%	bipyridine 40 mol%	AgOAc 2.3 equiv	dioxane/*o*-xylene[g]	32	11:89
21	$Pd(OAc)_2$ 10 mol%	bipyridine 40 mol%	AgOAc 2.3 equiv	dioxane/DMA[g]	22	20:80
22	$Pd(OAc)_2$ 10 mol%	bipyridine 40 mol%	AgOAc 2.3 equiv	dioxane/DMF[g]	42	25:75
23	$Pd(OAc)_2$ 10 mol%	bipyridine 40 mol%	AgOAc 2.3 equiv	dioxane/DMSO[g]	38	25:75
24	$Pd(OAc)_2$ 10 mol%	bipyridine 40 mol%	benzoquinone 2.3 equiv	dioxane	–	–
25	$Pd(OAc)_2$ 10 mol%	bipyridine 40 mol%	*t*$BuCO_2Bz$ 2.3 equiv	dioxane	–	–

[a] Reaction conditions: **1b** (0.25 mmol), **2** (1 mmol), additive (0.25 mmol), solvent (1 mL). [b] NMR yield. [c] Isolated yield. [d] Cs_2CO_3 as additive. [e] HOAc as additive. [f] Reaction conducted at 150 °C. [g] The ratio of co-solvent (1:1). BQ = benzoquinone. *t*BuO_2Bz = *tert*-butyl benzoyl peroxide.

We were satisfied to observe the C2 coupling product increased significantly when the 2,2'-bipyridine was introduced as a ligand (Table 5, entries 2 vs 1). Inspired by this, our continuing effort was made for screening to gain the switching of the C2/C3 selectivity. The silver salts were examined because Fagnou and DeBoef reported that 2-arylindoles were obtained in the presence of silver acetate.[59b, 61] Silver acetate may form a monometallic cluster with $Pd(OAc)_2$ that could prefer functionalization of the C2 position of indoles[61]. To our delight, The C3 arylation was further suppressed when silver salt was employed (entries 3 and 4). The reversed C2/C3 selectivity with modest yield was obtained in the presence of silver acetate (entry 3). The screening of oxidants revealed the importance of silver as oxidant, because the addition of other oxidants did not give any product (entries 24 and 25).

Control experiments were conducted to test if silver behaves as a catalyst in this transformation. Substrates **5b** and **1b** alone in the absence of palladium salt did not undergo any reaction, which indicates that palladium rather than silver acetate is essential for this transformation (entry 6).

The yield dropped in the absence of ligand (entry 5). Therefore we investigated ligands with different electronic properties. Neither electron-donating nor electron-withdrawing bipyridines did improve the yield compared with the unsubstitued bipyridine (entries 10–15). The same C2 and C3 mixture was afforded by using terpyridine as ligand (entry 10). The influence of steric factors of the ligand was also tested, 6,6'-dimethyl-2,2'-bipyridine led to decreased yield, which indicates that the the coordination ability of ligand to metal influences the catalytic reaction (entry 13).

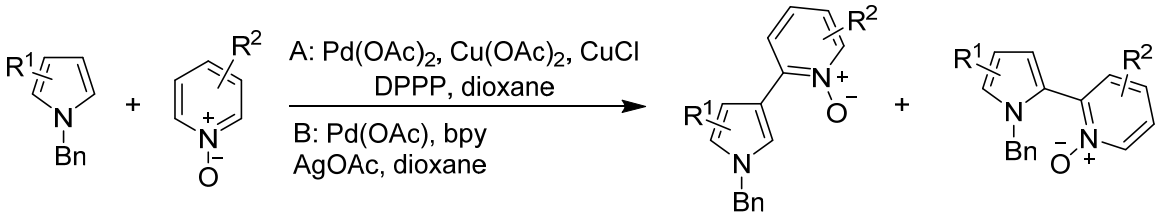
The influence of additives were examined. The acidic additive (HOAc) had minor influence and the basic addtive (Cs_2CO_3) decreased the yield (entries 16 and 17). Raising the reaction temperature resulted in slightly lower yield. The screening of solvent revealed that xylene as co-solvent slightly increased the ratio of C2/C3 product albeit decreasing the yield. Further solvents such as polar DMSO, DMF, and unpolar PhCl did not increase the yield (entries 18–23).

The influence of the catalyst and ligand loading were tested finally. We found the yield did not drop dramatically with the decreased amount of catalyst and ligand (entries 3, 8, and 9). The best

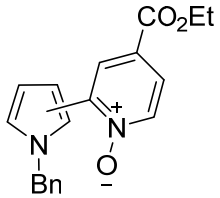
result was obtained by using 5 mol% $Pd(OAc)_2$ as catalyst, 40 mol% bipyridine as ligand, 2.3 equiv AgOAc as oxidant in dioxane solvent (entry 9).

2.3.4 The Regiocontrolled Oxidative Cross Coupling of *N*-Protecting Pyrroles with Pyridine *N*-Oxide Derivatives

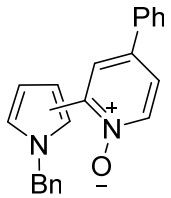
Scheme **85**: Substrate for the regiocontrolled oxidative coupling of pyrroles and pyridine *N*-oxides[a].



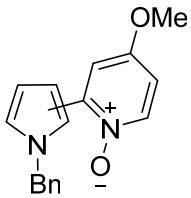
5 **1** **6** **7**



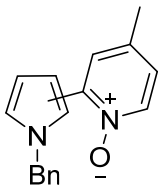
A: 64%, **6ba**:**7ba** = 90:10
B: 33%, **6ba**:**7ba** = 20:80



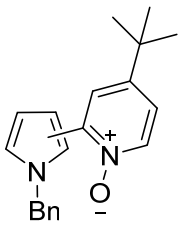
A: 68%, **6bh**:**7bh** = 94:6
B: 34%, **6bh**:**7bh** = 17:83



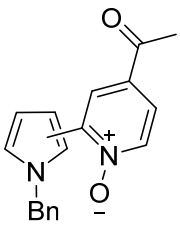
A: 42%, **6bg**:**7bg** = 89:11
B: 36%, **6bg**:**7bg** = 56:44



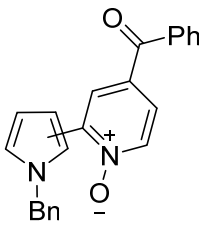
A: 59%, **6be**:**7be** = 95:5
B: 42%, **6be**:**7be** = 43:57



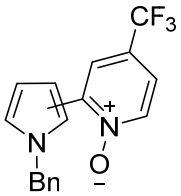
A: 61%, **6bf**:**7bf** = 95:5
B: 36%, **6bf**:**7bf** = 25:75



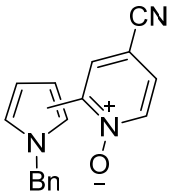
A: 69%, **6bk**:**7bk** = 92:8
B: 33%, **6bk**:**7bk** = 20:80



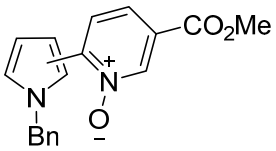
A: 68%, **6bl**:**7bl** = 96:4
B: 33%, **6bl**:**7bl** = 20:80



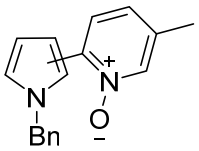
A: 60%, **6bu**:**7bu** = 90:10
B: 34%, **6bu**:**7bu** = 11:89



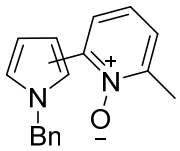
A: 24%, **6bo**:**7bo** = 75:25
B: 18%, **6bo**:**7bo** = 20:80



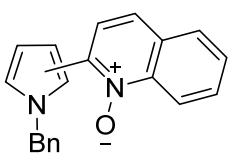
A: 45%, **6bc**:**7bc** = 52:48
B: 32%, **6bc**:**7bc** = 25:75



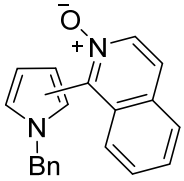
A: 45%, **6bv**:**7bv** = 75:25
B: 21%, **6bv**:**7bv** = 33:67



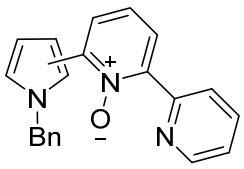
A: 38%, **6bd**:**7bd** = 89:11
B: 11%, **6bd**:**7bd** = 20:80



A: 48%, **6bj**:**7bj** = 50:50
B: 29%, **6bj**:**7bj** = 10:90

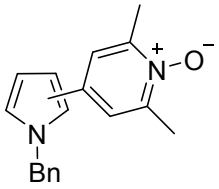


A: 50%, **6bi**:**7bi** = 75:25
B: 28%, **6bi**:**7bi** = 7:93

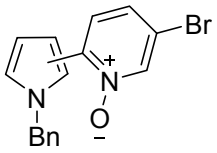


A: n.d.
B: 16%, **6bq**:**7bq** = 33:67

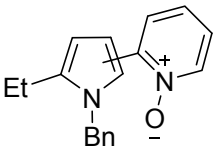
A: n.d.
B: 25%, **6bw**:**6bw** < 1:99



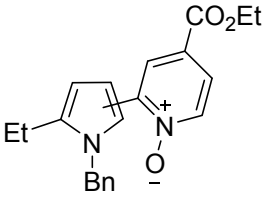
A: n.d.
B: n.d.



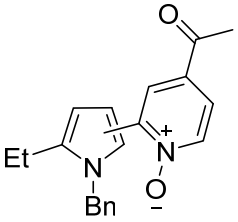
A: trace
B: trace



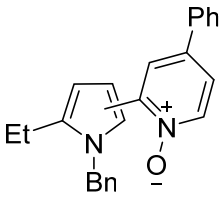
A: 60%, **6gb**:**7gb** = 84:16
B: 34%, **6gb**:**7gb** = 20:80



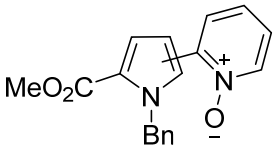
A: 80%, **6ga**:**7ga** = 94:6
B: 28%, **6ga**:**7ga** < 1:99



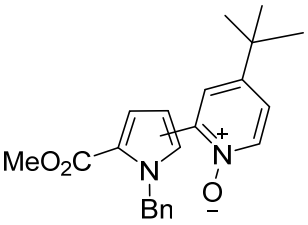
A: 74%, **6gk**:**7gk** = 91:9
B: 22%, **6gk**:**7gk** < 1:99



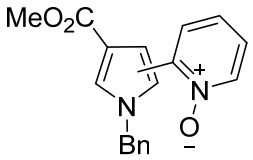
A: 79%, **6gh**:**7gh** > 99:1
B: 42%, **6gh**:**7gh** = 9:91



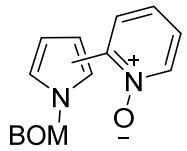
A: 45%, **6hb**:**7hb** = 93:7
B: 11%, **6hb**:**7hb** = 33:67



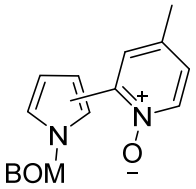
A: 57%, **6hf**:**7hf** > 99:1
B: trace



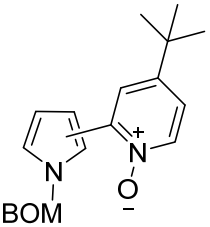
A: 26%, **6ib**:**7ib** < 1:99
B: 14%, **6ib**:**7ib** < 1:99



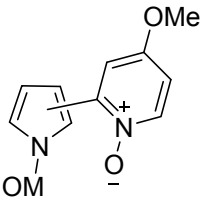
A[b]: 57%, **6jb**:**7jb** = 88:12
B: 37%, **6jb**:**7jb** = 25:75



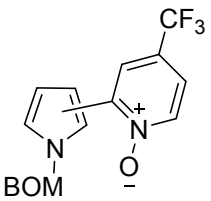
A[b]: 60%, **6je**:**7je** = 92:8
B: 35%, **6je**:**7je** = 57:43



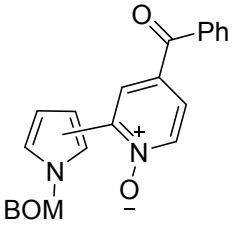
A[b]: 52%, **6jf**:**7jf** = 99:1
B: 37%, **6jf**:**7jf** = 33:67



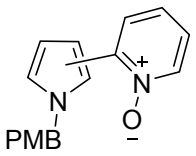
A[b]: 67%, **6jg**/**7jg** = 91:9
B: 45%, **6jg**/**7jg** = 55:45



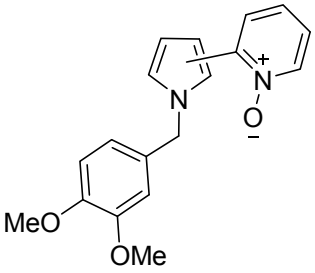
A[b]: 51%, **6ju**/**7ju** > 99:1
B: 41%, **6ju**/**7ju** = 25:75



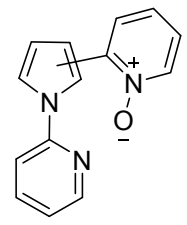
A[b]: 51%, **6jl**/**7jl** > 99:1
B: 43%, **6jl**/**7jl** = 33:67



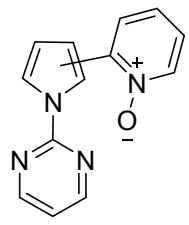
A[b]:60%, **6kb**/**7kb** = 93:7
B: 35%, **6kb**/**7kb** = 33:67



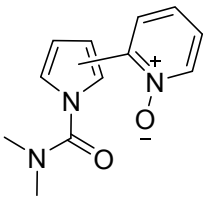
A[b]: 53%, **6lb**/**7lb** = 90:10
B: 33%, **6lb**/**7lb** = 38:62



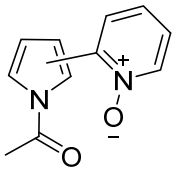
A:0%
B: 0%



A:trace
B: trace



B[c]: 22%, **6da**/**7da** = 50:50



B: trace

[a] Reaction conditions for (**A**): **4** (0.25 mmol), **5** (1 mmol), $Pd(OAc)_2$ (5 mol%), CuCl (10 mol%), dppp (5 mol%), $Cu(OAc)_2 \cdot H_2O$ (25 mol%), pyridine (1 equiv), HOAc (2 equiv) in dioxane(1 mL) at 110 ^oC for 60 h. [b] Reaction conditions for: **4** (0.25 mmol), **5** (1 mmol), $Pd(OAc)_2$ (5 mol%), CuCl (15 mol%), $Cu(OAc)_2 \cdot H_2O$ (25 mol%), pyridine (1 equiv), HOAc (2 equiv) in dioxane(1 mL) at 110 ^oC for 60 h. [c] NMR yield was reported.

The regioselectivity and reactivity was strongly depending on the reaction conditions (Scheme 85). We tested the substrate scope under the optimized reaction conditions. Most substituted pyridine *N*-oxides coupled with benzyl pyrrole in good to excellent yields under conditions **A**. Pyridine *N*-oxides with an ester, carbonyl, phenyl, *tert*-butyl, or trifluoro methyl group in the C4 position afforded the desired products in 64, 69, 68, 68, 61, and 60% yield respectively with high regioselectivity in favor of C3 position. The easy decomposition of pyrrole was suppressed under these conditions. Electron withdrawing substituents on pyridine *N*-oxides gave slightly higher yields than electron donating substituents (**6ba**/**7ba**, **6bk**/**7bk**, **6bl**/**7bl** vs **6bg**/**7bg**, **6be**/**7be**, **6bd**/**7bd**). We found deoxgenated starting material when 4-phenyl pyridine *N*-oxide and 4-benzoyl pyridine *N*-oxide were employed as substrate, resulting in 15% 4-phenyl pyridine and 49% 4-benzoyl pyridine to the corresponding pyridine *N*-oxides respectively. C3 substituted pyridine *N*-oxides afforded the product with low ratio of regioselectivity, the reaction proceeded at the C6 position of the pyridine oxides due to the steric hindrance by the C3 substituents (**6bc**/**7bc** and **6bv**/**7bv**). Quinoline and isoquinoline gave low selectivity slightly favored the C3 product, isoquinoline was selectively reacted at more reactive position (**6bj**/**7bj** and **6bi**/**7bi**). Moreover, under condition **B**, quinoline and isoquinoline led to much higher selectivity in favor of the C2 position. The functional groups such as carbonyl, ester and trifluoromethyl were tolerated. However, a low yield was obtained for cyano pyridine *N*-oxide with low conversion (**6bo**/**7bo**). A trace amount of product was observed and no halogen pyridine *N*-oxide was recovered, which indicated high incompatibility of halogen pyridine *N*-oxide under acidic and aerobic conditions. The unreactive 2,6-substitued pyridine oxides resulted in no conversion. Bipyridine *N*-oxides and pyrazine *N*-oxides were unreactive under these conditions. However, the corresponding product

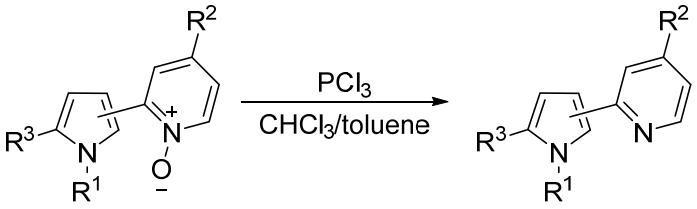
was formed under condition **B** (**6bq**/**7bq** and **7bw**). Satisfying result was obtained when electron rich pyrroles were employed (**6ga**/**7ga**, **6gb**/**7gb**, **6gk**/**7gk** and **6gh**/**7gh**). The impressive yield of 80% (**6ga**/**7ga**) and 79% with specific selectivity (**6gh**) was obtained for ethyl *N*-benzyl pyrrole, the ethyl group increased the electron density of the pyrrole ring to make it easy to undergo electrophilic aromatic substitution. In contrast, a relatively low yield was obtained by using electron poor 2-carboxylate *N*-benzyl pyrroles (**6hb**/**7hb**, **6hf**). Pyrroles with electron donating as well as protecting groups such as *N*-PMB, *N*-BOM, and *N*-(3,4-dimethoxylbenzyl) could also be coupled well with pyridine *N*-oxides to deliver the corresponding products in good yield and excellent C3 selectivity. These protecting groups are expected to be removed afterwards (**6jb**-**lb**/**7jb**-**lb**).

Under conditions **B**, the target compounds were formed in low to modest yield in favor of C2 heteroarylation. A significant amount of unreacted staring material was recovered under these conditions. Electron rich pyrroles had a better performance than electron poor pyrroles (**6gb**/**7gb**, vs **6hb**/**7hb** and **7ib**). 4-Ethoxycarbonyl pyridine *N*-oxide and 4-acetyl pyridine oxide gave the unique selective 2-arylated ethyl pyrrole, albeit in lower yield (**7ga** and **7gk**). When a C3 substituted pyrrole was used, the C2 product was exclusively detected under both conditions (**7ib**). While C2 ethyl substitued pyrrole led to high C2 selective products. 4-methoxypyridine *N*-oxides always afforded the C3 selective product when coupled with different substituted pyrroles. The effort by using directing group such as pyridiyl, acetyl, pyrimidyl, and dimethylcarboxamide to control the C2 selectivity under these conditions failed to achieve good reactivity, these substrates suffered from unreactivity or low yield. The structure of **7bg** was determined by single crystal X-ray diffraction.

2.3.5 Deoxygenation of Pyridine *N*-Oxides

The coupled pyridine oxides were easily reduced to the corresponding heteroarypyridines in good to excellent yield (Table 6). The effective deoxygenation was achieved by treatment with PCl_3. The *N*-protecting pyrrolopyridines were obtained under these conditions. Hydrogenation could also reduce the pyridine *N*-oxide in the prencense of Pd/C, however, full conversion was obtained for 12 h in 62 % yield with some perhaps decomposition product (Scheme 86).

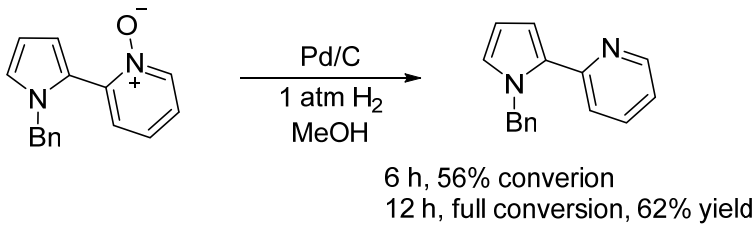
Table 6: Reduction of pyridine *N*-oxides.[a]



6/7 **8/9**

Entry	Pyridine *N*-oxides	R^1, R^2, R^3	Yield (%)[b]
1	**7bb**	Bn, H, H	86[c]
2	**7ga**	Bn, CO_2Et, Et	90
3	**7ba**	Bn, CO_2Et, H	72
4	**7bh**	Bn, Ph, H	90
5	**7ab**	Me, H, H	70
6[c]	**6bb**	Bn, H, H	85
7	**6ga**	Bn, CO_2Et, Et	87
8	**6ba**	Bn, CO_2Et, H	75
9	**6bh**	Bn, Ph, H	95
10	**6ab**	Me, H, H	72
11	**6kb**	PMB, H, H	92

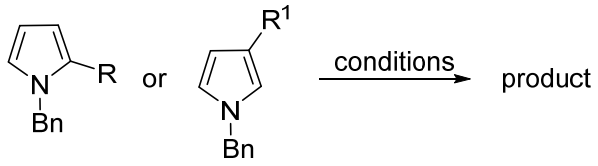
[a] Reactions were carried out with **6**/**7** (0.1 mmol), PCl_3 (4 equiv), in 10% $CHCl_3$/toluene, at room temperature. [b] Isolated yield was reported. [c] Reaction was carried out in toluene.



Scheme 86: Hydrogenation for reduction of pyridine *N*-oxide.

2.3.6 Deprotection of Pyrrole Nitrogen

Table 7: Conditions for debenzylation.



Entry	R or R^1	Conditions	Results
1	R = pyridine *N*-oxide	20 bar H_2, 10 mol% Pd/C, HOAc, 16 h	deoxygenation product (57%)[a]
2	R = pyridine *N*-oxide	35 bar H_2, 10 mol% Pd/C, HOAc, 24 h	decomposition of starting material
3	R^1 = 4-ethoxycarbonyl pyridine *N*-oxide	2 equiv $TiCl_3$-Li-THF-I_2, rt, 16 h	deoxygenation product (55%)[a]
4	R^1 = 4-ethoxycarbonyl pyridine	2 equiv $TiCl_3$-Li-THF-I_2, rt, 16 h	no conversition
5	R = Pyridine	10 equiv DMSO 7 equiv KO*t*Bu, O_2, 2 h	no conversition
6	R^1 = pyridine *N*-oxide	15 equiv CF_3CO_2H, 50 mol% H_2SO4 excess anisole, 90 °C, 3 days	10% conversion
7	R^1 = pyridine *N*-oxide	5 equiv $AlCl_3$ excess anisole, rt, 2 h	no conversion
8	R^1 = pyridine *N*-oxide	50 equiv HCl, MeOH, 4 h	no conversion
9	R^1 = pyridine	3 mol% AIBN, 2 equiv NBS, DCM, reflux, 10 h	bromination product on pyrrole

[a] Isolated yield. AIBN = azobisisobutyronitrile. NBS = *N*-bromosuccinimide.

Debenzylation of *N*-benzyl pyrrole **7bb** was found to be troublesome. Hydrogenation of **7bb** was carried out in an acetic acid solution at 20 bar hydrogen pressure using palladium on charcoal as catalyst resulting in 57% yield of reduced product **9bb** together with starting material (Table 7, entry 1). However, conducting the reaction at 35 bar hydrogen only led to the decomposition of starting material, which was not isolate (entry 2).

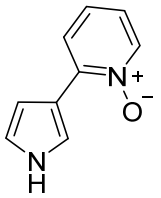
When 2-(1-benzyl-1*H*-pyrrol-3-yl)-4-(ethoxycarbonyl)pyridine *N*-oxide **6ba** was added to the $TiCl_3$-Li-THF-I_2 reagent[93], prepared from $TiCl_3$ with Li and I_2 in THF, the debenzylation did not

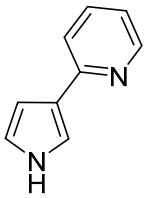
occur. However, deoxygenation product was obtained instead (entry 3). Due to the possible deactivation of the reducing agent by the pyridine *N*-oxide, 2-(1-benzyl-1*H*-pyrrol-3-yl)-4-(ethoxycarbonyl)pyridine **8ba** was employed as substrate under identical reaction conditions, disappointingly, it led to no conversion (entry 4).

We tried to remove the benzyl group using acid. However, neither sulfuric acid/trifluoroacetic acid with an excess of anisole[94] nor aluminum chloride with anisole [95]gave the product. A solution of HCl/ MeOH[96] failed to yield any product as well (entries 6–8). The potassium *tert*-butoxide/DMSO and oxygen conditions[97] were not viable for our desired purpose as well (entry 5), no conversion was observed in this case.

Another conceivable way to remove the benzyl group might be to introduce bromine in the benzylic position to form a intermediate via benzylic halogenation , which on aqueous work-up is expected to afford debenzylated product and benzaldehyde. However, bromination occurred on the more electrophilic pyrrole ring instead of the benzylic position resulting in C2 mono-brominated product (**13bb,14bb**) and 2,3- dibrominated product **12 bb** in 29% and 36% yield respectively (entry 9).

Table 8: Conditions for the removal of PMB group.

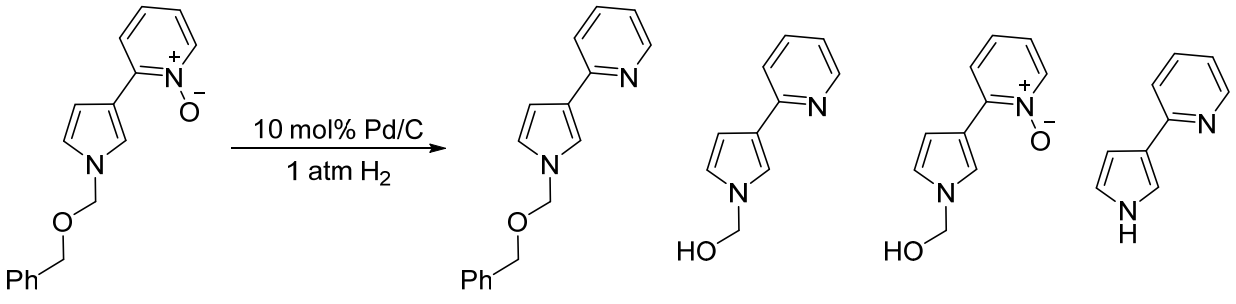
Entry	R	Conditions	Results
1	R = pyridine *N*-oxide	50 mol% H_2SO_4, excess CF_3CO_2H and anisole (1:1), 110 °C, 24 h	 35%[a]
2	R = pyridine *N*-oxide	DDQ, toluene, 80 °C, 24 h	–

3	R = pyridine	50 mol% H_2SO_4, excess CF_3CO_2H and anisole (1:1), 110 °C, 24 h	 44%[a]
4	R = pyridine *N*-oxide	50 mol% H_2SO_4, excess 1,3-dimethoxyl, benzene and CF_3CO_2H (1:1), 12 h, 110 °C	decomposition of starting matrial

[a] Isolated yield. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

The *N*-PMB pyrrole was reacting well with pyridine *N*-oxide as according to the reported method. Efforts were made to remove the PMB group due to its lower stability in comparison to a benzyl group. *N*-PMB pyrrolopyridine *N*-oxide gave the corresponding deprotected product in 35% yield after treatment with acid and anisole. Slightly higher yield was obtained for *N*-PMB pyrrolopyridine (44%, Table 8, entry 3). To further improve the yield, the more nucleophilic 1,3-dimethoxybenzene was used as scavenger for the putative cationic intermediate, which however resulted in no product. No signal of the pyrrole ring was observed in the crude NMR spectra, indicating decomposition of the starting material. The PMB group was also expected to be removed by oxidation under DDQ conditions and subsequent hydrolysis. However, it did not undergo any reaction.

Table 9: Conditions for the removel of BOM group.



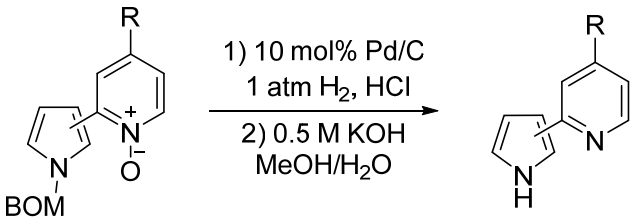
Entry	Conditions	Results[a]
1	MeOH, rt, 12h	A (full conversion)
2	10 equiv HCO_2H, rt, MeOH, 14 h	A:B = 1:0.56

3	10 equiv HCO_2H, rt, EtOH, 14 h	A (60% conversion)
4	10 equiv NH_4CO_2H, rt, MeOH, 16 h	A:B = 0.66:1
5	10 equiv NH_4CO_2H, reflux, MeOH, 4 h	A:B:D= 1:0.1:0.48
6	10 equiv HCl, MeOH, 16 h	B:C = 1:0.4
7	2.4 equiv HCl, MeOH:H_2O (1:4), 19 h	A:B = 1:5
8	2.4 equiv HCl, MeOH:H_2O (1:4), 21 h	B and some decomposed product

[a] The ratio was determined by NMR.

The initial attempt to remove the BOM group started from hydrogenation using palladium on charcoal. A mixture of debenzylated and deoxgenated product was observed (Table 9). Hydrogenation in methanol gave only the deoxygenated product. The addition of acid led to the debenzylation product to some degree. Therefore the influence of acid was investigated. Adding HCl resulted in complete debenzylation, however, not complete reduction of the pyridine *N*-oxide. Decreasing the amount of HCl and the addition of water gave 1-(hydroxymethyl)-pyrrole with high conversion. Full conversion was observed by extending the reaction time. However, the decomposed product was observed as well. The screening of reaction time, amount of acid and solvent is necessary for the different substrates to obtain a high conversion and avoid decomposition. To our delight, the removal of the *N*-BOM pyrrole was eventually achieved in good yields. Hydrogenation effectively reduced the pyridine *N*-oxide and removed the benzyl group to the corresponding 1-(hydroxymethyl)-pyrrole, subsequently the KOH was used to afford the desired product in good yield (Table 10, entries 1–8). While we observed the crude product underwent decomposition in some cases when performing it through column due to the instability of the pyrrole (entry 9).

Table 10: Deprotection of pyrroles.[a]

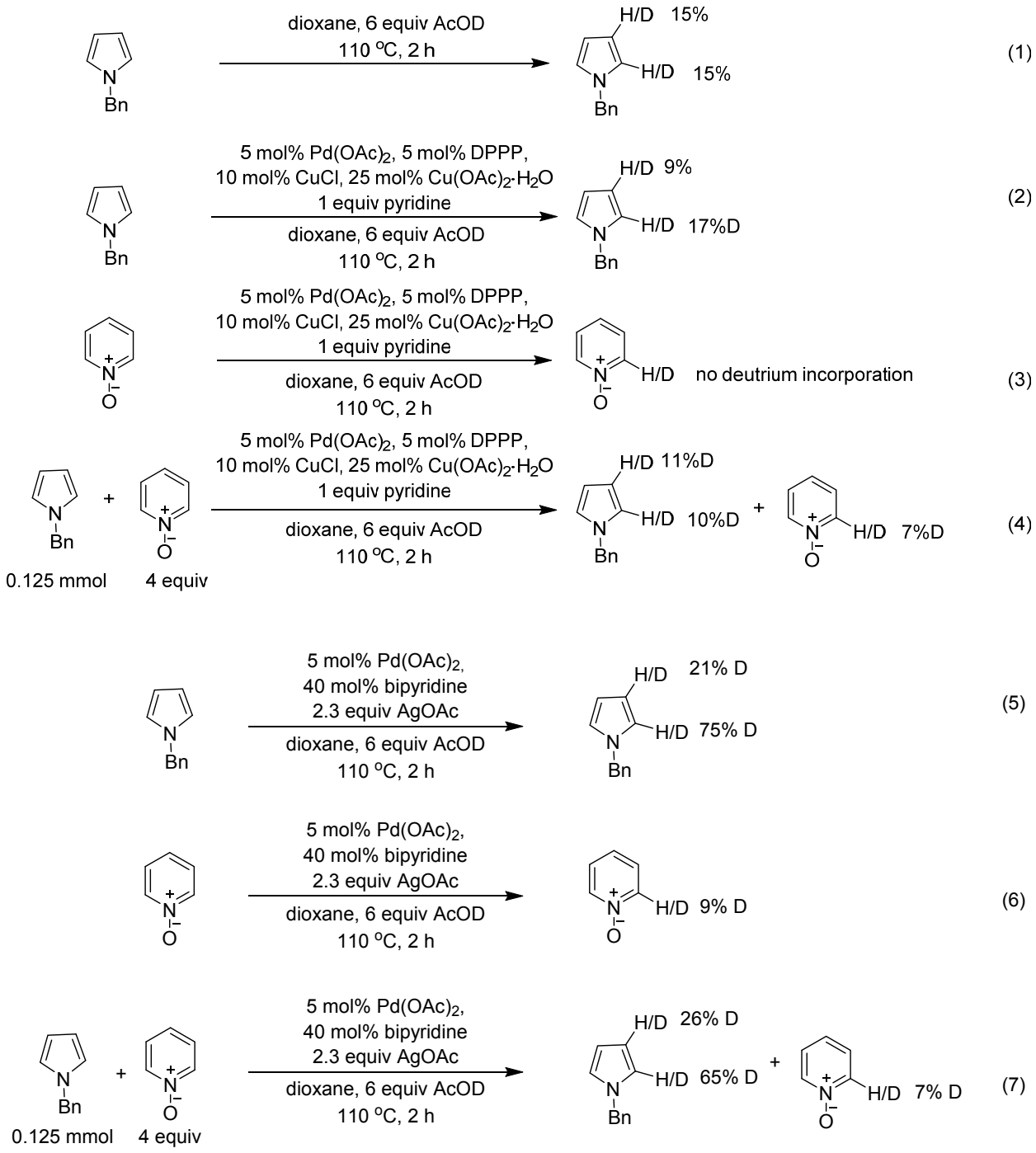


6/7 **10/11**

Entry	Starting Materials	R	Yield (%)[b]
1	**7jb**	H	61
2	**7je**	Me	88
3	**7jf**	*t*Bu	71
4	**7jg**	OMe	90
5	**6jb**	H	74
6	**6je**	Me	82
7	**6jf**	*t*Bu	60
8	**6jg**	OMe	84
9	**6ju**	CF_3	–[c]

[a] Reaction conditions: 1) 10 mol% Pd/C, 1 atm H_2, 0.05 M HCl in 2.5 mL MeOH/H_2O. 2) 0.5 M HCl in 2.5 mL MeOH/H_2O. [b] Isolated yield was reported. [c] Product was decomposed during column.

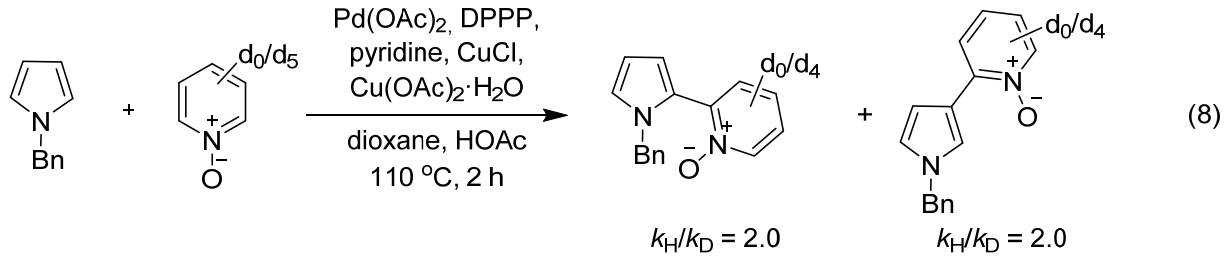
2.3.7 Mechanistic Study



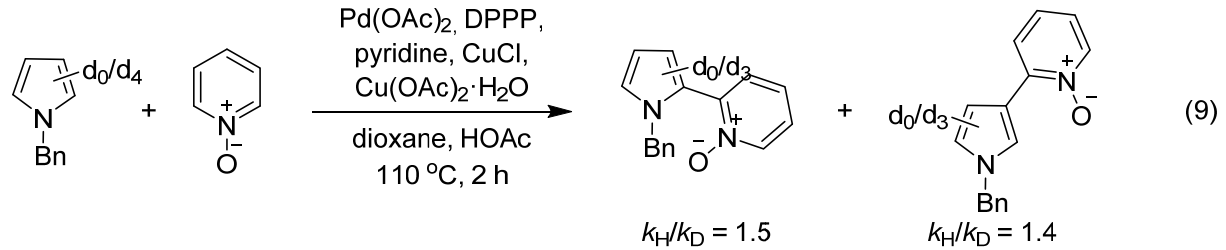
Scheme 87: H/D exchange experiments.

H/D exchange experiments were conducted (Scheme 87). The control experiments for benzyl pyrrole in deuterated acetic acid resulted in considerable deuterium incorporation compared to the deuterium incorporation in conditions **A**, which makes it hard to destinguish acid catalyzed

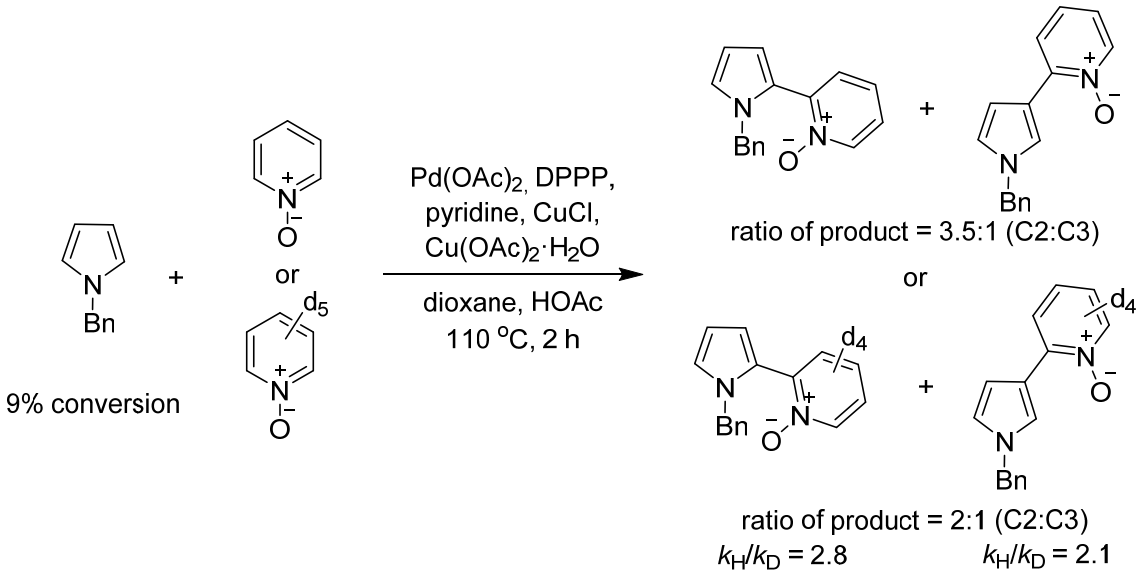
deuterium incorporation from metal mediated reversible C–H bond activation. In equation 2, The influence of the acid catalyst on deuterium incorporation of the two reactive position of pyrrole should be the same, however the deuterium incorporation on the two reactive site was different, which may indicated that the C–H bond activation on the C2 position was faster than the C3 position in the initial phase of the reaction. The exposure of benzyl pyrrole alone in the catalytic conditions **B** induced the rapid and significant H/D scrambling at the C2 position, which suggested the C–H bond activation of pyrrole on the C2 position was reversible. The magnitude of deuterium incorporation on C3 position was slightly higher than in the control experiments and comparable to the results in equation 7, which indicated that the C–H bond activation on the C3 pyrrole is reversible. The deuterium incorporation into pyridine *N*-oxide in the absence of pyrrole was comparable with the deuterium incorporation in the presence of pyrrole, which indicated the C–H bond activation of pyridine N-oxide under conditions **B** was reversible.



(8)

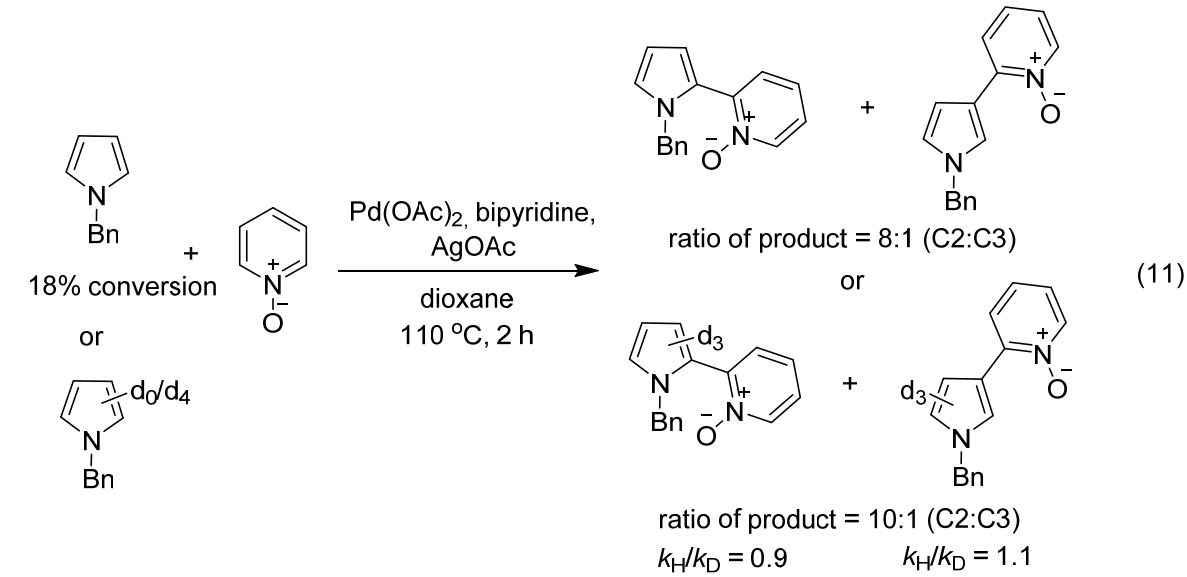


(9)

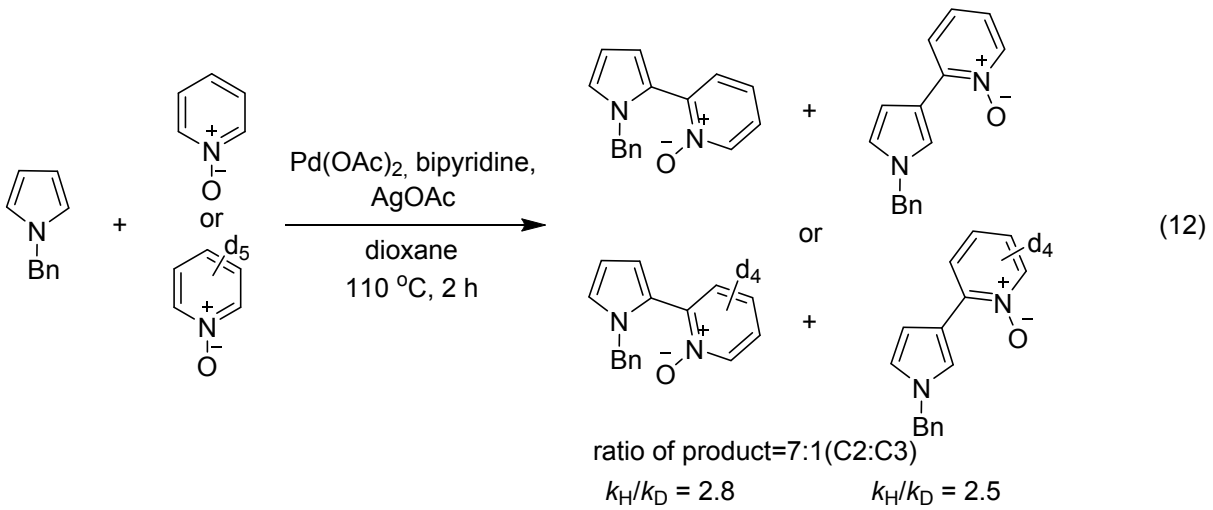


(10)

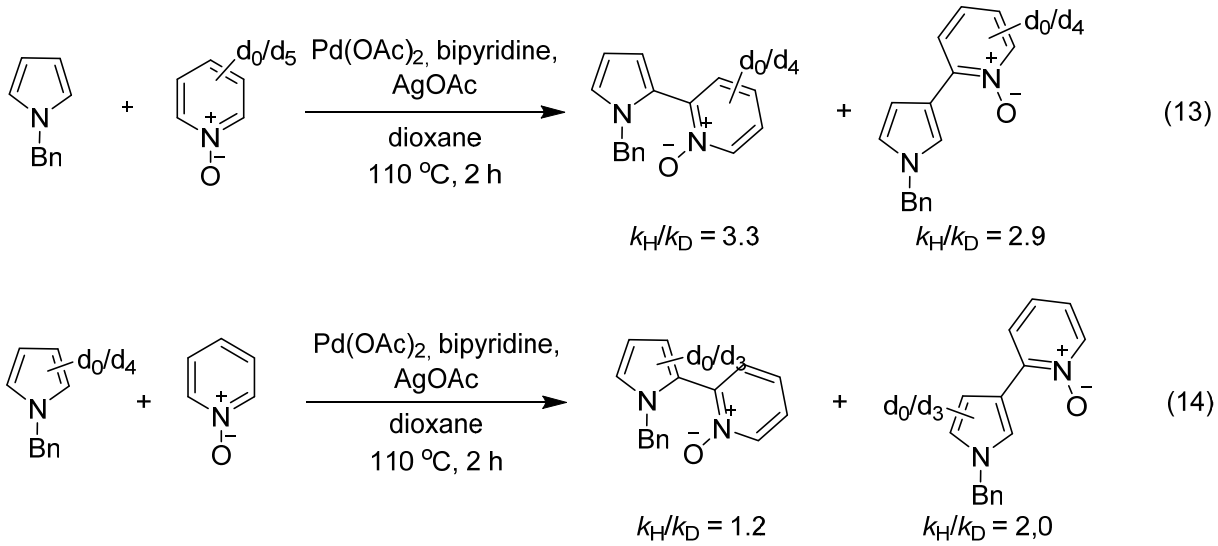
Scheme 88: Kinetic isotopic effect (KIE) investigation under condition **A**.



(11)



(12)



Scheme 89: Kinetic isotopic effect (KIE) investigation in condition **B**.

To get insight of the reaction mechanism, the kinetic isotopic effect (KIE) was investigated for both coupling partners under conditions **A** (Scheme 88). The intermolecular competition experiments revealed the kinetic isotopic effect (KIE) of 2.0 for pyridine *N*-oxide (equation 8), the primary KIE of 2.8 and 2.1 were observed in the two parallel experiments (equation 10), indicating the C–H bond activation of pyridine *N*-oxide occured during the rate determining step. In equation 10, the KIE of 1.5 and 1.4 for C2-pyrrole and C3-pyrrole ruled out the C–H bond cleavage of pyrrole involving in the rate determining step, the H/D exchange made the measured data larger than the real KIE, which might be in agreement with electrophilic substitution mechanism.

The isotopic effect was also investigated under conditions **B** (Scheme 89). The KIE of 0.9 and 1.1 excluded the C–H bond cleavage of pyrrole related to the rate determining step in parallel experiments (equation 11), and the KIE of 2.8 and 2.5 indicated the C–H bond cleavage of pyridine oxide occured during the rate determining step (equation 12). The KIE value on C3 position was unusual large might because the competition reaction on the C2 and C3 position, C–H bond activation on C3 position was slower than C2 position (equation 14).

2.4 Conclusion

In conclusion, a dehydrogenative two fold C–H bonds cross coupling of pyrroles with pyridine oxides was devoloped. The sensitive pyrroles were allowed under the reaction conditions. We were able to control the regioselectivity by using different conditions. The desired products with good yield and selectivity preferring the C3 position were achieved by using $Pd(OAc)_2$ (5 mol%), CuCl (10 mol%), DPPP (5 mol%), $Cu(OAc)_2 \cdot H_2O$ (25 mol%) as oxidant, both acetic acid and pyridine as additives in dioxane. whereas the C2 selectivity was controlled by using 5 mol% $Pd(OAc)_2$ as catalyst, 40 mol% bipyridine as ligand, 2.3 equiv AgOAc as oxidant in dioxane. A variety of substituted pyrroles and different pyridine *N*-oxides were tolerated in this method. Electron-donating pyrroles exhibited better reactivity than electron-withdrawing pyrroles. The reported method combined the subsequent hydrogenation to efficiently construct pyridopyrrole compounds.

Experimental Section

1 General Remarks

All reactions were carried out under anhydrous conditions in dried glasswares. Chemicals and solvents were commercially available. Dry solvents were taken from an MBRAUN *Solvent Purification System*.

Column chromatography was performed on *silica gel*. If deactivated silica gel was used column was first flushed with hexane/NEt_3 (10%) and hexane prior to use and the solvent was mixed with 0.1% NEt_3 during the seperation. TLC was performed on aluminium sheets with silica and fluorescence marker, or on aluminium sheets with aluminium oxide with fluorescence marker.

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded at room temperature using a *Jeol* ECX 400, *Jeol* ECP500, and *Bruker* AVANCE III 500. The chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS) and the coupling constants (*J*) are reported in Hertz (Hz). The spectra are referenced against residual solvent as internal standard according to the literature.[98] Multiplicity is reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. ^{13}C spectra are completely ^{1}H decoupled.

High resolution ESI-MS spectra were recorded on an Agilent 6210 ESI-TOF from *Agilent Technologies*. The applied charge is reported as positive (+). The spray charge was set to 4 kV. Data are reported in mass to charge (*m/z*). Electron impact ionization (EI) was recorded on a modified model MAT 711 from *Varian MAT* with a range of *m/z* 20 to 650.

Elemental analysis (C, H, N) were obtained on a Vario EL III elemental analyzer from *Varian Inc*.

GC-MS spectra were recorded on a Saturn 2100 from *Varian Inc*. with a range of *m/z* 20 to 650.

IR spectra were recorded in the range 4000–500 cm^{-1} with a ZnSe optical window. The absorption bands are given in wave numbers (cm^{-1}); intensities are reported as follows: s = strong, m = medium, w = weak.

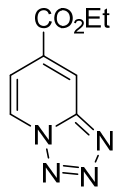
Melting points were measured on a *BÜCHI 510 melting point* apparatus and are uncorrected.

2 Experimental Section for Chapter I

2.1 Preparation of Tetrazolopyridines

General Procedure 1: To a teflon capped vial with a stir bar was added *N*-oxide (100 mg, 1.0 equiv), toluenesulfonyl chloride (5.0 equiv), sodium azide (5.0 equiv), and toluene (2 mL, 0.30 M in substrate). The resulting mixture was heated to 120 °C for 48 h and then cooled to room temperature. The reaction mixture was directly seperated by flash column chromatography on silica gel using ethyl acetate and hexane as eluent.

Ethyl tetrazolo[1,5-*a*]pyridine-7-carboxylate[99] **1027, 1036, 1079b**



2a

According to **General Procedure 1**, 4-ethyl carboxylate *N*-oxide (0.1 g, 0. 6 mmol), toluenesulfonyl chloride (0.57 g, 3 mmol), sodium azide (0.195 g, 3 mmol), toluene (2 mL, 0.3 M), column chromatography on silica gel (hexane:ethyl acetate = 2:1); white solid (110 mg, 0.57 mmol, 96%), (1.04 g, 91% for 6 mmol scale).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.87 (d, *J* = 7.0 Hz, 1H, PyH-6), 8.73 (d, *J* = 1.6 Hz, 1H, PyH-3), 7.81 (dd, *J* = 7.1, 1.6 Hz, 1H, PyH-5), 4.53 (q, *J* = 4.0 Hz, 2H, $\underline{CH_2}CH_3$), 1.46 (t, *J* = 4.0 Hz, 3H, $CH_2\underline{CH_3}$) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 163.5, 149.0, 134.6, 125.8, 118.6, 116.4, 63.2 ($\underline{CH_2}CH_3$), 14.6 ($CH_2\underline{CH_3}$) ppm.

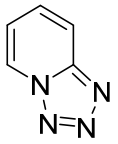
HRESI-MS: (+, 200V) m/z: $[M+H]^+$ Calcd. for $C_8H_9N_4O_2$ 193.0726; Found 193.0724. $[M+Na]^+$ Calcd. for $C_8H_8N_4O_2Na$ 215.0545; Found 215.0549.

IR (ν_{max}/cm^{-1}): 2962 (vw), 2150 (vw), 1717 (m), 1590 (w), 1487 (s), 1258 (m), 1189 (s), 1009 (s), 954 (s), 796 (s), 688 (s).

M.p.: 103–104 °C.

Elemental Analysis: Calcd. for $C_8H_8N_4O_2$: C, 50.00; H, 4.20; N, 29.15. Found: C, 50.37; H, 4.29; N, 29.17.

Tetrazolo[1,5-*a*]pyridine[33] **1041a**



2b

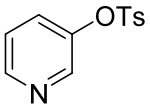
According to **General Procedure 1**, pyridine *N*-oxide (0.1 g, 1 mmol), toluenesulfonyl chloride (1 g, 5 mmol), sodium azide (0.34 g, 5 mmol), toluene (2 mL, 0.5 M), column chromatography on silica gel (hexane:ethyl acetate = 3:1–1:1); white solid (125 mg, 1 mmol, 99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (d, *J* = 6.9 Hz, 1H), 8.04 (d, *J* = 9.1 Hz, 1H), 7.75 – 7.61 (m, 1H), 7.27 – 7.21 (m, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.3, 132.3, 125.9, 117.0, 116.5 ppm.

HRESI-MS: (+, 200V) m/z: $[M+H]^+$ Calcd. for $C_5H_5N_4$ 121.0514; Found 121.0521.

pyridin-3-yl 4-methylbenzenesulfonate[100] **1041b**

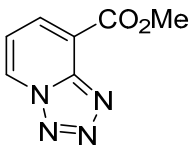


2bs

According to **General Procedure 1**, pyridine *N*-oxide (1 g, 10 mmol), toluenesulfonyl chloride (10 g, 10 mmol), sodium azide (3.4 g, 10 mmol), toluene (20 mL, 0.5 M), column chromatography on silica gel (hexane:ethyl acetate = 3:1–1:1); 2b (1.01g, 8 mmol, 80%) and white solid (100 mg, 0.4 mmol, 4%).

^{1}H NMR ($CDCl_3$) δ 8.50 (d, J = 4.7 Hz, 1 H), 8.14 (d, J = 2.7 Hz, 1 H), 7.70 (d, J = 8.3 Hz, 2 H), 7.47 (ddd, J = 8.2, 2.7, 1.4, Hz, 1 H), 7.28-7.34 (m, 2 H), 7.29 (dd, J = 8.4, 4.7 Hz, 1H), 2.45 (s, 3 H).

Methyl tetrazolo[1,5-*a*]pyridine-8-carboxylate[101] **1045**



2c

According to **General Procedure 1**, 3-methyl carboxylate *N*-oxide (0.1 g, 0.65 mmol), toluenesulfonyl chloride (0.62 g, 3.26 mmol), sodium azide (0.21 g, 3.23 mmol), toluene (2 mL, 0.32 M), column chromatography on silica gel (hexane:ethyl acetate = 2:1); white solid (45.3 mg, 0.25 mmol, 39%).

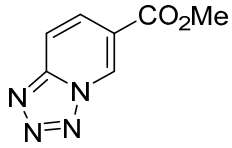
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (d, *J* = 4.0 Hz, 1H), 8.46 (d, *J* = 8.1 Hz, 1H), 7.36 (t, *J* = 7.0 Hz, 1H), 4.13 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.3, 147.2, 136.6, 129.6, 120.1, 116.3, 53.9 ppm.

HRESI-MS: (+, 200V) m/z: $[M+Na]^+$ Calcd. for $C_7H_6N_4O_2Na$ 201.0388; Found 201.0403.

M.p.: 170–171 °C.

Methyl tetrazolo[1,5-*a*]pyridine-6-carboxylate[99] **1045**



2c'

According to **General Procedure 1**, 3-methyl carboxylate *N*-oxide (0.1 g, 0.65 mmol), toluenesulfonyl chloride (0.62 g, 3.26 mmol), sodium azide (0.21 g, 3.23 mmol), toluene (2 mL, 0.32 M), column chromatography on silica gel (hexane:ethyl acetate = 2:1); yellow solid (60.5 mg, 0.34 mmol, 52%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.50 (d, *J* = 1.5 Hz, 1H, PyH-2), 8.22 (dd, *J* = 9.4, 1.5 Hz, 1H, PyH-4), 8.07 (d, *J* = 9.3 Hz, 1H, PyH-5), 4.04 (s, 3H, CH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.8 (CO), 149.7, 132.2, 129.2, 121.4, 116.0, 53.8 (CH_3) ppm.

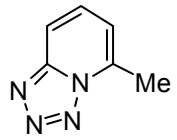
HRESI-MS: (+, 200V) m/z: $[M+Na]^+$ Calcd. for $C_7H_6N_4O_2Na$ 201.0388; Found 201.0393.

IR (ν_{max}/cm^{-1}): 3101 (w), 1715 (s), 1561 (s), 1438 (m), 1425 (m), 1339 (m), 1291 (s), 1259 (s), 1213 (s), 1000 (m), 997 (m), 842 (w), 796 (s), 772 (m).

M.p.: 117–118 °C.

Elemental Analysis: Calcd. for $C_7H_6N_4O_2$: C, 47.19; H, 3.39; N, 31.45. Found: C, 47.45; H, 3.81; N, 31.28.

5-Methyltetrazolo[1,5-*a*]pyridine[33] **1043**



2d

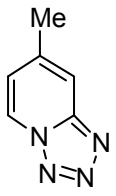
According to **General Procedure 1**, 2-methyl pyridine *N*-oxide (0.1 g, 0.92 mmol), toluenesulfonyl chloride (0.87 g, 4.6 mmol), sodium azide (0.29 g, 4.5 mmol), toluene (2 mL, 0.46 M), column chromatography on silica gel (hexane:ethyl acetate = 2:1–1:1); yellow solid (51.6 mg, 0.39 mmol, 42%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 9.0 Hz, 1H), 7.59 (dd, *J* = 9.0, 6.9 Hz, 1H), 7.00 (d, *J* = 6.9 Hz, 1H), 2.95 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.6, 136.6, 131.8, 115.3, 112.8, 17.2 ppm.

HRESI-MS: (+, 200V) m/z: $[M+H]^+$ Calcd. for $C_6H_7N_4$ 135.0671; Found 135.0674. $[M+Na]^+$ Calcd. for $C_6H_6N_4Na$ 157.0490; Found 157.0495.

7-Methyltetrazolo[1,5-*a*]pyridine[102] **1042**



2e

According to **General Procedure 1**, 4-methyl pyridine *N*-oxide (0.1 g, 0.92 mmol), toluenesulfonyl chloride (0.87 g, 4.6 mmol), sodium azide (0.29 g, 4.5 mmol), toluene (2 mL, 0.46

M), column chromatography on silica gel (hexane:ethyl acetate = 2:1–1:1); yellow solid (24.5 mg, 0.18 mmol, 21%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (d, *J* = 7.4 Hz, 1H, PyH-6), 7.77 (s, 1H, PyH-3), 7.04 (dd, *J* = 7.0, 1.5 Hz, 1H, PyH-5), 2.56 (s, 2H, CH_3) ppm.

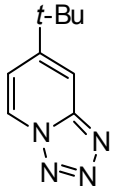
^{13}C NMR (101 MHz, $CDCl_3$): δ 149.3, 144.2, 124.7, 119.7, 114.3, 22.1 ppm.

HRESI-MS: (+, 200V) m/z: $[M+H]^+$ Calcd. for $C_6H_7N_4$ 135.0671; Found 135.0671. $[M+Na]^+$ Calcd. for $C_6H_6N_4Na$ 157.0490; Found 157.0495.

IR (ν_{max}/cm^{-1}): 2962 (w), 1633 (s), 1259 (s), 1213 (s), 1091 (m), 1015 (s), 997 (m), 863 (w), 795 (s).

M.p.: 97–98 °C.

7-(*tert*-Butyl)tetrazolo[1,5-*a*]pyridine[99] **1080**



2f

According to **General Procedure 1**, 4-*tert* butyl pyridine *N*-oxide (0.1 g, 0.68 mmol), toluenesulfonyl chloride (0.63 g, 3.3 mmol), sodium azide (0.22 g, 3.4 mmol), toluene (2 mL, 0.34 M), column chromatography on silica gel (hexane:ethyl acetate = 2:1); white solid (101 mg, 0.57 mmol, 87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (d, *J* = 7.3 Hz, 1H, PyH-6), 8.07 (d, *J* = 1.6 Hz, 1H, PyH-3), 7.25 (dd, *J* = 7.2, 1.6 Hz, 1H, PyH-5), 1.41 (s, 9H, $(\underline{CH_3})_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.8, 149.2, 124.5, 116.3, 110.3, 35.8, 30.4 ($(\underline{CH_3})_3$) ppm.

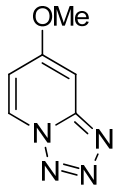
HRESI-MS: (+, 200V) m/z: $[M+H]^+$ Calcd. for $C_9H_{13}N_4$ 177.1140; Found 177.1140. $[M+Na]^+$ Calcd. for $C_9H_{12}N_4Na$ 199.0960; Found 199.0968.

IR (ν_{max}/cm^{-1}): 2965 (m), 2126 (vw), 1635 (s), 1532 (m), 1473 (s), 1375 (s), 1254 (m), 1160 (m), 1099 (s), 1002 (s), 881 (s), 810 (s), 667 (s).

M.p.: 101–102 °C.

Elemental Analysis: Calcd. for $C_9H_{12}N_4$: C, 61.34; H, 6.86; N, 31.79. Found: C, 61.33; H, 6.94; N, 31.63.

7-Methoxytetrazolo[1,5-*a*]pyridine[33] **1077**



2g

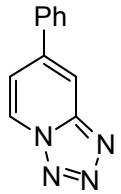
According to **General Procedure 1**, 4-methyoxyl pyridine *N*-oxide (0.1 g, 0.8 mmol), toluenesulfonyl chloride (0.76 g, 4 mmol), sodium azide (0.26 g, 4 mmol), toluene (2 mL, 0.4 M), column chromatography on silica gel (hexane:ethyl acetate = 1:1); white solid (20.4 mg, 0.14 mmol, 17%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 2.8 Hz, 1H), 6.86 (dd, *J* = 7.2, 2.8 Hz, 1H), 3.97 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.5, 125.5, 112.2, 100.1, 91.9, 56.6 ppm.

HRESI-MS: (+, 200V) m/z: $[M+H]^+$ Calcd. for $C_6H_7N_4O$ 151.0620; Found 151.0630. $[M+Na]^+$ Calcd. for $C_6H_6N_4ONa$ 173.0439; Found 173.0447.

7-Phenyltetrazolo[1,5-*a*]pyridine[33] **1044**



2h

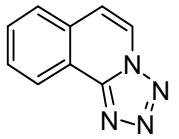
According to **General Procedure 1**, 4-phenyl pyridine *N*-oxide (0.1 g, 0.58 mmol), toluenesulfonyl chloride (0.56 g, 2.9 mmol), sodium azide (0.19 g, 2.9 mmol), toluene (2 mL, 0.29 M), column chromatography on silica gel (hexane:ethyl acetate = 2:1); white solid (105 mg, 0.54 mmol, 92%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.86 (dd, *J* = 7.2, 1.0 Hz, 1H), 8.18 – 8.17 (m, 1H), 7.70 – 7.68 (m, 2H), 7.58 – 7.53 (m, 3H), 7.48 (dd, *J* = 7.2, 1.5 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.6, 145.8, 137.1, 130.3, 129.9, 127.7, 125.5, 117.3, 112.4 ppm.

HRESI-MS: (+, 200V) m/z: $[M+H]^+$ Calcd. for $C_{11}H_9N_4$ 197.0827; Found 197.0834.

Tetrazolo[5,1-*a*]isoquinoline[33] **1046**



2i

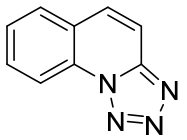
According to **General Procedure 1**, isoqunoline *N*-oxide (0.1 g, 0.7 mmol), toluenesulfonyl chloride (0.66 g, 3.4 mmol), sodium azide (0.23 g, 3.5 mmol), toluene (2 mL, 0.35 M), column chromatography on silica gel (hexane:ethyl acetate = 2:1); white solid (76.2 mg, 0.45 mmol, 65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81 – 8.72 (m, 1H), 8.55 (d, *J* = 7.3 Hz, 1H), 8.02 – 7.89 (m, 1H), 7.88 – 7.76 (m, 2H), 7.44 (d, *J* = 7.3 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 152.8, 148.2, 131.8, 130.0, 127.8, 125.4, 121.3, 120.1, 117.8 ppm.

HRESI-MS: (+, 200V) m/z: $[M+Na]^+$ Calcd. for $C_9H_6N_4Na$ 193.0490; Found 193.0500.

Tetrazolo[1,5-*a*]quinoline[33] **1078**



2j

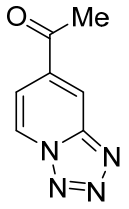
According to **General Procedure 1**, qunoline *N*-oxide (0.1 g, 0.7 mmol), toluenesulfonyl chloride (0.66 g, 3.4 mmol), sodium azide (0.23 g, 3.5 mmol), toluene (2 mL, 0.35 M), column chromatography on silica gel (hexane:ethyl acetate = 2:1); white solid (75 mg, 0.44 mmol, 64%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (d, *J* = 8.5 Hz, 1H), 8.02 – 7.93 (m, 2H), 7.91 – 7.83 (m, 2H), 7.73 – 7.72 (m, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 147.9, 133.8, 131.7, 131.3, 129.4, 128.5, 124.3, 117.3, 113.1 ppm.

HRESI-MS: (+, 200V) m/z: $[M+Na]^+$ Calcd. for $C_9H_6N_4Na$ 193.0490; Found 193.0482.

7-Acetyltetrazolo[1,5-*a*]pyridine[103] **1059**



2k

According to **General Procedure 1**, 4-acetyl pyridine *N*-oxide (0.1 g, 0.74 mmol), toluenesulfonyl chloride (0.70 g, 3.7 mmol), sodium azide (0.24 g, 3.7 mmol), toluene (2 mL, 0.37 M), column chromatography on silica gel (hexane:ethyl acetate = 1:1); white solid (105 mg, 0.65 mmol, 89%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.38 (d, *J* = 7.2 Hz, 1H, PyH-6), 8.95 (d, *J* = 1.7 Hz, 1H, PyH-2), 7.73 (dd, *J* = 7.2, 1.7 Hz, 1H, PyH-5), 2.75 (s, 3H, CH_3) ppm.

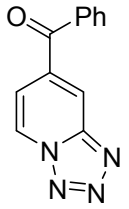
^{13}C NMR (101 MHz, DMSO-d_6): δ 196.1, 148.6, 139.6, 126.7, 117.0, 114.5, 26.8 ppm.

HRESI-MS: (+, 200V) m/z: $[M+H]^+$ Calcd. for $C_7H_7N_4O$ 163.0620; Found 163.0619.

IR (ν_{max}/cm^{-1}): 3041 (w), 1735 (s), 1685 (s), 1539 (m), 1476 (m), 1359 (m), 1314 (s), 1240 (s), 1215 (s), 1090 (m), 913 (m), 828 (s).

M.p.: 186–187 °C.

7-Benzoyltetrazolo[1,5-*a*]pyridine[99] **1060**



2l

According to **General Procedure 1**, 4-benzoyl pyridine *N*-oxide (0.1 g, 0.5 mmol), toluenesulfonyl chloride (0.48 g, 2.5 mmol), sodium azide (0.16 g, 2.5 mmol), toluene (2 mL, 0.25 M), column chromatography on silica gel (hexane:ethyl acetate = 2:1); white solid (110 mg, 0.49 mmol, 99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.94 (d, *J* = 7.1 Hz, 1H), 8.36 – 8.35 (m, 1H), 7.86 – 7.84 (m, 2H), 7.72 – 7.70 (m, 2H), 7.57 – 7.55 (m, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 193.0, 148.7, 140.8, 135.7, 134.5, 130.5, 129.4, 126.2, 118.6, 116.9 ppm.

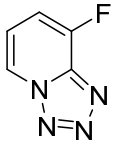
HRESI-MS: (+, 200V) m/z: $[M+Na]^+$ Calcd. for $C_{12}H_8N_4ONa$ 247.0596; Found 247.0595.

IR (ν_{max}/cm^{-1}): 3043 (w), 1652 (s), 1593 (m), 1529 (m), 1477 (m), 1444 (m), 1367 (w), 1324 (s), 1283 (s), 1250 (m), 1224 (w), 1088 (s), 911 (m), 894 (m), 826 (s), 716 (s).

M.p.: 116–117 °C.

Elemental Analysis: Calcd. for $C_{12}H_8N_4O$: C, 64.28; H, 3.60; N, 24.99. Found: C, 64.35; H, 3.46; N, 25.15.

8-Fluorotetrazolo[1,5-*a*]pyridine[33] **1062**



2m

According to **General Procedure 1**, 3-fluoropyridine *N*-oxide (0.1 g, 0.88 mmol), toluenesulfonyl chloride (0.84 g, 4.4 mmol), sodium azide (0.29 g, 4.5 mmol), toluene (2 mL, 0.44 M), column

chromatography on silica gel (hexane:ethyl acetate = 2:1); light yellow solid (103 mg, 0.75 mmol, 92%, **2m**:**2m'** = 77:15).

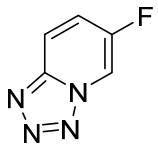
^{1}H NMR (400 MHz, DMSO-d_6): δ 9.24 (d, J = 6.7 Hz, 1H), 7.85 – 7.77 (m, 1H), 7.50 – 7.43 (m, 1H) ppm.

^{13}C NMR (101 MHz, CD_2Cl_2/DMSO-d_6): δ 149.7 (d, J = 258.0 Hz), 142.9 (d, J = 30.2 Hz), 122.9 (d, J = 5.7 Hz), 117.08 (d, J = 5.7 Hz), 115.57 (d, J = 15.9 Hz) ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ –122.1 ppm.

HRESI-MS: (+, 200V) m/z: $[M+H]^+$ Calcd. for $C_5H_4FN_4$ 139.0420; Found 139.0425.

6-Fluorotetrazolo[1,5-*a*]pyridine[33]



2m'

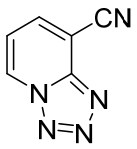
^{1}H NMR (400 MHz, DMSO-d_6): δ 9.73 (s, 1H), 8.35 (dd, J = 11.2, 5.3 Hz, 1H), 8.06 – 7.98 (m, 1H) ppm.

^{13}C NMR (101 MHz, CD_2Cl_2/DMSO-d_6): δ 155.1 (d, J = 245.6 Hz), 146.8, 125.1 (d, J = 26.5 Hz), 116.4 (d, J = 9.4 Hz), 113.9 (d, J = 41.6 Hz) ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ –132.5 ppm.

HRESI-MS: (+, 200V) m/z: $[M+H]^+$ Calcd. for $C_5H_4FN_4$ 139.0420; Found 139.0422.

Tetrazolo[1,5-*a*]pyridine-8-carbonitrile (2n)[8a] **1057, 1088**



2n

According to **General Procedure 1**, 3-cyanopyridine *N*-oxide (0.1 g, 0.83 mmol), toluenesulfonyl chloride (0.79 g, 4.2 mmol), sodium azide (0.27 g, 4.2 mmol), toluene (2 mL, 0.42 M), column chromatography on silica gel (hexane:ethyl acetate = 2:1, 10% Et_3N/hexane deactivate the

column); light yellow solid (44.7 mg, 0.31 mmol, 37%). Single crystals suitable for X-ray diffraction were obtained from DCM by slow evaporation of the solvent.

In CD_2Cl_2 solution a mixture of tetrazole and azide in a ratio of 17:1 was observed.

Tetrazole: **^{1}H NMR** (400 MHz, CD_2Cl_2): δ 9.08 (d, *J* = 7.0 Hz, 1H), 8.17 (d, *J* = 7.1 Hz, 1H), 7.39 (t, *J* = 7.0 Hz, 1H) ppm. **Azide**: δ 8.54 (dd, *J* = 4.8, 1.8 Hz, 1H), 7.94 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.19 (dd, *J* = 7.8, 5.0 Hz, 1H) ppm.

^{13}C NMR (126 MHz, CD_2Cl_2): δ 152.6, 147.5, 139.5, 135.0, 129.9, 129.8, 122.1, 119.8, 116.3, 112.8, 101.8, 100.0 ppm.

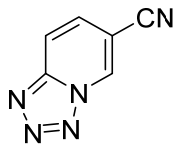
In DMSO-d_6 solution, only the tetrazole was detected.

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.65 (d, *J* = 7.6 Hz, 1H), 8.60 (d, *J* = 7.8 Hz, 1H), 7.61 (t, *J* = 7.0 Hz, 1H) ppm.

^{13}C NMR (101 MHz, DMSO-d_6/$CDCl_3$): δ 147.5, 141.4, 131.6, 117.1, 113.9, 99.8 ppm.

HRESI-MS: (+, 200V) m/z: $[M+Na]^+$ Calcd. for $C_6H_3N_5Na$ 168.0286; Found 168.0285.

Tetrazolo[1,5-*a*]pyridine-6-carbonitrile[8a]



2n'

According to **General Procedure 1**, 3-cyanopyridine *N*-oxide (0.1 g, 0.83 mmol), toluenesulfonyl chloride (0.79 g, 4.2 mmol), sodium azide (0.27 g, 4.2 mmol), toluene (2 mL, 0.42 M), column chromatography on silica gel (hexane:ethyl acetate = 2:1, 10% Et_3N/hexane deactivate the column); light yellow solid (15.7 mg, 0.11 mmol, 13%).

In $CDCl_3$ solution a mixture of tetrazole and azide in a ratio of 2.33:1 was observed.

Tetrazole: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.28 (q, *J* = 1.1 Hz, 1H), 8.19 (dt, *J* = 9.3, 1.0 Hz, 1H), 7.80 (ddd, *J* = 9.3, 1.5, 0.9 Hz, 1H) ppm. **Azide**: δ 8.62 (dt, *J* = 1.9, 0.9 Hz, 1H), 7.85 (ddd, *J* = 8.5, 2.2, 0.9 Hz, 1H), 6.88 (dt, *J* = 8.5, 0.9 Hz, 1H) ppm. Ratio tetrazole:azide = 2.33:1.

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.3, 152.7, 148.8, 141.7, 132.6, 131.8, 118.1, 117.0, 114.6, 114.2, 105.8, 104.0 ppm.

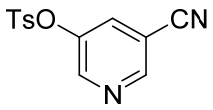
In DMSO-d_6 solution, only the tetrazole was detected.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.28 (d, *J* = 1.0 Hz, 1H), 8.41 (dd, *J* = 9.3, 1.0 Hz, 1H), 8.17 (dd, *J* = 9.3, 1.4 Hz, 1H) ppm.

^{13}C NMR (101 MHz, DMSO-d_6): δ 148.7, 134.6, 133.9, 117.0, 115.7, 102.9 ppm.

HRESI-MS: (+, 200V) m/z: $[M+Na]^+$ Calcd. for $C_6H_3N_5Na$ 168.0286; Found 168.0292.

5-cyanopyridin-3-yl 4-methylbenzenesulfonate **1057**



2ns

According to **General Procedure 1**, 3-cyanopyridine *N*-oxide (0.1 g, 0.83 mmol), toluenesulfonyl chloride (0.79 g, 4.2 mmol), sodium azide (0.27 g, 4.2 mmol), toluene (2 mL, 0.42 M), column chromatography on silica gel (hexane:ethyl acetate = 2:1, 10% Et_3N/hexane deactivate the column); **2n** (44.7 mg, 0.31 mmol, 37%); **2n'** (15.7 mg, 0.11 mmol, 13%) and yellow solid (15 mg, 0.06 mmol, 7%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (d, J = 1.7 Hz, 1H), 8.43 (d, J = 2.6 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.70 (dd, J = 2.6, 1.8 Hz, 1H), 7.41 – 7.35 (m, 2H), 2.49 (s, 3H).

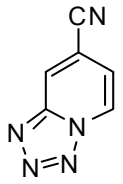
^{13}C NMR (101 MHz, $CDCl_3$) δ 150.57, 147.94, 146.95, 133.10, 131.12, 130.47, 128.60, 115.15, 21.93.

HRESI-MS: (+, 200V) m/z: $[M+Na]^+$ Calcd. for $C_{13}H_{10}N_2NaO_3S$ 297.0304; Found 297.0331.

IR (ν_{max}/cm^{-1}): 3073 (w), 1570 (s), 1425 (s), 1348 (s), 1246 (s), 1174 (s), 1091 (s), 959 (s), 821(s), 679 (s).

M.p.: 91–92 °C.

Tetrazolo[1,5-*a*]pyridine-7-carbonitrile[99] **1089**



2o

According to **General Procedure 1**, 3-cyanopyridine *N*-oxide (0.1 g, 0.83 mmol), toluenesulfonyl chloride (0.79 g, 4.2 mmol), sodium azide (0.27 g, 4.2 mmol), toluene (2 mL, 0.42 M), column chromatography on silica gel (hexane:ethyl acetate = 2:1, 10% Et_3N/hexane deactivate the column); light yellow solid (82.1 mg, 0.57 mmol, 68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.98 (dd, *J* = 7.1, 1.1 Hz, 1H, PyH-6), 8.48 (dd, *J* = 1.5, 1.1 Hz, 1H, PyH-3), 7.40 (dd, *J* = 7.1, 1.5 Hz, 1H, PyH-5) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.1, 127.4, 123.0, 117.3, 116.6, 115.3 ppm.

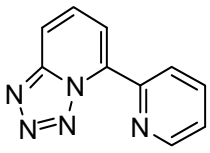
HRESI-MS: (+, 150V) m/z: $[M+Na]^+$ Calcd. for $C_6H_3N_5Na$ 168.0286; Found 168.0305.

IR (ν_{max}/cm^{-1}): 3058 (w), 2239 (w), 1640 (m), 1525 (s), 1482 (s), 1364 (s), 1174 (m), 1090 (s), 1004 (s), 900 (s), 801 (s), 756 (s), 708 (m).

M.p.: 129–130 °C.

Elemental Analysis: Calcd. for $C_6H_3N_5$: C, 49.66; H, 2.08; N, 48.26. Found: C, 49.67; H, 2.01; N, 48.34.

5-(Pyridin-2-yl)tetrazolo[1,5-*a*]pyridine[33] **1027, 1048**



2q

According to **General Procedure 1**, bipyridine *N*-oxide (0.1 g, 0.58 mmol), toluenesulfonyl chloride (0.56 g, 2.9 mmol), sodium azide (0.19 g, 2.9 mmol), toluene (2 mL, 0.29 M), column

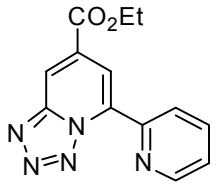
chromatography on silica gel (DCM:MeOH = 40:1); white solid (71 mg, 0.36 mmol, 62% in MeCN; 66.2 mg, 0.34 mmol, 56% in toluene).

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.83 (d, *J* = 4.7 Hz, 1H), 8.69 (d, *J* = 8.0 Hz, 1H), 8.32 (dd, *J* = 8.8, 4.7 Hz, 1H), 8.19 – 8.07 (m, 2H), 8.04 – 7.96 (m, 1H), 7.60 (ddd, *J* = 5.1, 4.6, 0.8 Hz, 1H) ppm.

^{13}C NMR (101 MHz, DMSO-d_6): δ 150.1, 149.6, 148.7, 137.2, 136.8, 132.1, 125.2, 125.1, 117.1, 115.6 ppm.

HRESI-MS: (+, 200V) m/z: $[M+Na]^+$ Calcd. for $C_{10}H_7N_5Na$ 220.0599; Found 220.0601.

Ethyl 5-(pyridin-2-yl)tetrazolo[1,5-*a*]pyridine-7-carboxylate[99] **1028**



2r

According to **General Procedure 1**, 4-(ethoxycarbonyl)-(2,2'-bipyridine) 1-oxide (0.05 g, 0.2 mmol), toluenesulfonyl chloride (0.20 g, 1.05 mmol), sodium azide (0.07 g, 1.07 mmol), CH_3CN (2 mL, 0.30 M), column chromatography on silica gel (hexane:ethyl acetate = 2:1–DCM:MeOH = 40:1, 10% Et_3N/hexane deactivate the column); yellow solid (28 mg, 0.1 mmol, 52%).

In $CDCl_3$ solution, a mixture of tetrazole and azide in a ration of 6.2:1 was observed.

Tetrazole: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.91 (dt, *J* = 8.1, 1.0 Hz, 1H, Ar'H-6), 8.85 (ddd, *J* = 4.7, 1.8, 1.0 Hz, 1H, Ar'H-3), 8.65 (d, *J* = 1.7 Hz, 1H, ArH-3), 8.61 (d, *J* = 1.6 Hz, 1H, ArH-5), 7.99 (td, *J* = 7.9, 1.8 Hz, 1H, Ar'H-5), 7.49 (ddd, *J* = 7.6, 4.7, 1.1 Hz, 1H, Ar'H-4), 4.51 (q, *J* = 7.1 Hz, 2H, CH_2), 1.47 (t, *J* = 7.2 Hz, 3H, CH_3) ppm. **Azide**: δ 8.69 (d, *J* = 1.3 Hz, 2H, ArH, Ar'H-6), 8.41 (dt, *J* = 8.0, 1.1 Hz, 1H, Ar'H-3), 7.84 (td, *J* = 7.7, 1.8 Hz, 1H, Ar'H-4), 7.37 (d, *J* = 1.3 Hz, 1H, ArH), 7.36 – 7.33 (m, 1H, Ar'H-5), 4.42 (q, *J* = 7.2 Hz, 2H, CH_2), 1.41 (t, *J* = 7.2 Hz, 3H, CH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.0, 163.8, 150.7, 150.1, 149.7, 147.8, 147.3, 142.3, 137.8 (tetrazole Ar'C-5), 137.7 (azide ArC), 135.0, 134.3, 132.9, 131.5, 125.9 (tetrazole Ar'C-6), 125.5 (tetrazole Ar'C-4), 124.9, 121.8 (azide, Ar'C-4), 117.7 (tetrazole ArC), 117.1 (azide ArC), 116.9 (tetrazole ArC), 114.4 (azide Ar'C-5), 63.2 (tetrazole CH_2), 62.5 (azide CH_2), 14.7, 14.7 ppm.

In DMSO-d_6 solution, only the tetrazole was detected.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.89 (dt, *J* =8.1, 0.9 Hz, 1H, Ar'H-6), 8.82 – 8.77 (m, 2H, ArH), 8.48 (ddd, *J* = 4.7, 1.7, 0.8 Hz, 1H, Ar'H-3), 8.15 (ddd, *J* = 8.1, 7.6, 1.8 Hz, 1H, Ar'H-5), 7.67 (ddd, *J* = 7.7, 4.8, 0.8 Hz, 1H, Ar'H-4), 447 (q, *J* = 7.1 Hz, 2H, CH_2), 1.41 (t, *J* =7.1 Hz, 3H, CH_3) ppm.

^{13}C NMR (101 MHz, DMSO-d_6): δ 163.5, 150.5, 149.7, 147.1, 137.9, 136.9, 134.1, 125.9, 125.1, 117.3, 115.8, 62.6, 14.2 ppm.

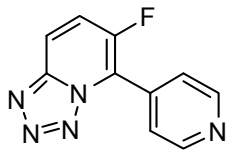
HRESI-MS: (+, 200V) m/z: $[M+Na]^+$ Calcd. for $C_{13}H_{11}N_5O_2Na$ 292.0810; Found 292.0806.

IR (ν_{max}/cm^{-1}): 2991 (vw), 1725 (s), 1575 (w), 1465 (m), 1408 (m), 1344 (m), 1267 (s), 1019 (m), 766 (s).

M.p.: 128–129 °C.

Elemental Analysis: Calcd. for $C_{13}H_{11}N_5O_2$: C, 57.99; H, 4.12; N, 26.01. Found: C, 57.93; H, 4.14; N, 26.07.

6-Fluoro-5-(pyridin-2-yl)tetrazolo[1,5-*a*]pyridine[99] **1032, 1096**



2s

According to **General Procedure 1**, 3-fluoro-(2,2'-bipyridine) 1-oxide (20 mg, 0.1 mmol), toluenesulfonyl chloride (10 mg, 0.05 mmol), sodium azide (3.4 mg, 0.05 mmol), CH_3CN (2 mL, 0.30 M), column chromatography on silica gel (hexane:ethyl acetate = 1:2, 10% Et_3N/hexane deactivate the column); yellow solid (11 mg, 0.05 mmol, 49%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (d, *J* =6.2 Hz, 2H, Ar'H), 8.45 (d, *J* = 5.1 Hz, 1H, ArH-4), 7.89 (d, *J* = 6.2 Hz, 2H, Ar'H), 7.11–7.01 (m, 1H, ArH-3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.0 (d, *J* = 260 Hz), 150.6 (Ar'C), 146.6 (d, *J* = 7.0 Hz, ArC-4), 144.7 (d, *J* = 8.3 Hz), 142.5 (d, *J* = 5.0 Hz), 138.2 (d, *J* = 10.2 Hz), 123.3 (d, *J* = 6.4 Hz, Ar'C), 116.2 (ArC-3) ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ –137.97 ppm.

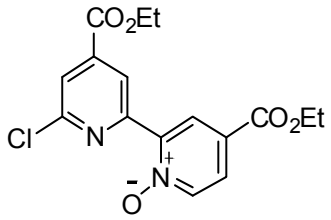
HRESI-MS: (+, 200V) m/z: $[M+H]^+$ Calcd. for $C_{10}H_7FN_5$ 216.0685; Found 216.0686.

IR (ν_{max}/cm^{-1}): 2925 (vw), 2128 (s), 1591 (s), 1547 (w), 1469 (m), 1434 (m), 1406 (m), 1332 (m), 1224 (m), 1187 (m), 825 (s), 734 (s).

M.p.: 100–101 °C.

Elemental Analysis: Calcd. for $C_{10}H_6FN_5$: C, 55.82; H, 2.81; N, 32.55. Found: C, 55.89; H, 3.03; N, 32.82.

6'-Chloro-4,4'-bis(ethoxycarbonyl)-[2,2'-bipyridine] 1-oxide[99] **1082**



3t

According to **General Procedure 1**, 4,4'-bis(ethoxycarbonyl)-[2,2'-bipyridine] 1,1'-dioxide (0.1 g, 0.3 mmol), toluenesulfonyl chloride (0.29 g, 1.5 mmol), sodium azide (0.1 g, 1.5 mmol), toluene (2 mL, 0.15 M), column chromatography on silica gel (hexane:ethyl acetate = 2:1); yellow solid (17 mg, 0.05 mmol, 16%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.29 (d, *J* = 1.2 Hz, 1H, Ar'H), 8.75 (d, *J* = 2.5 Hz,1H, ArH-3), 8.34 (dd, *J* = 6.8, 0.5 Hz, 1H, ArH-6), 7.97 (d, *J* = 1.2 Hz, 1H, Ar'H), 7.90 (dd, *J* = 6.8, 2.6 Hz, 1H, ArH-5), 4.44 (qd, *J* = 7.1, 2.5 Hz, 4H, CH_2), 1.42 (td, *J* = 7.1, 3.0 Hz, 6H, CH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 164.1 (CO), 163.9 (CO), 152.1, 150.6, 145.9, 141.8, 141.5 (ArC-6), 128.9 (ArC-3), 127.5, 126.2 (ArC-5), 125.5 (Ar'C), 123.7 (Ar'C), 62.9 (CH_2), 62.6 (CH_2), 14.7 (CH_3), 14.6 (CH_3) ppm.

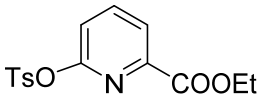
HRESI-MS: (+, 200V) m/z: $[M+Na]^+$ Calcd. for $C_{16}H_{15}N_2O_5ClNa$ 373.0567; Found 373.0567. $[M+K]^+$ Calcd. for $C_{16}H_{15}N_2O_5ClK$ 389.0307; Found 389.0298. $[M+H]^+$ Calcd. for $C_{16}H_{16}N_2O_5Cl$ 351.0748; Found 351.0746.

IR (ν_{max}/cm^{-1}): 3051 (vw), 1716(s), 1558 (s), 1359 (s), 1272 (m), 1015 (s), 901 (m), 862 (m), 805 (m), 767 (s), 743 (m).

M.p.: 135–136 °C.

Elemental Analysis: Calcd. for $C_{16}H_{15}N_2O_5Cl$: C, 54.79; H, 4.31; N, 7.99. Found: C, 54.79; H, 4.61; N, 8.19.

6- ethoxycarbnoyl pyridin-2-yl 4-methylbenzenesulfonate **1079**



2XS

According to **General Procedure 1**, 2-ethoxycarbnoyl *N*-oxide (0.1 g, 0.6 mmol), toluenesulfonyl chloride (0.57 g, 3 mmol), sodium azide (0.195 g, 3 mmol), toluene (2 mL, 0.3 M), column chromatography on silica gel (hexane:ethyl acetate = 2:1); white solid (13.3 mg, 0.05 mmol, 8%)

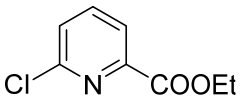
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (dd, J = 4.6, 1.4 Hz, 1H), 7.75 – 7.69 (m, 2H), 7.61 (dd, J = 8.4, 1.4 Hz, 1H), 7.45 (dd, J = 8.4, 4.6 Hz, 1H), 7.36 – 7.30 (m, 2H), 4.31 (q, J = 7.2 Hz, 2H), 2.45 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.99, 147.53, 145.90, 143.30, 132.11, 129.83, 128.52, 126.83, 62.05, 21.64, 13.94.

HRESI-MS: (+, 200V) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{16}NO_5S$ 322.0744; Found 322.0767.

IR (ν_{max}/cm^{-1}): 3023 (w), 1725 (s), 1525 (s), 1405 (s), 1364 (s), 1206 (m), 1174 (s).

ethyl 6-chloropicolinate[104] **1097**

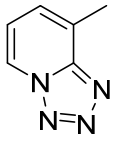


2xp

2-ethoxycarbnoyl N-oxide (0.1 g, 0.6 mmol), toluenesulfonyl chloride (0.57 g, 3 mmol), toluene (2 mL, 0.3 M), column chromatography on silica gel (hexane:ethyl acetate = 2:1); light yellow oil (40.8 mg, 0.05 mmol, 37%)

^{1}H NMR (400 MHz, Chloroform-d) δ 8.03 (d, J = 8.5 Hz, 1H), 7.84 – 7.73 (m, 1H), 7.50 (d, J = 8.9 Hz, 1H), 4.46 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H)

8-Methyltetrazolo[1,5-a]pyridine **1441F3**



2u

According to **General Procedure 1**, 3-methyl pyridine *N*-oxide (0.1 g, 0.92 mmol), toluenesulfonyl chloride (0.87 g, 4.6 mmol), sodium azide (0.29 g, 4.5 mmol), toluene (2 mL, 0.46 M), column chromatography on silica gel (hexane:ethyl acetate = 2:1–1:1); yellow solid (**2t**, 78 mg, 0.58 mmol, 63%), yellow solid (**2u**, 23.1 mg, 0.17 mmol, 18%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 6.8 Hz, 1H), 7.41 (d, *J* = 6.9 Hz, 1H), 7.13 (t, *J* = 6.9 Hz, 1H), 2.77 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.71, 130.53, 127.81, 123.32, 117.09, 17.41 ppm.

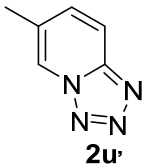
HRESI-MS: (+, 150V) m/z: $[M+H]^+$ Calcd. for $C_6H_7N_4$ 135.0671; Found 135.0642. $[M+Na]^+$ Calcd. for $C_6H_6N_4Na$ 157.0490; Found 157.0436.

HREI-MS: m/z: $[M]^+$ Calcd. for $C_6H_6N_4$ 134.0587; Found 134.0577.

IR (υ_{max}/cm^{-1}): 2920 (w), 1624 (m), 1498 (s), 1375 (m), 1164 (s), 1107 (s), 1045 (s), 880 (m), 764 (s).

M.p.: 122–123 °C.

6-Methyltetrazolo[1,5-a]pyridine **1441F5**



2u'

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.92 (d, *J* = 9.1 Hz, 1H), 7.51 (d, *J* = 9.8 Hz, 1H), 2.48 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.50, 134.83, 127.07, 122.67, 114.76, 17.89 ppm.

HRESI-MS: (+, 150V) m/z: $[M+H]^+$ Calcd. for $C_6H_7N_4$ 135.0671; Found 135.0666. $[M+Na]^+$ Calcd. for $C_6H_6N_4Na$ 157.0490; Found 157.0486.

HREI-MS: m/z: $[M]^+$ Calcd. for $C_6H_6N_4$ 134.0587; Found 134.0627.

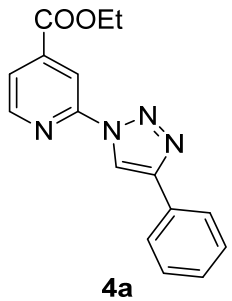
IR (υ_{max}/cm^{-1}): 2921 (w), 1624 (m), 1499 (s), 1333 (m), 1164 (s), 1090 (s), 819 (s), 765 (s).

M.p.: 135–136 °C.

2.2 Preparation of 1,2,3-pyridotriazoles

General procedure 2: In a glovebox, a teflon capped vial was charged with tetrazole (1.0 equiv), $Cu(OTf)_2 \cdot C_6H_6$ (10 mol%). Dry toluene (2 mL, 0.4 M) was added under inert atmosphere, followed by phenylacetylene (2.0 equiv). The reaction mixture was stirred at 80 °C for 12 h. After cooling to room temperature, toluene was removed under reduced pressure. The reaction mixture was diluted with DCM (30 mL), washed with water (2 × 30 mL), brine (30 mL) and dried (Na_2SO_4). The mixture was filtered and the filtrate was concentrated under reduced pressure. Chromatographic separation with silica gel gave pure product.

Ethyl 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)isonicotinate[99] **1066, 1099**



4a

According to **General Procedure 2**, ethyl tetrazolo[1,5-*a*]pyridine-7-carboxylate (150 mg, 0.8 mmol), $Cu(OTf)_2 \cdot C_6H_6$ (40.3 mg, 0.08 mmol), dry toluene (2 mL, 0.4 M), phenylacetylene (163 mg, 1.6 mmol), column chromatography on silica gel (hexane:ethyl acetate = 2:1); white solid (185 mg, 0.63 mmol, 81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (s, 1H, triazole H), 8.79 (dd, *J* = 1.4, 0.8 Hz, 1H, PyH-3), 8.67

(dd, *J* = 5.1, 0.8 Hz, 1H, PyH-5), 7.98 – 7.89 (m, 3H, PhH, PyH-6), 7.50 – 7.45 (m, 2H, PhH), 7.41 – 7.37 (m, 1H, PhH), 4.54 (q, *J* = 7.1 Hz, 1.4 Hz, 2H, CH_2), 1.46 (t, *J* = 7.1 Hz, 3H, CH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.9, 149.2, 141.0, 132.9, 130.5, 129.9, 129.0, 126.4, 123.2, 117.3, 113.4, 62.2, 14.0 ppm.

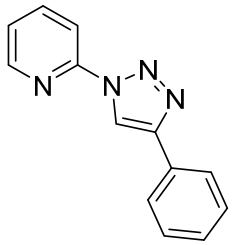
HRESI-MS: (+, 200V) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{15}N_4O_2$ 295.1195; Found 295.1190. $[M+Na]^+$ Calcd. for $C_{16}H_{14}N_4O_2Na$ 317.1014; Found 317.1014. $[M+K]^+$ Calcd. for $C_{16}H_{14}N_4O_2K$ 333.0754; Found 333.0801.

IR (ν_{max}/cm^{-1}): 3135 (vw), 1718 (s), 1606 (s), 1566 (s), 1466 (s), 1446 (s), 1370 (s), 1279 (s), 1237 (s), 1041 (s), 1010 (s), 896 (w), 774 (s).

M.p.: 174–175 °C.

Elemental Analysis: Calcd. for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04. Found: C, 65.72; H, 4.97; N, 19.40.

2-(4-phenyl-1H-1,2,3-triazol-1-yl)pyridine **1100**

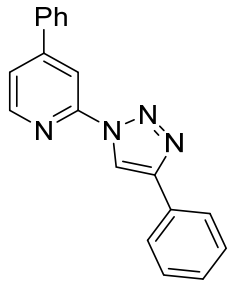


4b

According to General Procedure 2, tetrazole 2a (100 mg, 0.8 mmol), Cu(OTf)2·C6H6 (33.3 mg, 0.08 mmol), dry toluene (5 mL, 0.4 M), phenylacetylene (165 mg, 1.6 mmol), column chromatography on silica gel (hexane:ethyl acetate = 2:1, 10% Et3N/hexane deactivate the column); yellow solid (0,1 mg, 0.41 mmol, 50%).

^{1}H NMR (400 MHz, CDCl3) δ 8.82 (s, 1H), 8.53 (d, J = 4.4 Hz, 1H), 8.26 (d, J = 8.9 Hz, 1H), 7.97 – 7.91 (m, 3H), 7.47 (t, J = 7.4 Hz, 2H), 7.40 – 7.34 (m, 2H).

4-Phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)pyridine[99] **1110**



4h

According to **General Procedure 2**, tetrazole **2a** (58.8 mg, 0.3 mmol), $Cu(OTf)_2 \cdot C_6H_6$ (15.2 mg, 0.03 mmol), dry toluene (2 mL, 0.4 M), phenylacetylene (62 mg, 0.6 mmol), column chromatography on silica gel (hexane:ethyl acetate = 2:1, 10% Et_3N/hexane deactivate the column); yellow solid (56 mg, 0.18 mmol, 63%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.86 (d, *J* = 1.0 Hz, 1H, triazole H), 8.56 (d, *J* = 5.2 Hz, 1H, PyH-6), 8.52 – 8.46 (m, 1H, PyH-3), 7.97 (dq, *J* = 7.5, 1.3 Hz, 2H, PhH), 7.79 – 7.71 (m, 2H, Ph'H), 7.59 – 7.46 (m, 6H, PhH, Ph'H, PyH-5), 7.41 – 7.36 (m, 1H, Ph'H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 152.4, 149.4, 137.5, 136.8, 130.7, 130.3, 129.8, 129.4, 128.9, 127.6, 126.4, 121.9, 117.5, 112.0 ppm.

HRESI-MS: (+, 200 V) m/z: $[M+H]^+$ Calcd. for $C_{19}H_{15}N_4$ 299.1297; Found 299.1290. $[M+Na]^+$ Calcd. for $C_{19}H_{14}N_4Na$ 321.1116; Found 321.1116. $[M+K]^+$ Calcd. for $C_{19}H_{14}N_4K$ 337.0856; Found 337.0858.

IR (ν_{max}/cm^{-1}): 3135 (vw), 1600 (m), 1545 (m), 1466 (s), 1439 (w), 1260 (w), 1020 (s), 800 (w), 758 (s), 691 (s).

M.p.: 140–141 °C.

Elemental Analysis: Calcd. for $C_{19}H_{14}N_4$: C, 76.49; H, 4.73; N, 18.78. Found: C, 76.24; H, 4.97; N, 18.45.

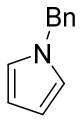
3 Experimental Section for Chapter Ⅱ

3.1 Synthesis of Starting Materials

General Procedure 3:[105] A Schlenk flask with a stir bar was charged with pyrrole (4 mmol, 1 equiv), KOH (2 equiv), RCl (1.1 equiv), DMSO (10 mL, 0.4 M), the reaction mixture was heated to 65 °C for 24 h under a N_2 atmosphere. The mixture was poured into water and extracted with DCM. The organic layer was washed with aqueous lithium chloride solution and aqueous sodium hydrogen carbonate solution, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by flash column chromatography.

General Procedure 4:[106] A Schlenk flask with a stir bar was charged with substituted pyrrol (2 mmol, 1 equiv), NaH (1.1 equiv), DMF (10 mL, 0.4 M) at 0 °C for 1 h, then BnBr (1.3 equiv) was added at room temperature for 12 h under a N_2 atmosphere. The mixture was poured into water and extracted with EtOAc. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by flash column chromatography.

1-Benzyl-1*H*-pyrrole[107] **1130a**

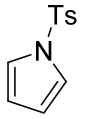


5b

According to **General Procedure 3**, pyrrole (264 mg, 4 mmol), KOH (448 mg, 8 mmol), BnCl (504 mg, 4.4 mmol), DMSO (10 mL, 0.4 M); a colorless oil (620 mg, 4 mmol, 99%) which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.28 (m, 3H), 7.19 – 7.07 (m, 2H), 6.71 (t, *J* = 2.1 Hz, 2H), 6.20 (t, *J* = 2.1 Hz, 2H), 5.08 (s, 2H) ppm.

1-Tosyl-1*H*-pyrrole[108] **1130c**

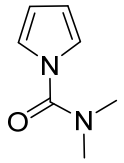


5c

A Schlenk flask with a stir bar was charged with pyrrole (264 mg, 4 mmol), KOH (448 mg, 8 mmol), TsCl (912 mg, 4.4 mmol), DCE (10 mL, 0.4 M) at rt for 24 h under a N_2 atmosphere. The mixture was extracted with DCM. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to afford white solid (830 mg, 3.8 mmol, 94%) which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.18 – 7.12 (m, 2H), 6.31 – 6.25 (m, 2H), 2.40 (s, 3H) ppm.

***N*,*N*-Dimethyl-1*H*-pyrrole-1-carboxamide[79]** **1142b**

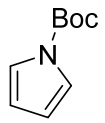


5d

A Schlenk flask with a stir bar was charged with pyrrole (264 mg, 4 mmol), THF (10 mL, 0.4 M), *n*-BuLi (1.6 M in hexane, 3.2 mL, 5.2 mmol) at –78 °C for 60 min, then dimethylcarbamic chloride (471 mg, 4.4 mmol) was added. The reaction stirred at 0 °C for 12 h. NH_4Cl was added to quench the reaction, followed by extraction with DCM. The organic phase was washed by water and brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure, the crude product was purified by column chromatography on silica gel (hexane:ethyl acetate = 5:1–2:1); colorless oil (441 mg, 3.2 mmol, 80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (t, *J* = 2.3 Hz, 2H), 6.30 – 6.17 (m, 2H), 3.09 (s, 6H) ppm.

tert-Butyl-1_H_-pyrrole-1-carboxylate[107] **1130b**



5e

A Schlenk flask with a stir bar was charged with pyrrole (264 mg, 4 mmol), DMAP (98 mg, 0.4 mmol), BocCl (1.05 g, 4.8 mmol), CH_3CN (10 mL, 0.4 M) at rt for 24 h under a N_2 atmosphere. The mixture was poured into water and extracted with DCM. The organic layer was washed with sodium hydrogen carbonate and brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure, the crude product was purified by column chromatography on silica gel (hexane:ethyl acetate = 5:1); colorless oil (846 mg, 2,8 mmol, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 – 7.21 (m, 2H), 6.24 – 6.19 (m, 2H), 1.59 (s, 9H) ppm.

1-Benzyl-2-ethyl-1_H_-pyrrole **1253A, 1247**

5g

According to **General Procedure 4**, 2-ethyl pyrrole (190 mg, 2 mmol), NaH (52.8 mg, 2.2 mmol), BnBr (445 mg, 2.6 mmol), DMF (0.4 M, 10 mL), column chromatography on silica gel (hexane:DCM = 6:1); colorless oil (222 mg, 1.2 mmol, 60%).

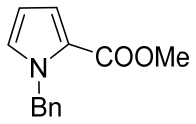
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.26 (m, 3H, Ph-H), 7.00 (d, *J* = 10.3 Hz, 2H, Ph-H), 6.64 (s, 1H, pyrroleH-5), 6.15 (d, *J* = 3.3 Hz, 1H, pyrroleH-4), 5.98 (d, *J* = 3.4 Hz, 1H, pyrroleH-3), 5.05 (s, 2H, $\underline{CH_2}$Ph), 2.48 (q, *J* = 7.9, 7.5 Hz, 2H, $\underline{CH_2}CH_3$), 1.20 (t, *J* = 7.5 Hz, 3H, $CH_2\underline{CH_3}$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 138.65, 135.26, 128.82, 127.42, 126.48, 121.02, 107.17, 105.19, 50.32, 19.54, 12.97 ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{13}H_{16}N$ 186.1277; Found 186.1290.

IR (υ_{max}/cm^{-1}): 2966 (w), 1700 (s), 1435 (m), 1326 (m), 1240 (s), 1105 (s), 1075 (s), 721 (s).

Methyl 1-benzyl-1*H*-pyrrole-2-carboxylate **1253B**



5h

According to **General Procedure 4**, 2-carboxylate pyrrole (250 mg, 2 mmol), NaH (52.8 mg, 2.2 mmol), BnBr (445 mg, 2.6 mmol), DMF (0.4 M, 10 mL), column chromatography on silica gel (hexane:DCM = 4:1–1:1); colorless oil (176 mg, 0.8 mmol, 41%).

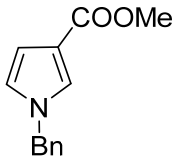
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.24 (m, 3H, Ph-H), 7.13 – 7.08 (m, 2H, Ph-H), 7.00 (dd, *J* = 4.0, 1.8 Hz, 1H, pyrroleH-3), 6.91 – 6.86 (m, 1H, pyrroleH-5), 6.19 (dd, *J* = 4.0, 2.6 Hz, 1H, pyrroleH-4), 5.57 (s, 2H, $\underline{CH_2}$-Ph), 3.77 (s, 3H, CO_2Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 161.64, 138.40, 129.18, 128.76, 127.56, 127.00, 122.15, 118.50, 108.65, 52.19 ($\underline{CH_2}$-Ph), 51.18 (CO_2Me) ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{13}H_{13}NO_2Na$ 238.0838; Found 238.0848.

IR (υ_{max}/cm^{-1}): 2949 (w), 1699 (s), 1437 (s), 1408 (s), 1326 (s), 1240 (s), 1105 (s), 1075 (s), 719 (s).

Methyl 1-benzyl-1*H*-pyrrole-3-carboxylate **1253C**



5i

According to **General Procedure 4**, 3-carboxylate pyrrole (250 mg, 2 mmol), NaH (52.8 mg, 2.2 mmol), BnBr (445 mg, 2.6 mmol), DMF (0.4 M, 10 mL), column chromatography on silica gel (hexane:DCM = 1:1–1:2); colorless oil (104 mg, 0.48 mmol, 24%).

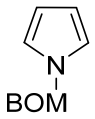
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.27 (m, 4H, Ph-H), 7.13 – 7.15 (m, 2H, Ph-H), 6.67 – 6.53 (m, 2H, pyrrole-H), 5.06 (s, 2H, $\underline{CH_2}$-Ph), 3.79 (s, 3H, CO_2Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.36, 136.79, 129.06, 128.28, 127.41, 126.49, 122.28, 116.30, 110.58, 54.00 ($\underline{CH_2}$-Ph), 51.15 (CO_2Me) ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{13}H_{13}NO_2Na$ 238.0838; Found 238.0838.

IR (υ_{max}/cm^{-1}): 2969 (w), 1700 (s), 1470 (s), 1408 (s), 1326 (s), 1194 (s), 1028 (s), 951 (m), 736 (s).

1-[(Benzyloxy)methyl]-1*H*-pyrrole **1401B**



5j

According to **General Procedure 4**, pyrrole (134 mg, 2 mmol), NaH (52.8 mg, 2.2 mmol), [(chloromethoxy)methyl]benzene (405 mg, 2.6 mmol), DMF (0.4 M, 10 mL), column chromatography on silica gel (hexane:DCM = 4:1–1:1); colorless oil (150 mg, 0.8 mmol, 40%).

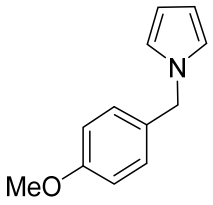
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.29 (m, 5H, Ph), 6.83 (t, *J* = 2.1 Hz, 2H, pyrroleH-2, H-5), 6.24 (t, *J* = 2.1 Hz, 2H, pyrroleH-3, H-4), 5.27 (s, 2H, $\underline{CH_2}$Ph), 4.41 (s, 2H, CH_2OPh) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 137.12, 128.64, 128.10, 128.09, 121.22, 109.45, 77.77, 69.69 ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{12}H_{14}NO$ 188.1070; Found 188.1077. $[M+Na]^+$ Calcd. for $C_{12}H_{13}NONa$ 210.0889; Found 210.0902.

IR (υ_{max}/cm^{-1}): 2927 (w), 1717 (m), 1495 (s), 1454 (m), 1378 (m), 1271 (s), 1068 (s), 951 (m), 696 (s).

1-(4-Methoxybenzyl)-1*H*-pyrrole[109] **1351A**



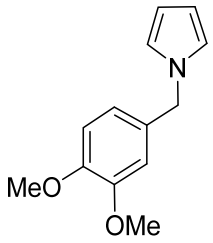
5k

A Schlenk flask with a stir bar was charged with 4-hydroxy-L-proline (0.25 g, 1.9 mmol), AcOH (7.5 mg, 0.13 mmol), DMF (5 mL, 0.4 M), the mixture was heated to reflux, then 4-methoxybenzaldehyde (0.17 g, 1.25 mmol) was added slowly by syringe pump for 1 h. After 2 h

the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 10:1); colorless oil (154 mg, 0.8 mmol, 66%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (d, *J* = 8.8 Hz, 2H), 7.00 – 6.92 (m, 2H), 6.77 (t, *J* = 2.1 Hz, 2H), 6.29 (t, *J* = 2.1 Hz, 2H), 5.07 (s, 2H), 3.86 (s, 3H) ppm.

1-(3,4-Dimethoxybenzyl)-1*H*-pyrrole[110] **1351B**

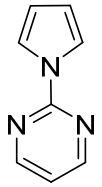


5l

A Schlenk flask with a stir bar was charged with 4-hydroxy-L-proline (1.9 mmol, 0.25 g), AcOH (7.5 mg, 10 mol%), DMF (5 mL, 0.4 M), the mixture was heated to reflux, then 3,4-dimethoxybenzaldehyde (0.21 g, 1.25 mmol) was added slowly by pump syringe for 1 h, after 2 h the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 10:1); colorless oil (237 mg, 1.09 mmol, 87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84 (d, *J* = 8.2 Hz, 1H), 6.76 – 6.64 (m, 4H), 6.20 (t, *J* = 2.3 Hz, 2H), 5.03 (s, 2H), 3.88 (s, 3H), 3.84 (s, 3H) ppm.

2-(1H-pyrrol-1-yl)pyrimidine[111] **1333**

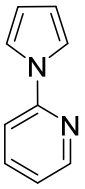


5p

According to **General Procedure 4**, pyrrole (268 mg, 4 mmol), NaH (106 mg, 4.4 mmol), 2-chloropyrimidine (593 mg, 5.2 mmol), DMF (0.4 M, 10 mL), column chromatography on silica gel (hexane:ethyl acetate = 3:1); colorless oil (244 mg, 1.7 mmol, 42%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 4.8 Hz, 2H), 7.83 – 7.74 (m, 2H), 7.05 (t, J = 4.8 Hz, 1H), 6.37 – 6.29 (m, 2H).

2-(1H-pyrrol-1-yl)pyridine[112] **1353**



5o

A Schlenk flask with a stir bar was charged with Cu_2O (66 mg, 10 mol%), Cs_2CO_3(3 g, 2equiv), 2-iodopyridine (0.95g, 4.66 mmol), pyrrole (474 mg, 1.5 equiv), DMSO (0.5 M, 10 mL) , the mixture heated at 100^{o}C for 24 hr, then the resulting mixture was diluted with DCM and filtered through a pad of celite, the combined organic layer dried over Na2SO4 before purified by chromatography on silica gel (hexane:ethyl acetate = 5:1); colorless oil (436 mg, 3.03 mmol, 65%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (ddd, J = 4.9, 2.0, 0.9 Hz, 1H), 7.74 (ddd, J = 8.3, 7.2, 1.8 Hz, 1H), 7.58 – 7.49 (m, 2H), 7.36 – 7.28 (m, 1H), 7.10 (ddd, J = 7.4, 4.9, 0.9 Hz, 1H), 6.41 – 6.32 (m, 2H).

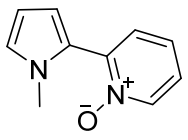
3.2 Oxidative Coupling of Substituted Pyridine Oxide with Pyrrole Derivatives

3.2.1 General Procedure and Experimental Data for the Oxidative Coupling of Pyridine Oxide with *N*-Substituted Pyrrole

General Procedure 5: To a teflon capped vial with a stir bar was added *N*-substituted pyrrole (0.25 mmol, 1.0 equiv), pyridine *N*-oxide (1 mmol, 4 equiv), $Pd(OAc)_2$ (5 mol%), CuBr (10 mol%),

$Cu(OAc)_2 \cdot H_2O$ (1.5 equiv), pyridine (1 equiv) and dioxane (0.25 M in substrate), the resulting mixture was heated to 110 °C for 48 h and then cooled to room temperature. The reaction mixture was directly purified by flash column chromatography.

2-(1-Methyl-1*H*-pyrrole-2-yl)pyridine 1-oxide **1114, 1134a**



7ab

According to **General Procedure 5**, *N*-methyl pyrrole (20.3 mg, 0.25 mmol), pyridine *N*-oxide (95 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuBr (3.6 mg, 0.025 mmol), $Cu(OAc)_2 \cdot H_2O$ (75 mg, 0.38 mmol), pyridine (20 mg, 0.25 mmol), dioxane (0.25 M, 1 mL), column chromatography on silica gel (hexane:ethanol = 10:1); yellow solid (C2 product, 4.4 mg, 0.025 mmol, 10%) and brown solid (C3 product, 17 mg, 0.1 mmol, 39%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 – 8.21 (m, 1H, PyH-6), 7.42 – 7.34 (m, 1H, PyH-3), 7.25 – 7.18 (m, 2H, PyH-4, PyH-5), 6.82 (t, *J* = 2.1 Hz, 1H, pyrroleH-5), 6.35 (dd, *J* = 3.3, 2.4 Hz, 1H, pyrroleH-4), 6.21 (t, *J* = 3.3 Hz, 1H, pyrroleH-3), 3.68 (s, 3H, *N*-Me) ppm.

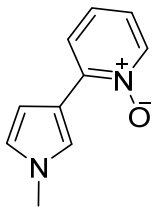
^{13}C NMR (101 MHz, $CDCl_3$): δ 143.73 (PyC-2), 140.25 (PyC-6), 129.14 (PyC-5), 125.54 (pyrroleC-2), 125.41 (pyrroleC-5), 125.14 (PyC-4), 124.78 (PhC-3), 112.74 (pyrroleC-4), 108.40 (pyrroleC-3), 35.86 (*N*-CH_3) ppm.

HRESI-MS: $[M+K]^+$ Calcd. for $C_{10}H_{10}N_2OK$ 213.0430; Found 213.0438. $[M+Na]^+$ Calcd. for $C_{10}H_{10}N_2ONa$ 197.0690; Found 197.0700. $[M+H]^+$ Calcd. for $C_{10}H_{11}N_2O$ 175.0871; Found 175.0874.

IR (υ_{max}/cm^{-1}): 2962 (w), 1600 (m), 1499 (s), 1428 (m), 1245 (s), 1039 (m), 948 (m), 838 (s), 776 (m), 723 (s).

M.p.: 85–86 °C.

2-(1-Methyl-1*H*-pyrrole-3-yl)pyridine 1-oxide



6ab

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (q, *J* = 1.8 Hz, 1H, pyrroleH-2), 8.25 (ddt, *J* = 6.6, 1.7, 0.8 Hz, 1H, PyH-3), 7.62 (dt, *J* = 8.1, 1.8 Hz, 1H, PyH-6), 7.24 – 7.14 (m, 1H, PyH-5), 7.00 – 6.91 (m, 1H, PyH-4), 6.66 (dd, *J* = 3.0, 2.1 Hz, 1H, pyrroleH-5), 6.59 (dt, *J* = 3.1, 1.5 Hz, 1H, pyrroleH-4), 3.71 (d, *J* = 1.6 Hz, 3H, *N*-CH_3) ppm.

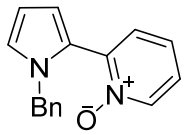
^{13}C NMR (101 MHz, $CDCl_3$): δ 145.40 (PyC-2), 140.89 (PyC-3), 127.50 (pyrroleC-2), 125.96 (PyC-5), 123.23 (PyC-6), 122.68 (pyrroleC-5), 120.83 (PyC-4), 115.19 (pyrroleC-3), 108.00 (pyrroleC-5), 36.97 (*N*-CH_3) ppm.

HRESI-MS: $[M+K]^+$ Calcd. for $C_{10}H_{10}N_2OK$ 213.0430; Found 213.0422. $[M+Na]^+$ Calcd. for $C_{10}H_{10}N_2ONa$ 197.0690; Found 197.0685. $[M+H]^+$ Calcd. for $C_{10}H_{11}N_2O$ 175.0871; Found 175.0862.

IR (υ_{max}/cm^{-1}): 2929 (w), 1602 (m), 1500 (s), 1485 (s), 1421 (s), 1246 (s), 1101 (m), 946 (m), 835 (m), 756 (s), 689 (s).

M.p.: 110–111 °C.

2-(1-Benzyl-1*H*-pyrrole-2-yl)pyridine 1-oxide **1133**



7bb

According to **General Procedure 5**, pyridine *N*-oxide (190 mg, 2 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), CuBr (7.2 mg, 0.05 mmol), $Cu(OAc)_2 \cdot H_2O$ (75 mg, 0.38 mmol), pyridine (40 mg, 0.5 mmol), dioxane (0.25 M, 2 mL), *N*-benzyl pyrrole (80 mg, 0.5 mmol), column chromatography on silica gel (hexane:ethanol = 10:1); brown solid (C2 product, 6.9 mg, 0.028 mmol, 6%) and red solid (C3 product, 57 mg, 0.23 mmol, 46%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, *J* = 6.9 Hz, 1H, PyH-6), 7.18 – 7.14 (m, 5H, PyH-4 and PhH- 2, 3), 7.09 (td, *J* = 7.6, 1.3 Hz, 1H, PyH-5), 6.95 (d, *J* = 1.7 Hz, 2H, PyH-3 and PhH4), 6.90 – 6.86 (m, 1H, pyrroleH-5), 6.37 (dd, *J* = 3.7, 1.8 Hz, 1H, pyrroleH-3), 6.29 – 6.24 (m, 1H, pyrroleH-4), 5.27 (s, 2H, CH_2Ph) ppm.

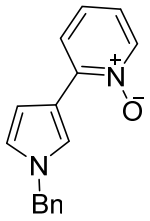
^{13}C NMR (101 MHz, $CDCl_3$): δ 144.02 (PyC-2), 140.01 (PyC-6), 138.60, 129.27, 128.50, 127.45, 127.07 (PyC-3), 125.34, 125.29 (PyC-5), 125.26 (pyrroleC-5), 124.72 (pyrroleC-2), 113.28 (pyrroleC-4), 108.82 (pyrroleC-3), 53.07 (CH_2Ph) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{16}H_{15}N_2O$ 251.1179; Found 251.1193. $[M+Na]^+$ Calcd. for $C_{16}H_{14}N_2ONa$ 273.0998; Found 273.0992.

IR (υ_{max}/cm^{-1}): 2930 (w), 1705 (m), 1602 (m), 1484 (s), 1436 (m), 1321 (m), 1237 (s), 1040 (m), 993 (m), 836 (s), 765 (s).

M.p.: 119–120 °C.

2-(1-Benzyl-1*H*-pyrrole-3-yl)pyridine 1-oxide



6bb

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (t, *J* = 1.8 Hz, 1H, pyrroleH-5), 8.24 (d, *J* = 6.5 Hz, 1H, PyH-6), 7.64 (dd, *J* = 8.2, 1.9 Hz, 1H, PyH-4), 7.33 – 7.28 (m, 3H, PhH), 7.22 – 7.17 (m, 3H, PyH-3 and PhH), 6.96 (td, *J* = 7.0, 1.9 Hz, 1H, PyH-5), 6.74 – 6.69 (m, 1H, pyrroleH-5), 6.64 (dd, *J* = 3.0, 1.6 Hz, 1H, pyrroleH-4), 5.11 (s, 2H, CH_2) ppm.

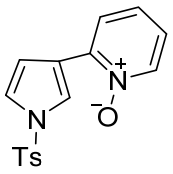
^{13}C NMR (126 MHz, $CDCl_3$): δ 140.84 (PyC-6), 137.52 (PyC-2), 129.18, 128.73, 128.26, 127.64, 127.05 (pyrroleC-2), 126.16, 123.23 (PyC-4), 121.92 (pyrroleC-5), 120.85 (PyC-5), 115.24 (pyrroleC-3), 108.38 (pyrroleC-4), 54.18 (CH_2Ph) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{16}H_{15}N_2O$ 251.1179; Found 251.1193. $[M+Na]^+$ Calcd. for $C_{16}H_{14}N_2ONa$ 273.0998; Found 273.0998.

IR (υ_{max}/cm^{-1}): 3062 (w), 1705 (m), 1603 (m), 1484 (s), 1436 (s), 1406 (s), 1321 (s), 1237 (s), 1077 (m), 993 (m), 837 (s), 765 (s), 715 (s).

M.p.: 104–105 °C.

2-(1-Tosyl-1*H*-pyrrole-3-yl)pyridine 1-oxide[73] **1132**



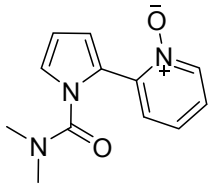
6cb

According to **General Procedure 5**, *N*-Ts pyrrole (55.3 mg, 0.25 mmol), pyridine *N*-oxide (95 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuBr (3.6 mg, 0.025 mmol), $Cu(OAc)_2 \cdot H_2O$ (75 mg, 0.38 mmol), pyridine (20 mg, 0.25 mmol), dioxane (0.25 M, 1 mL), column chromatography on silica gel (hexane:ethanol = 10:1); yellow solid (18.9 mg, 0.06 mmol, 24%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (s, 1H), 8.21 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.64 (s, 1H), 7.31 – 7.25 (m, 3H), 7.13 (s, 2H), 6.73 (d, *J* = 2.7 Hz, 1H), 2.38 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 145.91, 141.17, 136.00, 130.62, 127.70, 126.91, 126.31, 124.69, 124.23, 122.88, 121.28, 119.56, 112.11, 22.09 ppm.

2-(1-(DimethylcPhbamoyl)-1*H*-pyrrole-2-yl)pyridine 1-oxide **1150b**



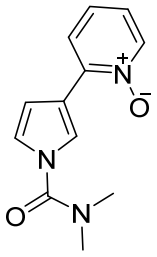
7db

According to **General Procedure 5**, *N*-dimethylcarbamoyl pyrrole (60 mg, 0.43 mmol), pyridine *N*-oxide (163 mg, 1.72 mmol), $Pd(OAc)_2$ (4.8 mg, 0.022 mmol), CuBr (6.2 mg, 0.043 mmol), $Cu(OAc)_2 \cdot H_2O$ (129 mg, 0.65 mmol), pyridine (34 mg, 0.43 mmol), dioxane (0.25 M, 1.6 mL), column chromatography on silica gel (ethyl acetate:EtOH = 10:1); yellow solid (C3 product, 9.3 mg, 0.04 mmol, 9%), a yellow oil (13.9 mg, 0.06 mmol, 14%, C2:C3 = 1:2.6) and yellow oil (99 mg, C2:pyridine oxide = 1:20, 0.05 mmol (C2), 11%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (ddd, *J* = 6.5, 1.3, 0.6 Hz, 1H, PyH-6), 7.51 – 7.44 (m, 1H, PyH-4), 7.24 (t, *J* = 7.5 Hz, 1H, PyH-3), 7.15 (ddd, *J* = 7.6, 6.5, 2.1 Hz, 1H, PyH-5), 7.02 (dd, *J* = 3.0, 1.6 Hz, 1H, pyrroleH-5), 6.48 (dd, *J* = 3.5, 1.6 Hz, 1H, pyrroleH-3), 6.26 (dd, *J* = 3.5, 3.0 Hz, 1H, pyrroleH-4).3.10 (s, 6H, NMe_2) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.13 (CO), 144.14, 140.77, 126.14, 124.71, 123.78, 121.82, 121.68, 116.69, 109.10, 38.86 (NMe_2) ppm.

2-(1-(Dimethylcarbamoyl)-1*H*-pyrrole-3-yl)pyridine 1-oxide



6db

Yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.77 (s, 1H, pyrrole H-2), 8.32 (d, *J* = 6.4 Hz, 1H, PyH-6), 7.72 – 7.65 (m, 1H), 7.29 (d, *J* = 7.6 Hz, 1H, PyH-3), 7.21 (dd, *J* = 3.3, 2.2 Hz, 1H, pyrroleH-4), 7.09 (td, *J* = 7.3, 1.7 Hz, 1H, PyH-4), 6.69 (s, 1H, pyrroleH-5), 3.15 (s, 6H, NMe_2) ppm.

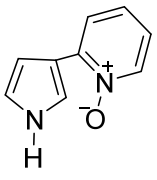
^{13}C NMR (101 MHz, $CDCl_3$): δ 154.93 (CO), 142.80, 139.76, 126.50, 125.72, 125.43, 124.14, 122.58, 115.16, 109.69, 39.00 (NMe_2) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{12}H_{14}N_3O_2$ 232.1081; Found 232.1096.

IR (υ_{max}/cm^{-1}): 2923 (w), 1667 (s), 1490 (m), 1389 (s), 1251 (s), 1185 (m), 982 (m), 825 (s), 747 (s).

Mp: 120 – 121 °C.

2-(1*H*-Pyrrole-3-yl)pyridine 1-oxide **1135**



6eb

According to **General Procedure 5**, *N*-Boc pyrrole (70 mg, 0.47 mmol), pyridine *N*-oxide (179 mg, 1.88 mmol), $Pd(OAc)_2$ (5.2 mg, 0.023 mmol), CuBr (6.7 mg, 0.047 mmol), $Cu(OAc)_2{\cdot}H_2O$ (141 mg, 0.7 mmol), pyridine (37 mg, 0.47 mmol), dioxane (0.25 M, 1.8 mL), column chromatography on silica gel (ethyl acetate:ethanol = 20:1); brown oil (10 mg, 0.06 mmol, 13%).

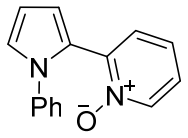
^{1}H NMR (400 MHz, MeOD): δ 8.24 (s, 2H, pyrroleH-2, PhH-6), 7.92 (d, *J* = 7.9 Hz, 1H, PhH-3), 7.48 (s, 1H, PhH-4), 7.20 (t, *J* = 5.9 Hz, 1H, PhH-5), 6.87 (d, *J* = 2.6 Hz, 1H, pyrroleH), 6.78 (d, *J* = 2.8 Hz, 1H, pyrroleH) ppm.

^{13}C NMR (101 MHz, DMSO-d_6): δ 140.43, 125.05, 123.41, 122.69, 121.38, 118.97, 114.82, 107.48, 99.87 ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_9H_9N_2O$ 161.0709; Found 161.0706.

IR (υ_{max}/cm^{-1}): 3172 (m), 3110 (m), 2923 (m), 1711 (m), 1605 (m), 1428 (s), 1222 (m), 1085 (s), 824 (m), 759 (s).

2-(1-Phenyl-1*H*-pyrrole-2-yl)pyridine 1-oxide **1238A**



7fb

According to **General Procedure 5**, *N*-Ph pyrrole (36 mg, 0.25 mmol), pyridine *N*-oxide (95 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuBr (3.6 mg, 0.025 mmol), $Cu(OAc)_2{\cdot}H_2O$ (75 mg, 0.38 mmol) pyridine (20 mg, 0.25 mmol), dioxane (0.25 M, 1 mL), column chromatography on silica gel (ethyl acetate:ethanol = 20:1); brown solid (C2 product, 6.6 mg, 0.03 mmol, 11%) and brown solid (C3 product,18.4 mg, 0.08 mmol, 32%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 7.1 Hz, 1H, PyH-6), 7.36 – 7.28 (m, 3H), 7.24 – 7.20 (m, 2H), 7.06 (dd, *J* = 5.9, 3.1 Hz, 4H), 6.98 (dd, *J* = 3.6, 1.7 Hz, 1H, pyrroleH-4), 6.44 (dd, *J* = 3.7, 2.8 Hz, 1H, pyrroleH-4) ppm.

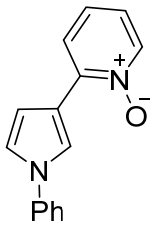
^{13}C NMR (101 MHz, $CDCl_3$): δ 146.49, 141.07, 140.73, 129.77, 128.49, 127.43, 125.96, 124.89, 124.62, 124.40, 124.17, 115.99, 110.33 ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{15}H_{13}N_2O$ 237.1022; Found 237.1013.

IR (υ_{max}/cm^{-1}): 3079 (w), 1453 (m), 1428 (m), 1295 (m), 1245 (s), 1100 (m), 1039 (m), 947 (m), 839 (s), 722 (s).

M.p.: 95–96 °C.

2-(1-Phenyl-1*H*-pyrrole-3-yl)pyridine 1-oxide



7fb

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93 – 8.86 (m, 1H, pyrroleH-2), 8.30 (d, *J* = 6.1 Hz, 1H, PyH-6), 7.69 (dd, *J* = 8.2, 1.9 Hz, 1H, PyH-3), 7.51 – 7.42 (m, 4H, Ph-H), 7.31 – 7.23 (m, 2H, PyH-4 and PhH), 7.16 (dd, *J* = 3.1, 2.3 Hz, 1H, pyrroleH-4), 7.03 (td, *J* = 7.3, 1.9 Hz, 1H, PyH-5), 6.80 (dd, *J* = 3.2, 1.6 Hz, 1H, pyrroleH-5) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 145.01 (PyC-2), 141.03 (PyC-6), 140.60 (PhC), 130.07 (PhC), 126.79, 126.00, 124.53 (pyrroleC-2), 123.58 (PyC-3), 121.43 (PyC-5), 121.21 (PhC), 120.46 (pyrroleC-4), 117.13 (pyrroleC-2), 109.87 (pyrroleC-5) ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{15}H_{12}N_2ONa$ 259.0842; Found 259.0843. $[M+H]^+$ Calcd. for $C_{15}H_{13}N_2O$ 237.1022; Found 237.1018.

IR (υ_{max}/cm^{-1}): 1596 (m), 1545 (m), 1449 (s), 1453 (m), 1245 (s), 1039 (m), 948 (m), 839 (s), 755 (s), 721 (s).

M.p.: 109–110 °C.

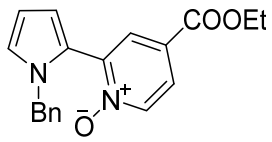
3.2.2 Oxidative Coupling of Substituted Pyridine Oxide with Pyrrole Derivatives

General Procedure 6: To a teflon capped vial with a stir bar was added, pyridine *N*-oxide (1 mmol, 4 equiv), $Pd(OAc)_2$ (5 mol%), CuCl (10 mol%), DPPP (5 mol%), $Cu(OAc)_2{\cdot}H_2O$ (25 mol%), pyridine (1 equiv), AcOH (2 equiv) and dioxane (0.25 M in substrate). The mixture was stirred for 10 minutes, then the substituted pyrrole (0.25 mmol, 1.0 equiv) was added, the resulting mixture was heated to 110 °C for 60 h and then cooled to room temperature. The reaction mixture was directly purified by flash column chromatography.

General Procedure 7: To a teflon capped vial with a stir bar was added, pyridine *N*-oxide (1 mmol, 4 equiv), $Pd(OAc)_2$ (5 mol%), bipyridine (40 mol%), and AgOAc (2.3 equiv) and dioxane

(0.25 M in substrate). The mixture was stirred for 10 minutes, then the substituted pyrrole (0.25 mmol, 1.0 equiv) was added, the resulting mixture was heated to 110 °C for 60 h and then cooled to room temperature. The reaction mixture was directly purified by flash column chromatography.

2-(1-Benzyl-1*H*-pyrrole-2-yl)-4-(ethoxycarbonyl)pyridine 1-oxide 1220B



6ba

According to **General Procedure 7**, 4-(ethoxycarbonyl)pyridine *N*-oxide (167 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (hexane:ethyl acetate = 2:1); brown oil (C2 product, 21.3 mg, 0.066 mmol, 26%) and yellow solid (C3 product, 5.3 mg, 0.016 mmol, 7%).

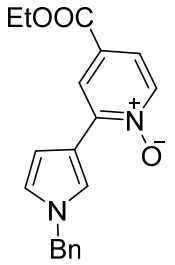
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, *J* = 6.8 Hz, 1H, PyH-6), 7.79 (d, *J* = 2.3 Hz, 1H, PyH-3), 7.72 (dd, *J* = 6.8, 2.6 Hz, 1H, PyH-5), 7.18 (d, *J* = 7.3 Hz, 3H, PhH), 6.98 – 6.93 (m, 2H, PhH), 6.92 – 6.87 (m, 1H, pyrroleH-5), 6.44 (dd, *J* = 3.7, 1.8 Hz, 1H, pyrroleH-3), 6.33 – 6.26 (m, 1H, pyrroleH-4), 5.21 (s, 2H, $\underline{CH_2}Ph$), 4.35 (q, *J* = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 1.36 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.65, 144.09, 140.11, 138.29, 129.37, 128.63, 127.63, 127.08, 126.36, 125.67, 124.58, 124.52, 113.93, 109.08, 61.98 ($\underline{CH_2}CH_3$), 53.16 ($\underline{CH_2}Ph$), 14.35 ($CH_2\underline{CH_3}$) ppm.

HRESI-MS: $[M+K]^+$ Calcd. for $C_{19}H_{18}N_2O_3K$ 361.0949; Found 361.0949. $[M+Na]^+$ Calcd. for $C_{19}H_{18}N_2O_3Na$ 345.1210; Found 345.1203. $[M+H]^+$ Calcd. for $C_{19}H_{19}N_2O_3$ 323.1390; Found 323.1381.

IR (υ_{max}/cm^{-1}): 2925 (vw), 1713 (s), 1443 (m), 1267 (s), 1233 (s), 1017 (m), 861 (m), 761 (s), 693 (s).

2-(1-Benzyl-1*H*-pyrrole-3-yl)-4-(ethoxycarbonyl)pyridine 1-oxide **1213**



6ba

According to **General Procedure 6**, 4-(ethoxycarbonyl)pyridine *N*-oxide (167 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (2.5 mg, 0.025 mmol), DPPP (5 mg, 0.013 mmol), $Cu(OAc)_2 \cdot H_2O$ (12.5 mg, 0.063 mmol), pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (hexane:ethyl acetate = 3:1); brown oil (C2 product, 5 mg, 0.016 mmol, 6%) and yellow solid (C3 product, 46.4 mg, 0.144 mmol, 58%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (t, *J* = 1.9 Hz, 1H, pyrroleH-2), 8.32 – 8.23 (m, 2H, PyH-3,6), 7.55 (dd, *J* = 6.8, 2.5 Hz, 1H, PyH-5), 7.36 – 7.28 (m, 3H, PhH), 7.22 – 7.16 (m, 2H, PhH), 6.74 (d, *J* = 2.1 Hz, 2H, pyrroleH4,5), 5.12 (s, 2H, $\underline{CH_2}$Ph), 4.40 (q, *J* = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 1.41 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$) ppm.

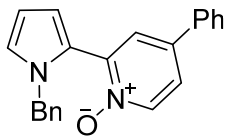
^{13}C NMR (126 MHz, $CDCl_3$): δ 164.06, 144.78, 140.40 (PyC-4), 136.90 (PhC), 128.73 (PhC), 127.85 (PhC), 127.15 (PhC), 126.37 (pyrroleC-2), 126.36 (PyC-2), 123.36 (PyC), 121.72 (pyrroleC), 119.92 (PyC-5), 114.50 (pyrroleC-3), 108.07 (pyrroleC), 61.61 ($\underline{CH_2}CH_3$), 53.76 ($\underline{CH_2}$Ph), 14.15 ($CH_2\underline{CH_3}$) ppm.

HRESI-MS: $[M+H]^+$Calcd. for $C_{19}H_{19}N_2O_3$ 323.1390; Found 323.1380.

IR (υ_{max}/cm^{-1}): 2927 (vw), 1711 (s), 1540 (s), 1394 (m), 1286 (s), 1259 (s), 1226 (s), 1020 (m), 761 (s), 693 (s).

M.p.: 109–110 °C.

2-(1-Benzyl-1*H*-pyrrole-2-yl)-4-phenylpyridine 1-oxide **1224B**



6bh

According to **General Procedure 7**, 4-phenyl pyridine *N*-oxide (171 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (hexane:ethyl acetate = 2:1); red oil (C2 product, 23.1 mg, 0.07 mmol, 28%) and red oil (C3 product, 4.6 mg, 0.014 mmol, 6%).

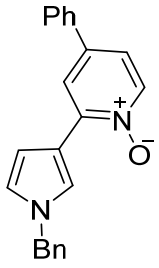
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, *J* = 6.0 Hz, 1H, PyH-6), 7.46 – 7.39 (m, 5H, PhH), 7.37 – 7.35 (m, 2H, PyH), 7.21 – 7.11 (m, 3H, PhH), 6.99 (d, *J* = 7.2 Hz, 2H, PhH), 6.93 – 6.88 (dd, *J* = 2.7, 1.8 Hz, 1H, pyrroleH-5), 6.45 (dd, *J* = 3.5, 1.9 Hz, 1H, pyrroleH-4), 6.30 (t, *J* = 3.3 Hz, 1H, pyrroleH-3), 5.31 (s, 2H, CH_2Ph) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.76, 139.93 (PyC-6), 138.56, 138.06, 136.41, 129.30, 129.02 (PhC), 128.52 (PhC), 127.48 (PhC), 127.11 (PhC), 126.73 (PyC), 126.47 (PhC), 125.32 (pyrroleC), 125.28 (pyrroleC-5), 122.37 (pyridineC), 113.28 (pyrroleC-4), 108.82 (pyrroleC-3), 53.05 (CH_2Ph) ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{22}H_{18}N_2ONa$ 349.1311; Found 349.1321. $[M+H]^+$ Calcd. for $C_{22}H_{19}N_2O$ 327.1492; Found 327.1505.

IR (υ_{max}/cm^{-1}): 3051 (vw), 1713 (s), 1558 (s), 1446 (m), 1248 (m), 1234 (s), 1015 (m), 767 (s), 695 (s).

2-(1-Benzyl-1*H*-pyrrole-3-yl)-4-phenylpyridine 1-oxide **1202**



6bh

According to **General Procedure 6**, 4-phenyl pyridine *N*-oxide (171 mg, 1 mmol, 4 equiv), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (2.5 mg, 0.025 mmol), DPPP (5 mg, 0.013 mmol), $Cu(OAc)_2 \cdot H_2O$ (12.5 mg, 0.063 mmol), pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (hexane:ethyl acetate = 2:1); red oil (C2 product, 3.3 mg, 0.01 mmol, 4%) and red oil (C3 product, 52.2 mg, 0.16 mmol, 64%).

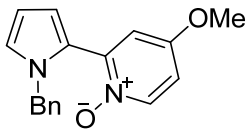
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (t, *J* = 1.8 Hz, 1H, pyrroleH-2), 8.29 (d, *J* = 6.9 Hz, 1H, PyH-6), 7.84 (d, *J* = 2.6 Hz, 1H, PyH-3), 7.65 – 7.60 (m, 2H, PhH), 7.51 – 7.46 (m, 2H, PhH), 7.44 – 7.41 (m, 1H, PhH), 7.35 – 7.28 (m, 3H, PhH), 7.20 (dd, *J* = 6.8, 2.1 Hz, 3H, PhH and PyH-5), 6.79 – 6.69 (m, 2H, pyrroleH), 5.13 (s, 2H, CH_2Ph) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 144.80 (PyC-6), 140.57, 138.45, 137.44, 137.29, 129.29 (PhC), 128.95 (PhC), 128.82 (PhC), 128.05 (PhC), 127.43 (pyrroleC-3), 126.89 (pyrroleC-2), 126.66 (PhC), 121.72 (pyrroleC), 120.55 (PyC), 118.80 (PyC), 115.17, 108.16 (pyrroleC), 53.99 (CH_2Ph) ppm.

HRESI-MS: $[M+K]^+$ Calcd. for $C_{22}H_{18}N_2OK$ 365.1051; Found 365.1069. $[M+Na]^+$ Calcd. for $C_{22}H_{18}N_2ONa$ 349.1311; Found 349.1316. $[M+H]^+$ Calcd. for $C_{22}H_{19}N_2O$ 327.1492; Found 327.1496.

IR (υ_{max}/cm^{-1}): 3048 (vw), 1712 (s), 1267 (m), 1232 (s), 1018 (m), 766 (s), 701 (s).

2-(1-Benzyl-1*H*-pyrrole-2-yl)-4-methoxypyridine 1-oxide **1222**



7bg

According to **General Procedure 7**, 4-methoxyl pyridine *N*-oxide (125 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (ethyl acetate:ethanol = 4:1); red solid (C2 product, 11.2 mg, 0.04 mmol, 16%) and red solid (C3 product, 14 mg, 0.05 mmol, 20%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 7.2 Hz, 1H, PyH-6), 7.21 – 7.13 (m, 3H, PhH), 6.95 (dd, *J* = 7.8, 1.7 Hz, 2H, PhH), 6.90 – 6.86 (m, 1H, pyrroleH-5), 6.71 (dd, *J* = 7.3, 3.5 Hz, 1H, PyH-5),

6.65 (d, *J* = 3.5 Hz, 1H, PyH-3), 6.39 (dd, *J* = 3.6, 1.8 Hz, 1H, pyrroleH-3), 6.29 – 6.23 (dd, *J* = 3.6, 2.7 Hz, 1H, pyrroleH-4), 5.33 (s, 2H, CH_2Ph), 3.72 (s, 3H, CH_3) ppm.

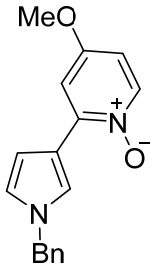
^{13}C NMR (126 MHz, $CDCl_3$): δ 157.13, 144.41, 140.71, 138.72, 128.53, 127.44, 127.11, 125.44, 125.36, 113.43, 113.27, 111.74, 108.78, 56.11 (OMe), 53.02 (CH_2Ph) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{17}H_{17}N_2O_2$ 281.1285; Found 281.1285.

IR (υ_{max}/cm^{-1}): 2927 (vw), 1709 (s), 1454 (m), 1221 (s), 1019 (m), 764 (s), 727 (s), 693 (s).

M.p.: 114–115 °C.

2-(1-Benzyl-1*H*-pyrrole-3-yl)-4-methoxypyridine 1-oxide **1201**



6bg

According to **General Procedure 6**, 4-methoxyl pyridine *N*-oxide (125 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (2.5 mg, 0.025 mmol), DPPP (5 mg, 0.013 mmol), $Cu(OAc)_2 \cdot H_2O$ (12.5 mg, 0.063 mmol), pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (ethyl acetate:ethanol = 4:1–3:1); red solid (C2 product, 3.5 mg, 0.0125 mmol, 5%) and red solid (C3 product, 25.9 mg, 0.093 mmol, 37%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.60 (s, 1H, pyrroleH-2), 8.13 (d, *J* = 7.3 Hz, 1H, PyH-6), 7.34 – 7.27 (m, 3H, PhH), 7.18 (d, *J* = 6.8 Hz, 2H, PhH), 7.08 (d, *J* = 3.4 Hz, 1H, PyH-3), 6.70 (dd, *J* = 3.0, 2.1 Hz, 1H, pyrroleH-4), 6.60 (dd, *J* = 3.1, 1.4 Hz, 1H, pyrroleH-5), 6.57 (dd, *J* = 7.2, 3.4 Hz, 1H, PyH-5), 5.10 (s, 2H, CH_2Ph), 3.86 (s, 3H, OCH_3) ppm.

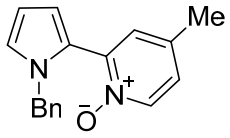
^{13}C NMR (126 MHz, $CDCl_3$): δ 157.51 (PyC-4), 141.33 (PyC-6), 137.25, 128.92 (PhH), 128.59, 128.02 (PhH), 127.42 (pyrroleC-2), 127.19 (PhH), 121.59 (pyrroleC-4), 115.10 (PyC-2), 108.25 (pyrroleC-5), 108.12 (PyC-5), 106.52 (PyC-3), 55.93 (OMe), 53.95 (CH_2Ph) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{17}H_{17}N_2O_2$ 281.1285; Found 281.1290.

IR (υ_{max}/cm^{-1}): 2927 (vw), 1711 (s), 1444 (m), 1232 (s), 1226 (s), 1018 (m), 763 (s), 694 (s).

M.p.: 85–86 °C.

2-(1-Benzyl-1*H*-pyrrole-2-yl)-4-methylpyridine 1-oxide **1206, 1226**



7be

According to **General Procedure 7**, 4-methyl pyridine *N*-oxide (109 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (ethyl acetate:ethanol = 4:1); gray solid (C2 product,15.7 mg, 0.06 mmol, 24%) and red oil (C3 product, 12.1 mg, 0.05 mmol, 18%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, *J* = 6.6 Hz, 1H, PyH), 7.21 – 7.14 (m, 3H, PhH), 7.00 – 6.90 (m, 4H, PhH and PyH), 6.89 – 6.82 (dd, *J* = 2.7, 1.8 Hz, 1H, pyrroleH-5), 6.34 (dd, *J* = 3.6, 1.7 Hz, 1H, pyrroleH-3), 6.29 – 6.22 (dd, *J* = 3.6, 2.7 Hz, 1H, pyrroleH-4), 5.28 (s, 2H, CH_2Ph), 2.23 (s, 3H, CH_3) ppm.

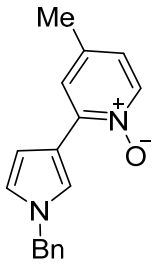
^{13}C NMR (101 MHz, $CDCl_3$): δ 143.18 (PyC), 139.33, 138.75, 136.77, 129.80, 128.50 (PhC), 127.38 (PhC), 127.14, 125.59 (pyrroleC-2), 125.50 (PhC), 125.08 (pyrroleC-5), 113.03 (pyrroleC-3), 108.79 (pyrroleC-4), 52.99 (CH_2Ph), 20.23 (CH_3) ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{17}H_{16}N_2ONa$ 287.1155; Found 287.1168.

IR (υ_{max}/cm^{-1}): 1713 (m), 1484 (m), 1454 (m), 1235 (s), 1019 (m), 830 (m), 792 (m), 727 (s), 691 (s).

M.p.: 119–120 °C.

2-(1-Benzyl-1*H*-pyrrole-3-yl)-4-methylpyridine 1-oxide **1206, 1215, 1226**



6be

According to **General Procedure 6**, 4-methyl pyridine *N*-oxide (109 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (2.5 mg, 0.025 mmol), DPPP (5 mg, 0.013 mmol), $Cu(OAc)_2 \cdot H_2O$ (12.5 mg, 0.063 mmol), pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (ethyl acetate:ethanol = 3:1); gray solid (C2 product, 2 mg, 0.008 mmol, 3%) and red oil (C3 product, 37 mg, 0.14 mmol, 56%).

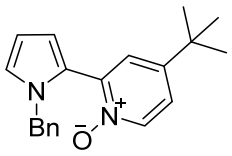
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (s, 1H, pyrroleH-2), 8.12 (d, *J* = 5.8 Hz, 1H, PyH-6), 7.43 (s, 1H, PyH-2), 7.35 – 7.27 (m, 3H, PhH), 7.18 (d, *J* = 8.5 Hz, 2H, PhH), 6.78 (d, *J* = 6.3 Hz, 1H, PyH-5), 6.70 (dd, *J* = 3.0 Hz, *J* = 2.1 Hz, 1H, pyrroleH-4), 6.63 (d, *J* = 2.8 Hz, 1H, pyrroleH-5), 5.10 (s, 2H, CH_2Ph), 2.34 (s, 3H, CH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 144.12 (PyC), 139.84 (PyC-6), 137.29, 136.71 (PyC), 128.86 (PhC), 127.94 (PhC), 127.37 (PhC), 126.80 (pyrroleC-2), 123.16 (PyC-2), 121.74 (pyrroleC-3), 121.50 (PyC-5), 115.02 (pyrroleC-4), 108.00 (pyrroleC-5), 53.88 (CH_2Ph), 20.54 (CH_3) ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{17}H_{16}N_2ONa$ 287.1155; Found 287.1154. $[M+H]^+$ Calcd. for $C_{17}H_{17}N_2O$ 265.1335; Found 265.1333.

IR (υ_{max}/cm^{-1}): 1712 (m), 1443 (m), 1268 (m), 1234 (s), 1019 (m), 767 (s), 729 (s), 694 (s).

2-(1-Benzyl-1*H*-pyrrole-2-yl)-4-(*tert*-butyl)pyridine 1-oxide **1225**



7bf

According to **General Procedure 7**, 4-(*tert*-butyl) pyridine *N*-oxide (151 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (ethyl acetate:ethanol = 10:1); red oil (C2 product, 20.7 mg, 0.07 mmol, 27%) and red oil (C3 product, 6.9 mg, 0.023 mmol, 9%).

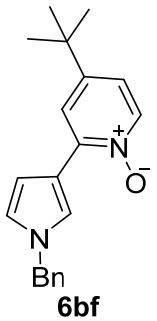
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 6.9 Hz, 1H, PyH-6), 7.15 – 7.08 (m, 4H, PhH), 7.01 (d, *J* = 2.9 Hz, 1H, PyH-3), 6.91 (dt, *J* = 7.6, 2.5 Hz, 3H, PhH, PyH-5, pyrroleH-5), 6.37 (dd, *J* = 3.6, 1.7 Hz, 1H, pyrroleH-3), 6.30 – 6.24 (dd, *J* = 3.6, 2.7 Hz, 1H, pyrroleH-4), 5.26 (s, 2H, $\underline{CH_2}$Ph), 1.17 (s, 9H, C($\underline{CH_3}$)$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.00($\underline{C}(CH_3)_3$), 142.95, 139.07 (PyC-6), 138.67, 128.42 (PhC), 127.43, 127.15 (PhC), 126.38 (PyC-3), 125.73, 125.08, 122.00 (PhC), 112.83 (pyrroleC-3), 108.51 (pyrroleC-4), 53.06 ($\underline{CH_2}$Ph), 34.43 ($\underline{C}(CH_3)_3$), 30.52 (C($\underline{C}H_3$)$_3$) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{20}H_{23}N_2O$ 307.1805; Found 307.1803.

IR (υ_{max}/cm^{-1}): 1703 (w), 1549 (m), 1237 (s), 981 (m), 823 (m), 704 (s), 686 (s), 665 (s).

2-(1-Benzyl-1*H*-pyrrole-3-yl)-4-(*tert*-butyl)pyridine 1-oxide 1225



6bf

According to **General Procedure 6**, 4-(*tert*-butyl) pyridine *N*-oxide (151 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (2.5 mg, 0.025 mmol), DPPP (5 mg, 0.013 mmol), $Cu(OAc)_2 \cdot H_2O$ (12.5 mg, 0.063 mmol), pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (ethyl acetate:ethanol = 10:1–5:1); red oil (2.3 mg, 0.008 mmol, 3%) and red oil (44.4 mg, 0.15 mmol, 58%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.55 (s, 1H, pyrroleH-2), 8.16 (d, *J* = 6.9 Hz, 1H, PyH-6), 7.58 (d, *J* = 2.7 Hz, 1H, PyH-3), 7.35 – 7.26 (m, 3H, PhH), 7.18 (d, *J* = 7.2 Hz, 2H, PhH), 6.97 (dd, *J* = 6.9,

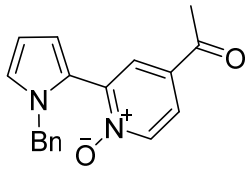
2.7 Hz, 1H, PyH-5), 6.74 – 6.70 (m, 1H, pyrroleH-5), 6.68 – 6.64 (m, 1H, pyrroleH-4), 5.11 (s, 2H, $\underline{CH_2}$Ph), 1.32 (s, 9H, C(CH_3)$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.93, 143.90 (PyC-6), 139.81, 137.41, 128.92 (PhC), 128.00 (PhC), 127.39 (PhC), 126.84 (pyrroleC-2), 121.52 (pyrroleC-5), 119.52 (PyC-3), 118.35 (PyC-5), 115.39, 108.02 (pyrroleC-4), 53.95 ($\underline{CH_2}$Ph), 34.59 ($\underline{C}(CH_3)_3$), 30.68 (C($\underline{C}H_3$)$_3$) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{20}H_{23}N_2O$ 307.1805; Found 307.1835.

IR (υ_{max}/cm^{-1}): 1614 (w), 1537 (m), 1393 (m), 1353 (m), 1252 (s), 1238 (s), 1166 (m), 955 (s), 806 (s), 732 (s), 689 (s).

4-Acetyl-2-(1-benzyl-1*H*-pyrrole-2-yl)pyridine 1-oxide **1229**



7bk

According to **General Procedure 7**, 4-acetyl pyridine *N*-oxide (137 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (cyclohexane:acetone = 5:1–2:1); brown solid (C2 product, 19 mg, 0.065 mmol, 26%) and red solid (C3 product, 5.1 mg, 0.017 mmol, 7%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, *J* = 6.8 Hz, 1H, PyH-6), 7.64 (dd, *J* = 6.8, 2.6 Hz, 1H, PyH-5), 7.60 (d, *J* = 2.6 Hz, 1H, PyH-3), 7.21 – 7.11 (m, 3H, PhH), 6.98 – 6.88 (m, 3H, PhH and pyrroleH-5), 6.45 (dd, *J* = 3.7, 1.8 Hz, 1H, pyrroleH-3), 6.31 (dd, *J* = 3.7, 2.7 Hz, 1H, pyrroleH-4), 5.21 (s, 2H, CH_2Ph), 2.44 (s, 3H, CH_3) ppm.

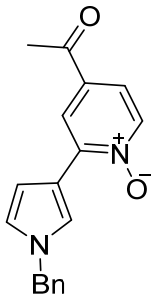
^{13}C NMR (101 MHz, $CDCl_3$): δ 194.01 (CO), 144.11 (PyC-2), 140.29 (PyC-6), 138.34 (PhC), 131.90 (PyC-4), 128.63 (PhC), 128.28 (PyC-3), 127.66 (PhC), 127.02 (pyrroleC-5), 125.81 (PhC), 124.42 (pyrroleC-2), 123.08 (PyC-5), 113.92 (pyrroleC-3), 109.05 (pyrroleC-4), 53.17 ($\underline{C}H_2$Ph), 26.31 (CH_3) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{18}H_{17}N_2O_2$ 293.1285; Found 293.1274.

IR (υ_{max}/cm^{-1}): 2924 (vw), 1682 (s), 1613 (m), 1451 (s), 1349 (s), 1248 (s), 1228 (s), 1071 (m), 840 (s), 693 (s).

M.p.: 104–105 °C.

4-Acetyl-2-(1-benzyl-1*H*-pyrrole-3-yl)pyridine 1-oxide **1229**



6bk

According to **General Procedure 6**, 4-acetyl pyridine *N*-oxide (151 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (2.5 mg, 0.025 mmol), DPPP (5 mg, 0.013 mmol), $Cu(OAc)_2 \cdot H_2O$ (12.5 mg, 0.063 mmol), pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (cyclohexane: acetone = 3:1–1:1); brown solid (C2 product, 3.7 mg, 0.013 mmol, 5%) and red oil (C3 product, 48.9 mg, 0.17 mmol, 64%).

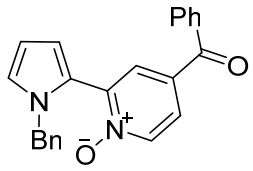
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (t, *J* = 2.0 Hz, 1H, pyrroleH-2), 8.28 (d, *J* = 6.8 Hz, 1H, PyH-6), 8.17 (d, *J* = 2.6 Hz, 1H, PyH-3), 7.48 (dd, *J* = 6.9, 2.5 Hz, 1H, PyH-5), 7.32 (ddd, *J* = 6.0, 4.7, 1.8 Hz, 3H, PhH), 7.25 – 7.16 (m, 2H, PhH), 6.81 – 6.68 (m, 2H, pyrrole H), 5.13 (s, 2H, CH_2Ph), 2.62 (s, 3H, CH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 194.80 (CO), 145.17 (PyC-6), 140.81 (PyC), 137.11 (PhC), 132.43 (PyC), 129.01 (PhC), 128.15, 127.42 (PhC), 126.67 (pyrrole C-2), 122.22 (PyC-3), 122.07 (pyrrole C), 119.00 (PyC-5), 114.72 (pyrrole C-3), 108.22 (pyrrole C), 54.05 ($\underline{C}H_2Ph$), 26.49 (CH_3) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{18}H_{17}N_2O_2$ 293.1285; Found 293.1291.

IR (υ_{max}/cm^{-1}): 2922 (vw), 1681 (s), 1612 (m), 1545 (m), 1349 (m), 1248 (s), 1228 (s), 1168 (m), 807 (s), 693 (s).

4-Benzoyl-2-(1-benzyl-1*H*-pyrrole-2-yl)pyridine 1-oxide **1230**



7bl

According to **General Procedure 7**, 4-benzoyl pyridine *N*-oxide (199 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (cyclohexane:acetone = 5:1–4:1); brown solid (C2 product, 23 mg, 0.065 mmol, 26%) and red solid (C3 product, 6.2 mg, 0.018 mmol, 7%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, *J* = 6.7 Hz, 1H, PyH-6), 7.64 – 7.56 (m, 4H, PyH-3,5 and COPhH), 7.50 – 7.44 (m, 3H, COPhH), 7.19 (d, *J* = 7.2 Hz, 3H, CH_2PhH), 7.01 – 6.90 (m, 3H, CH_2PhH and pyrrole H-5), 6.38 (dd, *J* = 3.7, 1.8 Hz, 1H, pyrrole H-3), 6.31 – 6.23 (m, 1H, pyrrole H-4), 5.27 (s, 2H, CH_2) ppm.

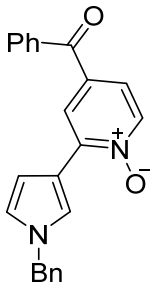
^{13}C NMR (101 MHz, $CDCl_3$): δ 192.11 (CO), 139.77 (PyC-6), 138.17, 135.93 (PhC), 133.54, 132.98 (PhC), 132.29 (PyC), 129.68 (PhC), 129.45 (PyC), 128.47 (PhC), 128.30 (PhC), 127.31 (PhC), 126.72 (PhC), 125.61 (pyrrole C-5), 124.71 (PyC), 124.07 (pyrrole C-2), 113.67 (pyrrole C-3), 108.60 (pyrrole C-4), 53.02 (CH_2) ppm.

HRESI-MS: $[M+K]^+$ Calcd. for $C_{23}H_{18}N_2O_2K$ 393.1000; Found 393.1010. $[M+Na]^+$ Calcd. for $C_{23}H_{18}N_2O_2Na$ 377.1260; Found 377.1250. $[M+H]^+$ Calcd. for $C_{23}H_{19}N_2O_2$ 355.1441; Found 355.1441.

IR (υ_{max}/cm^{-1}): 1654 (s), 1316 (m), 1243 (s), 1101 (m), 727 (s), 691 (s).

M.p.: 127–128 °C.

4-Benzoyl-2-(1-benzyl-1*H*-pyrrole-3-yl)pyridine 1-oxide **1230**



6bl

According to **General Procedure 6**, 4-benzoyl pyridine *N*-oxide (199 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (2.5 mg, 0.025 mmol), DPPP (5 mg, 0.013 mmol), $Cu(OAc)_2 \cdot H_2O$ (12.5 mg, 0.063 mmol), pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (pentane:acetone = 4:1–3:1); brown solid (C2 product, 2.7 mg, 0.008 mmol, 3%) and red solid (C3 product, 57.6 mg, 0.16 mmol, 65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (s, 1H, pyrroleH-2), 8.32 (d, *J* = 6.7 Hz, 1H, PyH-6), 8.08 (d, *J* = 2.2 Hz, 1H, PyH-3), 7.83 – 7.78 (m, 2H, PhH), 7.65 (t, *J* = 7.9 Hz, 1H, PhH), 7.53 (t, *J* = 7.5 Hz, 2H, PhH), 7.39 (dd, *J* = 6.7, 2.2 Hz, 1H, PyH-5), 7.35 – 7.29 (m, 3H, PhH), 7.23 – 7.16 (m, 2H, PhH), 6.78 – 6.72 (m, 1H, pyrroleH-5), 6.68 – 6.61 (m, 1H, pyrroleH-4), 5.13 (s, 2H, $\underline{CH_2}$Ph) ppm.

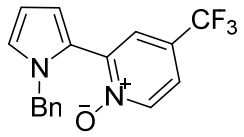
^{13}C NMR (101 MHz, $CDCl_3$): δ 192.93 (CO), 144.70, 140.23 (PyC-6), 136.80, 136.31, 132.90(PhC), 132.80, 129.55 (PhC), 128.69(PhC), 128.49 (PhC), 127.83 (PhC), 127.10, 126.49 (pyrroleC-2), 123.75 (PyC-3), 121.72 (PyC-5), 120.48, 114.37 (pyrroleC-5), 107.99 (pyrroleC-4), 53.73 ($\underline{CH_2}$Ph) ppm.

HRESI-MS: $[M+K]^+$ Calcd. for $C_{23}H_{18}N_2O_2K$ 393.1000; Found 393.0987. $[M+Na]^+$ Calcd. for $C_{23}H_{18}N_2O_2Na$ 377.1260; Found 377.1246. $[M+H]^+$ Calcd. for $C_{23}H_{19}N_2O_2$ 355.1441; Found 355.1427.

IR (υ_{max}/cm^{-1}): 2960 (vw), 1702 (s), 1546 (s), 1396 (m), 1236 (s), 1176 (m), 805 (m), 729 (s), 691 (s).

M.p.: 104–105 °C.

2-(1-Benzyl-1*H*-pyrrole-2-yl)-4-(trifluoromethyl)pyridine 1-oxide **1248**



7bu

According to **General Procedure 7**, 4-trifluoromethyl pyridine *N*-oxide (163 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (ethyl acetate:hexane = 2:1); red solid (C2 product, 24 mg, 0.075 mmol, 30%) and red oil (C3 product, 3.2 mg, 0.01 mmol, 4%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 – 8.25 (m, 1H, PyH-6), 7.31 (d, *J* = 3.0 Hz, 2H, PyH), 7.18 – 7.16 (m, 3H, PhH), 7.00 – 6.90 (m, 3H, pyrroleH-5, PhH), 6.43 (dd, *J* = 3.7, 1.8 Hz, 1H, pyrroleH-3), 6.35 – 6.22 (m, 1H, pyrroleH-4), 5.23 (s, 2H, CH_2) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 145.06 (CF_3), 140.74 (PyC-6), 138.43, 128.15 (d, *J* = 154.9 Hz), 128.12, 127.62 (PhC), 126.54, 126.07 (q, *J* = 3.9 Hz, PyC), 124.21, 124.11, 121.27 (q, *J* = 3.7 Hz, PyC), 114.92, 114.67 (pyrroleC-3), 109.44 (pyrroleC-4), 53.74 (CH_2) ppm.

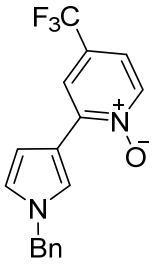
^{19}F NMR (376 MHz, $CDCl_3$): δ –63.55 ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{17}H_{13}F_3N_2ONa$ 341.0872; Found 341.0874.

IR (υ_{max}/cm^{-1}): 2927 (w), 1455 (m), 1322 (s), 1253 (s), 1111 (s), 1078 (s), 839 (m), 725 (s).

M.p.: 68–69 °C.

2-(1-Benzyl-1*H*-pyrrole-3-yl)-4-(trifluoromethyl)pyridine 1-oxide **1248**



6bu

According to **General Procedure 6**, 4-trifluoromethyl pyridine *N*-oxide (163 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (2.5 mg, 0.025 mmol), DPPP (5 mg, 0.013 mmol), $Cu(OAc)_2 \cdot H_2O$ (12.5 mg, 0.063 mmol), pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (ethyl acetate:hexane = 2:1 – ethyl acetate); red solid (C2 product, 4.8 mg, 0.015 mmol, 6%) and red oil (C3 product, 43 mg, 0.14 mmol, 54%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (t, *J* = 1.9 Hz, 1H, pyrroleH-2), 8.31 (d, *J* = 6.8 Hz, 1H, PyH-6), 7.83 (d, *J* = 2.4 Hz, 1H, PyH-3), 7.34 – 7.28 (m, 3H, PhH), 7.19 – 7.13 (m, 3H, PhH, PyH-5), 6.79 – 6.73 (m, 1H, pyrroleH-3), 6.66 (dd, *J* = 3.0, 1.7 Hz, 1H, pyrrole H-4), 5.12 (s, 2H, CH_2) ppm.

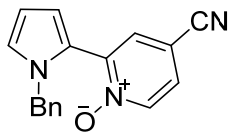
^{13}C NMR (101 MHz, $CDCl_3$): δ 145.48 (CF_3), 141.13 (PyC-6), 138.49 (d, *J* = 1.2 Hz), 137.01, 134.40, 128.23 (d, *J* = 163.1 Hz), 128.21 (PhC), 127.14 (PhC), 124.32, 122.28 (pyrroleC-3), 119.70 (q, *J* = 4.1 Hz, PyC-3), 116.57 (q, *J* = 3.5 Hz, PyC-5), 114.33, 108.21 (pyrroleC-4), 54.10 (CH_2) ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ –63.50 ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{17}H_{14}F_3N_2O$ 319.1053; Found 319.1077.

IR (υ_{max}/cm^{-1}): 2927 (w), 1542 (s), 1454 (s), 1313 (s), 1266 (s), 1169 (s), 1124 (s), 1078 (s), 716 (s).

2-(1-Benzyl-1*H*-pyrrole-2-yl)-4-cyanopyridine 1-oxide **1227**



7bo

According to **General Procedure 7**, 4-cyano pyridine *N*-oxide (120 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (ethyl acetate:hexane = 1:4–1:2); red oil (C2 product, 9.6 mg, 0.035 mmol, 14%) and brown solid (C3 product, 2.8 mg, 0.01 mmol, 4%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J* = 6.8 Hz, 1H, PyH-6), 7.34 (d, *J* = 2.5 Hz, 1H, PyH-3), 7.31 (dd, *J* = 6.7, 2.5 Hz, 1H, PyH-5), 7.23 – 7.16 (m, 3H, PhH), 6.99 – 6.86 (m, 3H, pyrroleH-5,

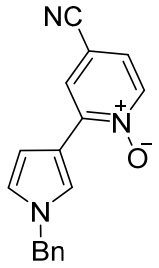
PhH), 6.42 (dd, *J* = 3.8, 1.7 Hz, 1H, pyrroleH-3), 6.34 – 6.25 (m, 1H, pyrroleH-4), 5.20 (s, 2H, CH_2) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 140.79 (CN), 137.99 (PyC-6), 131.56 (PyC-3), 128.71 (PhC), 127.94 (PhC), 126.99 (PhC), 126.67(pyrroleC-5), 126.50 (PyC-5), 126.43, 123.11, 115.97, 114.88 (pyrroleC-3), 109.32 (pyrroleC-4), 107.37, 53.55 (CH_2) ppm.

HRESI-MS: (+, 250V) m/z: $[M+Na]^+$ Calcd. for $C_{17}H_{13}N_3ONa$ 298.0951; Found 298.0955. $[M+H]^+$ Calcd. for $C_{17}H_{14}N_3O$ 276.1131; Found 276.1133.

IR (υ_{max}/cm^{-1}): 2922 (w), 1703 (s), 1542 (s), 1454 (s), 1396 (s), 1252 (s), 1236 (s), 1166 (s), 806 (s), 729 (s).

2-(1-Benzyl-1*H*-pyrrole-3-yl)-4-cyanopyridine 1-oxide **1227, 1205**



6bo

According to **General Procedure 6**, 4-cyano pyridine *N*-oxide (120 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (2.5 mg, 0.025 mmol), DPPP (5 mg, 0.013 mmol), $Cu(OAc)_2{\cdot}H_2O$ (12.5 mg, 0.063 mmol), pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (ethyl acetate:hexane = 1:1–2:1); red oil (C2 product, 4.1 mg, 0.015 mmol, 6%) and brown solid (C3 product, 12.4 mg, 0.045 mmol, 18%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (t, *J* = 1.9 Hz, 1H, pyrroleH-2), 8.26 (d, *J* = 6.9 Hz, 1H, PyH-6), 7.88 (d, *J* = 2.4 Hz, 1H, PyH-3), 7.36 – 7.30 (m, 3H, PhH), 7.20 – 7.14 (m, 3H, PhH, PyH-5), 6.78 – 6.74 (m, 1H, pyrroleH-5), 6.63 (dd, *J* = 3.0, 1.7 Hz, 1H, pyrroleH-4), 5.13 (s, 2H, CH_2) ppm.

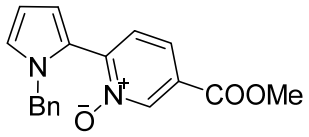
^{13}C NMR (101 MHz, $CDCl_3$): δ 146.10 (CN), 141.38 (PyC-6), 136.85 (PhC), 129.07 (PhC), 128.28, 127.44 (PhC), 127.14 (pyrroleC-2), 126.09 (PyC-3), 122.51 (pyrrole C-5), 121.96 (PyC-5), 116.77 (PyC), 113.67 (pyrroleC-3), 108.09, 107.88 (pyrrole C-4), 54.14 (CH_2) ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{17}H_{13}N_3ONa$ 298.0951; Found 298.0964. $[M+H]^+$ Calcd. for $C_{17}H_{14}N_3O$ 276.1131; Found 276.1139.

IR (υ_{max}/cm^{-1}): 2958 (w), 1705 (s), 1617 (m), 1543 (s), 1249 (s), 1179 (s), 825 (s), 708 (s), 667 (s).

M.p.: 125–126 °C.

2-(1-Benzyl-1*H*-pyrrol-2-yl)-5-(methoxycarbonyl)pyridine 1-oxide **1214**



7bc

According to **General Procedure 7**, 3-methoxycarbonyl pyridine *N*-oxide (153 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (hexane:ethyl acetate = 2:1–1:1); brown solid (C2 product, 18.5 mg, 0.06 mmol, 24%) and brown solid (C3 product, 6.2 mg, 0.02 mmol, 8%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.81 (d, *J* = 1.2 Hz, 1H, PyH-6), 7.64 (dd, *J* = 8.2, 1.4 Hz, 1H, PyH-4), 7.23 (d, *J* = 8.2 Hz, 1H, PyH-3), 7.19 – 7.13 (m, 3H, PhH), 6.97 – 6.89 (m, 3H, PhH, pyrroleH-5), 6.46 (dd, *J* = 3.7, 1.7 Hz, 1H, pyrroleH-3), 6.33 – 6.27 (m, 1H, pyrroleH-4), 5.31 (s, 2H, CH_2), 3.95 (s, 3H, CH_3) ppm.

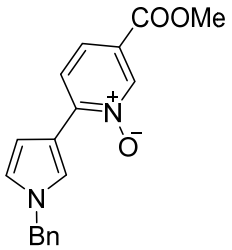
^{13}C NMR (101 MHz, $CDCl_3$): δ 163.67 (CO), 147.22, 141.15, 138.39, 128.60, 128.39, 127.80, 127.63, 126.99, 126.54, 125.54, 124.60, 114.84, 109.28, 53.47 (CH_2), 53.06 (CH_3) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{18}H_{17}N_2O_3$ 309.1234; Found 309.1228.

IR (υ_{max}/cm^{-1}): 2922 (w), 1715 (s), 1533 (s), 1432 (m), 1398 (m), 1284 (s), 1261 (s), 1108 (s), 806 (s), 756 (s).

M.p.: 87–88 °C.

2-(1-Benzyl-1*H*-pyrrole-3-yl)-5-(methoxycarbonyl)pyridine 1-oxide **1214**



6bc

According to **General Procedure 6**, 3-methoxycarbonyl pyridine *N*-oxide (153 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (2.5 mg, 0.025 mmol), DPPP (5 mg, 0.013 mmol), $Cu(OAc)_2 \cdot H_2O$ (12.5 mg, 0.063 mmol), pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (hexane:ethyl acetate = 1:1 – ethyl acetate); brown solid (C2 product, 16.2 mg, 0.05 mmol, 21%) and brown solid (C3 product, 18.5 mg, 0.06 mmol, 24%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81 (s, 1H, pyrroleH-2), 8.63 (s, 1H, PyH-2), 7.73 (d, *J* = 9.0 Hz, 1H, PyH), 7.64 (d, *J* = 8.8 Hz, 1H, PyH), 7.28 (d, *J* = 7.6 Hz, 3H, PhH), 7.18 – 7.11 (m, 2H, PhH), 6.72 – 6.68 (m, 1H, pyrroleH-5), 6.63 (dd, *J* = 3.7 Hz, *J* = 1.5 Hz, 1H, pyrroleH-4), 5.08 (s, 2H), 3.90 (s, 3H) ppm.

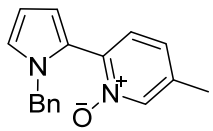
^{13}C NMR (101 MHz, $CDCl_3$): δ 164.18 (CO), 141.95, 136.95, 130.79, 129.03 (PhC), 128.21 (PyC-2), 128.10, 127.48 (PhC), 125.99, 123.75, 122.29 (pyrroleC-5), 122.25 (PyC-2), 114.66, 108.72 (pyrroleC-4), 54.12 (CH_2), 52.80 (CH_3) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{18}H_{17}N_2O_3$ 309.1234; Found 309.1223.

IR (υ_{max}/cm^{-1}): 2922 (w), 1716 (s), 1537 (s), 1432 (m), 1398 (m), 1285 (s), 1262 (s), 1109 (s), 986 (m), 806 (s), 755 (s), 691 (s).

M.p.: 80–81 °C.

2-(1-Benzyl-1*H*-pyrrole-2-yl)-5-methylpyridine 1-oxide **1232**



7bv

According to **General Procedure 7**, 3-methyl pyridine *N*-oxide (109 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (cyclohexane:acetone = 6:1); red oil (C2 product, 9.3 mg, 0.035 mmol, 14%) and red solid (C3 product, 4.6 mg, 0.017 mmol, 7%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 – 8.06 (m, 1H, PyH-6), 7.21 – 7.15 (m, 3H, PhH), 7.08 (d, *J* = 8.0 Hz, 1H, PyH-3), 6.96 – 6.91 (m, 3H, PyH-4, PhH), 6.85 (dd, *J* = 2.7, 1.8 Hz, 1H, pyrroleH-5),

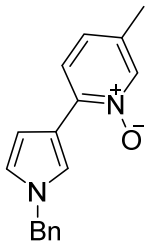
6.33 (dd, *J* = 3.6, 1.8 Hz, 1H, pyrroleH-3), 6.26 (dd, *J* = 3.6, 2.7 Hz, 1H, pyrroleH-4), 5.25 (s, 2H, CH_2), 2.28 (s, 3H, CH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 141.17 (PyC), 139.83 (PyC-6), 138.75 (PhC), 135.52 (PyC), 128.66 (PhC), 128.50 (PhC), 127.41 (PhC), 127.08 (PyC-4), 126.80 (PyC-3), 125.33 (pyrroleC-2), 124.88 (pyrroleC-5), 112.85 (pyrroleC-3), 108.77 (pyrroleC-4), 52.89 (CH_2), 18.20 (CH_3) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{17}H_{17}N_2O$ 265.1335; Found 265.1332. $[M+Na]^+$ Calcd. for $C_{17}H_{16}N_2ONa$ 287.1155; Found 287.1141.

IR (υ_{max}/cm^{-1}): 1713 (s), 1266 (s), 1250 (s), 1235 (s), 1018 (s), 951 (m), 797 (s), 729 (s), 690 (s).

2-(1-Benzyl-1*H*-pyrrole-3-yl)-5-methylpyridine 1-oxide **1232**



6bv

According to **General Procedure 6**, 3-methyl pyridine *N*-oxide (109 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (2.5 mg, 0.025 mmol), DPPP (5 mg, 0.013 mmol), $Cu(OAc)_2{\cdot}H_2O$ (12.5 mg, 0.063 mmol), pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (cyclohexane:acetone = 4:1); red oil (C2 product, 6 mg, 0.023 mmol, 9%) and red solid (C3 product, 23.8 mg, 0.09 mmol, 36%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (t, *J* = 2.0 Hz, 1H, pyrrole H-2), 8.11 (s, 1H, PyH-6), 7.54 (d, *J* = 8.5 Hz, 1H, PyH-3), 7.34 – 7.27 (m, 3H, PhH), 7.22 – 7.16 (m, 2H, PhH), 7.05 (d, *J* = 9.2 Hz, 1H, PyH-4), 6.73 – 6.68 (dd, *J* = 3.1 Hz, *J* = 2.0 Hz, 1H, pyrrole H-5), 6.62 (dd, *J* = 3.1 Hz, *J* = 1.3 Hz, 1H, pyrroleH-4), 5.11 (s, 2H, CH_2), 2.27 (s, 3H, CH_3) ppm.

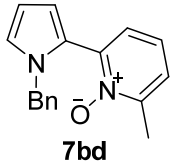
^{13}C NMR (101 MHz, $CDCl_3$): δ 142.50 (PyC), 140.24 (PyC-6), 137.38 (PhC), 131.04 (PyC), 128.93 (PhC), 128.00 (PhC), 127.54(PyC-4), 127.44 (PhC), 126.33 (pyrrole C-6), 122.44 (PyC-3), 121.48 (pyrroleC-5), 115.07 (pyrroleC-2), 107.94 (pyrroleC-4), 53.95 (CH_2), 17.90 (CH_3) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{17}H_{17}N_2O$ 265.1335; Found 265.1347.

IR (υ_{max}/cm^{-1}): 2922 (vw), 1706 (s), 1495 (m), 1234 (s), 1164 (s), 1075 (m), 693 (s), 670 (s).

M.p.: 139–140 °C.

2-(1-Benzyl-1*H*-pyrrole-2-yl)-6-methylpyridine 1-oxide **1231**



7bd

According to **General Procedure 7**, 2-methyl pyridine *N*-oxide (109 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (cyclohexane:acetone = 5:1–2:1); brown oil (C2 product, 5.9 mg, 0.022 mmol, 9%) and red oil (C3 product, 1.3 mg, 0.005 mmol, 2%).

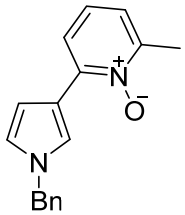
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 – 7.13 (m, 4H, PhH, PyH-3), 7.09 (dd, *J* = 7.9, 1.8 Hz, 1H, PyH-5), 6.99 (t, *J* = 7.5 Hz, 1H, PyH-4), 6.92 (dd, *J* = 7.7, 1.7 Hz, 2H, PhH), 6.87 – 6.82 (dd, *J* = 2.8, 1.7 Hz, 1H, pyrroleH-5), 6.34 (dd, *J* = 3.6, 1.8 Hz, 1H, pyrrole H-3), 6.25 (dd, *J* = 3.5, 2.8 Hz, 1H, pyrroleH-4), 5.25 (s, 2H, CH_2), 2.55 (s, 3H, CH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.27 (PyC), 143.65 (PyC), 138.46 (PhC), 128.15 (PhC), 127.06 (PhC), 126.76 (PyC), 126.57 (PyC), 125.68 (PhC), 124.88 (pyrroleC-5), 124.47 (PyC-4), 124.06 (pyrroleC), 112.62 (pyrroleC-3), 108.25 (pyrroleC-4), 52.71 (CH_2), 18.25 (CH_3) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{17}H_{17}N_2O$ 265.1335; Found 265.1351.

IR (υ_{max}/cm^{-1}): 2922 (vw), 1706 (s), 1546 (m), 1453 (m), 1273 (m), 1234 (s), 1164 (s), 951 (m), 813 (m), 714 (s).

2-(1-Benzyl-1*H*-pyrrole-2-yl)-6-methylpyridine 1-oxide **1231**



6bd

According to **General Procedure 6**, 2-methyl pyridine *N*-oxide (109 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (2.5 mg, 0.025 mmol), DPPP (5 mg, 0.013 mmol), $Cu(OAc)_2 \cdot H_2O$ (12.5 mg, 0.063 mmol), pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (cyclohexane:acetone = 2:1); brown oil (C2 product, 2.6 mg, 0.01 mmol, 4%) and red oil (C3 product, 22.4 mg, 0.08 mmol, 34%).

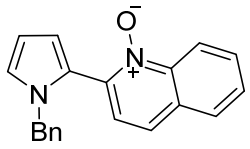
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (t, *J* = 2.0 Hz, 1H, pyrrole H-2), 7.58 (dd, *J* = 8.2, 1.8 Hz, 1H, PyH-3), 7.34 – 7.28 (m, 3H, PhH), 7.22 – 7.18 (m, 2H, PhH), 7.14 (t, *J* = 7.9 Hz, 1H, PyH-4), 7.01 (dd, *J* = 7.4, 1.6 Hz, 1H, PyH-5), 6.76 – 6.70 (m, 1H, pyrrole H-3), 6.65 (dd, *J* = 3.0, 1.7 Hz, 1H, pyrroleH-4), 5.11 (s, 2H, CH_2), 2.57 (s, 3H, CH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.68, 137.40, 128.96 (PhC), 128.24, 128.02 (PhC), 127.48 (PhC), 126.68, 125.00, 121.55, 121.18 (pyrroleC-3), 120.70, 115.64, 108.42 (pyrroleC-4), 54.03 (CH_2), 18.72 (CH_3) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{17}H_{17}N_2O$ 265.1335; Found 265.1337. $[M+Na]^+$ Calcd. for $C_{17}H_{16}N_2ONa$ 287.1155; Found 287.1156.

IR (υ_{max}/cm^{-1}): 2922 (vw), 1703 (s), 1543 (m), 1453 (m), 1396 (m), 1231 (s), 1207 (s), 1167 (s), 808 (m), 727 (s).

2-(1-Benzyl-1*H*-pyrrole-2-yl)quinoline 1-oxide **1233B**



7bj

According to **General Procedure 7**, quinoline *N*-oxide (145 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (cyclohexane:acetone = 4:1); brown oil (C2 product, 19.6 mg, 0.065 mmol, 26%) and brown solid (C3 product, 2.2 mg, 0.007 mmol, 3%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (dt, *J* = 8.8, 0.9 Hz, 1H, quinolineH-9), 7.80 (dd, *J* = 8.0, 1.3 Hz, 1H, quinolineH-6), 7.75 (dd, *J* = 8.7, 1.5 Hz, 1H, quinolineH-8), 7.64 – 7.58 (m, 1H, quinolineH-7), 7.54 (d, *J* = 8.8 Hz, 1H, quinolineH-3), 7.28-7.26 (m, 1H, quinolineH-4), 7.12 – 7.08 (m, 3H, PhH),

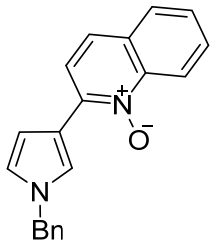
6.95 – 6.88 (m, 2H, PhH), 6.92 (dd, *J* = 2.7, 1.8 Hz, 1H, pyrroleH-5), 6.47 (dd, *J* = 3.7, 1.8 Hz, 1H, pyrroleH-3), 6.33 (dd, *J* = 3.7, 2.7 Hz, 1H, pyrroleH-4), 5.36 (s, 2H, CH_2) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 142.19, 138.85, 130.51, 129.69, 128.48, 128.41, 128.05 (PhC), 127.39, 127.00 (quinolineC-6), 126.42 (PhC), 125.37 (pyrroleC-5), 124.96 (quinolineC-3), 124.79 (quinolineC-4), 120.22 (quinolineC-9), 113.65 (pyrroleC-3), 109.20 (pyrroleC-4), 106.18, 53.46 (CH_2) ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{20}H_{16}N_2ONa$ 323.1155; Found 323.1149. $[M+H]^+$ Calcd. for $C_{20}H_{17}N_2O$ 301.1335; Found 301.1337.

IR (υ_{max}/cm^{-1}): 2923 (w), 1658 (m), 1595 (m), 1562 (m), 1326 (s), 1236 (m), 1064 (m), 813 (s), 712 (s).

2-(1-Benzyl-1*H*-pyrrole-3-yl)quinoline 1-oxide **1233A, 1233C**



6bj

According to **General Procedure 6**, quinoline *N*-oxide (109 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (2.5 mg, 0.025 mmol), DPPP (5 mg, 0.013 mmol), $Cu(OAc)_2 \cdot H_2O$ (12.5 mg, 0.063 mmol), pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (cyclohexane:acetone = 4:1); brown solid (C2 product, 14.3 mg, 0.048 mmol, 19%) and brown oil (C3 product, 21.8 mg, 0.073 mmol, 29%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (t, *J* = 2.0 Hz, 1H, pyrroleH-2), 8.83 – 8.68 (m, 1H, quinolineH-9), 7.80 – 7.71 (m, 3H, quinolineH), 7.66 (d, *J* = 9.2 Hz, 1H, quinolineH-6), 7.56 – 7.50 (m, 1H, quinolineH-4), 7.35 – 7.28 (m, 3H, PhH), 7.24 – 7.19 (m, 2H, PhH), 6.79 (s, 2H, pyrroleH), 5.15 (s, 2H, CH_2) ppm.

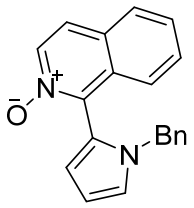
^{13}C NMR (101 MHz, $CDCl_3$): δ 142.45 (quinolineC), 141.32 (quinolineC), 137.22 (PhC), 130.41 (quinolineC), 128.98 (PhC), 128.09 (PhC), 127.86 (quinolineC), 127.81 (PhC), 127.66 (pyrroleC-2), 127.49, 127.13 (quinolineC-4), 125.53 (quinolineC-6), 121.87 (pyrroleC), 120.34 (quinolineC), 119.58 (quinolineC-9), 116.04 (pyrroleC-3), 108.94 (pyrroleC), 54.14 (CH_2) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{20}H_{17}N_2O$ 301.1335; Found 301.1344.

IR (υ_{max}/cm^{-1}): 2920 (w), 1702 (m), 1603 (m), 1540 (s), 1405 (s), 1330 (m), 1178 (m), 1063 (m), 799 (s), 706 (s).

M.p.: 96–97 °C.

1-(1-Benzyl-1*H*-pyrrole-2-yl)isoquinoline 2-oxide **1234B**



7bi

According to **General Procedure 7**, isoquinoline *N*-oxide (145 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (cyclohexane:acetone = 2:1 – acetone:ethyl acetate = 1:1); brown oil (C2 product, 19.5 mg, 0.065 mmol, 26%) and yellow oil (C3 product, 1.5 mg, 0.005 mmol, 2%).

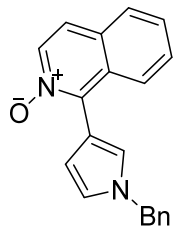
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 7.2 Hz, 1H, quinolineH-10), 7.65 (t, *J* = 9.6 Hz, 2H, quinolineH), 7.57 (d, *J* = 7.1 Hz, 1H, quinolineH-9), 7.49 – 7.36 (m, 2H, quinolineH), 7.04 – 6.85 (m, 6H, PhH, pyrroleH-2), 6.41 – 6.40 (m, 1H, pyrroleH), 6.38 – 6.37 (m, 1H, pyrroleH), 5.15 (s, 2H, CH_2) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 140.41, 138.05, 136.98 (quinolineC-10), 130.83, 129.30, 128.98, 128.86 (quinolineC), 128.28 (PhC), 127.29 (PhC), 127.11 (PhC), 126.52 (quinolineC), 126.25, 124.66 (pyrroleC-2), 123.73 (quinolineC-9), 121.41, 114.18 (pyrroleC), 108.65 (pyrroleC), 52.89 (CH_2) ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{20}H_{16}N_2ONa$ 323.1155; Found 323.1163. $[M+H]^+$Calcd. for $C_{20}H_{17}N_2O$ 301.1335; Found 301.1353.

IR (υ_{max}/cm^{-1}): 2913 (w), 1698 (m), 1395 (m), 1302 (s), 1169 (s), 1027 (m), 808 (s), 768 (s), 706 (s).

1-(1-Benzyl-1*H*-pyrrole-3-yl)isoquinoline 2-oxide **1234A**



6bi

According to **General Procedure 6**, isoquinoline *N*-oxide (109 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (2.5 mg, 0.025 mmol), DPPP (5 mg, 0.013 mmol), $Cu(OAc)_2{\cdot}H_2O$ (12.5 mg, 0.063 mmol), pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (cyclohexane:acetone = 2:1 – acetone:ethyl acetate = 1:1); brown oil (C2 product, 9.8 mg, 0.033 mmol, 13%) and yellow oil (C3 product, 27.8 mg, 0.093 mmol, 37%).

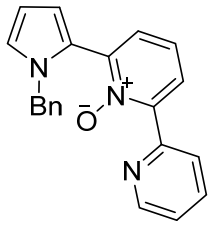
^{1}H NMR (400 MHz, MeOD): δ 8.23 (dd, *J* = 8.5, 1.1 Hz, 1H, quinolineH),8.19 (d, *J* = 7.1 Hz, 1H, quinolineH-2), 7.91 – 7.87 (m, 1H, quinolineH), 7.75 (d, *J* = 6.8 Hz, 1H, quinoline H-3), 7.68 – 7.54 (m, 3H, pyrrole H-2, quinolineH-6,7), 7.37 – 7.23 (m, 5H, PhH), 7.00 – 6.95 (dd, *J* = 2.9 Hz, *J* = 2.2 Hz, 1H, pyrroleH-5), 6.62 (dd, *J* = 2.9 Hz, *J* = 1.7 Hz, 1H, pyrroleH-4), 5.23 (s, 2H, CH_2) ppm.

^{13}C NMR (101 MHz, MeOD): δ 139.21 (quinolineC), 137.11 (quinolineC-2), 132.48 (quinolineC), 131.16 (quinolineC), 130.86 (PhC), 130.28 (quinolineC), 129.86 (PhC), 129.81 (quinoline C), 128.90 (PhC), 128.63 (quinolineC), 128.56 (PhC), 128.24 (quinolineC), 127.28 (pyrroleC), 123.32 (quinolineC-3), 122.67 (pyrroleC-5), 113.11 (pyrroleC-4), 112.48 (pyrrole C-3), 54.50 (CH_2) ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{20}H_{16}N_2ONa$ 323.1155; Found 323.1165. $[M+H]^+$ Calcd. for $C_{20}H_{17}N_2O$ 301.1335; Found 301.1324.

IR (υ_{max}/cm^{-1}): 2974 (w), 1701 (w), 1552 (m), 1494 (m), 1397 (m), 1304 (s), 1176 (m), 1117 (m), 973 (m), 809 (s), 707 (s).

6-(1-Benzyl-1*H*-pyrrole-2-yl)-[2,2'-bipyridine] 1-oxide **1240B**



7bq

According to **General Procedure 7**, bipyridine *N*-oxide (344 mg, 2 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (hexane:ethyl acetate = 1:1 – ethyl acetate); white solid (C2 product, 18 mg, 0.055 mmol, 11%) and brown oil (C3 product, 8 mg, 0.024 mmol, 5%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (d, *J* = 9.0 Hz, 1H, bpyH-6'), 8.73 (d, *J* = 6.3 Hz, 1H, bpyH-3'), 8.01 (dd, *J* = 7.1, 3.1 Hz, 1H, bpyH-4), 7.80 (td, *J* = 7.8, 1.8 Hz, 1H, bpyH-5'), 7.34 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, bpyH-4'), 7.22 – 7.13 (m, 5H,PhH, bpyH-3,5), 6.96 – 6.86 (m, 3H, pyrroleH-5, PhH), 6.39 (dd, *J* = 3.6, 1.8 Hz, 1H, pyrroleH-3), 6.28 (dd, *J* = 3.6, 2.7 Hz, 1H, pyrroleH-4), 5.22 (s, 2H, CH_2) ppm.

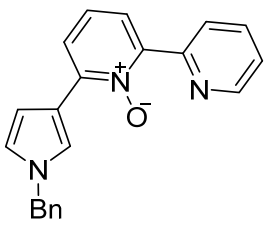
^{13}C NMR (101 MHz, $CDCl_3$): δ 150.52, 149.46 (bpyC-3'), 147.82, 144.81, 138.65, 136.26 (bpyC-5'), 128.86, 128.56, 127.47 (bpyC-4), 127.14 (PhC), 127.08, 125.78 (bpyC-6'), 125.69, 124.89 (pyrroleC-5), 124.84, 124.27 (bpyC-4'), 113.05 (pyrroleC-3), 108.70 (pyrroleC-4), 53.08 (CH_2) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{21}H_{18}N_3O$ 328.1444; Found 328.1414.

IR (υ_{max}/cm^{-1}): 1698 (m), 1538 (m), 1396 (s), 1348 (s), 1168 (s), 1090 (m), 1050 (s), 704 (s).

M.p.: 108–109 °C.

6-(1-Benzyl-1*H*-pyrrole-3-yl)-[2,2'-bipyridine] 1-oxide **1240**



6bq

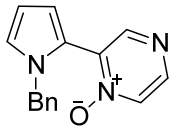
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (d, *J* = 4.8 Hz, 1H, bpy'C), 8.61 – 8.51 (m, 2H, pyrrole H-2, bpy'C), 7.82 (td, *J* = 7.8, 1.7 Hz, 1H, bpy'H), 7.73 (dd, *J* = 8.1, 2.0 Hz, 1H, bpyH), 7.67 (dd, *J* = 7.7, 2.1 Hz, 1H, bpyH), 7.34 – 7.28 (m, 5H, PhH, bpyH-4,4'), 7.21 – 7.16 (m, 2H, PhH), 6.78 – 6.67 (m, 2H, pyrroleH-4,5), 5.10 (s, 2H, CH_2) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.60, 149.43, 137.34, 136.11 (bpy'C), 128.96, 128.88, 128.05, 128.02, 127.71, 127.47 (PhH), 126.88 (pyrroleC-2), 125:86 (bpy'C), 123.87, 123.04 (bpyC), 122.91 (bpyC), 121.64 (pyrroleC-5), 115.44, 108.63 (pyrroleC-4), 54.04 (CH_2) ppm.

HRESI-MS: $[[M+H]^+$ Calcd. for $C_{21}H_{18}N_3O$ 328.1444; Found 328.1477.

IR (υ_{max}/cm^{-1}): 1701 (m), 1429 (m), 1396 (m), 1301 (s), 1168 (s), 1026 (m), 992 (s), 669 (s).

2-(1-Benzyl-1*H*-pyrrole-2-yl)pyrazine 1-oxide **1239**



7bw

According to **General Procedure 7**, pyrazine *N*-oxide (192 mg, 2 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), *N*-benzyl pyrrole (39.3 mg, 0.25 mmol), column chromatography on silica gel (DCM:methanol = 100:1); brown solid (15.7 mg, 0.06 mmol, 25%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (s, 1H, pyrazineH-3), 8.26 (d, *J* = 4.1 Hz, 1H, pyrazineH-6), 8.09 (dd, *J* = 4.1, 0.7 Hz, 1H, pyrazineH-5), 7.22 – 7.15 (m, 3H, PhH), 6.99 – 6.92 (m, 3H, PhH, pyrroleH-5), 6.45 (dd, *J* = 3.7, 1.8 Hz, 1H, pyrroleH-3), 6.32 (dd, *J* = 3.7, 2.7 Hz, 1H, pyrroleH-4), 5.19 (s, 2H, CH_2) ppm.

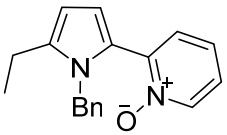
^{13}C NMR (101 MHz, $CDCl_3$): δ 149.94 (pyrazineC-3), 145.58 (pyrazineC-6), 139.69 (pyrazineC-2), 137.96 (PhC), 133.95 (pyrazineC-5), 128.71 (PhC), 127.86 (PhC), 126.95 (PhC), 126.63 (pyrroleC-5), 121.58 (pyrroleC-2), 114.56 (pyrroleC-3), 109.28 (pyrroleC-4), 53.34 (CH_2) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{10}H_{11}N_2O$ 252.1131; Found 252.1145.

IR (υ_{max}/cm^{-1}): 3061 (w), 1702 (m), 1544 (m), 1453 (m), 1294 (s), 1244 (m), 1042 (m), 861 (s), 842 (s), 670 (s).

M.p.: 80–81 °C.

2-(1-Benzyl-5-ethyl-1*H*-pyrrole-2-yl)pyridine 1-oxide **1250**



7gb

According to **General Procedure 7**, pyridine *N*-oxide (95 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), 2-ethyl *N*-benzyl pyrrole (46.3 mg, 0.25 mmol), column chromatography on silica gel (DCM:methanol = 50:1); yellow solid (C2 product, 18.8 mg, 0.07 mmol, 27%) and red oil (C3 product, 4.9 mg, 0.018 mmol, 7%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (dd, *J* = 6.3, 1.4 Hz, 1H, PyH-6), 7.21 – 7.04 (m, 6H, PhH, PyH-5), 6.75 (d, *J* = 5.9 Hz, 2H, PyH-3,4), 6.35 (d, *J* = 3.6 Hz, 1H, pyrroleH-3), 6.11 (d, *J* = 3.7 Hz, 1H, pyrroleH-4), 5.27 (s, 2H, CH_2), 2.55 (q, *J* = 7.4 Hz, 2H, $\underline{CH_2}CH_3$), 1.24 (t, *J* = 7.5 Hz, 3H, $CH_2\underline{CH_3}$) ppm.

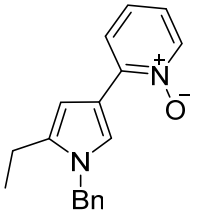
^{13}C NMR (101 MHz, $CDCl_3$): δ 144.38, 140.02, 139.36 (PyC-6), 139.27, 129.32, 128.51, 126.94, 125.83, 125.39, 124.92 (PyC-3, 4), 124.39, 112.20 (pyrroleC-3), 106.22 (pyrroleC-4), 49.19 (CH_2), 20.05 ($\underline{CH_2}CH_3$), 12.63 ($CH_2\underline{CH_3}$) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{18}H_{19}N_2O$ 279.1492; Found 279.1503.

IR (υ_{max}/cm^{-1}): 2927 (w), 1698 (s), 1448 (m), 1252 (s), 1144 (s), 1116 (m), 1039 (m), 841 (m), 808 (m), 759 (s), 720 (s).

M.p.: 89–90 °C.

2-(1-Benzyl-5-ethyl-1*H*-pyrrole-3-yl)pyridine 1-oxide **1250**



6gb

According to **General Procedure 6**, pyridine *N*-oxide (95 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (2.5 mg, 0.025 mmol), DPPP (5 mg, 0.013 mmol), $Cu(OAc)_2 \cdot H_2O$ (12.5 mg, 0.063 mmol), pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), 2-ethyl *N*-benzyl pyrrole (46.3 mg, 0.25 mmol), column chromatography on silica gel (DCM:methanol = 50:1); yellow solid (C2 product, 7 mg, 0.02 mmol, 10%) and red oil (C3 product, 34.8 mg, 0.12 mmol, 50%).

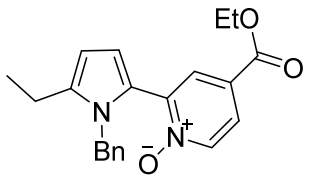
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (s, 1H, PyH-6), 8.22 (s, 1H, PyH), 7.69 (s, 1H, PyH), 7.37 – 7.27 (m, 3H, PhH), 7.23 (d, *J* = 7.2 Hz, 1H, PyH), 7.08 (d, *J* = 7.0 Hz, 2H, PhH), 6.98 (s, 1H, pyrroleH), 6.42 (s, 1H, pyrroleH), 5.11 (s, 2H, CH_2), 2.48 (q, *J* = 7.5 Hz, 2H, $\underline{CH_2}CH_3$), 1.22 (t, *J* = 7.5 Hz, 3H, $CH_2\underline{CH_3}$) ppm.

^{13}C NMR (101 MHz, CD_3CN): δ 141.36, 139.41, 136.91, 129.71, 129.54, 128.43 (PhC), 127.90, 127.70 (PhC), 126.99 (PhC), 123.50 (PyC), 121.37 (pyrroleC), 114.71, 105.39 (pyrroleC), 51.08 (CH_2), 19.95 ($\underline{CH_2}CH_3$), 13.12 ($CH_2\underline{CH_3}$) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{18}H_{19}N_2O$ 279.1492; Found 279.1502. $[M+Na]^+$ Calcd. for $C_{18}H_{18}N_2ONa$ 301.1311; Found 301.1323.

IR (υ_{max}/cm^{-1}): 2928 (w), 1698 (s), 1527 (s), 1430 (s), 1228 (m), 1174 (m), 1112 (m), 834 (m), 758 (s), 727 (s), 695 (s).

2-(1-Benzyl-5-ethyl-1*H*-pyrrole-2-yl)-4-(ethoxycarbonyl)pyridine 1-oxide 1257B



7ga

According to **General Procedure 7**, 4-ethoxycarbonyl pyridine *N*-oxide (167 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), 2-ethyl *N*-benzyl pyrrole (46.3 mg, 0.25 mmol), column chromatography on silica gel (hexane:ethyl acetate = 2:1); red oil (24 mg, 0.07 mmol, 28%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 6.7 Hz, 1H, PyH-6), 7.81 (d, *J* = 2.5 Hz, 1H, PyH-2), 7.67 (dd, *J* = 6.8, 2.5 Hz, 1H, PyH-5), 7.20 – 7.10 (m, 3H, PhH), 6.76 (d, *J* = 7.6 Hz, 2H, PhH), 6.43 (d, *J* = 3.7 Hz, 1H, pyrrole H-3), 6.14 (d, *J* = 4.1 Hz, 1H, pyrrole H-4), 5.20(s, 2H, CH_2), 4.38 – 4.30 (q, *J* = 8.0 Hz, 2H, $CO_2\underline{CH_2}CH_3$), 2.54 (q, *J* = 7.8, 2H, $\underline{CH_2}CH_3$), 1.35 (t, *J* = 7.1 Hz, 3H,

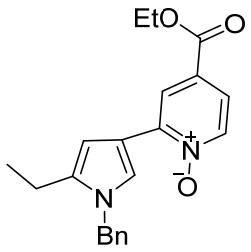
$CO_2CH_2\underline{CH_3}$), 1.26 – 1.21 (t, *J* = 8.0 Hz 3H, $CH_2\underline{CH_3}$) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 163.68(CO), 140.10, 139.81, 138.99, 130.30, 129.33, 128.63, 127.09, 126.47, 125.75, 124.20, 124.08, 112.97, 106.53, 61.91 ($CO_2\underline{CH_2}CH_3$), 49.31 (CH_2), 20.05 ($\underline{CH_2}CH_3$), 14.32 ($CO_2CH_2\underline{CH_3}$), 12.62 ($CH_2\underline{CH_3}$) ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{21}H_{22}N_2O_3Na$ 373.1523; Found 373.1541. $[M+H]^+$ Calcd. for $C_{21}H_{23}N_2O_3$ 351.1703; Found 351.1716.

IR (υ_{max}/cm^{-1}): 2968 (vw), 1715 (s), 1496 (m), 1236 (s), 1108 (s), 1020 (m), 763 (s), 720 (s), 695 (s).

2-(1-Benzyl-5-ethyl-1*H*-pyrrole-3-yl)-4-(ethoxycarbonyl)pyridine 1-oxide 1257A



6ga

According to **General Procedure 6**, 4-ethoxycarbonyl pyridine *N*-oxide (167 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (2.5 mg, 0.025 mmol), DPPP (5 mg, 0.013 mmol), $Cu(OAc)_2{\cdot}H_2O$ (12.5 mg, 0.063 mmol), pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), 2-ethyl *N*-benzyl pyrrole (46.3 mg, 0.25 mmol), column chromatography on silica gel (hexane:ethyl acetate = 2:1); red oil (C2 product, 2.6 mg, 0.007 mmol, 3%) and yellow solid (C3 product, 67.4 mg, 0.19 mmol, 77%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, *J* = 1.8 Hz, 1H, pyrrole H-2), 8.29 – 8.21 (m, 2H, PyH-3, 6), 7.52 (dd, *J* = 6.8, 2.4 Hz, 1H, PyH-5), 7.33 – 7.22 (m, 3H, PhH), 7.06 (d, *J* = 8.2 Hz, 2H, PhH), 6.50 (s, 1H, pyrroleH-4), 5.10 (s, 2H, CH_2), 4.41 (q, *J* = 7.1 Hz, 2H, $CO_2\underline{CH_2}CH_3$), 2.48 (q, *J* = 7.8 Hz, 2H, $\underline{CH_2}CH_3$), 1.41 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2\underline{CH_3}$), 1.23 (t, *J* = 7.5 Hz, 3H, $CH_2\underline{CH_3}$) ppm.

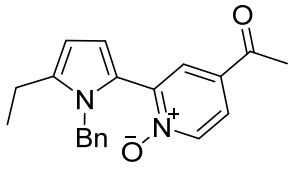
^{13}C NMR (101 MHz, $CDCl_3$): δ 164.38 (PyC-6), 145.07, 140.61 (PyC), 137.44 (PhC), 136.29 (pyrroleC), 128.90 (PhC), 127.68 (PhC), 127.36, 126.81 (pyrroleC-2), 126.55 (PhC), 123.46 (PyC-3), 119.75 (PyC-5), 113.34 (pyrroleC), 104.66 (pyrroleC-3), 61.82 ($CO_2\underline{CH_2}CH_3$), 50.91 (CH_2), 19.41 ($\underline{CH_2}CH_3$), 14.39 ($CO_2CH_2\underline{CH_3}$), 12.68 ($CH_2\underline{CH_3}$) ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{21}H_{22}N_2O_3Na$ 373.1523; Found 373.1506.

IR (υ_{max}/cm^{-1}): 2925 (vw), 1698 (s), 1433 (s), 1332 (s), 1212 (s), 1108 (s), 841 (s), 757 (s), 696 (m).

M.p.: 97–98 °C.

4-Acetyl-2-(1-benzyl-5-ethyl-1*H*-pyrrole-2-yl)pyridine 1-oxide **1267A**



7gk

According to **General Procedure 7**, 4-acetyl pyridine *N*-oxide (137 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), 2-ethyl *N*-benzyl pyrrole (46.3 mg, 0.25 mmol), column chromatography on silica gel (hexane:ethyl acetate = 2:1 – ethyl acetate); yellow oil (17.4 mg, 0.05 mmol, 22%).

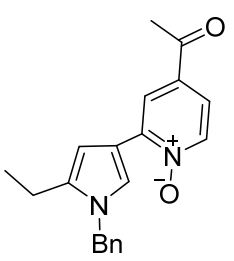
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, *J* = 6.7 Hz, 1H, PyH-6), 7.64 – 7.58 (m, 2H, PyH-3, 5), 7.14 (dd, *J* = 14.3, 7.5 Hz, 3H, PhH), 6.77 (d, *J* = 7.2 Hz, 2H, PhH), 6.45 (d, *J* = 3.7 Hz, 1H, pyrroleH-3), 6.15 (d, *J* = 4.1 Hz, 1H, pyrroleH-4), 5.19 (s, 2H, CH_2), 2.61 – 2.53 (q, *J* = 8.0 Hz, 2H, $\underline{CH_2}CH_3$), 2.39 (s, 3H, $CO\underline{CH_3}$), 1.26 (t, *J* = 7.5 Hz, 3H, $CH_2\underline{CH_3}$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 140.30, 139.87, 139.03, 132.00, 128.78, 128.67, 128.44, 128.19, 127.20, 125.78, 123.97, 122.67, 113.00, 106.52, 49.20 (CH_2), 26.27 ($\underline{CH_2}CH_3$), 20.07 ($CO\underline{CH_3}$), 12.70 ($CH_2\underline{CH_3}$) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{20}H_{21}N_2O_2$ 321.1598; Found 321.1621.

IR (υ_{max}/cm^{-1}): 2967 (vw), 1685 (s), 1496 (m), 1359 (m), 1266 (s), 1231 (s), 825 (m), 732 (s).

4-Acetyl-2-(1-benzyl-5-ethyl-1*H*-pyrrole-3-yl)pyridine 1-oxide **1267A**



6ga

According to **General Procedure 6**, 4-acetyl pyridine *N*-oxide (137 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (2.5 mg, 0.025 mmol), DPPP (5 mg, 0.013 mmol), $Cu(OAc)_2 \cdot H_2O$ (12.5 mg, 0.063 mmol), pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), 2-ethyl *N*-benzyl pyrrole (46.3 mg, 0.25 mmol), column chromatography on silica gel (hexane:ethyl acetate = 2:1–1:1); yellow oil (4 mg, 0.0125 mmol, 5%) and yellow solid (55.2 mg, 0.17 mmol, 69%).

^{1}H NMR (400 MHz, CD_3OD): δ 8.30 – 8.24 (m, 3H, pyrrole H-2, PyH-3,6), 7.59 (dd, *J* = 6.8, 2.5 Hz, 1H, PyH-5), 7.33 – 7.25 (m, 3H, PhH), 7.11 (d, *J* = 8.0 Hz, 2H, PhH), 6.63 (s, 1H, pyrroleH-4), 5.15 (s, 2H, CH_2), 2.63 (s, 3H, $COCH_3$), 2.51 (q, *J* = 7.7 Hz, 2H, $\underline{CH_2}CH_3$), 1.22 (t, *J* = 7.5 Hz, 3H, $CH_2\underline{CH_3}$) ppm.

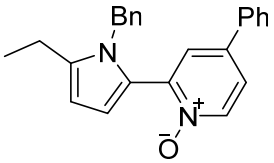
^{13}C NMR (101 MHz, $CDCl_3$): δ 194.95 (CO), 145.18 (PyC), 140.78 (PyC-6), 137.40 (PhC), 136.44 (pyrrole C), 132.43 (PyC), 128.93 (PhC), 127.73 (PhC), 126.90 (pyrrole C), 126.56 (PhC), 122.04 (PyC-3), 118.61 (PyC-5), 113.31 (pyrroleC), 104.56 (pyrrole C-4), 50.94 (CH_2), 26.54 ($COCH_3$), 19.43 ($\underline{CH_2}CH_3$), 12.68 ($CH_2\underline{CH_3}$) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{20}H_{21}N_2O_2$ 321.1598; Found 321.1609.

IR (υ_{max}/cm^{-1}): 2967 (vw), 1679 (s), 1606 (s), 1523 (s), 1370 (s), 1265 (s), 1238 (s), 1170 (m), 815 (s), 734 (s).

M.p.: 110–111 °C.

2-[1-Benzyl-5-ethyl-1*H*-pyrrole-2-yl]-4-phenylpyridine 1-oxide **1274B**



7gh

According to **General Procedure 7**, 4-phenyl pyridine *N*-oxide (171 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), 2-ethyl *N*-benzyl pyrrole (46.3 mg, 0.25 mmol), column chromatography on silica gel (hexane:ethyl acetate = 2:1–1:1); red oil (C2 product, 33.6 mg, 0.1 mmol, 38%) and red oil (C3 product, 3.5 mg, 0.01 mmol, 4%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 6.8 Hz, 1H, PyH-6), 7.44 – 7.37 (m, 6H, PhH, PyH-2),

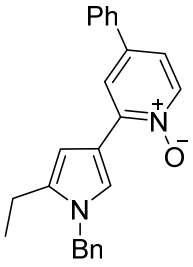
7.32 (dd, *J* = 6.8, 2.8 Hz, 1H, PyH-5), 7.17 (t, *J* = 7.9 Hz, 2H, Ph'H), 7.11 (d, *J* = 8.5 Hz, 1H, Ph'H), 6.81 (d, *J* = 8.1 Hz, 2H, Ph'H), 6.44 (d, *J* = 3.6 Hz, 1H, pyrrole H-3), 6.14 (d, *J* = 3.6 Hz, 1H, pyrroleH-4), 5.30 (s, 2H, CH_2), 2.57 (q, *J* = 7.9 Hz, 2H, $\underline{CH_2}CH_3$), 1.25 (q, *J* = 7.3 Hz, 3H, $CH_2\underline{CH_3}$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 139.99 (PyC-6), 139.35, 139.34, 138.12, 136.52, 129.30, 128.98 (Ph'C), 128.59, 127.01 (Ph'C), 126.71, 126.49, 126.18 (Ph'C), 125.90, 124.93, 122.02 (PyC-5), 112.36 (pyrroleC-3), 106.25 (pyrroleC-4), 49.22 (CH_2), 20.08 ($\underline{CH_2}CH_3$), 12.67 ($CH_2\underline{CH_3}$) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{24}H_{23}N_2O$ 355.1805; Found 355.1806. $[M+Na]^+$ Calcd. for $C_{24}H_{22}N_2ONa$ 377.1624; Found 377.1630.

IR (υ_{max}/cm^{-1}): 2966 (vw), 1495 (m), 1449 (s), 1246 (s), 908 (m), 754 (s), 724 (s), 693 (s).

2-[1-Benzyl-5-ethyl-1*H*-pyrrole-3-yl]-4-phenylpyridine 1-oxide **1274A**



6gh

According to **General Procedure 6**, 4-acetyl pyridine *N*-oxide (137 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (2.5 mg, 0.025 mmol), DPPP (5 mg, 0.013 mmol), $Cu(OAc)_2 \cdot H_2O$ (12.5 mg, 0.063 mmol), pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), 2-ethyl *N*-benzyl pyrrole (46.3 mg, 0.25 mmol), column chromatography on silica gel (hexane:ethyl acetate = 1:1 – ethyl acetate); red oil (70 mg, 0.2 mmol, 79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (s, 1H, pyrroleH-2), 8.28 (s, 1H, PyH-3), 7.88 (s, 1H, PyH-6), 7.63 (d, *J* = 7.4 Hz, 2H, Ph'H), 7.52 – 7.38 (m, 4H,Ph'H, PhH), 7.32 – 7.27 (m, 2H, PhH), 7.23 (d, *J* = 7.6 Hz, 1H, PyH-5), 7.08 (d, *J* = 8.1 Hz, 2H, PhH), 6.48 (s, 1H, pyrroleH-4), 5.12 (s, 2H, CH_2), 2.49 (q, *J* = 7.5 Hz, 2H, $\underline{CH_2}CH_3$), 1.23 (t, *J* = 7.5 Hz, 3H, $CH_2\underline{CH_3}$) ppm.

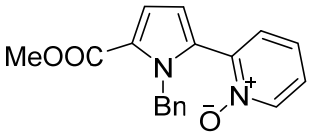
^{13}C NMR (101 MHz, $CDCl_3$): δ 137.58, 137.32 (pyrroleC), 136.04, 129.38, 129.21 (Ph'C), 128.83, 128.78 (PhC), 128.70 (Ph'C), 127.96, 127.70, 127.61 (PyC-5), 127.36 (PhC), 127.15 (pyrroleC-2), 126.74, 126.56 (PhC), 113.54 (pyrroleC), 104.57 (pyrroleC-4), 50.89 (CH_2), 19.40 ($\underline{CH_2}CH_3$), 12.69 ($CH_2\underline{CH_3}$) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{24}H_{23}N_2O$ 355.1805; Found 355.1817.

IR (υ_{max}/cm^{-1}): 2966 (vw), 1701 (m), 1546 (s), 1450 (s), 1241 (s), 1169 (m), 1015 (s), 907 (s), 761 (s), 725 (s), 694 (s).

M.p.: 135–136 °C.

2-[1-Benzyl-5-(methoxycarbonyl)-1*H*-pyrrole-2-yl]pyridine 1-oxide **1245B**



7hb

According to **General Procedure 7**, pyridine *N*-oxide (95 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), 2-methoxycarbonyl *N*-benzyl pyrrole (53.8 mg, 0.25 mmol), column chromatography on silica gel (hexane:ethyl acetate = 1:1 – ethyl acetate); yellow solid (C2 product, 5.3 mg, 0.017 mmol, 7%) and white solid (C3 product, 3 mg, 0.01 mmol, 4%).

^{1}H NMR (400 MHz, MeOD): δ 8.38 (d, *J* = 6.8 Hz, 1H, PyH-6), 7.51 – 7.45 (m, 1H, PyH-5), 7.41 – 7.35 (m, 1H, PyH-4), 7.28 (dd, *J* = 7.9, 2.4 Hz, 1H, PyH-3), 7.15 – 7.08 (m, 4H, PhH), 6.73 (dd, *J* = 6.6, 2.5 Hz, 2H, PhH, pyrroleH), 6.41 (d, *J* = 4.1 Hz, 1H, pyrroleH), 5.76 (s, 2H, CH_2), 3.82 (s, 3H, CH_3) ppm.

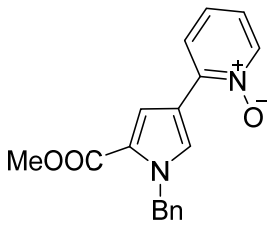
^{13}C NMR (101 MHz, $CDCl_3$): δ 161.58 (CO), 139.26, 133.31, 132.07, 129.75 (PhC), 128.41, 127.14, 127.04, 126.16 (pyrroleC), 125.82, 125.21, 124.99, 118.18 (PhC), 112.30, 51.48 (CH_3), 50.54 (CH_2) ppm.

HRESI-MS: $[M+Na]^+$Calcd. for $C_{18}H_{16}N_2O_3Na$ 331.1053; Found 331.1027.

IR (υ_{max}/cm^{-1}): 2923 (w), 1698 (s), 1433 (s), 1241 (s), 1142 (m), 1037 (m), 806 (m), 720 (s), 692 (s).

M.p.: 139–140 °C.

2-[1-Benzyl-5-(methoxycarbonyl)-1*H*-pyrrole-3-yl]pyridine 1-oxide 1245A



6hb

According to **General Procedure 6**, pyridine *N*-oxide (95 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (2.5 mg, 0.025 mmol), DPPP (5 mg, 0.013 mmol), $Cu(OAc)_2 \cdot H_2O$ (12.5 mg, 0.063 mmol), pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), 2-carbonyl *N*-benzyl pyrrole (53.8 mg, 0.25 mmol), column chromatography on silica gel (ethyl acetate – ethyl acetate:ethanol = 10:1); yellow solid (C2 product, 2.3 mg, 0.007 mmol, 3%) and white solid (C3 product, 32.3 mg, 0.1 mmol, 42%).

^{1}H NMR (400 MHz, MeCN-d_3): δ 8.63 (s, 1H, pyrroleH-2), 8.15 (s, 1H, PyH-6), 7.81 (s, 1H, PyH-4), 7.57 (s, 1H, pyrroleH-4), 7.35 – 7.24 (m, 4H, PhH, PyH-3), 7.17 (d, *J* = 8.3 Hz, 3H, PhH, PyH-5), 5.61 (s, 2H, CH_2), 3.76 (s, 3H, CO_2Me) ppm.

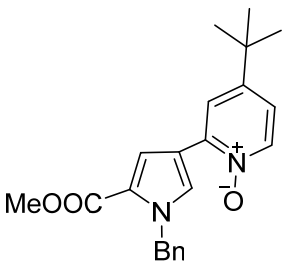
^{13}C NMR (101 MHz, CD_2Cl_2): δ 161.56 (CO), 147.30, 141.12, 138.57, 133.05 (pyrroleC-2), 129.15, 128.08, 127.43, 125.62, 123.42 (PyC-4), 122.87, 122.24, 117.19 (PyC-3), 115.49, 52.96 (CH_2), 51.78 (CH_3) ppm.

HRESI-MS: $[M+Na]^+$Calcd. for $C_{18}H_{16}N_2O_3Na$ 331.1053; Found 331.1062.

IR (υ_{max}/cm^{-1}): 2929 (w), 1698 (s), 1590 (s), 1497 (s), 1433 (m), 1292 (s), 1205 (m), 1104 (s), 842 (m), 754 (s), 727 (s), 692 (s).

M.p.: 147–148 °C.

2-[1-Benzyl-5-(methoxycarbonyl)-1*H*-pyrrole-3-yl]-4-(*tert*-butyl)pyridine 1-oxide 1268A



6hf

According to **General Procedure 6**, 4-*tert*- butyl pyridine *N*-oxide (151 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (2.5 mg, 0.025 mmol), DPPP (5 mg, 0.013 mmol), $Cu(OAc)_2 \cdot H_2O$ (12.5 mg, 0.063 mmol), pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), 2-carbonyl *N*-benzyl pyrrole (53.8 mg, 0.25 mmol), column chromatography on silica gel (ethyl acetate – ethyl acetate:ethanol = 20:1); yellow oil (51.9 mg, 0.14 mmol, 57%).

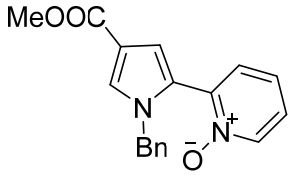
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (d, *J* = 1.8 Hz, 1H, pyrroleH-2), 8.17 (d, *J* = 6.9 Hz, 1H, PyH-6), 7.60 (d, *J* = 2.7 Hz, 1H, PyH-2), 7.46 (d, *J* = 1.8 Hz, 1H, pyrroleH-4), 7.29 – 7.22 (m, 3H, PhH), 7.19 – 7.14 (m, 2H, PhH), 7.03 (dd, *J* = 6.9, 2.7 Hz, 1H, PyH-5), 5.59 (s, 2H, CH_2), 3.80 (s, 3H, CO_2CH_3), 1.33 (s, 9H, $C(CH_3)_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 161.13 (CO), 150.19 (PhC), 142.67 (PyC-6), 139.81 (PyC), 137.60 (PhC), 133.09 (pyrroleC-2), 128.71 (PhC), 127.66 (PyC), 127.08 (PhC), 122.21 (pyrrole C), 119.71 (PyC-2), 119.40 (PyC-5), 116.89 (pyrrolC-4), 115.14 (pyrroleC), 52.65 (CH_2), 51.43 ($CO_2\underline{CH_3}$), 34.62 ($\underline{C}(CH_3)_3$), 30.64 ($C(\underline{CH_3})_3$) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{22}H_{25}N_2O_3$ 365.1860; Found 365.1878.

IR (υ_{max}/cm^{-1}): 2956 (w), 1704 (s), 1556 (s), 1486 (s), 1453 (s), 1375 (m), 1292 (m), 1246 (s), 1095 (s), 828 (s), 727 (s), 662 (s).

2-[1-Benzyl-4-(methoxycarbonyl)-1*H*-pyrrole-2-yl]pyridine 1-oxide 1251



7ib

According to **General Procedure 6**, pyridine *N*-oxide (95 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (2.5 mg, 0.025 mmol), DPPP (5 mg, 0.013 mmol), $Cu(OAc)_2 \cdot H_2O$ (12.5 mg, 0.063 mmol), pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), 3-carbonyl *N*-benzyl pyrrole (53.8 mg, 0.25 mmol), column chromatography on silica gel (ethyl acetate:ethanol = 10:1); red solid (20 mg, 26% 10.8 mg, 0.035 mmol, 14%).

According to **General Procedure 7**, pyridine *N*-oxide (57 mg), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL),

3-methoxycarbonyl *N*-benzyl pyrrole (53.8 mg, 0.25 mmol), column chromatography on silica gel (ethyl acetate:ethanol = 10:1); red solid (10.8 mg, 0,035 mmol, 14%).

^{1}H NMR (400 MHz, CD_3CN): δ 8.19 (d, *J* = 6.6 Hz, 1H, PyH-6), 7.55 (d, *J* = 1.9 Hz, 1H, pyrroleH-5), 7.29 (td, *J* = 6.8, 2.0 Hz, 1H, PyH-3), 7.21 – 7.12 (m, 5H, PhH, PyH-4,5), 6.95 (dd, *J* = 6.9, 2.7 Hz, 2H, PhH), 6.69 – 6.65 (m, 1H, pyrroleH-3), 5.25 (s, 2H, CH_2), 3.75 (s, 3H, CO_2Me) ppm.

^{13}C NMR (101 MHz, CD_3CN): δ 165.26 (CO), 140.74, 138.60, 130.50, 129.88, 129.48 (pyrroleC-5), 128.68, 128.29, 128.18, 127.09, 126.73, 125.98, 116.37, 114.11 (pyrroleC-3), 54.05 (CH_2), 51.59 (CH_3) ppm.

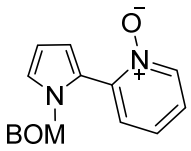
HRESI-MS: $[M+H]^+$ Calcd. for $C_{18}H_{17}N_2O_3$ 309.1234; Found 309.1248.

IR (υ_{max}/cm^{-1}): 2923 (vw), 1698 (s), 1517 (m), 1433 (s), 1212 (s), 1178 (s), 1002 (s), 841 (s), 758 (s).

M.p.: 161–162 °C.

General Procedure 8: To a teflon capped vial with a stir bar was added pyridine *N*-oxide (1 mmol, 4 equiv), $Pd(OAc)_2$ (5 mol%), CuCl (15 mol%), $Cu(OAc)_2 \cdot H_2O$ (25 mol%), pyridine (1 equiv) and AcOH (2 equiv) in dioxane (0.25 M in substrate), the mixture was stirred for 10 minutes, then the substituted pyrrole (0.25 mmol, 1.0 equiv) was added, the resulting mixture was heated to 110 °C for 60 h and then cooled to room temperature. The reaction mixture was directly purified by flash column chromatography.

2-{1-[(Benzyloxy)methyl]-1*H*-pyrrole-2-yl}pyridine 1-oxide 1382B, 1359B, 1377B



7jb

According to **General Procedure 7**, pyridine *N*-oxide (95 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), 1-[(benzyloxy)methyl]-1*H*-pyrrole (47 mg, 0.25 mmol), column chromatography on silica gel (ethyl

acetate:ethanol = 20:1); yellow solid (C2 product, 19.4 mg, 0.07 mmol, 28%) and yellow solid (C3 product, 6.5 mg, 0.02 mmol, 9%).

^{1}H NMR (400 MHz, MeOD): δ 8.30 (ddd, *J* = 6.5, 1.3, 0.6 Hz, 1H, PyH-6), 7.59 (ddd, *J* = 7.9, 2.2, 0.6 Hz, 1H, PyH-3), 7.53 (td, *J* = 7.7, 1.3 Hz, 1H, PyH-4), 7.44 (ddd, *J* = 7.5, 6.5, 2.2 Hz, 1H, PyH-5), 7.26 – 7.20 (m, 3H, PhH), 7.13 (dd, J = 2.8, 1.8 Hz, 1H, pyrrole H-5), 7.05 (dd, *J* = 7.2, 2.4 Hz, 2H, PhH), 6.53 (dd, *J* = 3.6, 1.7 Hz, 1H, pyrrole H-3), 6.30 (dd, *J* = 3.6, 2.8 Hz, 1H, pyrroleH-4), 5.48 (s, 2H, NCH_2), 4.24 (s, 2H, $O\underline{CH_2}Ph$) ppm.

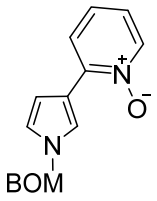
^{13}C NMR (126 MHz, MeOD): δ 144.98, 141.14, 138.49, 130.48, 130.05, 129.34, 128.79, 128.78, 126.82, 126.58, 125.55, 115.86, 110.11, 79.25 (NCH_2), 70.87 (OCH_2) ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{17}H_{16}N_2O_2Na$ 303.1104; Found 303.1097.

IR (υ_{max}/cm^{-1}): 3062 (vw), 1560 (m), 1486 (s), 1309 (s), 1239 (s), 1093 (s), 948 (s), 825 (s), 733 (s).

M.p.: 85–86 °C.

2-{1-[(Benzyloxy)methyl]-1*H*-pyrrole-3-yl}pyridine 1-oxide 1382, 1364B, 1359A, 1377A



6jb

According to **General Procedure 8**, pyridine *N*-oxide (95 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (3.8 mg, 0.038 mmol), $Cu(OAc)_2{\cdot}H_2O$ (12.5 mg, 0.063 mmol), pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), 1-[(benzyloxy)methyl]-1*H*-pyrrole (47 mg, 0.25 mmol), column chromatography on silica gel (ethyl acetate:ethanol = 20:1); yellow solid (5 mg, 0.018 mmol, 7%) and yellow solid (34.9 mg, 0.12 mmol, 50%).

^{1}H NMR (400 MHz, MeOD): δ 8.41 (t, *J* = 1.9 Hz, 1H, pyrroleH-2), 8.32 (d, *J* = 6.6 Hz, 1H, PyH-6), 7.95 (dd, *J* = 8.2, 2.0 Hz, 1H, PyH-3), 7.58 – 7.53 (m, 1H, PyH-4), 7.34 – 7.23 (m, 6H, PyH-5, PhH), 7.07 – 7.02 (m, 1H, pyrroleH-4), 6.88 (dd, *J* = 3.1, 1.7 Hz, 1H, pyrroleH-5), 5.41 (s, 2H, NCH_2), 4.49 (s, 2H, $O\underline{CH_2}Ph$) ppm.

^{13}C NMR (101 MHz, MeOD): δ 141.56 (PyC-6), 138.54 (PyC), 137.06 (PhC), 130.49 (PyC-4), 129.46 (PhC), 129.04 (PhC), 128.93 (PhC), 127.63 (pyrroleC-2), 125.12 (PyC-3), 123.35

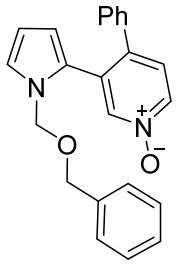
(pyrroleC-4), 122.87 (PyC-5), 116.38 (pyrrole C), 110.19 (pyrrole C-5), 79.34 (NCH_2), 71.18 (OCH_2) ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{17}H_{16}N_2O_2Na$ 303.1104; Found 303.1144.

IR (υ_{max}/cm^{-1}): 2923 (vw), 1707 (s), 1544 (m), 1430 (s), 1259 (m), 1182 (m), 1066 (s), 760 (s).

M.p.: 87–88 °C.

2-{1-[(Benzyloxy)methyl]-1*H*-pyrrol-2-yl}-4-phenylpyridine 1-oxide 1387B



7jh

According to **General Procedure 7**, 4-phenyl pyridine *N*-oxide (171 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), 1-[(benzyloxy)methyl]-1*H*-pyrrole (47 mg, 0.25 mmol), column chromatography on silica gel (ethyl acetate:ethanol = 20:1); yellow oil (C2 product, 25.6 mg, 0.072 mmol, 29%) and yellow oil (C3 product, 12.6 mg, 0.04 mmol, 14%).

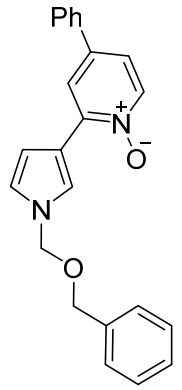
^{1}H NMR (400 MHz, MeOD): δ 8.28 (d, *J* = 6.9 Hz, 1H, PyH-6), 7.81 (d, *J* = 2.7 Hz, 1H, PyH-3), 7.67 – 7.62 (m, 3H, PyH-5, PhH), 7.46 – 7.41 (m, 3H, PhH), 7.15 – 7.09 (m, 4H, pyrroleH-5, PhH), 7.02 (dd, *J* = 6.6, 3.1 Hz, 2H, PhH), 6.64 (dd, *J* = 3.6, 1.7 Hz, 1H, pyrroleH-3), 6.30 (dd, *J* = 3.6, 2.9 Hz, 1H, pyrroleH-4), 5.49 (s, 2H, NCH_2), 4.29 (s, 2H, $\underline{CH_2}$Bn) ppm.

^{13}C NMR (101 MHz, MeOD): δ 144.65, 142.50, 141.16 (PyC-6), 138.45, 137.04, 130.57, 130.38 (PhC), 129.31, 128.75 (PhC), 128.21 (PhC), 127.81, 127.44 (PyC-3), 127.02 (pyrrole C-5), 125.50, 123.70, 116.20 (pyrroleH-3), 110.07 (pyrroleH-4), 79.15 (NCH_2), 70.88 ($\underline{CH_2}$Bn) ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{23}H_{20}N_2O_2Na$ 379.1417; Found 379.1425. $[M+H]^+$ Calcd. for $C_{23}H_{21}N_2O_2$ 357.1598; Found 357.1598.

IR (υ_{max}/cm^{-1}): 3059 (vw), 1710 (m), 1556 (m), 1450 (s), 1318 (m), 1242 (s), 1070 (s), 852 (m), 731 (s).

2-{1-[(Benzyloxy)methyl]-1*H*-pyrrol-3-yl}-4-phenylpyridine 1-oxide **1387A**



6jh

According to **General Procedure 8**, 4-phenyl pyridine *N*-oxide (171 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (3.8 mg, 0.038 mmol), $Cu(OAc)_2 \cdot H_2O$ (12.5 mg, 0.063 mmol), pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), 1-[(benzyloxy)methyl]-1*H*-pyrrole (47 mg, 0.25 mmol), column chromatography on silica gel (hexane:ethyl acetate = 1:1 – ethyl acetate:ethanol = 20:1); yellow oil (45.4 mg, 0.13 mmol, 51%).

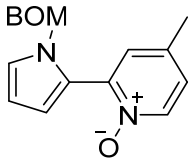
^{1}H NMR (400 MHz, MeOD): δ 8.41 (s, 1H, pyrroleH-2), 8.29 (d, *J* = 6.9 Hz, 1H, PyH-6), 8.04 (d, *J* = 2.5 Hz, 1H, PyH-3), 7.73 (d, *J* = 7.1 Hz, 2H, PhH), 7.50 – 7.41 (m, 5H, PhH), 7.29 – 7.25 (m, 4H, PhH), 7.02 – 6.99 (m, 1H, pyrroleH), 6.94 (s, 1H, pyrroleH), 5.34 (s, 2H, NCH_2), 4.44 (s, 2H, $\underline{CH_2}$Bn) ppm.

^{13}C NMR (101 MHz, MeOD): δ 146.36, 142.91, 141.56, 138.50, 137.68, 130.40, 130.33, 129.47, 129.01, 128.91, 127.87, 127.69, 123.32, 122.00, 120.58, 116.47, 110.38, 79.32 (NCH_2), 71.16 ($\underline{CH_2}$Bn) ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{23}H_{20}N_2O_2Na$ 379.1417; Found 379.1417. $[M+H]^+$ Calcd. for $C_{23}H_{21}N_2O_2$ 357.1598; Found 357.1591.

IR (υ_{max}/cm^{-1}): 3030 (vw), 1712 (m), 1552 (s), 1448 (s), 1348 (m), 1241 (s), 1174 (s), 1072 (s), 810 (s), 695 (s).

2-{1-[(Benzyloxy)methyl]-1*H*-pyrrole-2-yl}-4-methylpyridine 1-oxide 1389



7je

According to **General Procedure 7**, 4-methyl pyridine *N*-oxide (109 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), 1-[(benzyloxy)methyl]-1*H*-pyrrole (47 mg, 0.25 mmol), column chromatography on silica gel (ethyl acetate:ethanol = 3:1); yellow oil (C2 product, 14.7 mg, 0.05 mmol, 20%) and yellow oil (C3 product, 11.2 mg, 0.04 mmol, 15%).

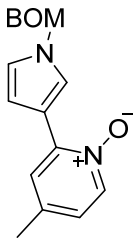
^{1}H NMR (500 MHz, MeOD): δ 8.18 (d, *J* = 6.7 Hz, 1H, PyH-6), 7.39 (d, *J* = 2.5 Hz, 1H, PyH-3), 7.30 – 7.23 (m, 4H, PyH-5, PhH), 7.14 (dd, *J* = 2.9, 1.8 Hz, 1H, pyrrole H-5), 7.09 – 7.04 (m, 2H, PhH), 6.52 (dd, *J* = 3.6, 1.7 Hz, 1H, pyrrole H-3), 6.31 (dd, *J* = 3.6, 2.8 Hz, 1H, pyrrole H-4), 5.51 (s, 2H, NCH_2), 4.27 (s, 2H, OCH_2), 2.38 (s, 3H, CH_3) ppm.

^{13}C NMR (101 MHz, MeOD): δ 144.13, 142.68 (PyC), 140.23 (PyC-6), 138.46, 130.83 (PyC-3), 129.25, 128.70 (PhC), 128.68 (PhC), 127.24 (PhC), 126.64 (PyC-5), 125.49 (pyrrole C-5), 115.67 (pyrrole C-3), 109.99 (pyrrole C-4), 79.19 (NCH_2), 70.68 (OCH_2), 20.23 (CH_3) ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{18}H_{18}N_2O_2Na$ 317.1260; Found 317.1262.

IR (υ_{max}/cm^{-1}): 3030 (vw), 1623 (m), 1507 (s), 1453 (m), 1346 (m), 1206 (s), 1070 (s), 809 (s), 737 (s).

2-{1-[(Benzyloxy)methyl]-1*H*-pyrrole-3-yl}-4-methylpyridine 1-oxide 1389



6je

According to **General Procedure 8**, 4-methyl pyridine *N*-oxide (109 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (3.8 mg, 0.038 mmol), $Cu(OAc)_2 \cdot H_2O$ (12.5 mg, 0.063 mmol), pyridine (20

mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), 1-[(benzyloxy)methyl]-1*H*-pyrrole (47 mg, 0.25 mmol), column chromatography on silica gel (ethyl acetate:ethanol = 3:1); yellow oil (C2 product, 3.7 mg, 0.013 mmol, 5%) and yellow oil (C3 product, 40.4 mg, 0.14 mmol, 55%).

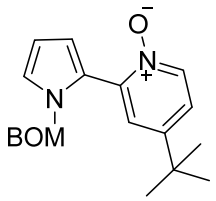
^{1}H NMR (500 MHz, MeOD): δ 8.38 (s, 1H, pyrroleH-2), 8.15 (d, *J* = 6.7 Hz, 1H, PyH-6), 7.73 (d, *J* = 2.3 Hz, 1H, PyH-3), 7.33 – 7.25 (m, 5H, PhH), 7.05 (dd, *J* = 6.1, 2.3 Hz, 1H, PyH-5), 7.00 (dd, *J* = 3.0, 1.6 Hz, 1H, pyrroleH-5), 6.86 (d, *J* = 3.1 Hz, 1H, pyrrole H-4), 5.36 (d, *J* = 1.2 Hz, 2H, NCH_2), 4.45 (s, 2H, OCH_2), 2.38 (s, 3H, CH_3) ppm.

^{13}C NMR (101 MHz, MeOD): δ 145.79 (PyC), 142.78 (PyC), 140.77 (PyC-6), 138.49 (PhC), 129.41 (PhC), 128.97 (PhC), 128.87 (PhC), 127.60 (pyrroleC-2), 125.12 (PyC-3), 123.83 (PyC-5), 123.21 (pyrroleC-5), 116.27 (pyrroleC-3), 110.23 (pyrrole C-4), 79.28 (NCH_2), 71.11 (OCH_2), 20.44 (CH_3) ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{18}H_{18}N_2O_2Na$ 317.1260; Found 317.1254.

IR (υ_{max}/cm^{-1}): 2919 (vw), 1710 (m), 1547 (s), 1453 (m), 1346 (m), 1236 (s), 1165 (s), 1070 (s), 737 (s).

2-{1-[(Benzyloxy)methyl)]-1*H*-pyrrole-2-yl}-4-(*tert*-butyl)pyridine 1-oxide 1392



7jf

According to **General Procedure 7**, 4-*tert*-butyl pyridine *N*-oxide (151 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), 1-[(benzyloxy)methyl]-1*H*-pyrrole (47 mg, 0.25 mmol), column chromatography on silica gel (hexane:ethyl acetate = 1:2 – ethyl acetate); yellow oil (C2 product, 20.7 mg, 0.06 mmol, 25%) and yellow oil (C3 product, 10.3 mg, 0.03 mmol, 12%).

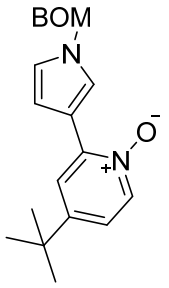
^{1}H NMR (500 MHz, MeOD): δ 8.21 (dd, *J* = 6.9, 0.5 Hz, 1H, PyH-6), 7.58 (dd, *J* = 2.8, 0.5 Hz, 1H, PyH-3), 7.47 (dd, *J* = 6.9, 2.8 Hz, 1H, PyH-5), 7.22 – 7.18 (m, 3H, PhH), 7.13 (dd, *J* = 2.8, 1.7 Hz, 1H, pyrroleH-5), 7.06 – 7.01 (m, 2H, PhH), 6.58 (dd, *J* = 3.7, 1.7 Hz, 1H, pyrroleH-3), 6.29 (dd, *J* = 3.7, 2.8 Hz, 1H, pyrroleH-4), 5.49 (s, 2H, NCH_2), 4.27 (d, *J* = 0.6 Hz, 2H, OCH_2), 1.29 (s, 9H, $C(CH_3)_3$) ppm.

^{13}C NMR (101 MHz, MeOD): δ 155.30 (PyC-4), 143.98 (PyC-2), 140.37 (PyC-6), 138.55 (PhC), 129.34 (PhC), 128.77 (PhC), 128.70 (PhC), 127.23 (PyC-3), 126.91 (pyrroleC-5), 125.68 (pyrroleC), 123.85 (PyC-5), 116.02 (pyrroleC-3), 109.97 (pyrroleC-4), 79.20 (NCH_2), 70.86 (OCH_2), 35.73 ($\underline{C}(CH_3)_3$), 30.69 ($C(\underline{CH_3})_3$) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{21}H_{25}N_2O_2$ 337.1911; Found 337.1910.

IR (υ_{max}/cm^{-1}): 2959 (vw), 1715 (s), 1551 (s), 1364 (s), 1236 (s), 1182 (s), 1076 (s), 746 (s).

2-{1-[(Benzyloxy)methyl]-1*H*-pyrrole-3-yl}-4-(*tert*-butyl)pyridine 1-oxide 1392



6jf

According to **General Procedure 8**, 4-*tert*-butyl pyridine *N*-oxide (151 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (3.8 mg, 0.038 mmol), $Cu(OAc)_2 \cdot H_2O$ (12.5 mg, 0.063 mmol), pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), 1-[(benzyloxy)methyl]-1*H*-pyrrole (47 mg, 0.25 mmol), column chromatography on silica gel (hexane:ethyl acetate = 1:2 – ethyl acetate); yellow oil (C2 product, 0.7 mg, 0.002 mmol, 1%) and yellow oil (C3 product, 43 mg, 0.13 mmol, 51%).

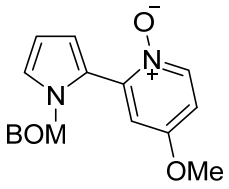
^{1}H NMR (500 MHz, MeOD): δ 8.39 (s, 1H, pyrroleH-2), 8.22 (s, 1H, PyH-6), 7.82 (d, *J* = 2.5 Hz, 1H, PyH-3), 7.32 – 7.25 (m, 6H, PyH-5, PhH), 7.03 (s, 1H, pyrroleH), 6.89 (d, *J* = 2.6 Hz, 1H, pyrroleH), 5.38 (s, 2H, NCH_2), 4.47 (s, 2H, OCH_2), 1.37 (s, 9H, $C(CH_3)_3$) ppm.

^{13}C NMR (101 MHz, MeOD): δ 155.40 (PyC), 145.69 (PyC-6), 140.88, 138.52 (PhC), 129.44 (PhC), 129.01, 128.90, 127.56 (pyrroleC-2), 123.29 (pyrrole C), 121.46 (PyC-3), 120.59 (PyC-5), 116.55 (pyrroleC-3), 110.20 (pyrroleC), 79.32 (NCH_2), 71.14 (OCH_2), 35.78 ($\underline{C}(CH_3)_3$), 30.75 ($C(\underline{CH_3})_3$)ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{21}H_{25}N_2O_2$ 337.1911; Found 337.1913.

IR (υ_{max}/cm^{-1}): 2922 (vw), 1619 (s), 1479 (s), 1245 (s), 1027 (s), 827 (s), 746 (s).

2-{1-[(Benzyloxy)methyl]-1*H*-pyrrole-2-yl}-4-methoxypyridine 1-oxide 1391, 1404



7jg

According to **General Procedure 7**, 4-methoxyl pyridine *N*-oxide (125 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), 1-[(benzyloxy)methyl]-1*H*-pyrrole (47 mg, 0.25 mmol), column chromatography on silica gel (ethyl acetate:ethanol = 3:1); yellow oil (C2 product, 15.5 mg, 0.05 mmol, 20%) and yellow solid (C3 product, 19.3 mg, 0.06 mmol, 25%).

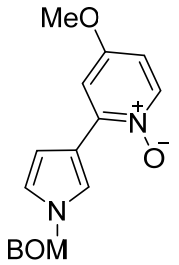
^{1}H NMR (400 MHz, MeOD): δ 8.19 (d, *J* = 7.5 Hz, 1H, PyH-6), 7.26 – 7.22 (m, 3H, PhH), 7.18 (d, *J* = 3.5 Hz, 1H, PyH-3), 7.15 (dd, *J* = 2.8, 1.7 Hz, 1H, pyrrole H-5), 7.09 (dd, *J* = 7.0, 2.1 Hz, 2H, PhH), 7.05 (dd, *J* = 7.3, 3.5 Hz, 1H, PyH-5), 6.62 (dd, *J* = 3.6, 1.7 Hz, 1H, pyrrole H-3), 6.31 (dd, *J* = 3.6, 2.9 Hz, 1H, pyrrole H-4), 5.51 (s, 2H, NCH_2), 4.31 (s, 2H, OCH_2), 3.87 (s, 3H, OCH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 157.60, 141.65, 141.02, 137.15, 128.51, 127.96, 127.84, 125.48, 125.01, 114.69, 113.14, 111.50, 109.42, 78.31 (NCH_2), 70.03 (OCH_2), 56.23 (OCH_3) ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{18}H_{18}N_2O_3Na$ 333.1210; Found 333.1242. $[M+H]^+$ Calcd. for $C_{18}H_{19}N_2O_3$ 311.1390; Found 311.1420.

IR (υ_{max}/cm^{-1}): 3086 (vw), 1639 (s), 1483 (s), 1291 (s), 1027 (s), 792 (s), 737 (s).

2-{1-[(Benzyloxy)methyl]-1*H*-pyrrole-3-yl}-4-methoxypyridine 1-oxide 1391,1404



6jg

According to **General Procedure 8**, 4-methoxyl pyridine *N*-oxide (125 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (3.8 mg, 0.038 mmol), $Cu(OAc)_2{\cdot}H_2O$ (12.5 mg, 0.063 mmol),

pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), 1-[(benzyloxy)methyl]-1*H*-pyrrole (47 mg, 0.25 mmol), column chromatography on silica gel (ethyl acetate:ethanol = 2:1); yellow oil (4.6 mg, 0.015 mmol, 6%) and yellow solid (47 mg, 0.15 mmol, 61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (s, 1H, pyrroleH-2), 8.19 (d, *J* = 7.4 Hz, 1H, PyH-6), 7.36 – 7.29 (m, 5H, PhH), 7.12 (d, *J* = 3.3 Hz, 1H, PyH-3), 6.93 – 6.89 (m, 1H, pyrroleH), 6.67 (d, *J* = 3.0 Hz, 1H, pyrroleH), 6.63 (dd, *J* = 7.3, 3.3 Hz, 1H, PyH-5), 5.32 (s, 2H, NCH_2), 4.46 (s, 2H, OCH_2), 3.90 (s, 3H, OCH_3) ppm.

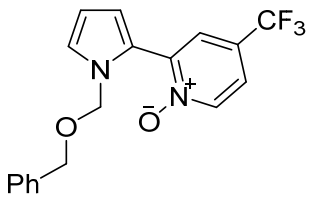
^{13}C NMR (101 MHz, $CDCl_3$): δ 162.54, 158.09 (PyC), 141.47 (PyC-6), 136.80 (PhC), 128.69 (PhC), 128.17, 128.14 (PhC), 127.11 (pyrroleC-2), 121.41 (pyrroleC), 115.42 (pyrroleC), 109.07 (pyrroleC), 108.51 (PyC-5), 106.96 (PyC-3), 78.26 (NCH_2), 70.15 (OCH_2), 56.07 (OCH_3) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{18}H_{19}N_2O_3$ 311.1390; Found 311.1401.

IR (υ_{max}/cm^{-1}): 2939 (vw), 1623 (s), 1547(m), 1483 (s), 1426 (m), 1349 (s), 1210 (s), 1165 (s), 1071 (s), 1027 (s), 737 (s), 697 (s).

M.p.: 68–69 °C

2-{1-[(Benzyloxy)methyl]-1*H*-pyrrol-3-yl}-4-trifluoromethylpyridine 1-oxide 1390, 1403



7ju

According to **General Procedure 7**, 4-trifluromethyl pyridine *N*-oxide (163 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58), dioxane (0.25 M, 1 mL), 1-[(benzyloxy)methyl]-1*H*-pyrrole (47 mg, 0.25 mmol), 10 mol% Et_3N/hexane deactivated column chromatography on silica gel (hexane:ethyl acetate = 4:1, (0.1% Et_3N)); yellow oil (C2 product, 27 mg, 0.08 mmol, 31%) and yellow solid (C3 product, 9 mg, 0.03 mmol, 10%).

^{1}H NMR (500 MHz, MeOD): δ 8.43 (d, *J* = 6.8 Hz, 1H, PyH-6), 7.84 (s, 1H, PyH-3), 7.67 (dd, *J* = 6.8, 2.7 Hz, 1H, PyH-5), 7.26 – 7.22 (m, 3H, PhH), 7.21 – 7.19 (m, 1H, pyrroleH-5), 7.06 (dd, *J* = 6.6, 3.0 Hz, 2H), 6.66 (dd, *J* = 3.7, 1.7 Hz, 1H, pyrroleH-3), 6.36 – 6.33 (m, 1H, pyrroleH-4), 5.52

(s, 2H, N$\underline{H_2}$), 4.31 (s, 2H, $\underline{CH_2}$Ph) ppm.

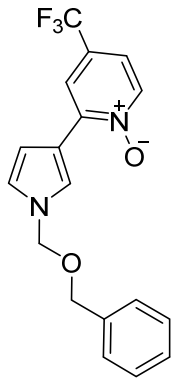
^{13}C NMR (126 MHz, MeOD): δ 145.72, 142.16 (PyC-6), 138.36, 129.33, 129.02 (d, *J* = 76.9 Hz, PyC-4), 128.85 (PhH), 128.82 (PhH), 127.51 (pyrrole C-5), 126.47 (d, *J* = 3.8 Hz, PyC-3), 125.01, 124.45, 122.57 (d, *J* = 3.7 Hz, PyC-5), 116.84 (pyrrole C-3), 110.25 (pyrrole C-4), 79.54 ($\underline{CH_2}$OBn), 70.91 ($\underline{CH_2}$Ph) ppm.

^{19}F NMR (471 MHz, MeOD): δ –64.98 ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{18}H_{15}F_3N_2O_2Na$ 371.0978; Found 371.0987.

IR (υ_{max}/cm^{-1}): 2923 (vw), 1543 (s), 1311 (s), 1259 (s), 1169 (s), 1072 (s), 943 (s), 834 (s), 735 (s).

2-{1-[(Benzyloxy)methyl]-1*H*-pyrrol-3-yl}-4-trifluoromethylpyridine 1-oxide 1390, 1403



6ju

According to **General Procedure 8**, 4- trifluromethyl pyridine *N*-oxide (163 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (3.8 mg, 0.038 mmol), $Cu(OAc)_2 \cdot H_2O$ (12.5 mg, 0.063 mmol), pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), 1-[(benzyloxy)methyl]-1*H*-pyrrole (47 mg, 0.25 mmol), 10% Et_3N/hexane deactivated column chromatography on silica gel (hexane:ethyl acetate = 4:1, (0.1% Et_3N)); yellow solid (44 mg, 0.13 mmol, 51%).

^{1}H NMR (500 MHz, MeOD): δ 8.50 (t, *J* = 1.6 Hz, 1H, pyrroleH-2), 8.45 (d, *J* = 6.8 Hz, 1H, PyH-6), 8.15 (s, 1H, PyH-3), 7.47 (d, *J* = 8.5 Hz, 1H, PyH-5), 7.35 – 7.27 (m, 5H, PhH), 7.06 (t, *J* = 2.6 Hz, 1H, pyrroleH-4), 6.95 (dd, *J* = 3.0, 1.5 Hz, 1H, pyrroleH-5), 5.41 (s, 2H, $\underline{CH_2}$N), 4.48 (s, 2H, $\underline{CH_2}$Ph) ppm.

^{13}C NMR (126 MHz, MeOD): δ 142.56 (PyC-6), 138.48, 131.81, 130.96 (PhC), 129.24 (d, *J* = 55.3 Hz, PyC-4), 128.94, 128.12 (pyrroleC-2), 126.74, 123.67 (pyrroleC-4), 123.12, 121.42 (d, *J* = 3.9

Hz, PyC-3), 118.52 (d, *J* = 3.2 Hz, PyC-5), 115.81, 110.15 (pyrroleC-5), 79.39 ($\underline{CH_2}$N), 71.27 ($\underline{CH_2}$Ph) ppm.

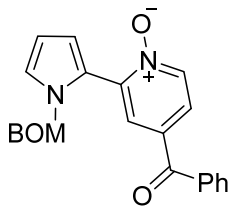
^{19}F NMR (471 MHz, MeOD): δ –65.13 ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{18}H_{15}F_3N_2O_2Na$ 371.0978; Found 371.0989.

IR (υ_{max}/cm^{-1}): 2852 (vw), 1624 (m), 1547 (m), 1348 (s), 1259 (s), 1124 (s), 1078 (s), 902 (s), 731 (s), 697 (s).

M.p.: 81–82 °C.

2-{1-[(Benzyloxy)methyl]-1*H*-pyrrol-2-yl}-4-benzoylpyridine 1-oxide 1388



7jl

According to **General Procedure 7**, 4-(benzyloxy)methyl pyridine *N*-oxide (398 mg, 2 mmol), $Pd(OAc)_2$ (5.6 mg, 0.026 mmol), bipyridine (32 mg, 0.2 mmol), AgOAc (192 mg, 1.16 mmol), dioxane (0.25 M, 2 mL), 1-[(benzyloxy)methyl]-1*H*-pyrrole (94 mg, 0.5 mmol), column chromatography on silica gel (hexane:ethyl acetate = 1:1); yellow oil (56 mg, 0.15 mmol, 29%) and yellow oil (26 mg, 0.07 mmol, 14%).

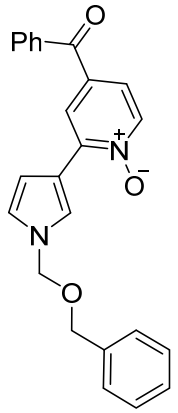
^{1}H NMR (400 MHz, MeOD): δ 8.39 (d, *J* = 6.7 Hz, 1H, PyH-6), 7.78 – 7.68 (m, 3H), 7.64 (dd, *J* = 6.7, 2.6 Hz, 1H, PyH-5), 7.63 (d, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.16 – 7.13 (m, 4H), 7.01 (dd, *J* = 7.6, 1.8 Hz, 2H), 6.60 (dd, *J* = 3.7, 1.7 Hz, 1H, pyrroleH-3), 6.29 (dd, *J* = 3.6, 2.8 Hz, 1H, pyrroleH-4), 5.50 (s, 2H, $\underline{CH_2}$N), 4.26 (s, 2H, $\underline{CH_2}$Ph) ppm.

^{13}C NMR (101 MHz, MeOD): δ 193.80, 144.90, 141.41, 138.47, 137.32, 136.30, 134.54, 130.86, 130.37, 129.86, 129.34, 128.77, 128.63, 127.20, 126.28, 124.90, 116.42, 110.14, 79.51 ($\underline{CH_2}$N), 70.91 ($\underline{CH_2}$Ph).ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{24}H_{20}N_2O_3Na$ 407.1366; Found 407.1391.

IR (υ_{max}/cm^{-1}): 2870 (vw), 1713 (s), 1656 (s), 1446 (s), 1318 (m), 1250 (s), 1070 (s), 948 (s), 730 (s), 697 (s).

2-{1-[(Benzyloxy)methyl]-1*H*-pyrrol-3-yl}-4-benzoylpyridine 1-oxide **1388**



6jl

According to **General Procedure 8**, 4- (benzyloxy)methyl pyridine *N*-oxide (398 mg, 2 mmol), $Pd(OAc)_2$ (5.6 mg, 0.026 mmol), CuCl (7.2 mg, 0.072 mmol), $Cu(OAc)_2 \cdot H_2O$ (25 mg, 0.13 mmol), pyridine (40 mg, 0.5 mmol), AcOH (60 mg, 1 mmol), dioxane (0.25 M, 2 mL), 1-[(benzyloxy)methyl]-1*H*-pyrrole (94 mg, 0.5 mmol), column chromatography on silica gel (hexane:ethyl acetate = 1:1); yellow oil (109 mg, 0.28 mmol, 51%).

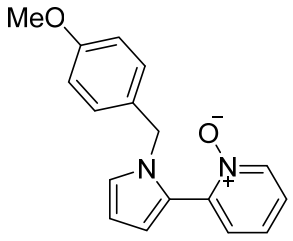
^{1}H NMR (400 MHz, MeOD): δ 8.43 (s, 1H, pyrroleH-5), 8.37 (d, *J* = 6.7 Hz, 1H, PyH-6), 8.14 (d, *J* = 2.1 Hz, 1H, PyH-3), 7.84 – 7.80 (m, 2H, PhH), 7.68 (t, *J* = 8.1 Hz, 1H, PhH), 7.56 (t, *J* = 7.6 Hz, 2H, PhH), 7.47 (d, *J* = 6.4 Hz, 1H, PyH-5), 7.28 (td, *J* = 6.8, 2.2 Hz, 5H, PhH), 7.00 (s, 1H, pyrroleH), 6.77 (d, *J* = 2.9 Hz, 1H, pyrroleH), 5.36 (s, 2H, $\underline{CH_2}$N), 4.45 (s, 2H, $\underline{CH_2}$Ph) ppm.

^{13}C NMR (101 MHz, MeOD): δ 194.37(CO), 141.70, 138.48, 137.48, 136.79, 134.83, 134.53, 130.95, 129.87, 129.45, 129.01, 128.92, 127.70, 125.26, 123.51, 122.46, 116.11, 109.99, 79.34 ($\underline{CH_2}$N), 71.19 ($\underline{CH_2}$Ph).ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{24}H_{20}N_2O_3Na$ 407.1366; Found 407.1389.

IR (υ_{max}/cm^{-1}): 2928 (vw), 1713 (s), 1547 (m), 1447 (m), 1258 (s), 1177 (s), 1069 (s), 817 (s), 732 (s), 696 (s).

2-[1-(4-Methoxybenzyl)-1*H*-pyrrol-2-yl]pyridine 1-oxide **1339B**



7kb

According to **General Procedure 7**, pyridine *N*-oxide (95 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), 1-(4-methoxybenzyl)-1*H*-pyrrole (47 mg, 0.25 mmol), column chromatography on silica gel (ethyl acetate:ethanol =10:1); yellow oil (C2 product, 16.4 mg, 0.06 mmol, 23%) and yellow solid (C3 product, 8 mg, 0.03 mmol, 12%).

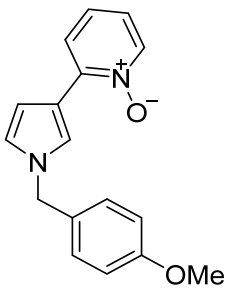
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, *J* = 6.4 Hz, 1H, PyH-6), 7.20 – 7.14 (m, 2H, PyH), 7.11 (t, *J* = 7.5 Hz, 1H, PyH-3), 6.91 (d, *J* = 8.7 Hz, 2H, PhH), 6.87 – 6.85 (m, 1H, pyrroleH-5), 6.72 – 6.69 (m, 2H, PhH), 6.35 (dd, *J* = 3.6, 1.8 Hz, 1H, pyrroleH-3), 6.25 (dd, *J* = 3.6, 2.8 Hz, 1H, pyrrole H-4), 5.19 (s, 2H, $\underline{CH_2}$Ar), 3.73 (s, 2H, CH_3) ppm.

^{13}C NMR (101 MHz, MeOD): δ 159.00, 140.07, 130.60, 129.26, 128.60, 125.26, 125.17, 124.99, 124.71, 121.97, 113.89, 113.19, 108.68, 55.36 ($\underline{CH_2}$Ar), 52.52 (CH_3) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{17}H_{17}N_2O_2$ 281.1285; Found 281.1311. $[M+Na]^+$ Calcd. for $C_{17}H_{16}N_2O_2Na$ 303.1104; Found 303.1136.

IR (υ_{max}/cm^{-1}): 2931 (vw), 1609 (s), 1510 (m), 1433 (s), 1242 (s), 1174 (s), 1028 (s), 836 (s), 763 (s), 721 (s).

2-[1-(4-Methoxybenzyl)-1*H*-pyrrol-3-yl]pyridine 1-oxide **1339A, 1354D**



6kb

According to **General Procedure 8**, pyridine *N*-oxide (95 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), CuCl (3.8 mg, 0.038 mmol), $Cu(OAc)_2 \cdot H_2O$ (12.5 mg, 0.063 mmol), pyridine (20 mg, 0.25 mmol), AcOH (30 mg, 0.5 mmol), dioxane (0.25 M, 1 mL), 1-(4-methoxybenzyl)-1*H*-pyrrole (47 mg, 0.25 mmol), column chromatography on silica gel (ethyl acetate:ethanol = 10:1); yellow oil (C2 product, 4.9 mg, 0.018 mmol, 4%) and yellow oil (C3 product, 39 mg, 0.14 mmol, 56%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (s, 1H, pyrroleH-2), 8.22 (s, 1H, PyH-6), 7.61 (d, *J* = 7.2 Hz, 1H, PyH-3), 7.12 (d, *J* = 8.6 Hz, 3H, PhH, PyH-4), 6.93 (t, *J* = 5.6 Hz, 1H, PyH-5), 6.82 (d, *J* = 8.7 Hz, 2H, PhH), 6.67 (d, *J* = 2.8 Hz, 1H, pyrroleH), 6.61 (s, 1H, pyrroleH), 5.00 (s, 2H, $\underline{CH_2}Ar$), 3.74 (s, 3H, CH_3) ppm.

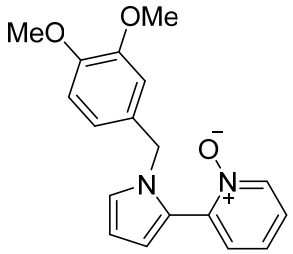
^{13}C NMR (101 MHz, MeOD): δ 159.30, 145.34, 140.95, 129.18, 128.81, 126.46, 125.91, 122.64, 121.32, 120.29, 114.69, 114.17, 107.95, 55.27 ($\underline{CH_2}Ar$), 53.29 (CH_3) ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{17}H_{16}N_2O_2Na$ 303.1104; Found 303.1145.

IR (υ_{max}/cm^{-1}): 2932 (vw), 1609 (s), 1541 (s), 1511 (s), 1428 (s), 1397 (s), 1244 (s), 1176 (s), 1029 (s), 830 (s), 759 (s).

M.p.: 95–96 °C

2-[1-(3,4-Dimethoxybenzyl)-1*H*-pyrrol-2-yl]pyridine 1-oxide **1360B**



7Ib

According to **General Procedure 7**, pyridine *N*-oxide (95 mg, 1 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), bipyridine (15.6 mg, 0.1 mmol), AgOAc (95.6 mg, 0.58 mmol), dioxane (0.25 M, 1 mL), 1-(3,4-dimethoxybenzyl)-1*H*-pyrrole (52.3 mg, 0.25 mmol, 1.0 equiv), column chromatography on silica gel (ethyl acetate:ethanol = 20:1); yellow oil (C2 product, 15.8 mg, 0.05 mmol, 20%) and yellow oil (C3 product, 10 mg, 0.03 mmol, 13%).

^{1}H NMR (500 MHz, MeOD): δ 8.22 (s, 1H, PyH), 7.43 (s, 1H, PyH), 7.36 – 7.22 (m, 2H, PyH), 7.05 (s, 1H, PhH-2), 6.69 (d, *J* = 8.2 Hz, 1H, PhH), 6.50 (s, 1H, Pyrrole H), 6.46 (d, *J* = 8.2 Hz, 1H,

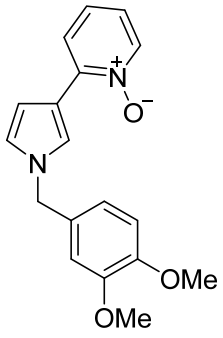
PhH), 6.38 (s, 1H, pyrrole H), 6.24 (s, 1H, pyrroleH), 5.20 (s, 2H, $\underline{CH_2}$Ar), 3.71 (s, 3H, OMe), 3.65 (s, 3H, OMe) ppm.

^{13}C NMR (101 MHz, MeOD): δ 150.38, 149.87, 148.47, 136.30, 132.61, 129.58, 128.41, 126.95, 123.61, 120.73, 115.10, 112.68, 111.93, 110.69, 109.39, 56.40 ($\underline{CH_2}$Ar), 56.30 (OMe), 53.77 (OMe) ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{18}H_{18}N_2O_3Na$ 333.1210; Found 333.1216.

IR (υ_{max}/cm^{-1}): 2939 (vw), 1513 (s), 1419 (s), 1259 (s), 1137 (s), 1092 (s), 1021 (s), 797 (s), 765 (s).

2-[1-(3,4-Dimethoxybenzyl)-1*H*-pyrrol-3-yl]pyridine 1-oxide **1354E**



6Ib

According to **General Procedure 8**, pyridine *N*-oxide (190 mg, 2 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), CuCl (7.6 mg, 0.076 mmol), $Cu(OAc)_2 \cdot H_2O$ (25 mg, 0.13 mmol), pyridine (40 mg, 0.5 mmol) and AcOH (60 mg, 1 mmol) in dioxane (0.25 M, 2 mL), 1-(3,4-dimethoxybenzyl)-1*H*-pyrrole (105 mg, 0.5 mmol), column chromatography on silica gel (ethyl acetate:ethanol = 20:1); yellow oil (8 mg, 0.026 mmol, 5%) and yellow oil (74 mg, 0.24 mmol, 48%).

^{1}H NMR (400 MHz, MeOD): δ 8.32 – 8.18 (m, 2H, pyrroleH-3, PyH-6), 7.85 (dd, *J* = 8.3, 1.7 Hz, 1H, PyH), 7.45 (t, *J* = 7.8 Hz, 1H, PyH), 7.19 – 7.11 (m, 1H, PyH), 6.86 – 6.84 (m, 3H, pyrroleH, PhH), 6.82 – 6.75 (m, 2H, pyrroleH, PhH), 5.05 (s, 2H, $\underline{CH_2}$Ar), 3.76 (s, 3H, OMe), 3.75 (s, 3H, OMe) ppm.

^{13}C NMR (101 MHz, MeOD): δ 150.69, 150.27, 146.89, 141.48, 131.66, 130.42, 127.45, 124.75, 123.31, 122.32, 121.42, 115.61, 112.93, 112.57, 109.54, 56.42, 56.38, 54.30 ppm.

HRESI-MS: $[M+Na]^+$ Calcd. for $C_{18}H_{18}N_2O_3Na$ 333.1210; Found 333.1215.

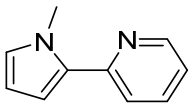
IR (υ_{max}/cm^{-1}): 2933 (vw), 1681 (s), 1542 (s), 1513 (s), 1429 (s), 1396 (s), 1259 (s), 1136 (s), 1023

(s), 800 (s), 755 (s), 697 (s).

3.3 Reduction of Pyridine Oxides

General Procedure 9:[51] Phosphorus trichloride (4 equiv) was added dropwise to a solution of pyridine oxides (1 equiv) in solvent (1 mL, 0.1 M). The resulting orange mixture was stirred for 4–12 h at room temperature, then a saturated aqueous $NaHCO_3$ solution was slowly added. The mixture was extracted with DCM twice, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The pure product was obtained by flash column chromatography.

2-(1-Methyl-1*H*-pyrrole-2-yl)pyridine[113] **1315**

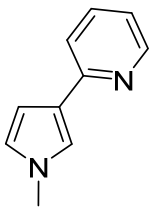


9ab

According to **General Procedure 9**, phosphorus trichloride (54.8 mg, 0.4 mmol), 2-(1-methyl-1*H*-pyrrol-2-yl)pyridine oxide (17.4 mg, 0.1 mmol), 10% $CDCl_3$/toluene (1 mL, 0.1 M), 10 h, column chromatography on silica gel (hexane:ethyl acetate = 1:1); brown oil (10.8 mg, 0.07 mmol, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 – 8.52 (m, 1H), 7.64 (dddd, *J* = 8.0, 7.4, 1.9, 0.6 Hz, 1H), 7.54 (dq, *J* = 8.0, 0.9 Hz, 1H), 7.07 (dddd, *J* = 7.4, 4.9, 1.3, 0.6 Hz, 1H), 6.75 (t, *J* = 2.2 Hz, 1H), 6.59 (ddd, *J* = 3.8, 1.8, 0.6 Hz, 1H), 6.20 (ddd, *J* = 3.8, 2.6, 0.6 Hz, 1H), 4.02 (d, *J* = 0.6 Hz, 3H) ppm.

2-(1-Methyl-1*H*-pyrrole-3-yl)pyridine **1315B**



8ab

According to **General Procedure 9**, phosphorus trichloride (54.8 mg, 0.4 mmol), 2-(1-methyl-1*H*-pyrrol-3-yl)pyridine oxide (17.4 mg, 0.1 mmol), 10% $CDCl_3$/toluene (1 mL, 0.1 M), 10 h, column chromatography on silica gel (hexane:ethyl acetate = 1:1); brown oil (11.3 mg, 0.072 mmol, 72%).

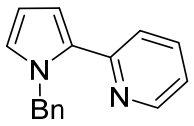
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (dd, *J* = 4.1, 0.9 Hz, 1H, pyrroleH-6), 7.63 – 7.54 (m, 1H, PyH-3), 7.43 (d, *J* = 8.7 Hz, 1H, PyH-6), 7.27 – 7.26 (m, 1H, pyrroleH-2), 7.00 (dd, *J* = 7.3, 5.0 Hz, 1H, PyH-4), 6.62 (dt, *J* = 7.4, 2.2 Hz, 2H, pyrroleH-5, PyH-5), 3.69 (s, 3H, CH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.74, 149.35, 136.46, 125.17, 123.05, 121.27, 120.13, 118.94, 106.94, 36.55 (CH_3) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{10}H_{11}N_2$ 159.0917; Found 159.0927.

IR (υ_{max}/cm^{-1}): 1560 (s), 1542 (m), 1487 (s), 1455 (s) 1437 (m), 1325 (m), 768 (m), 716 (s).

2-(1-Benzyl-1*H*-pyrrole-2-yl)pyridine[114] **1262**

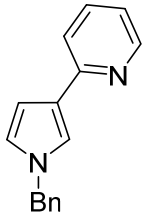


9bb

According to **General Procedure 9**, phosphorus trichloride (54.8 mg, 0.4 mmol), 2-(1-benzyl-1*H*-pyrrol-2-yl)pyridine oxide (25 mg, 0.1 mmol), toluene (1 mL, 0.1 M), 4 h, pure product obtained as a brown oil (20 mg, 0.086 mmol, 86%) without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.59 (ddd, *J* = 8.0, 7.4, 1.9 Hz, 1H), 7.50 (dt, *J* = 8.1, 1.1 Hz, 1H), 7.26 – 7.15 (m, 3H), 7.08 – 7.00 (m, 3H), 6.81 (dd, *J* = 2.6, 1.8 Hz, 1H), 6.62 (dd, *J* = 3.7, 1.8 Hz, 1H), 6.24 (dd, *J* = 3.7, 2.7 Hz, 1H), 5.78 (s, 2H) ppm.

2-(1-Benzyl-1*H*-pyrrole-3-yl)pyridine **1305B, 1297**



8bb

According to **General Procedure 9**, phosphorus trichloride (0.28 mg, 0.2 mmol), 2-(1-benzyl-1*H*-pyrrol-3-yl)pyridine oxide (0.13 g, 0.5 mmol), toluene (1 mL, 0.1 M), 4 h, column chromatography on silica gel (hexane:ethyl acetate = 2:1); yellow oil (102 mg, 0.44 mmol, 85%).

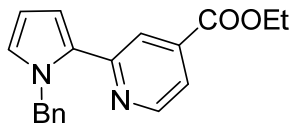
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1H, PyH-6), 7.60 (ddd, *J* = 8.0, 7.4, 1.9 Hz, 1H, PyH-4), 7.45 (dt, *J* = 8.0, 1.1 Hz, 1H, PyH-3), 7.38 – 7.28 (m, 4H, PhH), 7.19 (ddt, *J* = 7.3, 1.5, 0.7 Hz, 2H, pyrroleH-2, PhH), 7.01 (ddd, *J* = 7.4, 4.9, 1.2 Hz, 1H, PyH-5), 6.74 – 6.71 (m, 1H, pyrroleH-4), 6.67 (dd, *J* = 2.8, 1.8 Hz, 1H, pyrroleH-5), 5.09 (s, 2H, CH_2Ph) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.62, 151.35, 149.37, 137.59, 136.63, 128.94, 127.99, 127.39, 122.57, 120.76, 120.24, 119.06, 107.28, 53.91 (CH_2Ph) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{16}H_{15}N_2$ 235.1230; Found 235.1241.

IR (υ_{max}/cm^{-1}): 1702 (m), 1587 (s), 1428 (s), 1358 (m), 1235 (m), 1095 (m), 769 (s), 692 (s).

Ethyl 2-(1-benzyl-1*H*-pyrrole-2-yl)isonicotinate **1348**



9ba

According to **General Procedure 9**, phosphorus trichloride (82.2 mg, 0.64 mmol), 2-(1-benzyl-1*H*-pyrrol-2-yl)-4-(ethoxycarbonyl)pyridine 1-oxide (50 mg, 0.16 mmol), 10% $CDCl_3$/toluene (1.5 mL, 0.1 M), overnight, column chromatography on silica gel (hexane:ethyl acetate = 2:1); red oil (34 mg, 0.11 mmol, 72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, *J* = 4.9 Hz, 1H, PyH-6), 8.06 (s, 1H, PyH-3), 7.55 (dd, *J* = 5.1, 1.4 Hz, 1H, PyH-5), 7.25 – 7.20 (m, 3H, PhH), 7.03 (d, *J* = 6.9 Hz, 2H, PhH), 6.88 – 6.84 (m, 1H, pyrroleH-5), 6.81 – 6.76 (m, 1H, pyrroleH-3), 6.27 (dd, *J* = 3.8, 2.7 Hz, 1H, pyrroleH-4), 5.77 (s, 2H, $\underline{CH_2}$Ph), 4.40 (q, *J* = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 1.40 (t, *J* = 7.1 Hz, 3H, CH_3) ppm.

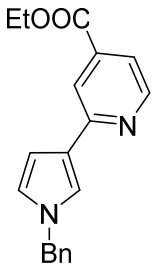
^{13}C NMR (101 MHz, $CDCl_3$): δ 165.34 (CO), 153.18, 149.06, 139.28, 138.34, 131.09, 128.54, 127.17, 127.06, 126.85, 120.84, 119.16, 112.70, 108.87, 61.87 ($\underline{CH_2}CH_3$), 52.25 ($\underline{CH_2}$Ph), 14.33 (CH_3) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{19}H_{19}N_2O_2$ 307.1441; Found 307.1467.

IR (υ_{max}/cm^{-1}): 1723 (s), 1597 (s), 1553 (s), 1440 (s), 1287 (m), 1241 (s), 1112 (s), 1020 (s), 719

(s), 694 (s).

Ethyl 2-(1-benzyl-1*H*-pyrrole-3-yl)isonicotinate **1305A**



8ba

According to **General Procedure 9**, phosphorus trichloride (137 mg, 2.72 mmol), 2-(1-benzyl-1*H*-pyrrol-3-yl)-4-(ethoxycarbonyl)pyridine 1-oxide (220 mg, 0.68 mmol), 10% $CDCl_3$/toluene (7 mL, 0.1 M), overnight, column chromatography on silica gel (hexane:ethyl acetate = 2:1 – ethyl acetate); red oil (154 mg, 0.5 mmol, 75%).

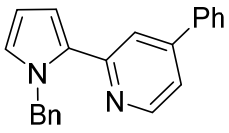
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (d, *J* = 5.1 Hz, 1H, PyH-6), 7.99 (s, 1H, pyrrole H-2), 7.56 (d, *J* = 5.1 Hz, 1H, PyH-5), 7.46 (s, 1H, PyH-3), 7.37 – 7.29 (m, 3H, PhH), 7.23 – 7.17 (m, 2H, PhH), 6.81 – 6.70 (m, 2H, pyrrole H-4,5), 5.11 (s, 2H, $\underline{CH_2}$Ph), 4.42 (q, *J* = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 1.42 (t, *J* = 7.1 Hz, 3H, CH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.65 (CO), 149.70, 138.47, 137.38, 129.00, 128.76, 128.49, 128.10, 127.41, 122.97, 121.46, 119.12, 118.57, 107.62, 61.87 ($\underline{CH_2}CH_3$), 54.00 ($\underline{CH_2}$Ph), 14.38 (CH_3) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{19}H_{19}N_2O_2$ 307.1441; Found 307.1452.

IR (υ_{max}/cm^{-1}): 1704 (s), 1600 (s), 1550 (s), 1394 (s), 1108 (m), 1017 (m), 760 (s).

2-(1-Benzyl-1*H*-pyrrole-2-yl)-4-phenylpyridine **1347**



9bh

According to **General Procedure 9**, phosphorus trichloride (82.5 mg, 0.6 mmol), 2-(1-benzyl-1*H*-pyrrole-2-yl)-4-phenylpyridine 1-oxide (50 mg, 0.15 mmol), 10% $CDCl_3$/toluene

(1.5 mL, 0.1 M), 4 h, pure product obtained as a red oil (43 mg, 0.14 mmol, 90%) without further purification.

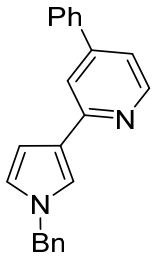
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.57 (dd, *J* = 5.2, 0.8 Hz, 1H, PyH-6), 7.73 (dd, *J* = 1.7, 0.8 Hz, 1H, PyH-2), 7.63 (dd, *J* = 8.3, 1.4 Hz, 2H, PhH), 7.46 (ddd, *J* = 10.0, 6.6, 6.1 Hz, 3H, PhH), 7.26 (s, 3H, PhH), 7.20 (d, *J* = 6.5 Hz, 1H, PyH-5), 7.10 (dd, *J* = 8.2, 1.4 Hz, 2H, PhH), 6.86 – 6.83 (m, 1H, pyrroleH-5), 6.71 (dd, *J* = 3.7, 1.8 Hz, 1H, pyrroleH-3), 6.28 (dd, *J* = 3.7, 2.7 Hz, 1H, pyrroleH-4), 5.82 (s, 2H, CH_2) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 153.22, 149.21, 148.78, 139.62, 138.67, 132.42, 129.16, 129.02, 128.55, 127.14, 127.10, 127.03, 126.02, 119.64, 118.68, 111.44, 108.59, 52.04 (CH_2) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{22}H_{19}N_2$ 311.1543; Found 311.1546.

IR (υ_{max}/cm^{-1}): 1591 (s), 1542 (s), 1481 (s), 1261 (s), 1075 (s), 718 (s), 693 (s).

2-(1-Benzyl-1*H*-pyrrole-3-yl)-4-phenylpyridine **1347**



8bh

According to **General Procedure 9**, phosphorus trichloride (247 mg, 1.8 mmol), 2-(1-benzyl-1*H*-pyrrole-2-yl)-4-phenylpyridine 1-oxide (150 mg, 0.45 mmol), toluene (4.5 mL, 0.1 M), 4 h, pure product obtained as a red oil (144 mg, 0.45 mmol, 100%) without further purification.

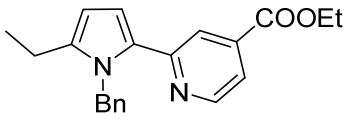
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (d, *J* = 5.2 Hz, 1H, PyH-6), 7.69 – 7.64 (m, 3H), 7.55 (s, 1H), 7.51 – 7.44 (m, 3H), 7.37 – 7.27 (m, 4H), 7.22 – 7.18 (m, 2H), 6.77 – 6.73 (m, 2H, pyrrole H-4,5), 5.09 (s, 2H, CH_2) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.36, 149.72, 148.64, 138.52, 137.40, 129.09, 128.87, 128.28, 127.95, 127.33, 127.09, 125.36, 122.71, 121.44, 118.44, 117.21, 107.44, 53.86 ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{22}H_{19}N_2$ 311.1543; Found 311.1550.

IR (υ_{max}/cm^{-1}): 1594 (s), 1539 (s), 1395 (m), 1348 (m), 1258 (s), 1076 (s), 1013 (s), 789 (s), 694 (s).

2-(1-Benzyl-5-ethyl-1*H*-pyrrole-2-yl)-4-(ethoxycarbonyl)pyridine 1350



9ga

According to **General Procedure 9**, phosphorus trichloride (34 mg, 0.24 mmol), 2-(1-benzyl-5-ethyl-1*H*-pyrrole-2-yl)-4-(ethoxycarbonyl)pyridine 1-oxide (20 mg, 0.06 mmol), 10% $CDCl_3$/toluene (1 mL, 0.06 M), 4 h, column chromatography on silica gel (hexane:ethyl acetate = 2:1); red oil (18 mg, 0.054 mmol, 90%).

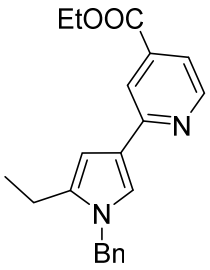
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (dd, *J* = 5.1, 0.8 Hz, 1H, PyH-6), 8.07 – 8.04 (m, 1H, PyH-3), 7.48 (dd, *J* = 5.1, 1.5 Hz, 1H, PyH-5), 7.20 (d, *J* = 6.0 Hz, 2H, PhH), 7.15 (d, *J* = 8.5 Hz, 1H, PhH), 6.88 (d, *J* = 8.4 Hz, 2H, PhH), 6.73 (d, *J* = 3.8 Hz, 1H, pyrrole H), 6.09 (d, *J* = 3.8 Hz, 1H, pyrrole H), 5.85 (s, 2H, CH_2), 4.36 (s, 2H, $CO_2\underline{CH_2}CH_3$), 2.50 (t, *J* = 7.5 Hz, 2H, $\underline{CH_2}CH_3$), 1.39 (d, *J* = 7.1 Hz, 3H, $CO_2CH_2\underline{CH_3}$), 1.22 (t, *J* = 7.5 Hz, 3H, $CH_2\underline{CH_3}$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.62 (CO), 153.93, 149.31, 140.62, 139.68, 138.06, 131.36, 128.54, 126.73, 126.00, 120.79, 118.69, 111.86, 106.27, 61.79 ($CO_2\underline{CH_2}CH_3$), 48.15 (CH_2Ph), 20.08 ($\underline{CH_2}CH_3$), 14.37 ($CO_2CH_2\underline{CH_3}$), 12.73 ($CH_2\underline{CH_3}$) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{21}H_{23}N_2O_2$ 335.1754; Found 335.1766.

IR (υ_{max}/cm^{-1}): 1724 (s), 1596 (s), 1556 (s), 1495 (s), 1287 (s), 1106 (s), 1020 (s), 759 (s).

2-(1-Benzyl-5-ethyl-1*H*-pyrrole-3-yl)-4-(ethoxycarbonyl)pyridine 1-oxide 1350



8ga

According to **General Procedure 9**, phosphorus trichloride (84 mg, 0.64 mmol), 2-(1-benzyl-1*H*-pyrrole-2-yl)-4-phenylpyridine 1-oxide (50 mg, 0.14 mmol), 10% $CDCl_3$/toluene (1.5 mL, 0.1 M), 4 h, column chromatography on silica gel (hexane:ethyl acetate = 2:1); red oil (41 mg, 0.12 mmol, 87%).

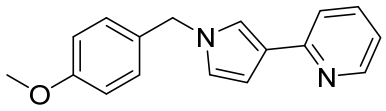
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.64 (d, *J* = 5.1 Hz, 1H, PyH-6), 8.02 (s, 1H, PyH-3), 7.57 (dd, *J* = 5.2, 1.5 Hz, 1H, PyH-5), 7.47 (s, 1H, pyrroleH-2), 7.35 – 7.31 (m, 2H, PhH), 7.29 – 7.27 (m, 1H, PhH), 7.09 (d, *J* = 7.1 Hz, 2H, PhH), 6.59 (s, 1H, pyrrole H-4), 5.09 (s, 2H, CH_2Ph), 4.44 (q, *J* = 7.1 Hz, 2H, $CO_2\underline{CH_2}CH_3$), 2.51 (q, *J* = 7.4 Hz, 2H, $\underline{CH_2}CH_3$), 1.44 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2\underline{CH_3}$), 1.27 (t, *J* = 7.5 Hz, 3H, $CH_2\underline{CH_3}$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.88 (CO), 155.93 (PyC-6), 150.08 (PyC-2), 138.06 (PyC-4), 137.78, 137.03 (pyrroleC-2), 128.94 (PhC), 127.69 (PhC), 126.66 (PhC), 123.38, 120.97 (PhC), 118.83 (PyC-5), 118.20 (PyC-3), 104.20 (pyrroleC-4,5), 61.74 ($CO_2\underline{CH_2}CH_3$), 50.75 (CH_2Ph), 19.59 ($\underline{CH_2}CH_3$), 14.40 ($CO_2CH_2\underline{CH_3}$), 12.75 ($CH_2\underline{CH_3}$) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{21}H_{23}N_2O_2$ 335.1754; Found 335.1741.

IR (υ_{max}/cm^{-1}): 1702 (s), 1594 (s), 1546 (s), 1394 (s), 1259 (s), 1016 (s), 1020 (s), 795 (s).

2-[1-(4-Methoxybenzyl)-1*H*-pyrrol-3-yl]pyridine **1362**



8kb

According to **General Procedure 9**, phosphorus trichloride (64 mg, 0.48 mmol), 2-[1-(4-methoxybenzyl)-1*H*-pyrrol-3-yl]pyridine 1-oxide (33 mg, 0.12 mmol), 50% $CDCl_3$/toluene (1.5 mL, 0.08 M), 4 h, pure product obtained as a yellow oil (30 mg, 0.11 mmol, 92%) without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (s, 1H, pyrrole H-2), 7.64 (t, *J* = 7.5 Hz, 1H, PyH-6), 7.46 (d, *J* = 8.3 Hz, 2H, PyH-3,4), 7.14 (d, *J* = 8.7 Hz, 2H, PhH), 7.03 (ddd, *J* = 7.4, 5.0, 1.2 Hz, 1H, PyH-5), 6.86 (d, *J* = 8.7 Hz, 2H, PhH), 6.69 (dd, *J* = 2.8, 2.2 Hz, 1H, pyrroleH-4), 6.65 (dd, *J* = 2.9, 1.7 Hz, 1H, pyrroleH-5), 5.01 (s, 2H, CH_2), 3.78 (s, 3H, CH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 159.45, 153.97, 148.17, 145.08, 137.45, 129.37, 128.95, 122.51, 121.24, 120.22, 119.38, 114.31, 107.34, 55.42 (CH_2), 53.43 (CH_3) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{17}H_{17}N_2O$ 265.1335; Found 265.1359.

IR (υ_{max}/cm^{-1}): 2927 (w), 1702 (s), 1589 (s), 1511 (s), 1395(m), 1245 (s), 1175 (m), 1027 (m), 769 (s).

3.4 Deprotection of Pyrroles

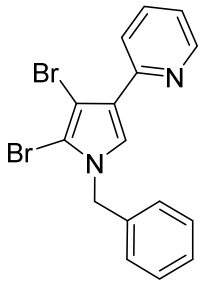
General Procedure 10: Deprotection of *N*-BOM pyrroles

Pyrrole (0.05 mmol, 1 equiv) was acidified by the addition of aqueous hydrogen chloride (0.05 M, in 2.5 mL MeOH/H_2O) and hydrogenated under atmospheric pressure in the presence of Pd-C catalyst (10 wt %, 10–15 mol%) for 11–19 h. The catalyst was filtered off through a celite pad and rinsed with excess methanol. The filtrate was concentrated under reduced pressure, followed by the addition of 0.5 M KOH solution (MeOH/H_2O, 20%–100%, 2.5 mL), the mixture was heated to reflux overnight. The reaction mixture was concentrated before taking up in DCM, the organic layer was washed with H_2O and brine and dried over $NaSO_4$ before evaporating the solvent under reduced pressure. The crude product was purified by flash column chromatography.

General Procedure 11: Deprotection of *N*-PMB Pyrrole

2-[1-(4-Methoxybenzyl)-1*H*-pyrrol-3-yl]pyridine (0.1 mmol, 1 equiv) was dissolved in the mixture of 1:1 CF_3CO_2H/anisole (2 mL, 0.05 M), concentrated sulfuric acid (0.5 equiv) was added in the solution, the mixture stired at 110 ^oC for 24 h, after the solution cooled to room temperature, Na_2CO_3 was added to neutralize the acid solution, followed by extraction by DCM. The organic layer was washed with H_2O and brine, dried over $NaSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography.

2-(1-benzyl-4,5-dibromo-1H-pyrrol-3-yl)pyridine **1309**



12bb

A soultion of **8bb** (0.3 mmol, 70.2 mg) in chlorobenzene containg NBS (53.4 mg, 1equiv), AIBN (9.84 mg, 20 mol%) was heated to reflux under argon, further AIBN (5 mg, 0.1 equiv) and NBS (11 mg, 0.2 equiv) were added after 4h, the solution was heated overnight and filtration. Et_2O and

H_2O were added to the residue which was stirred for 4h, the organic layer was separated and concentrated, the crude product purified by column gave the red oil (42 mg, 0.11 mmol, 36%) and brown oil (27.2 mg, 0.09 mmol, 29%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, J = 5.0 Hz, 1H), 8.00 (s, 1H), 7.92 – 7.84 (m, 1H), 7.30 (dd, J = 13.7, 7.2 Hz, 5H), 7.10 (d, J = 8.8 Hz, 2H), 5.34 (s, 2H).

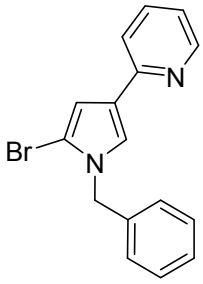
^{13}C NMR (101 MHz, CDCl3) δ 150.71, 146.92, 139.20, 135.84, 128.90, 128.69, 127.86, 126.50, 122.13, 121.82, 113.22, 104.82, 102.71, 51.00.

HRESI-MS: [M+H]+ Calcd. for $C_{16}H_{13}Br_2N_2$ 390.9440; Found 390.9694

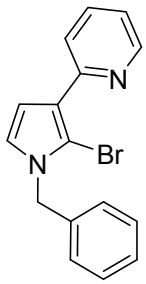
IR (υmax/cm-1): 2921 (m), 1697 (s), 1590 (s), 1452 (s), 1342 (m), 1270 (m), 772 (s), 728 (s), 696 (s).

2-(1-benzyl-5-bromo-1H-pyrrol-3-yl)pyridine + 2-(1-benzyl-2-bromo-1H-pyrrol-3-yl)pyridine

1097



13bb



14bb

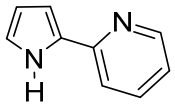
^{1}H NMR (400 MHz, CDCl3) δ 8.67 (d, J = 6.0 Hz, 1H), 8.53 (d, J = 7.8 Hz, 2H), 7.94 (d, J = 8.1 Hz, 1H), 7.85 – 7.75 (m, 4H), 7.50 (d, J = 9.0 Hz, 2H), 7.31 (d, J = 18.1 Hz, 10H), 7.19 (d, J = 7.3 Hz, 7H), 7.13 (d, J = 9.4 Hz, 2H), 6.98 (d, J = 3.3 Hz, 1H), 6.90 (d, J = 3.3 Hz, 1H), 6.78 (d, J = 2.1 Hz, 2H), 5.20 (s, 2H), 5.16 (s, 4H). The ratio of **13bb**: **14bb**=2:1

^{13}C NMR (101 MHz, CDCl3) δ 152.52, 151.56, 147.82, 146.25, 139.50, 137.88, 136.70, 136.41, 128.98, 128.93, 128.10, 127.94, 127.32, 127.02, 126.71, 126.48, 123.67, 123.54, 121.70, 121.11, 120.92, 120.03, 110.52, 109.98, 104.84, 102.58, 52.48, 52.26.

HRESI-MS: [M+H]+ Calcd. for $C_{16}H_{14}BrN_2$ 313.0335; Found 313.0413

IR (υmax/cm-1): 2929 (m), 1702 (s), 1589 (s), 1384 (m), 1214 (m), 771 (s), 723 (s), 698 (s).

2-(1*H*-Pyrrole-2-yl)pyridine[86] **1384B, 1385, 1386C**

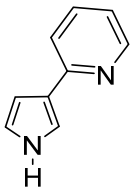


11jb

According to **General Procedure 10**, **4ja** (7 mg, 0.025 mmol), Pd-C (2.7 mg, 10 mol%), 0.05 M HCl in MeOH/H_2O (1:4, 1.25 mL), 14 h; 0.5 M KOH solution (MeOH/H_2O, 1:4, 1.25 mL), overnight, 10% Et_3N/hexane deactivated column chromatography on silica gel (hexane:ethyl acetate = 4:1); white solid (2.3 mg, 0.015 mmol, 61%).

^{1}H NMR (500 MHz, MeOD): δ 8.41 (ddd, *J* = 5.0, 1.8, 1.0 Hz, 1H), 7.71 (ddd, *J* = 8.1, 7.4, 1.8 Hz, 1H), 7.61 (dt, *J* = 8.1, 1.1 Hz, 1H), 7.09 (ddd, *J* = 7.4, 5.0, 1.2 Hz, 1H), 6.89 (dd, *J* = 2.6, 1.5 Hz, 1H), 6.75 (dd, *J* = 3.6, 1.5 Hz, 1H), 6.20 (dd, *J* = 3.6, 2.6 Hz, 1H) ppm.

2-(1*H*-Pyrrole-3-yl)pyridine **1384C, 1365A, 1381B, 1386A**



10jb

According to **General Procedure 10**, **3ja** (7 mg, 0.025 mmol), Pd-C (2.7 mg, 10 mol%), 0.05 M HCl in MeOH/H_2O (1:1.5, 2.5 mL), 19 h; 0.5 M KOH solution (MeOH/H_2O, 1:4, 2.5 mL), overnight, 10% Et_3N/hexane deactivated column chromatography on silica gel (hexane:ethyl acetate = 1:1);white solid (2.7 mg, 0.019 mmol, 74%).

According to **General Procedure 11**, the same product (3.5 mg, 0.024 mmol, 44%) was delivered from the compound **5ka** (13.2 mg, 0.05 mmol).

^{1}H NMR (400 MHz, MeOD): δ 8.35 (ddd, *J* = 5.0, 1.8, 0.9 Hz, 1H, PyH-6), 7.70 (ddd, *J* = 8.1, 7.4, 1.8 Hz, 1H, PyH-4), 7.59 (dt, *J* = 8.1, 1.1 Hz, 1H, PyH-3), 7.38 (s, 1H, pyrrole H-2), 7.09 (ddd, *J* = 7.4, 5.0, 1.2 Hz, 1H, PyH-5), 6.79 (dd, *J* = 2.9, 2.0 Hz, 1H, pyrrole H-5), 6.63 (dd, *J* = 2.9, 1.6 Hz, 1H, pyrrole H-4) ppm.

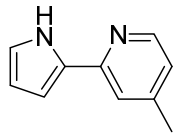
^{13}C NMR (101 MHz, MeOD): δ 156.62, 149.31, 138.50, 124.98, 121.24, 120.91, 120.24, 118.67, 107.29 ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_9H_9N_2$ 145.0760; Found 145.0762.

IR (υ_{max}/cm^{-1}): 2921 (m), 1696 (m), 1590 (s), 1557 (s), 1431 (s), 1259 (s), 1017 (s), 921 (s), 797 (s).

M.p.: 114–115 °C.

4-Methyl-2-(1*H*-pyrrole-2-yl)pyridine **1396B**



11je

According to **General Procedure 10**, **4je** (13.44 mg, 0.04 mmol), Pd-C (4.24 mg, 10 mol%), 0.05 M HCl in MeOH/H_2O (1:4, 2.1 mL), 11 h; 0.5 M KOH solution (MeOH/H_2O, 4:1, 2.1 mL), 12 h, 10% Et_3N/hexane deactivated column chromatography on silica gel (hexane:ethyl acetate = 1:2); white solid (5.9 mg, 0.037 mmol, 88%).

^{1}H NMR (500 MHz, MeOD): δ 8.26 (d, *J* = 5.1 Hz, 1H, PyH-6), 7.48 (s, 1H, PyH-3), 6.96 (ddd, *J* = 5.2, 1.6, 0.7 Hz, 1H, PyH-5), 6.88 (dd, *J* = 2.6, 1.5 Hz, 1H, pyrrole H-5), 6.75 (dd, *J* = 3.6, 1.5 Hz, 1H, pyrrole H-3), 6.19 (dd, *J* = 3.6, 2.6 Hz, 1H, pyrrole H-4), 2.37 (s, 3H, CH_3) ppm.

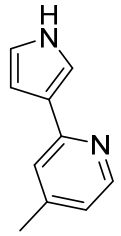
^{13}C NMR (101 MHz, MeOD): δ 152.51, 149.78, 149.43, 132.22, 122.58, 121.44, 120.06, 110.54, 109.12, 21.11 ppm.

HRESI-MS: [M+H]+ Calcd. for $C_{10}H_{11}N_2$ 159.0917; Found 159.0929.

IR (υmax/cm-1): 2921 (m), 1608 (s), 1547 (s), 1482 (m), 1447 (s), 1286 (m), 1124 (s), 1036 (s), 994 (m), 818 (s), 716 (s).

M.p.: 78–79 °C.

4-Methyl-2-(1*H*-pyrrole-3-yl)pyridine **1396E, 1395A**



10je

According to **General Procedure 10**, **3je** (14.7 mg, 0.05 mmol), Pd-C (0.53 mg, 10 mol%), 0.05 M HCl in MeOH/H_2O (1:4, 2.5 mL), 19 h; 0.5 M KOH solution (MeOH/H_2O, 4:1, 2.5 mL), overnight, 10% Et_3N/hexane deactivated column chromatography on silica gel (hexane:ethyl acetate = 1:2); yellow oil (6.5 mg, 0.04 mmol, 82%).

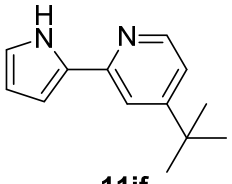
^{1}H NMR (500 MHz, MeOD): δ 8.22 (d, *J* = 5.9 Hz, 1H, PyH-6), 7.47 – 7.43 (m, 1H, PyH-3), 7.38 (t, *J* = 1.7 Hz, 1H, pyrrole H-2), 6.96 (dd, *J* = 5.0, 1.7 Hz, 1H, PyH-5), 6.80 – 6.77 (m, 1H, pyrrole H), 6.64 (dd, *J* = 2.8, 1.5 Hz, 1H, pyrrole H), 2.37 (s, 3H, CH_3) ppm.

^{13}C NMR (101 MHz, MeOD): δ 150.30, 148.69, 122.35, 121.59, 120.20, 118.75, 112.94, 108.57, 107.31, 21.14 ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{10}H_{11}N_2$ 159.0917; Found 159.0916.

IR (υ_{max}/cm^{-1}): 2919 (m), 1604 (s), 1555 (s), 1503 (m), 1442 (m), 1287 (m), 1077 (s), 1038 (s), 996 (m), 943 (m), 791 (s).

4-(*tert*-Butyl)-2-(1*H*-pyrrole-2-yl)pyridine **1397j**



11jf

According to **General Procedure 10**, **4jf** (16.8 mg, 0.05 mmol), Pd-C (5.3 mg,10 mol%), 0.05 M HCl in MeOH/H_2O (1:1.3, 2.5 mL), 12 h; 0.5 M KOH solution (MeOH/H_2O, 2:1, 2.5 mL), 8.5 h, 10% Et_3N/hexane deactivated column chromatography on silica gel (hexane:ethyl acetate = 2:1); colorless oil (7.1 mg, 0.071 mmol, 71%).

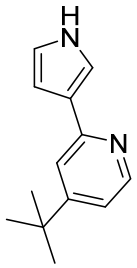
^{1}H NMR (500 MHz, MeOD): δ 8.32 (d, *J* = 5.4 Hz, 1H, PyH-6), 7.64 (d, *J* = 2.4 Hz, 1H, PyH-3), 7.16 (dd, *J* = 5.4, 1.9 Hz, 1H, PyH-5), 6.89 (dd, *J* = 2.6, 1.5 Hz, 1H, pyrrole H-5), 6.77 (dd, *J* = 3.6, 1.5 Hz, 1H, pyrroleH-3), 6.20 (dd, *J* = 3.6, 2.6 Hz, 1H, pyrrole H-4), 1.36 (s, 9H, $(CH_3)_3$) ppm.

^{13}C NMR (101 MHz, MeOD): δ 162.65, 152.60, 149.58, 132.52, 121.42, 118.94, 116.25, 110.55, 109.09, 35.76, 30.84 ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{13}H_{17}N_2$ 201.1386; Found 201.1381.

IR (υ_{max}/cm^{-1}): 2962 (m), 1697 (m), 1601 (s), 1539 (s), 1437 (s), 1127 (m), 1034 (m), 883 (m), 830 (m), 722 (s).

4-(*tert*-Butyl)-2-(1*H*-pyrrole-3-yl)pyridine **1397k**



10jf

According to **General Procedure 10**, **3jf** (16.8 mg, 0.05 mmol), Pd-C (5.3 mg, 10 mol%), 0.05 M HCl in MeOH/H_2O (1:1.5, 2.5 mL), 19 h; 0.5 M KOH solution (MeOH/H_2O, 2:1, 2.5 mL), 8 h, 10% Et_3N/hexane deactivated column chromatography on silica gel (hexane:ethyl acetate = 1:2); yellow oil (6 mg, 0.03 mmol, 60%).

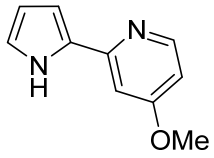
^{1}H NMR (500 MHz, MeOD): δ 8.27 (dd, *J* = 5.5, 0.7 Hz, 1H, PyH-6), 7.59 (dd, *J* = 1.9, 0.7 Hz, 1H, PyH-3), 7.38 (t, *J* = 1.8 Hz, 1H, pyrrole H-2), 7.16 (dd, *J* = 5.5, 1.9 Hz, 1H, PyH-5), 6.81 – 6.77 (m, 1H, pyrrole H), 6.64 (dd, *J* = 2.9, 1.6 Hz, 1H, pyrrole H), 1.36 (s, 9H, $(CH_3)_3$) ppm.

^{13}C NMR (101 MHz, MeOD): δ 162.67, 156.46, 149.17, 125.19, 120.11, 118.63, 118.54, 117.61, 107.29, 35.69, 30.86 ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{13}H_{17}N_2$ 201.1386; Found 201.1420.

IR (υ_{max}/cm^{-1}): 2962 (m), 1660 (s), 1540 (s), 1400 (m), 1262 (m), 1078 (m), 1038 (m), 850 (m), 798 (m), 681 (s).

4-Methoxy-2-(1*H*-pyrrole-2-yl)pyridine **1408**



11jg

According to **General Procedure 10**, **4jd** (15.5 mg, 0.05 mmol), Pd-C (5.3 mg, 10 mol%), 0.05 M HCl in MeOH/H_2O (1:4, 2.5 mL), 12 h; 0.25 M KOH solution (MeOH/H_2O, 1:1, 2.5 mL), overnight, 10% Et_3N/hexane deactivated column chromatography on silica gel (hexane:ethyl acetate = 3:1); white solid (7.8 mg, 0.045 mmol, 90%).

^{1}H NMR (400 MHz, MeOD): δ 8.23 (d, *J* = 5.9 Hz, 1H, PyH-6), 7.17 (d, *J* = 2.4 Hz, 1H, PyH-3), 6.89 (dd, *J* = 2.6, 1.5 Hz, 1H, pyrroleH-5), 6.77 (dd, *J* = 3.6, 1.5 Hz, 1H, pyrroleH-3), 6.71 (dd, *J* = 5.9, 2.5 Hz, 1H, PyH-5), 6.19 (dd, *J* = 3.6, 2.6 Hz, 1H, pyrroleH-4), 3.90 (s, 3H, OCH_3) ppm.

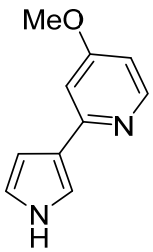
^{13}C NMR (101 MHz, MeOD): δ 168.30, 154.28, 151.00, 132.16, 121.54, 110.56, 109.43, 108.50, 104.52, 55.86 ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{10}H_{11}N_2O$ 175.0866; Found 175.0873.

IR (υ_{max}/cm^{-1}): 3100 (w), 1594 (s), 1559 (s), 1454 (s), 1314 (s), 1266 (s), 1223 (s), 1124 (s), 1031 (s), 843 (s), 804 (m), 724 (s).

M.p.: 95–96 °C.

4-Methoxy-2-(1*H*-pyrrole-3-yl)pyridine **1407**



10jg

According to **General Procedure 10**, **3jd** (15.5 mg, 0.05 mmol), Pd-C (5.3 mg, 10 mol%), 0.5 M HCl in MeOH/H_2O (1:4, 2.5 mL), 19 h; 0.25 M KOH solution (MeOH/H_2O, 1:1, 2.5 mL), overnight, 10% Et_3N/hexane deactivated column chromatography on silica gel (hexane:ethyl acetate = 1:2); blue oil (7.3 mg, 0.042 mmol, 84%).

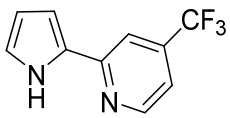
^{1}H NMR (400 MHz, MeOD): δ 8.18 (d, *J* = 6.0 Hz, 1H, PyH-6), 7.37 (t, *J* = 1.8 Hz, 1H, pyrrole H-2), 7.10 (d, *J* = 2.5 Hz, 1H, PyH-3), 6.78 (dd, *J* = 2.9, 2.0 Hz, 1H, pyrrole H-5), 6.70 (dd, J = 5.9, 2.5 Hz, 1H, PyH-5), 6.62 (dd, *J* = 2.9, 1.6 Hz, 1H, pyrroleH-4), 3.89 (s, 3H, OMe) ppm.

^{13}C NMR (101 MHz, MeOD): δ 196.57, 186.36, 178.68, 152.95, 148.27, 146.96, 136.24, 135.52, 134.07, 83.96 ppm.

HRESI-MS: [M+H]+ Calcd. for $C_{10}H_{11}N_2O$ 175.0866; Found 175.0871.

IR (υmax/cm-1): 3156 (w), 1593 (s), 1559 (s), 1474 (m), 1329 (m), 1297(s), 1223 (s), 1039 (s), 791 (s).

2-(1*H*-Pyrrol-2-yl)-4-(trifluoromethyl)pyridine **1400E, F, 1406**

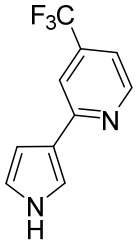


11ju

According to **General Procedure 10**, **4ji** (8.7 mg, 0.025 mmol), Pd-C (4 mg, 15 mol%), 0.24 M HCl in 1 mL MeOH, 12 h; 0.5 M KOH solution (MeOH, 2 mL), overnight, a yellow oil (decomposition during column chromatography).

^{1}H NMR for crude product (500 MHz, MeOD): δ 8.65 (d, *J* = 5.2 Hz, 1H), 7.83 (s, 1H), 7.30 (d, *J* = 5.2 Hz, 1H), 6.94 (dd, *J* = 2.6, 1.4 Hz, 1H), 6.88 (dd, *J* = 3.6, 1.4 Hz, 1H), 6.23 (dd, *J* = 3.7, 2.6 Hz, 1H) ppm.

2-(1*H*-Pyrrol-3-yl)-4-(trifluoromethyl)pyridine **1400D, G**



10ju

According to **General Procedure 10**, **3ji** (8.7 mg, 0.05 mmol), Pd-C (4 mg, 15 mol%), 0.24 M HCl in 2 mL MeOH, 12 h, 0.5 M KOH solution (MeOH, 2.5 mL), overnight; yellow oil still contained impurties after column.

^{1}H NMR (500 MHz, MeOD): δ 8.63 – 8.58 (m, 1H), 7.80 (s, 1H), 7.51 (t, *J* = 1.8 Hz, 1H), 7.34 (d, *J* = 6.8 Hz, 1H), 6.84 (dd, *J* = 2.9, 2.0 Hz, 1H), 6.72 (dd, *J* = 2.9, 1.6 Hz, 1H) ppm.

HRESI-MS: $[M+H]^+$ Calcd. for $C_{18}H_8F_3N_2$ 213.0634; Found 213.0637.

A1 X-Ray Crystal Structure Data

A1.1 X-Ray Crystal Data of Product 2n

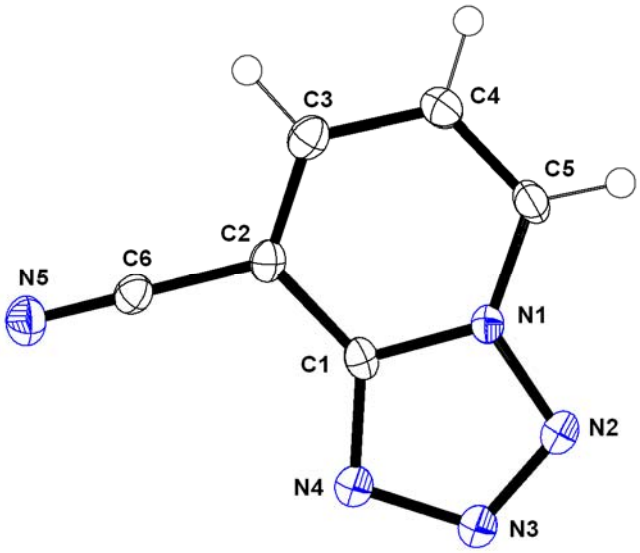


Figure S1: Crystal structure of compound **2n** (CCDC 983711, crystallographic atom numbering, thermal ellipsoids are shown at a 50% probability level). Selected bond distances [Å]: N1−C1 1.362(2), C1−C2 1.419(2), C2−C3 1.362(2), C3−C4 1.420(2), C4−C5 1.354(2), C5−N1 1.373(2), N1−N2 1.364(1), N2−N3 1.302(1), N3−N4 1.356(1), N4−C1 1.338(2).

Table S1: Crystal data and structure refinement for compound **2n**.

Bond precision:	C-C = 0.0018 A Wavelength = 0.71073
Cell:	a = 8.739(4) b = 10.227(5) c = 7.217(3)
alpha = 90	beta = 98.656(9) gamma = 90
Temperature:	100 K
Volume	637.7(5)
Space group	P2(1)/c
Sum formula	C6 H3 N5
Mr	145.13
Dx,g cm-3	1.512
Z	4
Mu (mm^{-1})	0.106

F000	296.0
h,k,lmax	10, 12, 8
Nref	6202
Tmin, Tmax	0.659, 0.746

Correction method = MULTI-SCAN

Data completeness = 5.464

Theta (max) = 25.020

R (reflections) = 0.0544(4884)

wR2 (reflections) = 0.1667(6202)

S = 1.075

Npar = 101

Table S2: Bond lengths [Å].

Atom1	Atom2	Length
N5	C6	1.152(2)
N3	N4	1.356(1)
N3	N2	1.302(1)
N4	C1	1.338(2)
N2	N1	1.364(1)
N1	C1	1.362(2)
N1	C5	1.373(2)
C6	C2	1.444(2)
C2	C3	1.362(2)
C2	C1	1.419(2)
C3	H3	0.950(1)
C3	C4	1.420(2)
C4	H4	0.950(1)
C4	C5	1.354(2)
C5	H5	0.950(1)

Table S3: Bond l angles [°].

Atom1	Atom2	Atom3	Angle
N4	N3	N2	112.79(9)
N3	N4	C1	104.99(9)
N3	N2	N1	105.47(9)
N2	N1	C1	108.24(9)
N2	N1	C5	127.2(1)
C1	N1	C5	124.6(1)
N5	C6	C2	179.0(1)
C6	C2	C3	122.3(1)
C6	C2	C1	119.2(1)
C3	C2	C1	118.5(1)
C2	C3	H3	119.6(1)
C2	C3	C4	120.8(1)
H3	C3	C4	119.6(1)
C3	C4	H4	119.6(1)
C3	C4	C5	120.9(1)
H4	C4	C5	119.5(1)
N4	C1	N1	108.5(1)
N4	C1	C2	133.4(1)
N1	C1	C2	118.1(1)
N1	C5	C4	117.2(1)
N1	C5	H5	121.4(1)
C4	C5	H5	121.4(1)

Table S4: Anisotropic displacement parameters ($Å^2 x\ 10^3$).

Atom1	Atom2	Atom3	Atom4	Torsion
N2	N3	N4	C1	-0.4(1)
N4	N3	N2	N1	0.3(1)
N3	N4	C1	N1	0.3(1)
N3	N4	C1	C2	179.5(1)

N3	N2	N1	C1	-0.1(1)
N3	N2	N1	C5	180.0(1)
N2	N1	C1	N4	-0.1(1)
N2	N1	C1	C2	-179.5(1)
C5	N1	C1	N4	179.8(1)
C5	N1	C1	C2	0.4(2)
N2	N1	C5	C4	179.2(1)
N2	N1	C5	H5	-0.8(2)
C1	N1	C5	C4	-0.7(2)
C1	N1	C5	H5	179.3(1)
N5	C6	C2	C3	95(7)
N5	C6	C2	C1	-84(7)
C6	C2	C3	H3	0.5(2)
C6	C2	C3	C4	-179.5(1)
C1	C2	C3	H3	179.6(1)
C1	C2	C3	C4	-0.4(2)
C6	C2	C1	N4	0.1(2)
C6	C2	C1	N1	179.3(1)
C3	C2	C1	N4	-179.0(1)
C3	C2	C1	N1	0.1(2)
C2	C3	C4	H4	-179.9(1)
C2	C3	C4	C5	0.1(2)
H3	C3	C4	H4	0.1(2)
H3	C3	C4	C5	-179.9(1)
C3	C4	C5	N1	0.4(2)
C3	C4	C5	H5	-179.6(1)
H4	C4	C5	N1	-179.6(1)
H4	C4	C5	H5	0.4(2)

A1.2 Compound 7bg

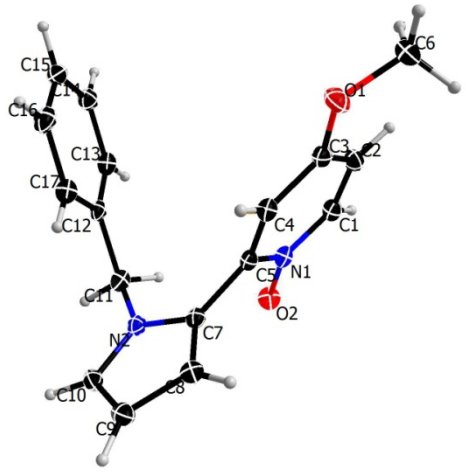


Figure S2: Crystal structure of compound **7bg**.

Table S5: Crystal data and structure refinement for compound **7bg**.

Bond precision:	C-C = 0.0019 A Wavelength = 0.71073		
Cell:	a = 5.9622(1)	b = 8.7942(1)	c = 14.4090(2)
	alpha = 107.424(1)	beta = 97.165(1)	gamma = 95.541(1)
Temperature:	100 K		
Volume	708.017(18)		
Space group	P -1		
Hall group	-P 1		
Moiety formula	C17 H16 N2 O2		
Sum formula	C17 H16 N2 O2		
Mr	280.32		
Dx,g cm-3	1.315		
Z	2		
Mu (mm-1)	0.087		
F000	296.0		

h,k,lmax	7,11,18
Nref	2902
Tmin, Tmax	0.667,0.745

Correction method = MULTI-SCAN

Data completeness = 0.993 Theta (max) = 26.449

R (reflections) = 0.0452 (2679) wR2 (reflections) = 0.1253(2902)

S = 1.148

NpPh = 192

Table S6: Bond lengths [Å].

Atom1	Atom2	Length
C1	H1	0.95
C1	C2	1.380(2)
C1	N1	1.355(2)
C2	H2	0.95
C2	C3	1.397(2)
C3	C4	1.390(2)
C3	O1	1.356(2)
C4	H4	0.951
C4	C5	1.383(2)
C5	C7	1.469(2)
C5	N1	1.378(2)
C6	H6A	0.98
C6	H6B	0.98
C6	H6C	0.981
C6	O1	1.435(2)
C7	C8	1.379(2)
C7	N2	1.379(1)
C8	H8	0.95
C8	C9	1.418(2)

C9	H9	0.95
C9	C10	1.373(2)
C10	H10	0.949
C10	N2	1.370(2)
C11	H11A	0.99
C11	H11B	0.99
C11	C12	1.514(2)
C11	N2	1.457(2)
C12	C13	1.391(2)
C12	C17	1.397(2)
C13	H13	0.95
C13	C14	1.389(2)
C14	H14	0.95
C14	C15	1.391(2)
C15	H15	0.95
C15	C16	1.387(2)
C16	H16	0.95
C16	C17	1.392(2)
C17	H17	0.949
N1	O2	1.321(2)

Table S7: Bond l angles [°].

Atom1	Atom2	Atom3	Angle
H1	C1	C2	118.9
H1	C1	N1	118.8
C2	C1	N1	122.3(1)
C1	C2	H2	120.4
C1	C2	C3	119.1(1)
H2	C2	C3	120.4
C2	C3	C4	118.0(1)

C2	C3	O1	125.8(1)
C4	C3	O1	116.2(1)
C3	C4	H4	119.1
C3	C4	C5	121.8(1)
H4	C4	C5	119.1
C4	C5	C7	120.3(1)
C4	C5	N1	119.1(1)
C7	C5	N1	120.5(1)
H6A	C6	H6B	109.4
H6A	C6	H6C	109.5
H6A	C6	O1	109.5
H6B	C6	H6C	109.4
H6B	C6	O1	109.5
H6C	C6	O1	109.5
C5	C7	C8	126.5(1)
C5	C7	N2	125.0(1)
C8	C7	N2	108.0(1)
C7	C8	H8	126.3
C7	C8	C9	107.3(1)
H8	C8	C9	126.4
C8	C9	H9	126.3
C8	C9	C10	107.3(1)
H9	C9	C10	126.4
C9	C10	H10	125.7
C9	C10	N2	108.6(1)
H10	C10	N2	125.7
H11A	C11	H11B	107.7
H11A	C11	C12	108.9
H11A	C11	N2	108.9

H11B	C11	C12	108.9
H11B	C11	N2	108.9
C12	C11	N2	113.4(1)
C11	C12	C13	118.7(1)
C11	C12	C17	122.5(1)
C13	C12	C17	118.8(1)
C12	C13	H13	119.5
C12	C13	C14	121.0(1)
H13	C13	C14	119.5
C13	C14	H14	120
C13	C14	C15	120.0(1)
H14	C14	C15	120
C14	C15	H15	120.3
C14	C15	C16	119.4(1)
H15	C15	C16	120.3
C15	C16	H16	119.7
C15	C16	C17	120.6(1)
H16	C16	C17	119.7
C12	C17	C16	120.2(1)
C12	C17	H17	119.9
C16	C17	H17	119.9
C1	N1	C5	119.7(1)
C1	N1	O2	119.9(1)
C5	N1	O2	120.4(1)
C7	N2	C10	108.8(1)
C7	N2	C11	125.8(1)
C10	N2	C11	124.9(1)
C3	O1	C6	117.4(1)

Table S8: Anisotropic displacement parameters ($Å^2 x\ 10^3$).

Atom1	Atom2	Atom3	Atom4	Torsion
H1	C1	C2	H2	-0.4
H1	C1	C2	C3	179.5
N1	C1	C2	H2	179.6
N1	C1	C2	C3	-0.5(2)
H1	C1	N1	C5	179.7
H1	C1	N1	O2	1.7
C2	C1	N1	C5	-0.3(2)
C2	C1	N1	O2	-178.3(1)
C1	C2	C3	C4	1.2(2)
C1	C2	C3	O1	-177.3(1)
H2	C2	C3	C4	-178.8
H2	C2	C3	O1	2.7
C2	C3	C4	H4	178.8
C2	C3	C4	C5	-1.2(2)
O1	C3	C4	H4	-2.6
O1	C3	C4	C5	177.4(1)
C2	C3	O1	C6	-15.5(2)
C4	C3	O1	C6	166.0(1)
C3	C4	C5	C7	175.9(1)
C3	C4	C5	N1	0.5(2)
H4	C4	C5	C7	-4.1
H4	C4	C5	N1	-179.5
C4	C5	C7	C8	-49.7(2)
C4	C5	C7	N2	121.9(1)
N1	C5	C7	C8	125.7(1)
N1	C5	C7	N2	-62.8(2)
C4	C5	N1	C1	0.3(2)
C4	C5	N1	O2	178.3(1)

C7	C5	N1	C1	-175.1(1)
C7	C5	N1	O2	2.9(2)
H6A	C6	O1	C3	-175.7
H6B	C6	O1	C3	64.3
H6C	C6	O1	C3	-55.7
C5	C7	C8	H8	-7.2
C5	C7	C8	C9	172.8(1)
N2	C7	C8	H8	-179.9
N2	C7	C8	C9	0.1(1)
C5	C7	N2	C10	-172.3(1)
C5	C7	N2	C11	-0.7(2)
C8	C7	N2	C10	0.5(1)
C8	C7	N2	C11	172.2(1)
C7	C8	C9	H9	179.3
C7	C8	C9	C10	-0.7(1)
H8	C8	C9	H9	-0.7
H8	C8	C9	C10	179.3
C8	C9	C10	H10	-178.9
C8	C9	C10	N2	1.0(2)
H9	C9	C10	H10	1.1
H9	C9	C10	N2	-179
C9	C10	N2	C7	-1.0(1)
C9	C10	N2	C11	-172.7(1)
H10	C10	N2	C7	179
H10	C10	N2	C11	7.2
H11A	C11	C12	C13	-82.9
H11A	C11	C12	C17	96.5
H11B	C11	C12	C13	34.3
H11B	C11	C12	C17	-146.3

N2	C11	C12	C13	155.6(1)
N2	C11	C12	C17	-24.9(2)
H11A	C11	N2	C7	170.9
H11A	C11	N2	C10	-18.7
H11B	C11	N2	C7	53.7
H11B	C11	N2	C10	-136
C12	C11	N2	C7	-67.7(2)
C12	C11	N2	C10	102.7(1)
C11	C12	C13	H13	-0.2
C11	C12	C13	C14	179.8(1)
C17	C12	C13	H13	-179.6
C17	C12	C13	C14	0.4(2)
C11	C12	C17	C16	180.0(1)
C11	C12	C17	H17	0
C13	C12	C17	C16	-0.6(2)
C13	C12	C17	H17	179.5
C12	C13	C14	H14	-179.9
C12	C13	C14	C15	0.1(2)
H13	C13	C14	H14	0.1
H13	C13	C14	C15	-179.9
C13	C14	C15	H15	179.6
C13	C14	C15	C16	-0.4(2)
H14	C14	C15	H15	-0.4
H14	C14	C15	C16	179.5
C14	C15	C16	H16	-179.8
C14	C15	C16	C17	0.2(2)
H15	C15	C16	H16	0.2
H15	C15	C16	C17	-179.8
C15	C16	C17	C12	0.3(2)

C15	C16	C17	H17	-179.8
H16	C16	C17	C12	-179.7
H16	C16	C17	H17	0.3

Bibliography

[1] E. F. V. Scriven, K. Turnbull, *Chem. Rev.* **1988**, *88*, 297-368.

[2] S. X. Cai, D. J. Glenn, K. R. Gee, M. Yan, R. E. Cotter, N. L. Reddy, E. Weber, J. F. W. Keana, *Bioconjugate Chem.* **1993**, *4*, 545-548.

[3] S. X. Cai, D. J. Glenn, M. Kanskar, M. N. Wybourne, J. F. W. Keana, *Chem. Mat.* **1994**, *6*, 1822-1829.

[4] E. W. Meijer, S. Nijhuis, F. C. B. M. Van Vroonhoven, *J. Am. Chem. Soc.* **1988**, *110*, 7209-7210.

[5] S. X. Cai, D. J. Glenn, J. F. W. Keana, *J. Org. Chem.* **1992**, *57*, 1299-1304.

[6] J. Yang, X. Gong, G. Wang, *RSC Adv.* **2015**, *5*, 9503-9509.

[7] A. Messmer, G. Hajos, *J. Org. Chem.* **1981**, *46*, 843-846.

[8] a) C. Addicott, C. Wentrup, *Aust. J. Chem.* **2008**, *61*, 592-599; b) C. K. Lowe-Ma, R. A. Nissan, W. S. Wilson, *J. Org. Chem.* **1990**, *55*, 3755-3761.

[9] R. A. Evans, C. Wentrup, *J. Chem. Soc., Chem. Commun.* **1992**, 1062-1064.

[10] D. Zornik, R. M. Meudtner, T. El Malah, C. M. Thiele, S. Hecht, *Chem. Eur. J.* **2011**, *17*, 1473-1484.

[11] T. Sasaki, K. Kanematsu, M. Murata, *Tetrahedron* **1971**, *27*, 5359-5366.

[12] a) D. Simoni, R. Rondanin, G. Furnò, E. Aiello, F. P. Invidiata, *Tetrahedron Lett.* **2000**, *41*, 2699-2703; b) C. Wentrup, H. W. Winter, *J. Am. Chem. Soc.* **1980**, *102*, 6159-6161; c) A. Reisinger, R. Koch, C. Wentrup, *J. Chem. Soc., Perkin Trans. 1* **1998**, 2247-2250.

[13] J. Boyer, M. Chang, R. Reinisch, *J. Org. Chem.* **1960**, *25*, 286-287.

[14] A. Messmer, G. Hajos, Z. Juhasz-Riedl, P. Sohar, *J. Org. Chem.* **1988**, *53*, 973-975.

[15] A. Messmer, G. Hajós, J. Fleischer, M. Czugler, *Monatsh. Chem.* **1985**, *116*, 1227-1231.

[16] P. K. Dutt, H. R. Whitehead, A. Wormall, *J. Chem. Soc., Perkin Trans.* **1921**, *119*, 2088-2094.

[17] S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem. Int. Ed.* **2005**, *44*, 5188-5240.

[18] S. M. Capitosti, T. P. Hansen, M. L. Brown, *Org. Lett.* **2003**, *5*, 2865-2867.

[19] A. A. Siddiki, B. S. Takale, V. N. Telvekar, *Tetrahedron Lett.* **2013**, *54*, 1294-1297.

[20] a) P. A. S. Smith, C. D. Rowe, L. B. Bruner, *J. Org. Chem.* **1969**, *34*, 3430-3433; b) P. A. S. Smith, G. F. Budde, S. S. P. Chou, *J. Org. Chem.* **1985**, *50*, 2062-2066.

[21] Q. Liu, Y. Tor, *Org. Lett.* **2003**, *5*, 2571-2572.

[22] a) Y. H. Kim, K. Kim, S. B. Shim, *Tetrahedron Lett.* **1986**, *27*, 4749-4752; b) M. De Rosa, P. Haberfield, *J. Org. Chem.* **1981**, *46*, 2639-2643; c) V. Pozsgay, H. J. Jennings, *Tetrahedron Lett.* **1987**, *28*, 5091-5092.

[23] B. R. Cho, C.-O. M. Yoon, K. S. Song, *Tetrahedron Lett.* **1995**, *36*, 3193-3196.

[24] B. Chattopadhyay, C. I. R. Vera, S. Chuprakov, V. Gevorgyan, *Org. Lett.* **2010**, *12*, 2166-2169.

[25] J. K. Laha, G. D. cuny, *Synthesis* **2008**, 4002-4006.

[26] O. Seide, *Ber. Dtsch. Chem. Ges.* **1926**, *59*, 2465-2473.

[27] M. M. Boudakian, F. F. Frulla, D. F. Gavin, J. A. Zaslowsky, *J. Heterocycl. Chem.* **1967**, *4*, 375-376.

[28] a) J. Alcázar, J. M. Alonso, J. M. Bartolomé, L. Iturrino, E. Matesanz, *Tetrahedron Lett.* **2003**, *44*, 8983-8986; b) D. Cuperly, P. Gros, Y. Fort, *J. Org. Chem.* **2002**, *67*, 238-241.
[29] O. García Mancheño, C. Bolm, *Org. Lett.* **2007**, *9*, 2951-2954.
[30] K. S. Reddy, U. T. Bnalerao, D. S. Iyengar, *Chem. Lett.* **1983**, 1745-1748.
[31] I. M. Kozaburo Nishiyama, *Bull. Chem. Soc. Jpn.* **1985**, *58*.
[32] N. Sato, N. Miwa, N. Hirokawa, *J. Chem. Soc., Perkin Trans. 1* **1994**, 885-888.
[33] J. M. Keith, *J. Org. Chem.* **2006**, *71*, 9540-9543.
[34] a) H. C. Bertrand, S. Clède, R. Guillot, F. Lambert, C. Policar, *Inorg. Chem.* **2014**, *53*, 6204-6223; b) S. Jindabot, K. Teerachanan, P. Thongkam, S. Kiatisevi, T. Khamnaen, P. Phiriyawirut, S. Charoenchaidet, T. Sooksimuang, P. Kongsaeree, P. Sangtrirutnugul, *J. Organomet. Chem.* **2014**, *750*, 35-40; c) I. Stengel, A. Mishra, N. Pootrakulchote, S.-J. Moon, S. M. Zakeeruddin, M. Gratzel, P. Bauerle, *J. Mater. Chem.* **2011**, *21*, 3726-3734; d) S. Gu, H. Xu, N. Zhang, W. Chen, *Chem.Asian J.* **2010**, *5*, 1677-1686.
[35] W. K. C. Lo, G. S. Huff, J. R. Cubanski, A. D. W. Kennedy, C. J. McAdam, D. A. McMorran, K. C. Gordon, J. D. Crowley, *Inorg. Chem.* **2015**, *54*, 1572-1587.
[36] T. Wang, in *U.S. Pat. Appl. Publ.,*, **2008**.
[37] J. M. Keith, *J. Org. Chem.* **2010**, *75*, 2722-2725.
[38] C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057-3064.
[39] V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596-2599.
[40] a) P. Wu, A. K. Feldman, A. K. Nugent, C. J. Hawker, A. Scheel, B. Voit, J. Pyun, J. M. J. Fréchet, K. B. Sharpless, V. V. Fokin, *Angew. Chem. Int. Ed.* **2004**, *43*, 3928-3932; b) Q. Wang, T. R. Chan, R. Hilgraf, V. V. Fokin, K. B. Sharpless, M. G. Finn, *J. Am. Chem. Soc.* **2003**, *125*, 3192-3193.
[41] a) M. Köhn, R. Breinbauer, *Angew. Chem. Int. Ed.* **2004**, *43*, 3106-3116; b) W. G. Lewis, L. G. Green, F. Grynszpan, Z. Radić, P. R. Carlier, P. Taylor, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 1053-1057.
[42] Y. Liu, X. Wang, J. Xu, Q. Zhang, Y. Zhao, Y. Hu, *Tetrahedron* **2011**, *67*, 6294-6299.
[43] L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315-1345.
[44] E. Beck, M. Gaunt, in *C-H Activation, Vol. 292* (Eds.: J.-Q. Yu, Z. Shi), Springer Berlin Heidelberg, **2010**, pp. 85-121.
[45] G. Rousseau, B. Breit, *Angew. Chem. Int. Ed.* **2011**, *50*, 2450-2494.
[46] D. Leow, G. Li, T.-S. Mei, J.-Q. Yu, *Nature* **2012**, *486*, 518-522.
[47] J. W. Daly, H. Martin Garraffo, T. F. Spande, in *Alkaloids: Chemical and Biological Perspectives, Vol. Volume 13* (Ed.: S. W. Pelletier), Pergamon, **1999**, pp. 1-161.
[48] a) R. Suresh, S. Muthusubramanian, R. Senthilkumaran, *Synlett* **2014**, *25*, 2064-2066; b) R. Suresh, S. Muthusubramanian, R. S. Kumaran, G. Manickam, *Asian J. Org. Chem.* **2014**, *3*, 604-608.
[49] K. S. Kanyiva, Y. Nakao, T. Hiyama, *Angew. Chem. Int. Ed.* **2007**, 46, 8872–8874. **2007**, *119*, 9028-9030.
[50] Z. Wu, C. Pi, X. Cui, J. Bai, Y. Wu, *Adv. Synth. Catal.* **2013**, *355*, 1971-1976.
[51] S. H. Cho, S. J. Hwang, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 9254-9256.
[52] P. Xi, F. Yang, S. Qin, D. Zhao, J. Lan, G. Gao, C. Hu, J. You, *J. Am. Chem. Soc.* **2010**, *132*, 1822-1824.

[53] W. Liu, Y. Li, Y. Wang, C. Kuang, *Org. Lett.* **2013**, *15*, 4682-4685.
[54] W. Liu, X. Yu, Y. Li, C. Kuang, *Chem. Commun.* **2014**, *50*, 9291-9294.
[55] a) X. Qin, H. Liu, D. Qin, Q. Wu, J. You, D. Zhao, Q. Guo, X. Huang, J. Lan, *Chem. Sci.* **2013**, *4*, 1964-1969; b) X.-P. Fu, Q.-Q. Xuan, L. Liu, D. Wang, Y.-J. Chen, C.-J. Li, *Tetrahedron* **2013**, *69*, 4436.
[56] N. J. Willis, J. M. Smith, *RSC Adv.* **2014**, *4*, 11059-11063.
[57] Y. Shang, X. Jie, H. Zhao, P. Hu, W. Su, *Org. Lett.* **2014**, *16*, 416-419.
[58] G. Bartoli, G. Bencivenni, R. Dalpozzo, *Chem. Soc. Rev.* **2010**, *39*, 4449-4465.
[59] a) R. J. Phipps, N. P. Grimster, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 8172-8174; b) D. R. Stuart, E. Villemure, K. Fagnou, *J. Am. Chem. Soc.* **2007**, *129*, 12072-12073; c) E. Capito, J. M. Brown, A. Ricci, *Chem. Commun.* **2005**, 1854-1856.
[60] a) N. P. Grimster, C. Gauntlett, C. R. A. Godfrey, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2005**, *44*, 3125-3129; b) D. R. Stuart, K. Fagnou, *Science* **2007**, *316*, 1172-1175.
[61] S. Potavathri, A. S. Dumas, T. A. Dwight, G. R. Naumiec, J. M. Hammann, B. DeBoef, *Tetrahedron Lett.* **2008**, *49*, 4050-4053.
[62] D. Wang, Y. Izawa, S. S. Stahl, *J. Am. Chem. Soc.* **2014**, *136*, 9914-9917.
[63] E. M. Beck, N. P. Grimster, R. Hatley, M. J. Gaunt, *J. Am. Chem. Soc.* **2006**, *128*, 2528-2529.
[64] M. Zhang, P. Hu, J. Zhou, G. Wu, S. Huang, W. Su, *Org. Lett.* **2013**, *15*, 1718-1721.
[65] L. Yang, L. Zhao, C.-J. Li, *Chem. Commun.* **2010**, *46*, 4184-4186.
[66] L. Filippini, M. Gusmeroli, R. Riva, *Tetrahedron Lett.* **1992**, *33*, 1755-1758.
[67] P. Ehlers, A. Petrosyan, J. Baumgard, S. Jopp, N. Steinfeld, T. V. Ghochikyan, A. S. Saghyan, C. Fischer, P. Langer, *ChemCatChem* **2013**, *5*, 2504-2511.
[68] J. Roger, H. Doucet, *Adv. Synth. Catal.* **2009**, *351*, 1977-1990.
[69] J. Wen, R.-Y. Zhang, S.-Y. Chen, J. Zhang, X.-Q. Yu, *J. Org. Chem.* **2012**, *77*, 766-771.
[70] B. Saoudi, A. Debache, J.-F. Soule, H. Doucet, *RSC Adv.* **2015**, *5*, 65175-65183.
[71] K. Ueda, K. Amaike, R. M. Maceiczyk, K. Itami, J. Yamaguchi, *J. Am. Chem. Soc.* **2014**, *136*, 13226-13232.
[72] Z. Wang, K. Li, D. Zhao, J. Lan, J. You, *Angew. Chem. Int. Ed.* **2011**, *50*, 5365-5369.
[73] A. D. Yamaguchi, D. Mandal, J. Yamaguchi, K. Itami, *Chem. Lett.* **2011**, *40*, 555-557.
[74] S.-D. Yang, C.-L. Sun, Z. Fang, B.-J. Li, Y.-Z. Li, Z.-J. Shi, *Angew. Chem. Int. Ed.* **2008**, *47*, 1473-1476.
[75] A. Honraedt, M.-A. Raux, E. L. Grognec, D. Jacquemin, F.-X. Felpin, *Chem. Commun.* **2014**, *50*, 5236-5238.
[76] S. Gowrisankar, J. Seayad, *Chem. Eur. J.* **2014**, *20*, 12754-12758.
[77] Y. Kita, K. Morimoto, M. Ito, C. Ogawa, A. Goto, T. Dohi, *J. Am. Chem. Soc.* **2009**, *131*, 1668-1669.
[78] A. García-Rubia, R. G. Arrayás, J. C. Carretero, *Angew. Chem. Int. Ed.* **2009**, *48*, 6511-6515.
[79] B. Li, J. Ma, W. Xie, H. Song, S. Xu, B. Wang, *Chem. Eur. J.* **2013**, *19*, 11863-11868.
[80] J. P. Brand, C. Chevalley, R. Scopelliti, J. Waser, *Chem. Eur. J.* **2012**, *18*, 5655-5666.
[81] Y.-M. Su, Y. Hou, F. Yin, Y.-M. Xu, Y. Li, X. Zheng, X.-S. Wang, *Org. Lett.* **2014**, *16*, 2958-2961.
[82] M. F. Semmelhack, A. Chlenov, D. M. Ho, *J. Am. Chem. Soc.* **2005**, *127*, 7759-7773.

[83] M. Böttger, B. Wiegmann, S. Schaumburg, P. G. Jones, W. Kowalsky, H.-H. Johannes, *Beilstein J. Org. Chem.* **2012**, *8*, 1037-1047.
[84] J. Roppe, N. D. Smith, D. Huang, L. Tehrani, B. Wang, J. Anderson, J. Brodkin, J. Chung, X. Jiang, C. King, B. Munoz, M. A. Varney, P. Prasit, N. D. P. Cosford, *J. Med. Chem.* **2004**, *47*, 4645-4648.
[85] E. T. Nadres, A. Lazareva, O. Daugulis, *J. Org. Chem.* **2011**, *76*, 471-483.
[86] A. Spaggiari, D. Vaccari, P. Davoli, F. Prati, *Synthesis* **2006**, *2006*, 995-998.
[87] B. A. Trofimov, A. b. I. Mikhaleva, A. V. Ivanov, V. S. Shcherbakova, I. A. Ushakov, *Tetrahedron* **2015**, *71*, 124-128.
[88] O. L. Eliseev, P. E. Ivashkin, A. G. Ostapenko, A. V. Lesiv, Y. A. Khomutova, S. L. Ioffe, A. L. Lapidus, *Synlett* **2006**, *2006*, 2239-2240.
[89] D. Savoia, V. Concialini, S. Roffia, L. Tarsi, *J. Org. Chem.* **1991**, *56*, 1822-1827.
[90] N. D. Smith, D. Huang, N. D. P. Cosford, *Org. Lett.* **2002**, *4*, 3537-3539.
[91] a) Z. Zhang, Z. Hu, Z. Yu, P. Lei, H. Chi, Y. Wang, R. He, *Tetrahedron Lett.* **2007**, *48*, 2415-2419; b) M. V. Nikulin, A. Y. Lebedev, A. Z. Voskoboinikov, I. P. Beletskaya, *Dokl. Chem.* **2008**, *423*, 326-329.
[92] Y. Ji, R. E. Plata, C. S. Regens, M. Hay, M. Schmidt, T. Razler, Y. Qiu, P. Geng, Y. Hsiao, T. Rosner, M. D. Eastgate, D. G. Blackmond, *J. Am. Chem. Soc.* **2015**, *137*, 13272-13281.
[93] S. Talukdar, S. K. Nayak, A. Banerji, *J. Org. Chem.* **1998**, *63*, 4925-4929.
[94] M. I. Jones, C. Froussios, D. A. Evans, *J. Chem. Soc., Chem. Commun.* **1976**, 472-473.
[95] A. Fürstner, H. Weintritt, *J. Am. Chem. Soc.* **1998**, *120*, 2817-2825.
[96] a) P. Gao, Y. Liu, L. Zhang, P.-F. Xu, S. Wang, Y. Lu, M. He, H. Zhai, *J. Org. Chem.* **2006**, *71*, 9495-9498; b) A. Merz, T. Meyer, *Synthesis* **1999**, *1999*, 94-99.
[97] A. A. Haddach, A. Kelleman, M. V. Deaton-Rewolinski, *Tetrahedron Lett.* **2002**, *43*, 399-402.
[98] H. E. Gottlieb, V. Kotlyar, A. Nudelman, *J. Org. Chem.* **1997**, *62*, 7512-7515.
[99] S. Liu, D. Lentz, C. C. Tzschucke, *J. Org. Chem.* **2014**, *79*, 3249-3254.
[100] a) T. Ogata, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 13848-13849; b) J.-i. Kuroda, K. Inamoto, K. Hiroya, T. Doi, *Eur. J. Org. Chem.* **2009**, *2009*, 2251-2261.
[101] G. Berionni, B. Pégot, R. Goumont, *Magn. Reson. Chem.* **2010**, *48*, 101-110.
[102] A. S. Kiselyov, *Tetrahedron Lett.* **2005**, *46*, 4851-4854.
[103] M. H. Fisher, M. J. Wyvratt, *J. Eur. Pat. Appl.* **1989**, EP 318092 A318092 19890531.
[104] B. Riflade, D. Lachkar, J. Oble, J. Li, S. Thorimbert, B. Hasenknopf, E. Lacôte, *Org. Lett.* **2014**, *16*, 3860-3863.
[105] W. T. Lim, S. Y. Choi, B. J. Kim, C. M. Kim, I. S. Lee, S. H. Kim, N. H. Heo, *Bull. Korean Chem. Soc.* **2005**, *26*, 1090-1096.
[106] N. Kuhl, M. N. Hopkinson, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 8230-8234.
[107] J. E. Taylor, M. D. Jones, J. M. J. Williams, S. D. Bull, *Org. Lett.* **2010**, *12*, 5740-5743.
[108] C. Zonta, F. Fabris, O. De Lucchi, *Org. Lett.* **2005**, *7*, 1003-1006.
[109] G. Satish, K. H. V. Reddy, K. Ramesh, B. S. P. A. Kumar, Y. V. D. Nageswar, *Tetrahedron Lett.* **2014**, *55*, 2596-2599.
[110] Z. Zou, Z. Deng, X. Yu, M. Zhang, S. Zhao, T. Luo, X. Yin, H. Xu, W. Wang, *Sci. China Chem.* **2012**, *55*, 43-49.
[111] X. Hong, H. Wang, B. Liu, B. Xu, *Chem. Commun.* **2014**, *50*, 14129-14132.

[112] H. Sharghi, P. Shiri, *Synthesis* **2015**, *26*, 1131-1146.
[113] J. D. Fourneron, A. Archelas, R. Furstoss, *J. Org. Chem.* **1989**, *54*, 2478-2483.
[114] W. von der Saal, R. Reinhardt, J. Stawitz, H. Quast, *Eur. J. Org. Chem.* **1998**, *1998*, 1645-1652.

List of Publication

1. S. Liu, D. Lentz, C. C. Tzschucke, Conversion of Pyridine *N*-Oxides to Tetrazolopyridines, *J. Org. Chem.* **2014**, *79*, 3249-3254.

Curriculum Vitae

The curriculum vitae is not available in the online version due to data protection.

Der Lebenslauf ist in der Online-Version aus Gründen des Datenschutzes nicht enthalten.