Synthesis of Aromatic Heterocycles by Palladium(0)-Catalyzed Domino Reactions and Cyclization of Hydrazone Dianions

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Declaration

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

Erklärung

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

Rostock, September 2016

Thang N. Ngo

Abstract

This dissertation focuses on the development of new and convenient synthetic approaches for important or new aromatic heterocycles, which are potential for drug discovery and advanced materials. Based on selective Pd(0)-catalyzed reactions of easily accessible starting materials, the precursors with desired active centers were set up for further domino reactions towards target molecules. This strategy was successfully applied in the development of new synthetic methods for chromeno[3,4-*b*]pyrrol-4(3*H*)-ones, indolo[1,2-*f*]phenanthridines, azaindolo[1,2-*f*]phenanthridines, and naphtho-fused heterocycles. Furthermore, a convenient synthesis of fluorinated pyrazoles based on one-pot domino reaction of dianinons was developed.

Zusammenfassung

Diese Dissertation beschäftigt sich mit der Entwicklung neuer und zugleich einfacher synthetischer Zugänge von wichtigen bzw. neuen aromatischen Heterozyklen, welche von Interesse für die Entwicklung neuer Wirkstoffe oder Materialien sind. Mittels selektiver Pd(0) katalysierter Reaktionen von einfach zugänglichen Startmaterialien wurden Vorstufen synthetisiert, welche im Anschluss durch Domino-Reaktionen zu den entsprechenden Zielprodukten umgesetzt wurden. Diese Strategie wurde erfolgreich angewendet zur Darstellung von Chromeno[3,4-*b*]pyrrol-4(3*H*)-onen, Indolo[1,2-*f*]phenanthridinen, Azaindolo[1,2-*f*]phenanthridinen und Naphthalin-annellierten Heterozyklen. Außerdem wurde ein praktischer Zugang zu fluorierten Pyrazolen, basierend auf einer Ein-Topf-Domino-Reaktion entwickelt.

Table of Contents

List of abbreviations

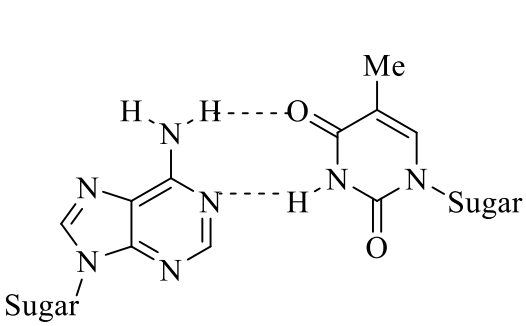
°C	Degrees Celsius
^{13}C	Carbon 13
^{19}F	Fluorine 19
^{1}H	Hydrogen, proton
Å	Angstrom, 10^{-8} m
Ac	Acetyl
AcO	Acetate
Ar	Aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Boc	*N*-*tert*-butoxycarbonyl
Calcd	Calculated
CataCXium A	Di(1-adamantyl)-*n*-butylphosphine
CI	Chemical Ionization
cm^{-1}	Wavenumber
Cy	Cyclohexane
DavePhos	2-Dicyclohexylphosphino-2′-(*N,N*-dimethylamino)biphenyl
dba	Dibenzylideneacetone
DMA	Dimethylacetamide
DMF	*N,N*-Dimethylformamide
DPEPhos	(Oxydi-2,1-phenylene)bis(diphenylphosphine)
Dppe	1,2-Bis(diphenylphosphino)ethane
Dppf	1,1'- Bis(diphenylphosphanyl)ferrocene
EI	Electron Ionization
EI-MS	Electron Ionization - Mass Spectrometry
Equiv.	Equivalent
ESI	Electrospray Ionization
Et_3N	Triethylamine
GC	Gas Chromatography
h	Hour
HMBC	Heteronuclear Multiple-bond Correlation Spectroscopy
HOMO	Highest Occupied Molecular Orbital

HSQC	Heteronuclear Single Quantum Coherence Spectroscopy
Hz	Hertz (S^{-1})
IR	Infrared Spectroscopy
J	Coupling Constant
L	Ligand
LCD	Liquid Crystal Display
LUMO	Lowest Unoccupied Molecular Orbital
m/z	Mass-to-charge Ratio
MeCN	Acetonitrile
mp	Melting Point
MS	Mass Spectrometry
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
Nu	Nucleophile
ORTEP	Oak Ridge Thermal Ellipsoid Plot
OTf	Triflate (Trifluoromethanesulfonate)
Ph	Phenyl
PPh_3	Triphenylphosphine
ppm	Parts per Million
rt	Room temperature
RuPhos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
SPhos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
Tf_2O	Trifluoromethanesulfonic anhydride
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilane
UV/Vis	Ultraviolet and visible absorption spectroscopy
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
λ	Wavelength
ϕ	Fluorescence quantum yield

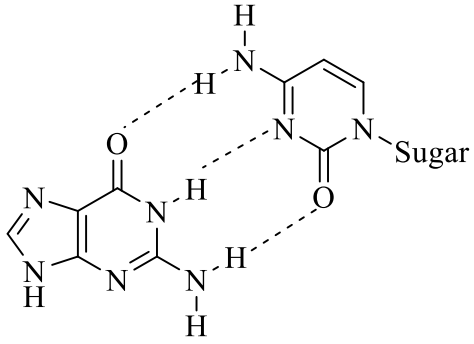
1. General introduction

1.1. The importance of heterocycles

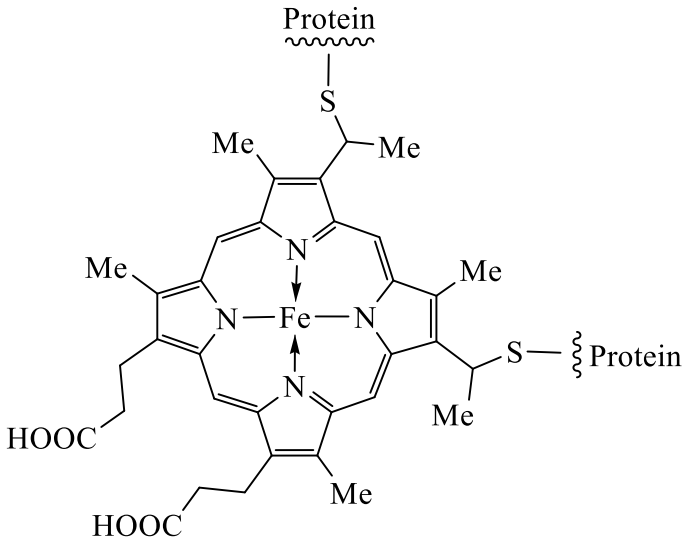
Heterocyclic molecules could be figuratively compared to jewelry rings ornamented with gemstones.[1] By introducing one or more heteroatoms to an aromatic carbocyclic system, both chemical and physical properties change significantly, making the ring system more "precious". For example, pyridine, formed by replacing one CH unit in benzene by one nitrogen, could act as a base or nucleophile while the α-hydrogens could undergo substitution by strong base such as sodium amide. Another example is pyrrole, an electron-rich five-membered ring heterocycle, formed by replacing two CH units in benzene by one NH unit, which is prone to electrophilic reactions, or tend to be oxidized more easily. In addition, heteroatom that possesses one or more unshared electron pairs, as of pyridine, imidazole, or pyrazole, can take part in weak interactions such as hydrogen bonds or form complexes with metal ions, playing crucial roles in human biological systems. Although activities of aromatic systems are improved by incorporation of heteroatoms, the thermal stability is still retained in molecules of heteroaromatic systems.[1][2]



Adenine - Thymine



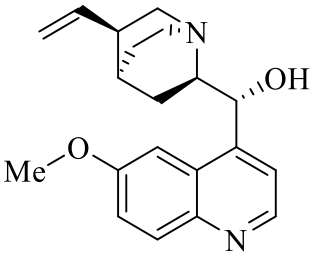
Guanine - Cytosine



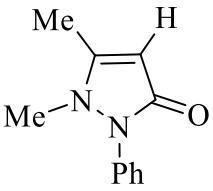
Heme C

Figure 1.1: Heterocycles in hydrogen-bonding interaction and complex with metal cation

Aromatic heterocycles are ubiquitous in life and society and found crucial applications in medicine, agriculture, and technology. From natural sources, a great number of heteroaromatic compounds have been discovered and many of them have been used as drugs or lead compounds for drug discovery. For instance, extracts from the bark of cinchona tree have been used to prevent or cure malaria since 1632. Later studies showed that the main active component of them is quinine, a quinoline derivative.[3] Quinine then was recommended as a first-line treatment for malaria by WHO until 2006. Moreover, synthetic aromatic heterocycles also lead to the discovery of many new drugs. For example, phenazone, known as an anti-inflammatory and antipyretic drug, is a pyrazole derivative first synthesized by Lugwig Knorr in 1887.[4]



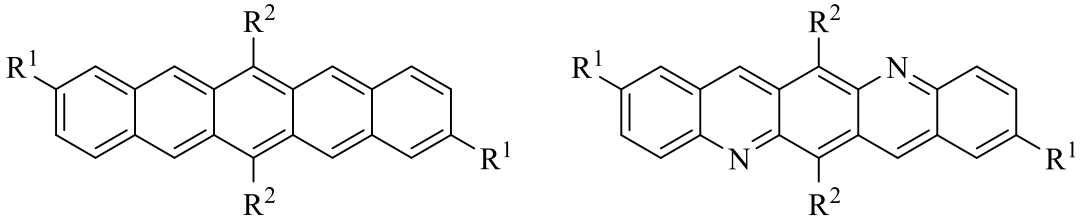
Quinine



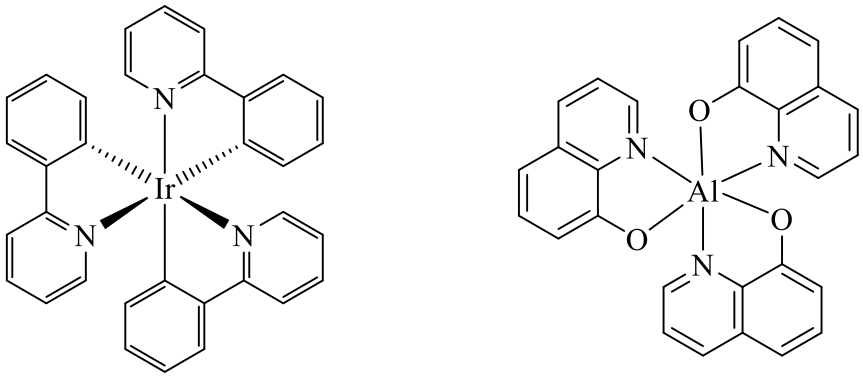
Phenazone

Figure 1.2: Aromatic heterocycles as drugs

Furthermore, synthetic aromatic polyheterocycles are essential components in developing advanced materials. They are applied in numerous types of light-emitting diodes (OLEDs), organic photovoltaic devices (OPVs), and organic field effect transistors (OFETs).[5] Heteroatoms help improving stability, charge mobility, and molecular packing of aromatic heterocycles over corresponding polycyclic aromatic hydrocarbons (PAHs).[6] For example, pentacene, a linear PAH consisting of five fused benzene rings, known as an organic semiconductor with high charge mobility, is vulnerable to oxidation, which slowly degrades under air and light exposure; therefore, its applications is practically limited.[7] By introducing heteroatoms to pentacene systems, the stability of obtained derivatives is improved as well as other properties such as charge mobility, solubility, or molecular packing. Numerous pentacene derivatives have been discovered by this strategy which possess potential electronic, photophysical, and optical properties.[8] Moreover, heteroaromatic compounds can form organometallic chelates with remarkable charge transport and luminescent properties. Among them, Alq_3 (tris(8-hydroxyquinolinato)aluminium), a common component of small molecule OLEDs, has been used as the emission and electron transport layers.[9] And $Ir(ppy)_3$ (Tris[2-phenylpyridinato-C^2,*N*)iridium(III)), a green emitting complex, is used as the dopant in phosphorescent organic light-emitting diode (PHOLED).[10]



Pentacene and derivatives



$Ir(ppy)_3$ **Alq_3**

Figure 1.3: Aromatic heterocycles applied in organic materials

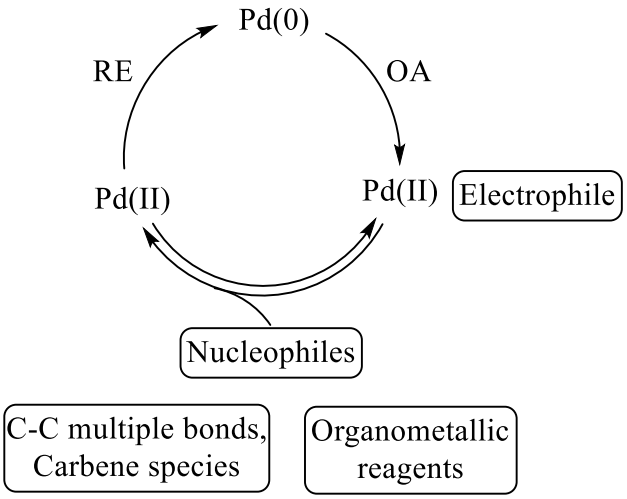
Due to their gravity in modern life, extensive effort has been devoted to the development of synthetic methods and characteristic studies of aromatic heterocycles. Recently, synthetic methods of heterocyclic and polyheterocyclic compounds have been blooming in the light of transition metal-catalyzed reactions.[11] Among them, palladium(0) – catalyzed reactions have been well-studied and found important practical applications.[12–14]

1.2. Palladium(0) catalytic cycle

The chemistry of palladium(0)-catalyzed reaction was incubated in the late 1960s and has been growing rapidly since then. Because of its practical importance to human life, in 2010, the Nobel Prize in chemistry was dedicated to professors Heck, Negishi, and Suzuki for their contribution to the development in the field.[15]

In general, a palladium(0)-catalyzed reaction is a catalytic cycle that includes 3 basic stages: oxidative addition, reactions of Pd(II) complexes with appropriate nucleophiles, and reductive elimination. Firstly, the catalytic cycle starts with a Pd(0) species that is oxidized by substrates to generate a Pd(II) complex, which is called oxidative addition (OA). The new generated Pd(II) species now behaves as an electrophile. Depending on the nature of nucleophiles, different processes can take place, such as ligand substitution, transmetalation, or migratory insertion. Finally, expected products are formed by reductive elimination (RE) of Pd(II) complexes, along

with the regeneration of [Pd(0)] catalyst to start a new catalytic cycle. In the case of migratory insertion, the product and a hydridopalladium(II) halide complex are obtained after *β*-hydride elimination, then the hydridopalladium(II) halide complex undergoes reductive elimination to recreate the [Pd(0)] catalyst.[13,16]

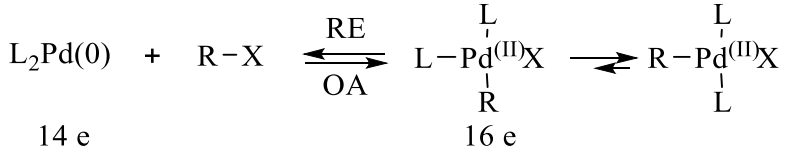


Transformations of Pd(II) complexes

Figure 1.4: A general Pd(0)-catalytic cycle

1.2.1. Oxidative addition and reductive elimination

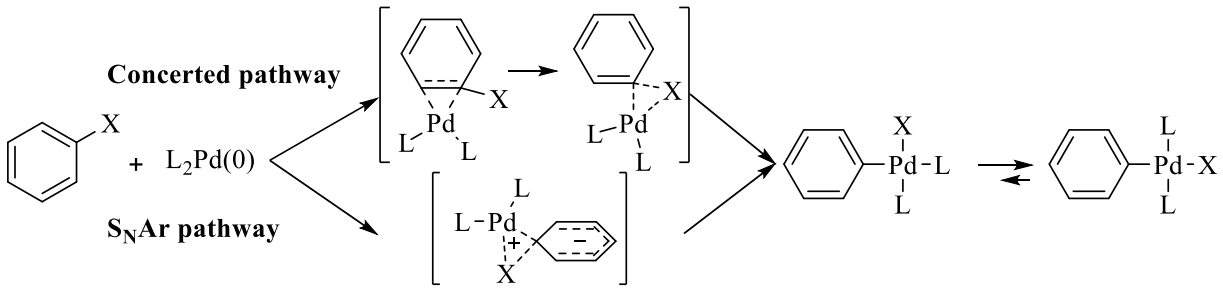
Oxidative addition (OA) and reductive elimination (RE), which are microscopic reverse, are involved in all Pd(0)-catalytic cycles.



Scheme 1.1: Oxidative addition and reductive elimination

The process above describes the oxidative addition of R-X to a Pd(0) center. After OA, both coordination number and oxidative state of metal increase by 2 units. According to the 18-electron rule, Pd(0) with d^{10} configuration requires 8 more electrons to reach the configuration of Xe, thus the coordination number of Pd(0) is four. For the oxidative addition to occur, the metal center must have a lone pair of electrons and a vacant site, that means 16-electron or lower complex is required. For instance, a typical Pd(0) catalyst is $Pd(PPh_3)_4$; before OA can be performed, at least one ligand (PPh_3) must leave to activate the catalyst. As studies have shown, a small amount of $Pd(PPh_3)_2$ was found in equilibrium with $Pd(PPh_3)_3$. The two-coordinated species is more reactive than the three-coordinated complex and plays the main

role in oxidative addition. The highly active 14-electron Pd(0) species then performs OA with the substrate, Pd(0) is oxidized to Pd(II) and the coordination number increases by two units, resulting in a 16-electron square-planar Pd(II) complex, then isomerizes to the more stable *trans* complex. Oxidative addition can undergo through 4 types of mechanisms: concerted, substitution S_N2, radical, or ionic mechanisms. In the case of aryl or vinyl halide (pseudohalide), the mechanism oxidative addition to Pd(0) is widely accepted as concerted pathway for non-polar substrates or substitution *via* S_NAr for polar substrates.[16,17]



Scheme 1.2: Mechanisms of oxidative addition

Noteworthy, when the substrates contain two or more reactive centers for OA, controlling the selectivity of OA is very important to obtained desired products. Generally, the rate of OA for different halogens or pseudohalogens follows this trend: C_{Ar}-I > C_{Ar}-OTf > C_{Ar}- Br >> C_{Ar}-Cl >>> C_{Ar}-F. C_{Ar}-F bonds, on the other hand, is relatively inert for OA. With a same halogen, the electron density and steric effect of substituents around C-X decide the selectivity of the reaction. OA favors less sterically hindered and more electron-positive carbon. For example, by utilizing chemo-selectivity or site-selectivity on 2,3-dihalogenopyridine, different products of cross-coupling reactions can be prepared depending on the synthetic strategy. Since C_{Ar}-Br is more reactive than C_{Ar}-Cl, the first OA takes place at the 3rd position of 3-bromo-2-chloropyridine. However, with 2,3-dibromopyridine, the first OA takes place at the 2nd position which is more electron-positive.[18] Another demonstration is 5,7-dibromo-8-(trifluoromethylsulfonyloxy)quinolone. In this molecule, there are three reactive centers for cross-coupling reactions, for example, Suzuki-Miyaura reaction. Evaluating these three reactive centers, Br^5 and Br^7 are more reactive than OTf and Br^5 is less sterically hindered than Br^7. Therefore, the reactivity order for OA is: C-Br^5, C-Br^7, and finally C-OTf. [19] (figure 1.5)

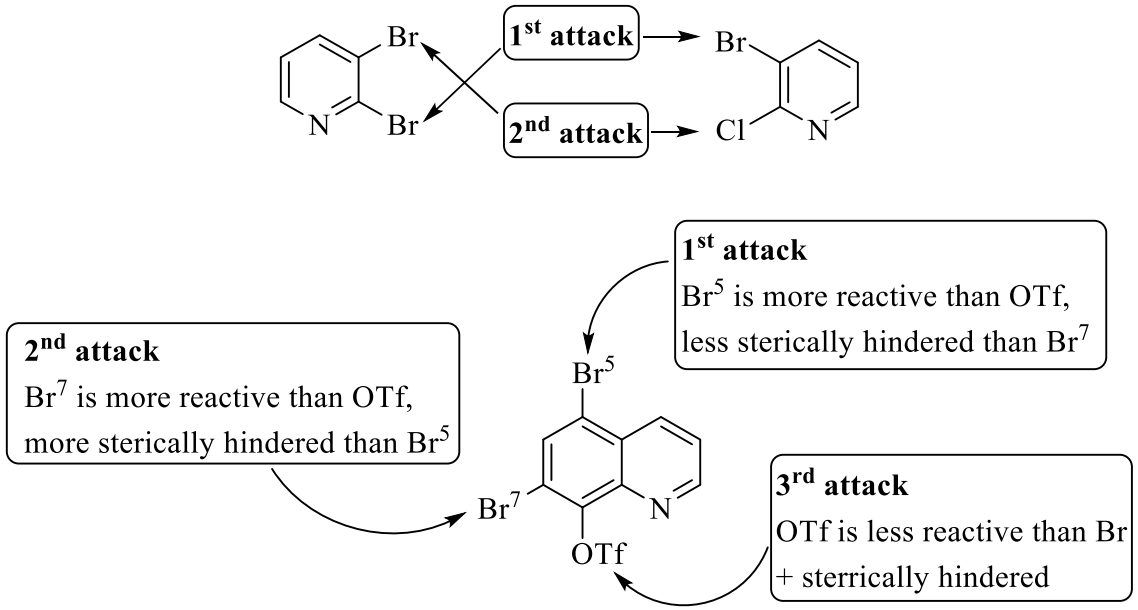


Figure 1.5: Selectivity of oxidative addition on substrates with many reactive centers

Reductive elimination is the reverse of oxidative addition to regenerate Pd(0) catalyst from Pd(II) complex, and in most cases, forms new bond in the product structure. Since RE is the microscopic reverse of OA, RE can run through those mechanisms as OA, however, the most important one is concerted pathway. Moreover, *cis*-coordination of the groups being eliminated is required for RE. Therefore, in order for RE to perform, the *trans* Pd(II) complex must isomerize to *cis* configuration. If a *β*-H is present in the molecular, *β*-hydride elimination may compete with reductive elimination.

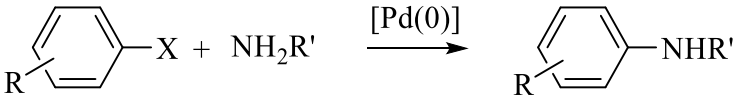
Reductive eliminations which involve H, such as H-H, H-R, H-COR, are particularly fast. Reductive eliminations involving $C(sp^2)$-$C(sp^2)$ bond formation usually take part in cross-coupling reactions such as Suzuki-Miyaura, Negishi, Stills, Kumada, Hiyama couplings. Sonogashira coupling, on the other hand, produces C(sp)-$C(sp^2)$ bond. Representative examples for reductive elimination involving $C(sp^2)$-N or $C(sp^2)$-O bond formation are those of Buchwald-Hartwig reaction.[20]

1.2.2. Reactions of Pd(II) complexes

As mentioned earlier, depending on the nature of nucleophiles interacting with the Pd(II) complex, the catalytic cycle can run in different directions. Most important are ligand substitution, demonstrated in Buchwald-Hartwig reaction, transmetalation in cross-coupling reactions involving an organometallic reagent as the nucleophile, and migratory insertion in Heck-type reactions or carbene insertion. Those transformations and their demonstration in reactions utilized in this dissertation will be the main concern of this section.

Ligand substitution: Buchwald-Hartwig reaction

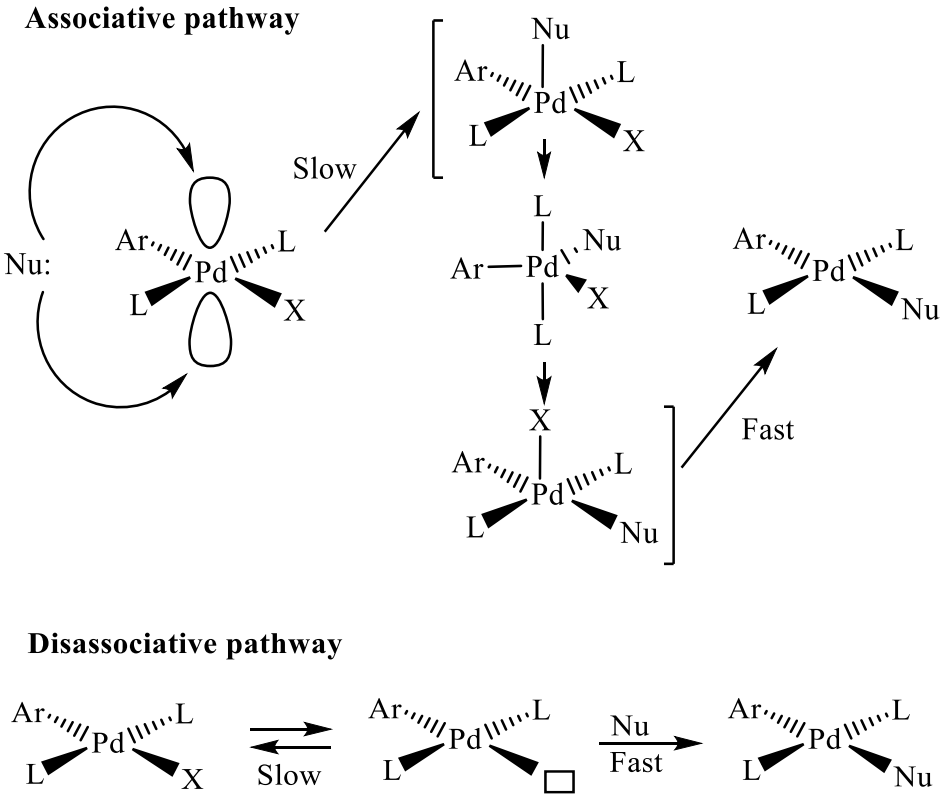
Ligand exchange is an important process for cross-coupling reactions involving C-heteroatom bond formations such as C-N, C-S, C-O, C-P bonds.[21] One of the most important reactions is Buchwald-Hartwig amination, in which amines are employed as nucleophiles.[22]



R = Alkyl, CN, COR,...
R' = Alkyl, Aryl, COR

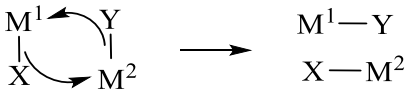
Scheme 1.3: Buchwald-Hartwig reaction

As described previously, the four-coordinated Pd(II) complex formed by OA is a 16-electron square-planar complex. Ligand substitution of Pd(II) complexes can occur *via* two mechanisms: associative pathway or dissociative pathway. In associative pathway, nucleophile forms a penta-coordinated square-pyramidal Pd(II) complex by σ-bonding with empty p_z orbital of Pd. The 18-electron square-pyramidal complex then rearranges the configuration in which the leaving ligand (usually X) is being on the top of the pyramid *via* a trigonal bipyramid intermediate. Finally, the leaving ligand disassociates to form a new square-planar Pd(II) complex. This process can be considered as an analog of S_N2 reaction, in which Pd(II) center is a soft electrophile. However, when the attack of nucleophile is sterically hindered or the formation of penta-coordinated square-pyramidal complex is not favored by energy, ligand exchange prefers *via* dissociative pathway. In this mechanism, the Pd-X bond is fully broken to form a T-shaped intermediate, then the nucleophile attacks to the empty site left by X to form the new square-planar complex. The dissociative pathway is similar to S_N1 reaction. There is no change in oxidation state at the Pd center through ligand substitution.



Scheme 1.4: Mechanisms of ligand exchange

Transmetalation: Suzuki and Sonogashira reaction



Scheme 1.5: Transmetalation

Transmetalation is an irreversible process involving the transfer of ligands from one metal to another. Similar to ligand substitution, there is no change of oxidation state of the metal centers. In this process, Pd(II) is an electrophilic center while R^2-M bond is a nucleophile. Therefore, increasing the nucleophilicity of R^2 and electrophilicity of Pd(II) center accelerate transmetalation. For transmetalation to proceed, Pd must be more electronegative than M. For example, Pd(II) complexes participate in transmetalation with organometallic compounds of metals such as Cu, B, Si, Zn, Al, Sn. Cross-coupling reactions involving transmetalation of different organometallic reagents with Pd(II) complexes are summarized in figure 1.6.[23]

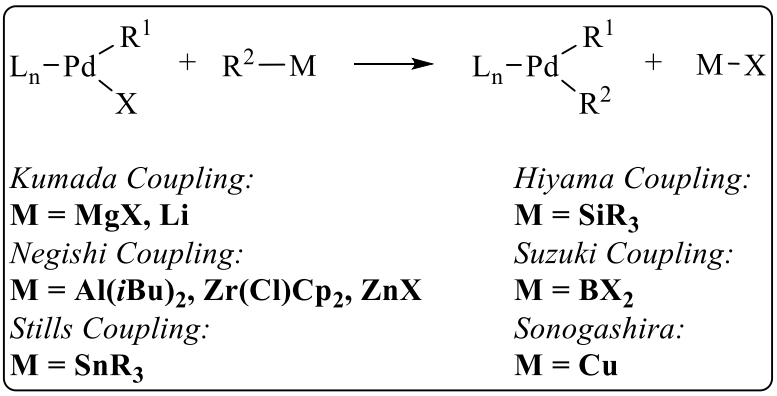
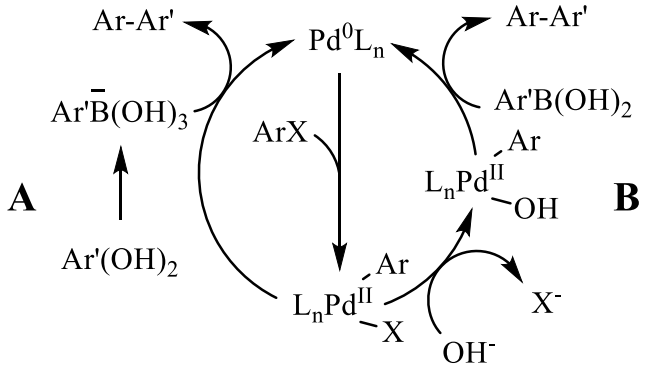


Figure 1.6: Cross-coupling reaction involving transmetalation

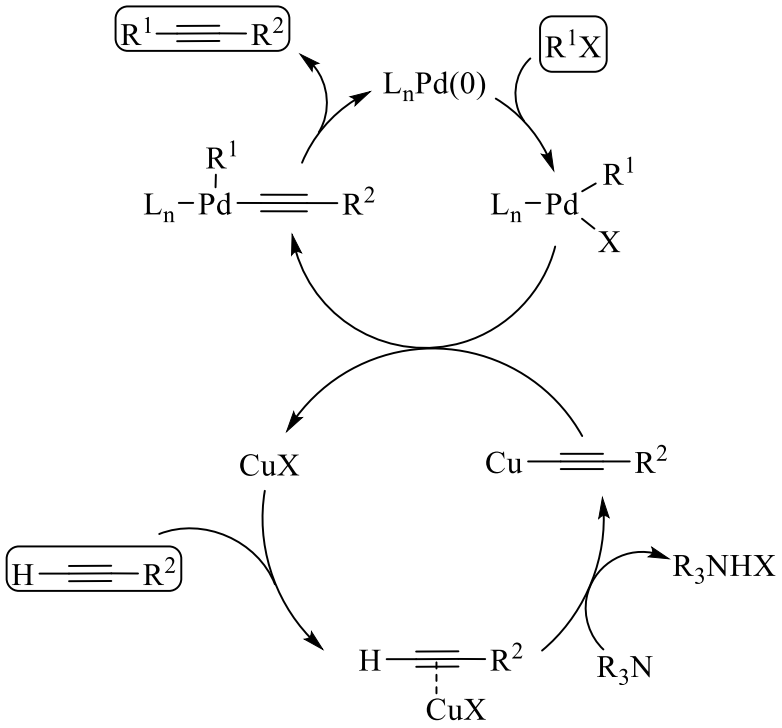
Among them, Suzuki-Miyaura cross-coupling reaction is one of the most popular methods for constructing C(sp2)-C(sp2) bonds.[24] This method employs organoborons as the coupling partner, which are easily accessible, air and moisture stable, less toxic, and safer for environment than other organometallic compounds such as organostannane or organozinc. Since the C-B bond is considered to be highly covalent, R^2BX_2 is a weak nucleophilic reagent. Hence, to promote transmetalation, adding a nucleophile or base is often required to increase the nucleophilicity of B-R^2. In fact, many studies show that, without the presence of base, organoboron compounds do not undergo transmetalation. A nucleophilic base can participate in the reaction by two ways described in scheme 1.6. Following path A, organoboron compound is activated by adding one base to the boron center, which is more readily to undergo transmetalation. In path B, the nucleophilic base replaces X of Pd(II) complex and transforms it to a new Pd(II) complex that is capable of coordinating to the boron center of organoborane. The product of transmetalation then arranges to *cis* configuration for reductive elimination, affording the product and regenerating Pd(0) catalyst.



Scheme 1.6: Roles of base in Suzuki-Miyaura reaction

While Suzuki-Miyaura reaction is widely used for constructing C(sp2)-C(sp2) bonds, Sonogashira reaction is the most convenient method for forming C(sp2)-C(sp) bonds.[14,25] The reaction utilizes organocopper compounds as the coupling partner, generated *in situ* from

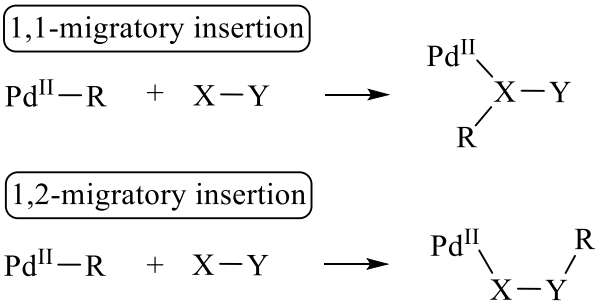
terminal alkyne and CuX in the presence of an amine base. In this reaction, CuX is used as catalytic amount, integrating with Pd cycle as shown in scheme 1.7.



Scheme 1.7: Mechanism of Sonogashira reaction

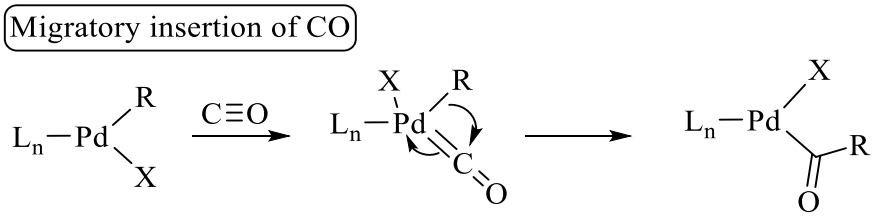
Insertion and elimination: Heck-type reactions and cross-coupling reactions of *N*-tosylhydrazone

In organometallic chemistry, migratory insertion is an inserting process of a ligand to metal complexes which results in bond formation of it with another ligand on the metal complex. By that definition, migratory insertion of a ligand to Pd(II) complex can take place commonly in two main ways: 1,1- and 1,2-migratory insertion. As depicted in scheme 1.8, 1,1-migratory insertion results in bond formation of R with ligand X-Y at the same position with Pd while 1,2- migratory insertion gives bond at the neighboring atom.

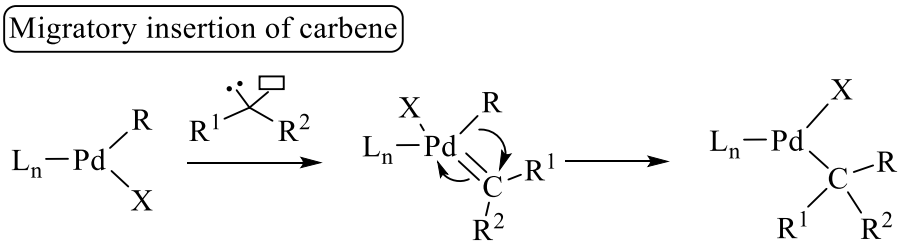


Scheme 1.8: Migratory insertions

Ligands that have both donor and acceptor centers at the same atom usually undergo 1,1-migratory insertion. For example, CO gives 1,1-migratory insertion, in which both Pd and R^1 end up attached to carbon of CO.[26]

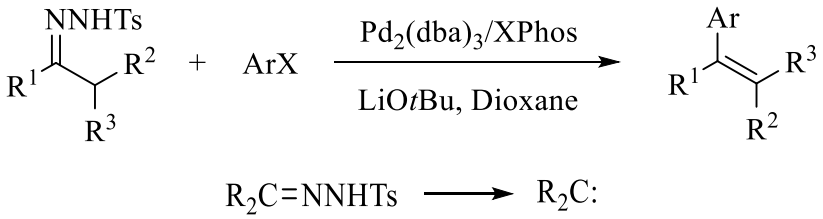


Scheme 1.9: Migratory insertion of CO



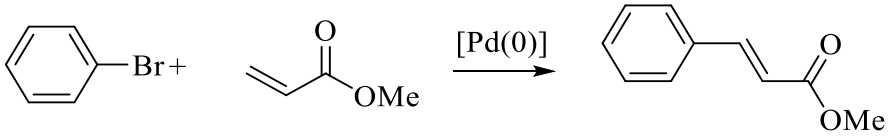
Scheme 1.10: Migratory insertion of carbene

Another important example is the migratory insertion of carbenes R_2C, which possess a lone pair electron that can act as a σ-donor and an empty orbital that can act as an acceptor at carbon atom. Recently, the coupling reactions of aryl halide and diazo compound to synthesize substituted olefins, in which carbene is generated *in situ*, have been attracting a lot of attention.[27–29] Among them, cross-coupling reactions utilizing *N*-tosylhydrazone as the coupling partner have been prove to be efficient to synthesized substituted olefins.[30,31] In this reaction, under the high temperature and in the presence of a base, such as LiO*t*Bu, a carbene is generated *in situ* from *N*-tosylhydrazones.



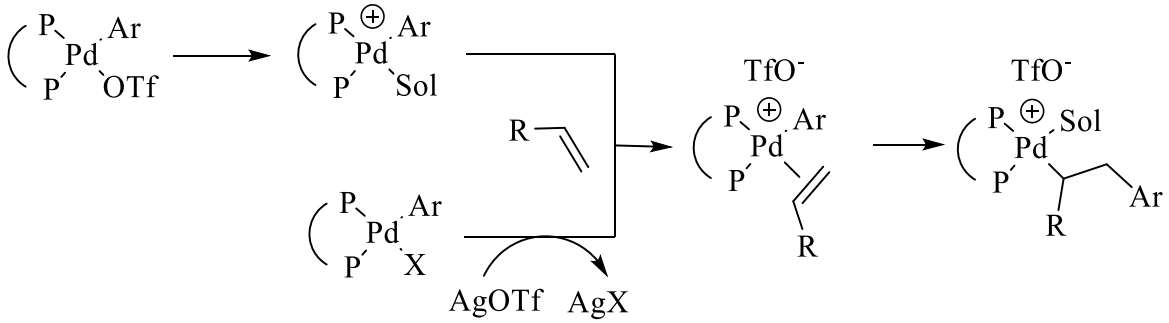
Scheme 1.11: Cross-coupling reaction of *N*-tosylhydrazones involving carbene

On the other hand, 1,2-migratory insertion takes place when η^2-ligands, such as alkenes, react with Pd(II) complexes. A typical example of 1,2-migratory insertion is the insertion of double bond to Pd(II) complexes, an important step in Heck-Mizoroki cross-coupling reaction.[32]



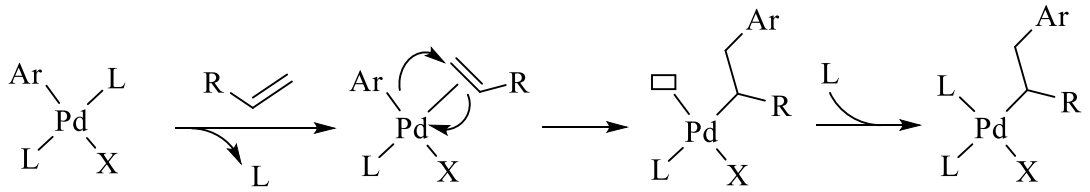
Scheme 1.12: Heck-Mizoroki reaction

Migratory insertion in Heck-Mizoroki reactions can undergo *via* three mechanisms: cationic, neutral, or anionic pathways. Cationic mechanism takes place when Heck reactions of aryl triflates or aryl halides are catalyzed by palladium-diphosphine in the presence of Ag(I) or Tl(I) salts. Dissociation of OTf or X anion leaves Pd(II) center a positive charge and a vacant site, that is attached by the double bond of an alkene. Then migratory insertion of double bond to PdAr proceeds, forming new Pd(II) complex. During migratory insertion, both Pd-P bonds stay intact so the enantioselectivity of the product can be achieved by utilizing chiral diphosphine ligands.



Scheme 1.13: Cationic mechanism of 1,2-migratory insertion

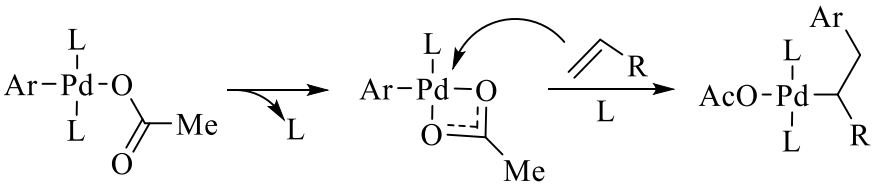
Regularly, without the presence of Ag(I) or Tl(I) salt, migratory insertion of alkenes is considered undergoing neutral pathway. This mechanism involves the dissociation of one neutral ligand (phosphine ligand) to create a vacant site for the coordination of double bond with Pd(II) center, leading to 1,2-migratory insertion of C=C to Ar-Pd.



Scheme 1.14: Neutral mechanism of 1,2-migratory insertion

Recent studies show that the combination of phosphine ligands and $Pd(OAc)_2$ as precatalyst may generate an anionic species $[Pd(L)_2OAc]^-$ for oxidative addition of ArX, in which acetate anion act as a bystander ligand. The product of oxidative addition is believed existing as a penta-coordinated Pd(II) complex, which is short-live and easy to dissociate X^- anion to form neutral *trans*-$ArPd(OAc)L_2$ as the key reactive intermediate. The reaction of this Pd(II) species

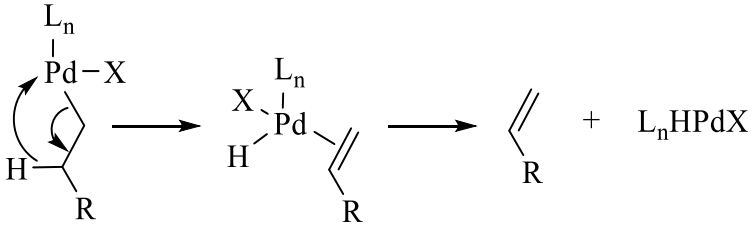
is the rate-determining step of the Heck reactions underwent anionic pathway. Acetate ligand facilitates the dissociation of one phosphine ligand because of its bidentate nature.



Scheme 1.15: Anionic mechanism of 1,2-migratory insertion

In all three mechanisms, product of insertion is *syn*-addition of alkene to PdR. Regiochemistry depends on the mechanism of insertion. Regioselectivity is under the influence of steric factor when the reaction passes *via* neutral Pd complexes, which Ar prefer to attach to less hindered carbon. On the other hand, regioselectivity is governed by electronic factor in mechanisms involving cationic Pd complexes, which Ar favorably bonds with the less electron-density carbon.

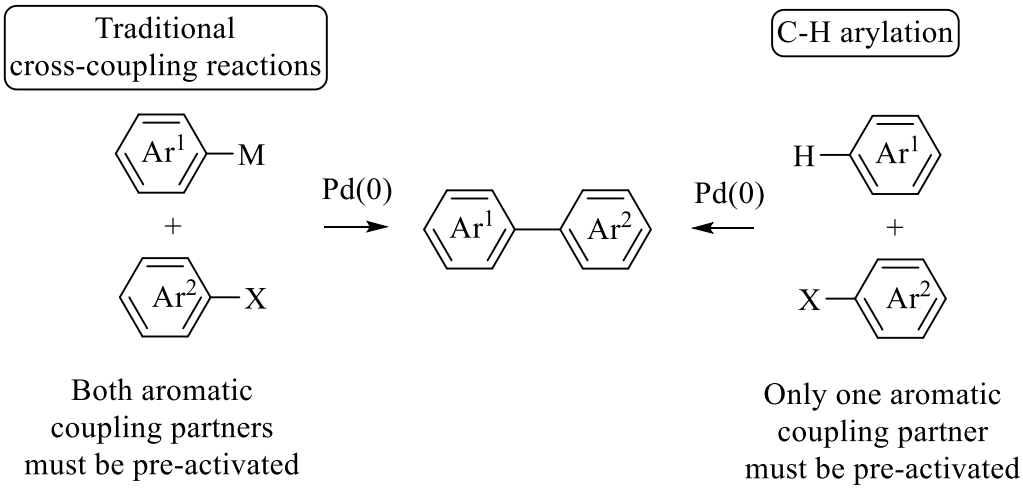
The reverse process of 1,2-migratory insertion, *β*-hydride elimination, is a process in which a metal alkyl is converted to a hydro metal alkene complex. In order for *β*-hydride elimination to process, a vacant site on Pd that is *cis* to the alkyl group is required, and Pd-C-C-H must arrange on a coplanar conformation to bring *β*-H atom close enough to Pd to form an agostic interaction. The Heck reaction is stereoselective for E olefin because the transition state of it is more favored by energy. In addition, Z-configurated olefin, which is the minor product, can react with H-Pd to form thermodynamically more stable E-isomer.



Scheme 1.16: *β*-hydride elimination

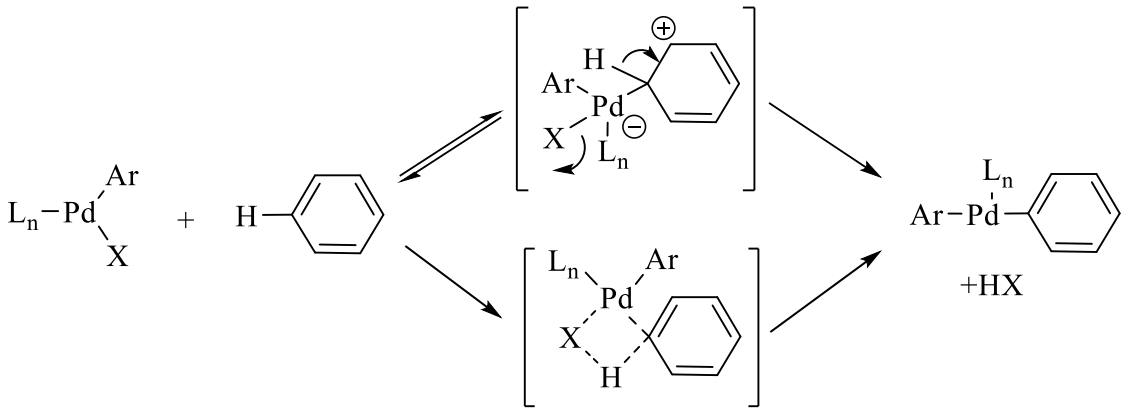
β-Hydride elimination produces olefin and hydridopalladium(II) halide complex, which undergoes reductive elimination to regenerate Pd(0) catalyst.

An analogue of Heck reaction is the direct arylation of aryl halides and arenes without pre-functionalized, affording biaryl compounds. This reaction has many advantages over traditional cross-coupling reactions such as utilizing unactivated arenes instead of pre-functionalized arenes for transmetalation.[33]



Scheme 1.17: C-H arylation vs traditional cross-coupling reactions

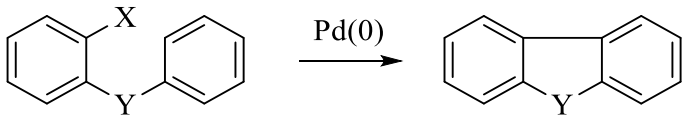
The reaction of Ar[Pd]X with arenes can be considered as electrophilic aromatic substitution S_EAr, Heck-like, or concerted metalation-deprotonation (CMD). Studies have supported that it is reasonable to describe direct arylation of electron-rich, π-nucleophilic heteroarenes as S_EAr and that of electron-deficient benzenes as CMD.



Scheme 1.18: Mechanisms C-H arylation

Owning to the fact that there might be more than one C-H site in the structure of arene, more than one biaryl products could be formed. In general, considering CMD pathway, the more acidic the C-H bond, the more active it is in C-H activation reaction. On the other hand, the Heck-like pathway favors the more stable intermediate, in which the positive charge is more stabilized. Moreover, a strategy to achieve selectivity is to employ directing groups. Normally, directing groups can coordinate to the Pd center, therefore limit it to a certain geometry, which can selectively reach to the desired C-H site. For example, ester, amide, carbamate, nitro can be used as directing groups, in which the *ortho* C-H to the directing group is usually the reacting site. After the reaction, directing groups can be removed or transform to other functional groups.[34]

Furthermore, intramolecular direct arylation is often utilized in constructing aromatic polyheterocyles due to its convenience, which is important in developing synthetic methods in this dissertation.[35]



X = Hal
Y = O, S, NMe, CH_2, OCH_2, OCH_2CH_2,...

Scheme 1.19: Intramolecular direct arylation

1.2.3. Effects of ligands: Phosphine ligands

Ligands are usually used in combination with Pd catalyst to achieve selectivity and reactivity. In oxidative addition, Pd center of Pd(0) complexes acts as a nucleophile. Strong σ-donating ligands such as alkyl phosphines and carbenes increase electron density at the Pd(0) center; hence, facilitate oxidative addition. On the other hand, strong π-acceptor ligands such as CO, however, slow the process down. Bulky ligands help pushing the equilibrium of Pd(0) complexes to the two-coordinated 14-electron complex, or in some cases, generating monoligated 12-electron complexes, which are highly active for OA. Bulky ligands also force other ligands close together to facilitate reductive elimination. The Pd center of Pd(II) complexes, on the other hand, is electrophilic and should be sterically accessible for the incoming nucleophiles. Therefore, controlling the electronic and steric properties of ligands is crucial for optimizing reaction conditions. In this dissertation, phosphine ligands were mainly employed because of their availability and many advantages.

Phosphine ligands R_3P, known as σ-donating and weak π-accepting ligands (d to σ* of P-R), are widely used in Pd(0)-catalyzed cross-coupling reaction because they could be conveniently synthesized in series. Furthermore, their electronic and steric properties could be modified systematically and predictably by changing R. In addition, phosphines normally exist in crystal form, are air and thermal stable. Therefore, they are easy to handle and stable under a wide range of reaction conditions. Notably, in 1998, Fu reported a series of bulky, electron-rich phosphines, such as $P(t\text{Bu})_3$ and PCy_3, used in combination with Pd(0) precatalysts to produce biaryls from unactivated chloroarenes and arylboronic acid in good yield.[36] At about the same time, Buchwald also reported comparable results with the discovery of dialkyl biaryl phosphine ligands.[37] Those ligands have been applying widely in Pd(0)-catalyzed C-C, C-N, C-O bond-forming reactions.[38]

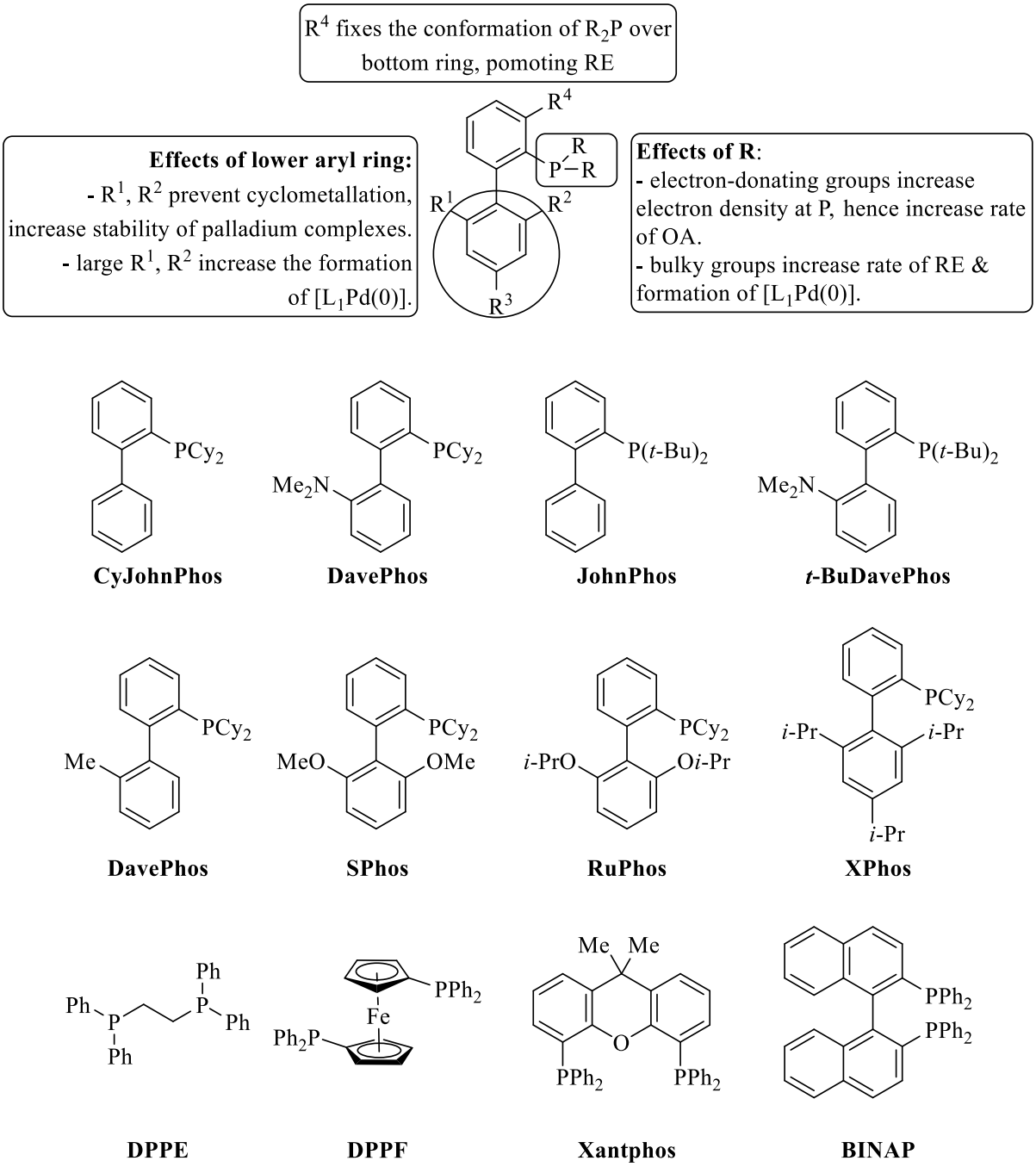


Figure 1.7: Phosphine ligands

Moreover, Beller showed that turnover numbers of Suzuki-Miyaura couplings of unactivated and deactivated chloroarenes could be achieved at 20000 when di-(1-adamanyl)-*n*-butylphosphine (cataCXium® A) is used as the ligand.[39] Bulky ligands are believed to promote the formation of highly active monoligated 12-electron Pd(0) catalyst.[40]

In addition, diphosphines such as $Ph_2P(CH_2)_nPPh_2$, which are bidentate ligands, also play an important role in Pd-catalyzed reactions. This type of ligands force Pd(II) complexes to the *cis* arrangement which accelerate both OA and RE. Bite angle is an important parameter regarding bidentate ligands and easily modified combining with steric effect of substituents. Many studies

have shown that bidentate ligands with large bite angles have an impact on selectivity and reactivity of the reaction.[41]

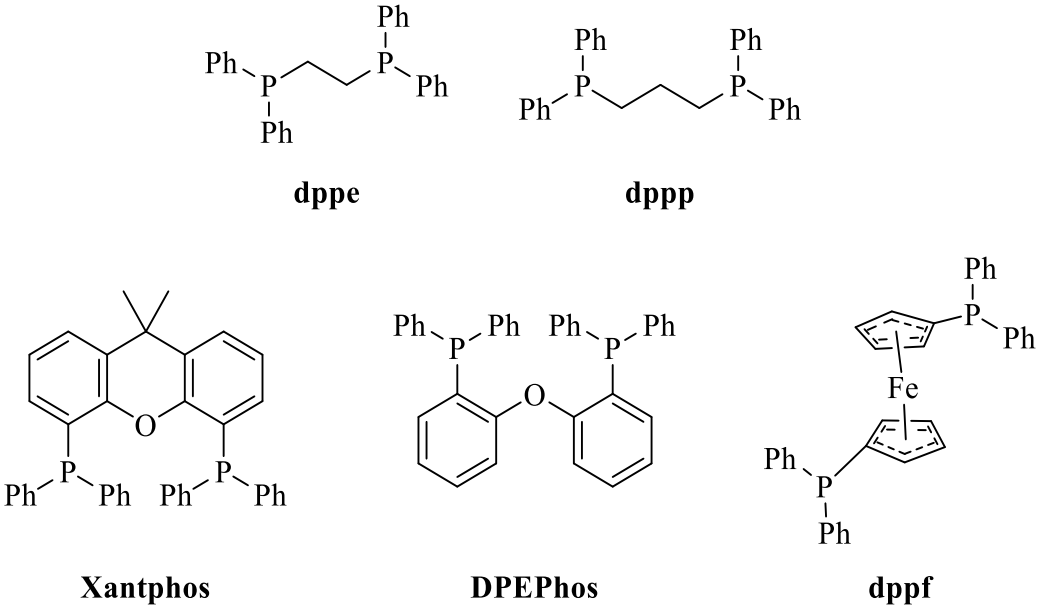


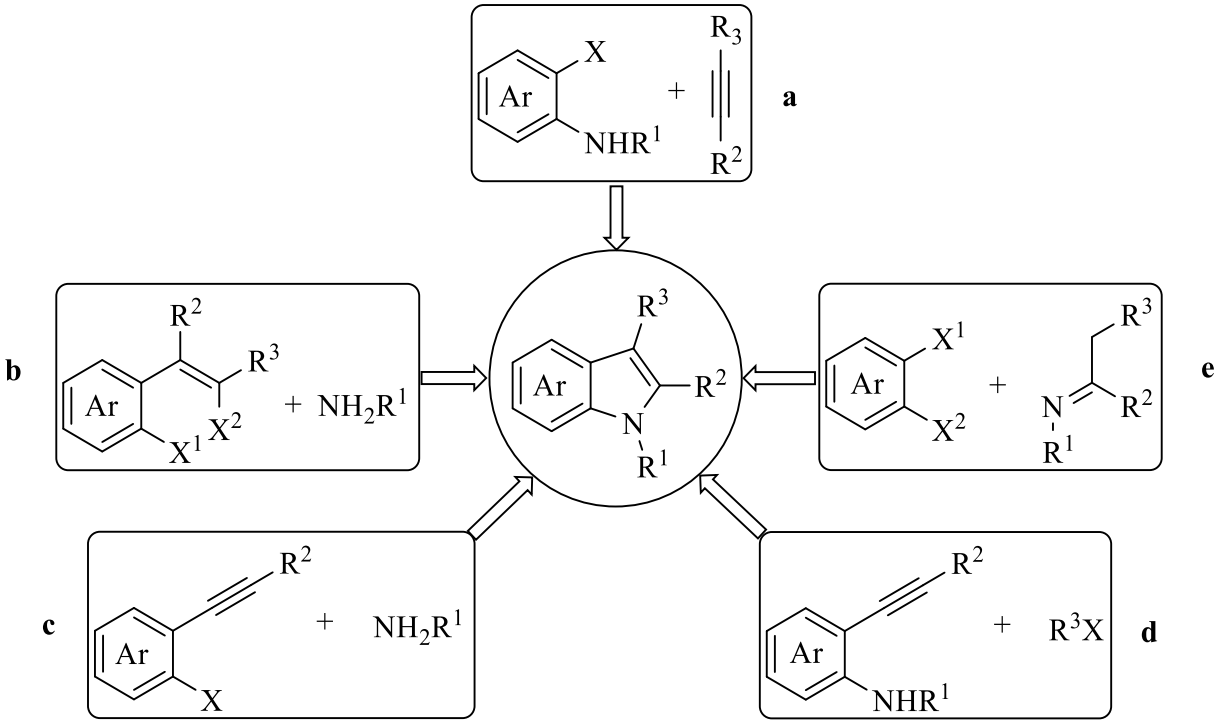
Figure 1.8: Diphosphine ligands

1.3. Palladium(0)-catalyzed domino reactions in constructing important heterocycles

Among synthetic approaches, methods that involve one-pot multistep reactions have been proved to be effective, in which two or more reactions are carried out continuously without isolating the intermediates. One-pot reactions bring several advantages over stepwise reactions such as reduction in time, cost, and waste production. They help approaching complex structures via more effective and shorter pathways, which are favored in industrial applications. In particularly, if the reaction proceeds through many steps under the same reaction conditions without adding additional reagents, the terms domino, cascade, tandem, or sequential catalysis are used. Domino reactions can be classified as cationic, anionic, radical, pericyclic, transition metal catalyzed, or enzymatic domino reaction.[42] Benefiting from the advance of transition metal catalyzed reactions, especially Pd(0)-catalyzed reactions, a great number of Pd(0)-catalyzed domino or one-pot reactions have been developed, providing practical tools for construction of heteroaromatic systems.[43] Pd(0)-catalyzed domino reactions could be seen as continuous Pd(0) catalytic cycles promoted by a single catalytic system. Some notable examples will be discussed in following parts to demonstrate their utility.

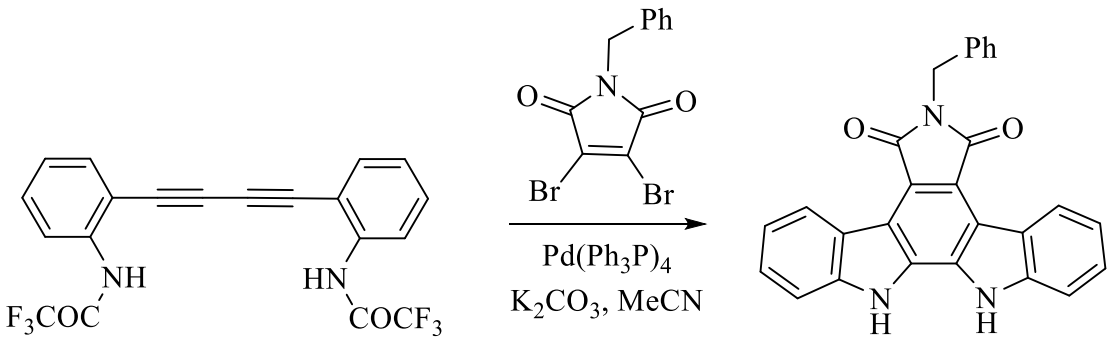
One of the most important class of compounds which is present widely in biologically active and naturally occurring compounds are indoles and indole-based structures.[44] In the past, indoles were prepared by Fisher synthesis from phenylhydrazine and aldehyde or ketone

under acidic conditions. However, phenylhydrazine is very toxic, and the Fisher's conditions are somehow harsh. Later a lot of modifications have been studied to improve Fisher synthesis,[45] such as Buchwald modification, in which involves Pd-catalyzed cross-coupling of aryl bromide and hydrazones.[46]



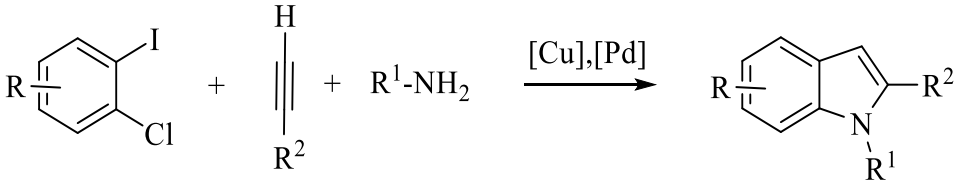
Scheme 1.20: Approaches to the synthesis of indoles by Pd(0)-catalyzed domino reactions:

Recently, many convenient methods based on Pd(0)-catalyzed domino reactions have been developed for the synthesis of indoles.[47] Among them, Larock's method has proved to be superior (**a**, figure 1.9).[48] The domino reaction initiates by oxidative addition of 2-halogenoaniline to form Pd(II) species, followed by regioselective insertion of alkyne to the Pd(II) center, and subsequent intramolecular palladium displacement by amino group, affording 2,3-disubstituted indoles in good yields. A similar strategy starting from *ortho*-alkynyltrifluoroacetanilides and aryl halides was reported by Cacchi (**d**).[49] The methodology was well demonstrated in synthesizing the complex structure of indolo[2,3-*a*]carbazole in a single step from 1,3-diaceylene precursor.[50]



Scheme 1.21: Synthesis of indolo[2,3-*a*]carbazoles by Cacchi

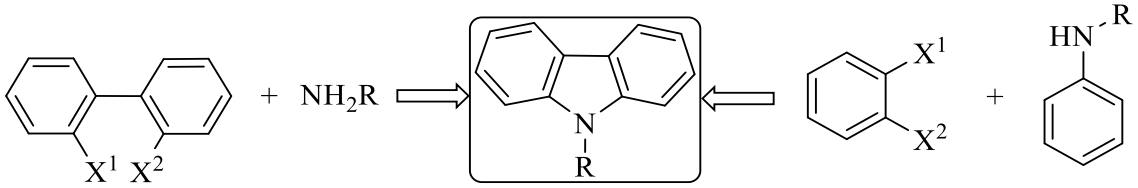
Starting from *ortho*-alkynylhalogenoarenes, Ackermann has combined Buchwald-hartwig amination and intramolecular hydroamination to synthesize 2-substituted indoles with excellent yields. Moreover, *ortho*-alkynylhalogenoarenes are easily obtained by Sonogashira reaction of *ortho*-dihalogenoarenes and terminal alkynes (**c**).[51] Later, Ackemann has reported an improvement that started straightforward from *ortho*-dihalogenoarenes, terminal alkyenes, and amines in a one-pot three-component reaction.[52]



Scheme 1.22: Synthesis of indoles by one-pot three-component reaction by Ackemann

In addition, recently methods are also worth mentioning, for example, strategies that employ aryl and alkenyl C-N bond formation (**b**)[53] or subsequently C-C and C-N bond formation from imines and *ortho*-dihaloarenes (**e**).[54]

Furthermore, an important class of compounds derived from indole ring is carbazoles, which are found in many natural alkaloids and some of them possess potential bioactivity.[55] Carbazoles can be synthesized efficiently by Pd(0)-catalyzed domino reaction, for instance, two-fold C-N bond formation by Buchwald-Hartwig reaction[56] or C-N and C-C bond formation by subsequent Buchwald-Hartwig and C-H arylation reactions.[57]



Scheme 1.23: Approaches to the synthesis of carbazoles

1.4. The aim of dissertation

Motivated by the importance of aromatic heterocycles, the aim of this dissertation is to develop new and convenient approaches for important or new aromatic heterocycles, mainly nitrogen-containing. Compounds targeted in this work are potential for drug discovery and advanced materials. Regarding biologically active compounds, the structures based on natural products, which possess highly therapeutic activity, and drugs or novel drug candidates will be explored. For discovering new organic material, aromatic polyheterocyclic compounds, which have been proved to be crucial in advanced materials, will be the spotlight.

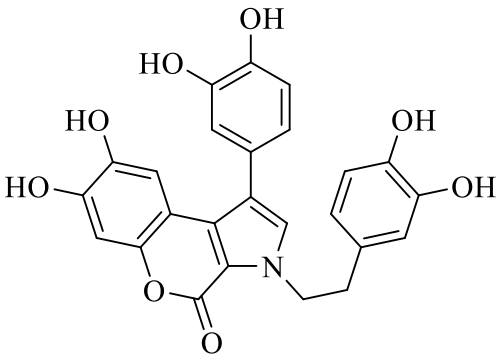
The synthetic methods developed for desired compounds are aiming to be convenient and practical. My strategy is based on the selectivity of Pd(0)-catalyzed reactions of easily accessible starting materials to set up the precursors with desired active centers for further domino reactions. The precursors then will be converted to target molecules by designed Pd(0)-catalyzed domino reactions. This strategy will be demonstrated throughout chapter 2 to chapter 4. Chapter 5 is about domino reactions of dianions for the synthesis of fluorinated compounds.

In addition, selected synthesized compounds will be submitted to biological studies in collaboration with the group of Dr. Jamshed Iqbal (Centre for Advanced Drug Research, COMSATS Institute of Information Technology, Abbottabad, Pakistan). And compounds with potential application in developing advanced materials will be examined physical properties in collaboration with the group of Prof. Stefan Lochbrunner (Institut für Physik, Universität Rostock).

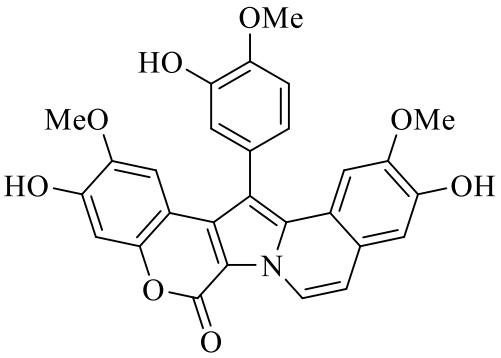
2. Synthesis of pyrrolocoumarins via palladium(0)-catalyzed domino C-N coupling/hydroamination reactions

2.1. Introduction

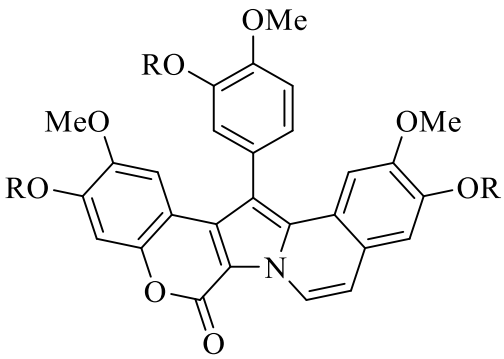
Pyrrolocoumarin is a privileged scaffold formulated from coumarin moiety fused with a pyrrole unit which widely occurs in biologically active compounds. Notably, chromeno[3,4-*b*]pyrrol-4(3*H*)-one, recognized as the core structure in molecules of marine alkaloids ningalin B[58] and lamellarin,[59,60] exhibits potent pharmacological properties such as immunomodulatory activity, cytotoxicity,[60] and HIV-1 integrase inhibition.[61] Some of them are novel drug candidates or lead compounds for drug discovery. For example, synthetic modification of lamellarin D leads to a series of Topoisomerase 1 inhibitors.[62]



Ningalin B



Lamellarin D

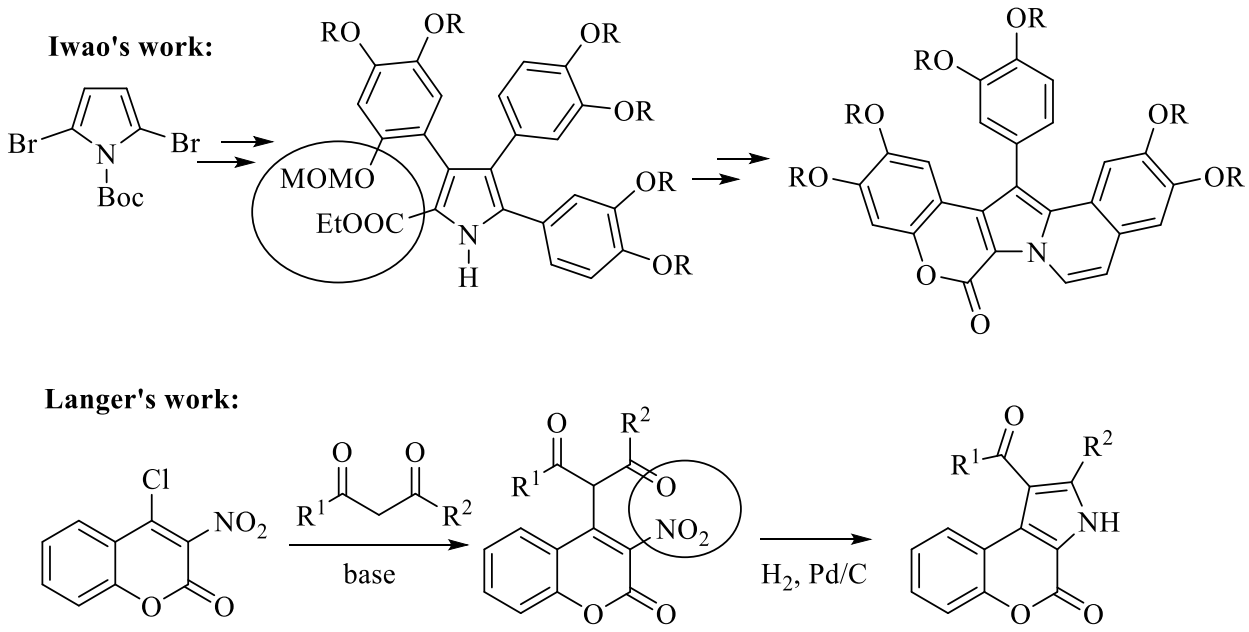


R= H, $COCH_3$, SO_2CH_3, $COCH_2CH_2Ph$,

Figure 2.1: Ningalin B and Lamellarin D derivatives

The diversity of their bioactivities has motivated many researches to develop efficient synthetic routes for constructing the chromeno[3,4-*b*]pyrrol-4(3*H*)-one subunit. Generally, there are two main strategies for the synthesis of this unique scaffold.[63] Firstly, synthesis of chromeno[3,4-*b*]pyrrol-4(3*H*)-ones can be derived from regioselectively constructing functionalized pyrrole moiety, following by lactonizing to afford the desired structure. This

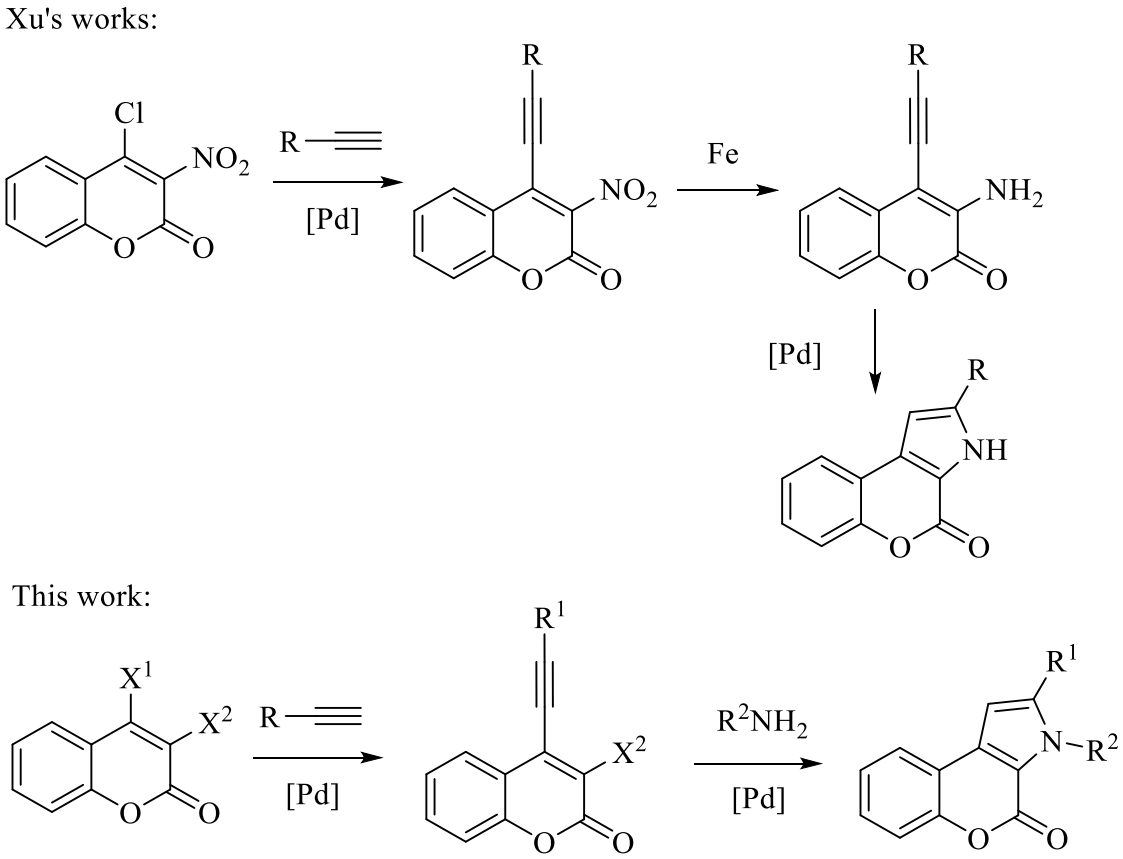
approach is effectively demonstrated in the works of Iwao.[64] The second approach originated from isoquinolines as starting materials.[65] Recently, synthesis of chromeno[3,4-*b*]pyrrol-4(3*H*)-ones starting from coumarins has attracted a lot of attention. For example, Langer group has reported a new approach to this scaffold by cyclocondensation reactions of 1,3-dicarbonyl compounds with 4-chloro-3-nitrocoumarin.[66]



Scheme 2.1: Synthesis of chromeno[3,4-*b*]pyrrol-4(3*H*)-ones

Moreover, catalytic hydroamination of alkynes has recently become a valuable synthetic tool in the synthesis of fused nitrogen-containing heterocycles. Several catalytic systems have been utilized for this type of cyclization such as palladium, gold, mercury, copper, zinc, rhodium, platinum, indium, and iridium salts.[67] Among them, Pd(II) has been proved its versatility. For example, Xu and co-workers reported an elegant approach to pyrrolocoumarins by Pd-catalyzed intramolecular hydroamination of acetylenic aminocoumarins obtained from 4-chloro-3-nitrocoumarin.[68] Interestingly, Ackermann reported that the combination of Pd(0)-catalyzed Buchwald-Hartwig amination and intramolecular hydroamination of *o*-alkynylanilines with amines works harmoniously to form pyrrole-fused systems.[51,69] Considering this strategy, I believe that it is plausible to obtain the pyrrolocoumarin framework starting from a *ortho*-dihalogenated coumarin, following by mono-Sonogashira coupling reaction to obtain key intermediate *o*-alkynyl bromocoumarin. The key step then relies on forming fused-pyrrole ring via palladium catalyzed sequential C-N coupling/intramolecular hydroamination of *o*-alkynyl bromocoumarins with amines. After reviewing many reported synthetic approaches, I found that 3-bromo-4-(trifluoromethanesulfonyloxy)coumarin **2.3**

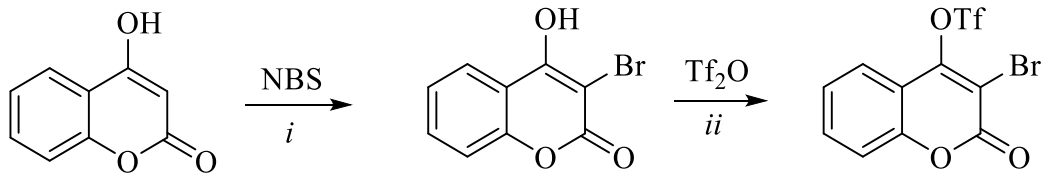
would be the most suitable educt for synthesizing various analogues of pyrrolocoumarin (scheme 2.3).



Scheme 2.2: Synthesis of chromeno[3,4-*b*]pyrrol-4(3*H*)-ones by hydroamination

2.2. Synthesis of chromeno[3,4-*b*]pyrrol-4(3*H*)-ones

Starting from commercially available 4-hydroxycoumarin **2.1**, bromination was carried out in MeCN at 20 °C by using NBS, affording brominated product **2.2** after 45 minutes with 91% yield. 3-Bromo-4-hydroxycoumarin **2.2** was then easily transformed into its corresponding triflate **2.3** by using triflic anhydride in dry DCM. Interestingly, the yield raised up from 55% to 80% by reducing the temperature to -20 °C compared to 0 °C of the originally published procedure (Scheme 2.3).[70]

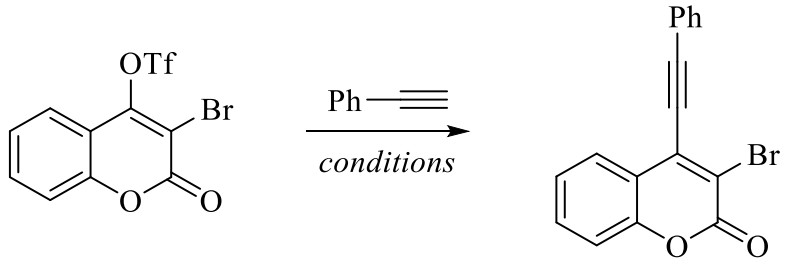


2.1 **2.2 (91%)** **2.3 (80%)**

Scheme 2.3: Synthesis of 3-bromo-4-(trifluoromethanesulfonyloxy)coumarin. *Conditions*: *i,* NH_4OAc, MeCN, 45 min, 20 °C. *ii,* **1** (1 equiv.), Tf_2O (1.2 equiv.), Et_3N (3 equiv.), CH_2Cl_2, -20 °C to 20 °C.

Then, the selective Sonogashira cross-coupling reaction of 3-bromo-4-(trifluoromethanesulfonyloxy)coumarin **2.2** with phenylacetylene was studied as the model reaction. Since C-OTf is more favored than C-Br in Sonogashira reaction plus the C4 is more electron-positive than C3, the mono-coupling is expected at C4-OTf. At the first attempt, the general procedure using $Pd(PPh_3)_2Cl_2$/CuI in THF at room temperature (20 °C) was applied, but the result was disappointing with only 7% yield of isolated product yield (entry 1, table 2.1). Only trace of product was detected when $Pd(PPh_3)_4$ was used as the catalyst (entry 2 and 3, table 2.1). After studying various conditions, $Pd(CH_3CN)_2Cl_2$ proved to be the best catalyst for this reaction so far. The reaction proceeded smoothly in NEt_3/DMF (3:2) at room temperature catalyzed by 5% of $Pd(CH_3CN)_2Cl_2$ and 10% CuI in 75% yield (entry 7, table 2.1). DMF must be added to overcome the low solubility of **2.3** in NEt_3. Other attempts to raise the temperature or to change the catalyst resulted in poor yields.

Table 2.1: Optimization for the synthesis of **2.4a**



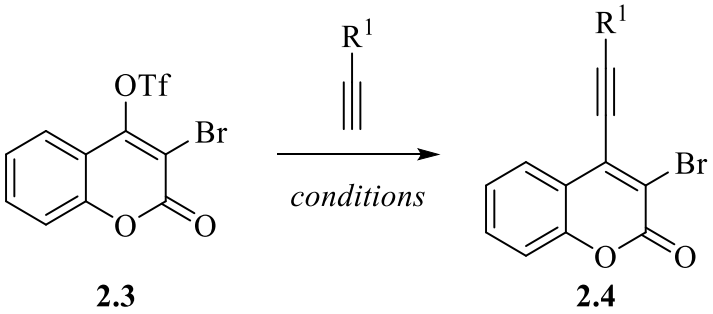
2.3 **2.4a**

No.	**Catalyst** (5 mol%), CuI (10%)	**Base**	**Solvent**	**Time (h)**	**Yield (%)**
1	$Pd(PPh_3)_2Cl_2$	NEt_3	THF	4	**7**
2	$Pd(PPh_3)_3$	NEt_3	THF	4	trace
3	$Pd(PPh_3)_4$	NEt_3	CH_3CN	4	trace
4	$Pd(PPh_3)_2Cl_2$	NEt_3	CH_3CN	4	15
5	$Pd(PPh_3)_2Cl_2$	NEt_3	DMF	4	23
6	$Pd(PPh_3)_2Cl_2$	DIPEA	DMF	4	20
7	$Pd(CH_3CN)_2Cl_2$	NEt_3	DMF	2	75

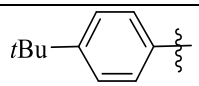
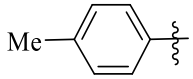
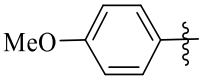
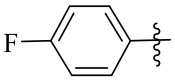
Conditions: **2.3** (1 equiv.), alkyne (1.2 equiv.), NEt_3/DMF (3:2), 20 °C

Applying the optimized conditions, I prepared various alkynylated coumarins **2.4b-g**. Both aromatic and aliphatic alkynes could be employed to achieve desired products (Table 2.2).

Table 2.2: Synthesis of **2.4**



2.3 **2.4**

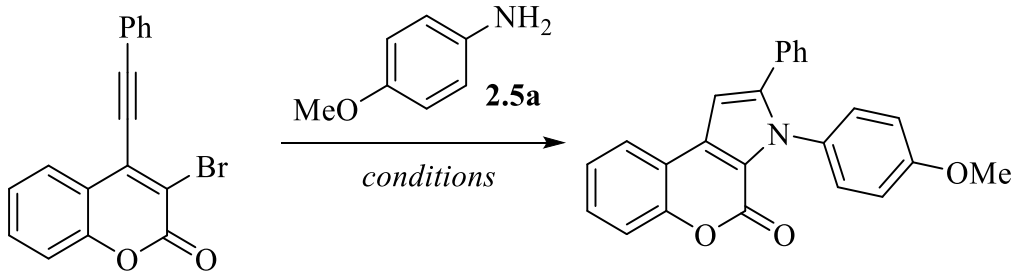
2.4	**R^1**	**Yield (%)**
b		56
c		22
d		53
e		41
f	$CH_3(CH_2)_2$-	47
g	$CH_3(CH_2)_3$-	45

Conditions: **2.3** (1 equiv.), alkyne (1.2 equiv.), $Pd(CH_3CN)_2Cl_2$ (5% mol), CuI (10 % mol), NEt_3/DMF (3:2), 20 °C, 2 h.

With the alkynylated coumarins in hand, the reaction of alkynylated coumarins **2.4** with amines **2.5** affording pyrrolocoumarins **2.6** was investigated. Compound **2.4a** and 4-methoxyaniline were firstly used as model substrates for the optimization of the reaction conditions. During the studies, it became apparent that strong bases, such as NaO*t*Bu or KO*t*Bu, should be avoided, because of decomposition of the coumarin ring under these conditions. Therefore, mild inorganic bases, such as Cs_2CO_3, K_2CO_3, and K_3PO_4, were utilized. The reaction was first studied in toluene as the solvent using $Pd(OAc)_2$ (5%) as the catalytic source and different phosphine ligands (10%). It is important to note that we could only obtain the desired product, albeit in only 12% yield when SPhos (2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl) was used as the ligand and Cs_2CO_3 as the base (entry 4, table 2.3). However, the yield could be improved when DMF or DMA was used as the solvent. The best result (64% yield) was obtained when the catalyst loading was increased to 10% and CuI (20%) was used as an additive (entry 14, table 2.3). The role of CuI might be to promote the hydroamination step. The use of CuI as the catalyst in combination with ligands

also resulted in the formation of the product as well, however, only in 23% yield (entry 15, table 2.3).

Table 2.3: Optimization of **2.6a**



2.4a **2.6a**

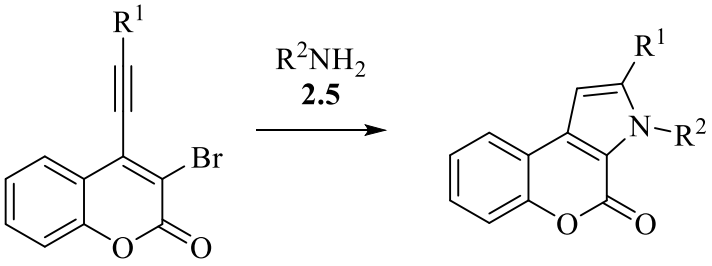
No.	Catalyst (5%)	Ligand (10%)	Base	Solvent	Temp. (°C)	Time (h)	Yield (%)
1	$Pd(OAc)_2$	XantPhos[a]	Cs_2CO_3	Toluene	110	8	-
2	$Pd(OAc)_2$	$(t\text{Bu})_3P\cdot HBF_4$	Cs_2CO_3	Toluene	110	8	-
3	$Pd(OAc)_2$	Cy_3P	Cs_2CO_3	Toluene	110	8	-
4	$Pd(OAc)_2$	SPhos	Cs_2CO_3	Toluene	110	8	12
5	$Pd(OAc)_2$	XPhos	Cs_2CO_3	Toluene	110	8	5
6	$Pd(OAc)_2$	SPhos	K_3PO_4	Toluene	110	8	-
7	$Pd(OAc)_2$	SPhos	K_2CO_3	Toluene	110	8	-
8	$Pd(OAc)_2$	XPhos	K_3PO_4	Toluene	110	8	-
9	$Pd(OAc)_2$	XPhos	K_2CO_3	Toluene	110	8	-
10	$Pd(OAc)_2$	SPhos	Cs_2CO_3	DMF	110	2	39
11	$Pd(OAc)_2$	SPhos	Cs_2CO_3	DMA	110	2	35
12	$Pd(OAc)_2$	SPhos	Cs_2CO_3	DMSO	110	8	-
13	$Pd(OAc)_2$[c]	SPhos[b]	Cs_2CO_3	DMF	80	4	52
14	$Pd(OAc)_2$[c] CuI[b]	SPhos[b]	Cs_2CO_3	DMF	80	4	64
15	CuI[c]	1,10-phenantroline[b]	Cs_2CO_3	DMF	110	8	23

16	CuI[c]	1*H*-Benzotriazole-1-methanol[b]	Cs_2CO_3	DMF	110	8	15
17	CuI[c]	1,2-DMEDA[b]	Cs_2CO_3	DMF	110	8	17
18	CuI[c]	TMEDA[b]	Cs_2CO_3	DMF	110	8	11

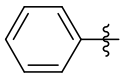
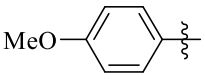
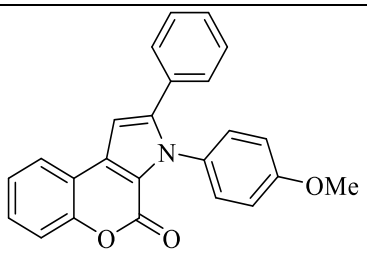
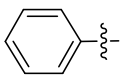
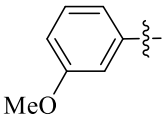
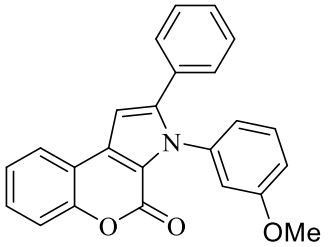
Conditions: **2.4a** (0.1 mmol, 1 equiv.), **2.5a** (0.12 mmol, 1.2 equiv.), base (0.25 mmol, 2.5 equiv.), solvent 2 mL
[a]5%, [b]20%, [c]10%

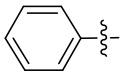
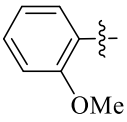
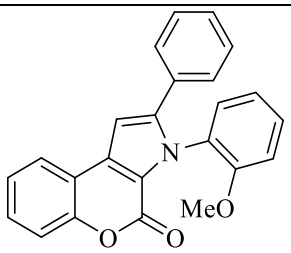
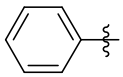
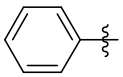
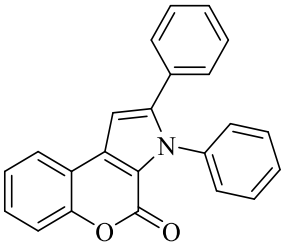
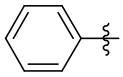
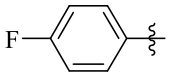
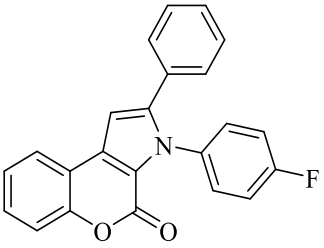
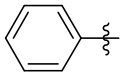
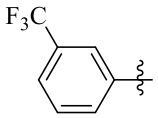
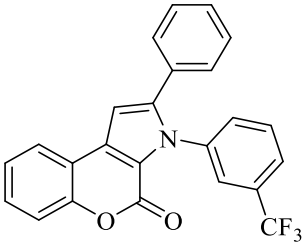
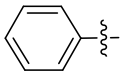
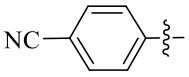
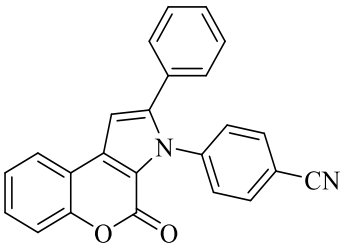
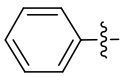
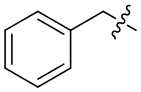
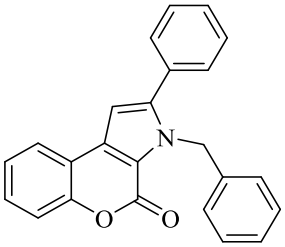
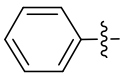
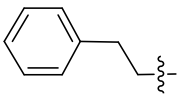
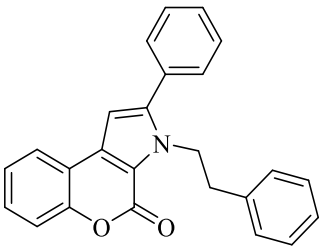
With the optimized conditions in hand, we extended the scope of the reaction to synthesize a series of pyrrolocoumarins **2.6b-q** using various amines (Table 2.4). The employment of anilines containing electron donating substituents (more nucleophilic) generally resulted in better yields than of anilines containing electron withdrawing groups. No product was isolated from 4-nitroaniline. Aliphatic amines were successfully employed in the reactions, affording desired products in good yields.

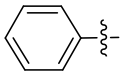
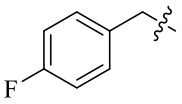
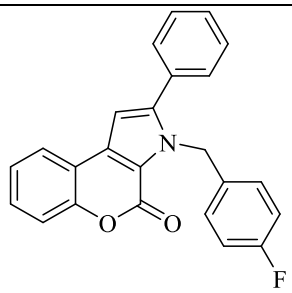
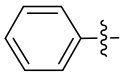
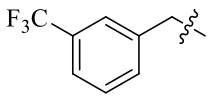
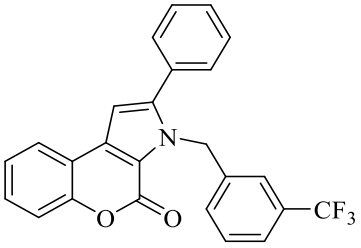
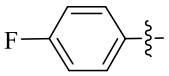
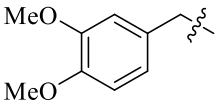
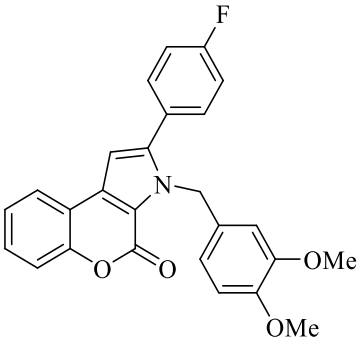
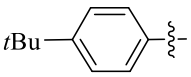
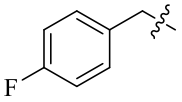
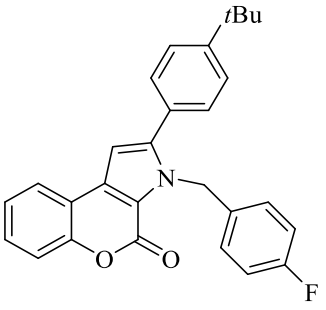
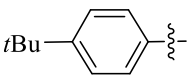
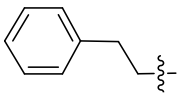
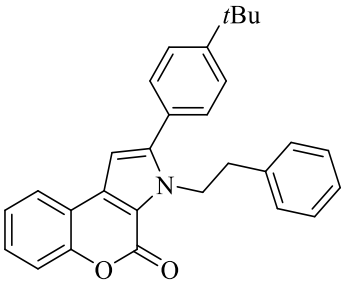
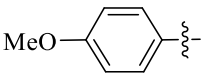
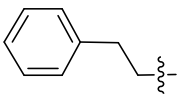
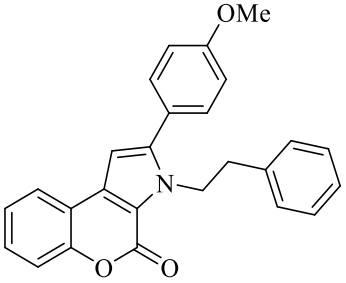
Table 2.4: Synthesis of chromeno[3,4-*b*]pyrrol-4(3*H*)-ones

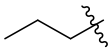
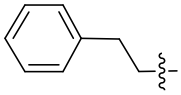
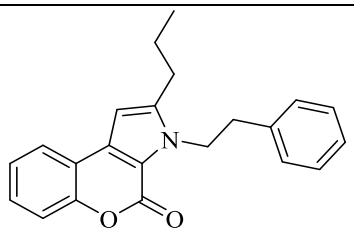
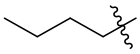
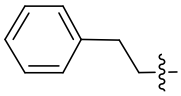
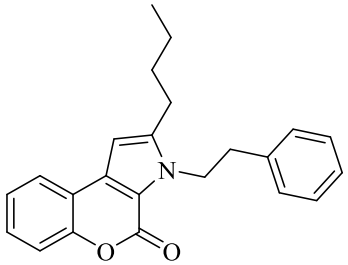
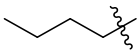
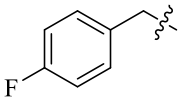
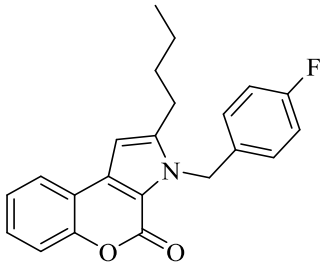


2.4 **2.6**

Compound	R^1	R^2	Structure	Yield (%)
2.6a				64
2.6b				47

2.6c				61
2.6d				52
2.6e				41
2.6f				35
2.6g				40
2.6h				82
2.6i				76

2.6j				61
2.6k				46
2.6l				57
2.6m				47
2.6n				65
2.6o				69

2.6p				62
2.6q				65
2.6r				51

Conditions: **2.4a-g** (0.2 mmol, 1 equiv.), R'NH_2 (0.24 mmol, 1.2 equiv.), $Pd(OAc)_2$ (0.02 mmol, 10 mol%), SPhos 0.04 (mmol, 20 mol%), Cs_2CO_3 (0.5 mmol, 2.5 equiv.), DMF (4 mL), 80 °C, 4 h.

The structures of all products were confirmed by spectroscopic methods. The structure of **2.6j** was independently confirmed by X-ray crystal structure analysis (Figure 2.2).

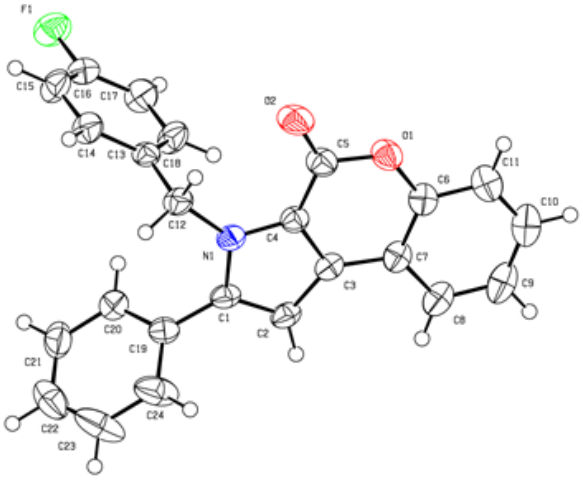


Figure 2.2: X-ray structure of **2.6j**

2.3. Bioactivity and docking study

Synthesized compounds were tested for cholinesterase (acetylcholinesterase and butyrylcholinesterase, obtained from *electric eel* and equine serum) and monoamine oxidase

(A & B) inhibition. Cholinesterase inhibition is known as one of the most powerful approaches for the treatment of Alzheimer's disease.[71] Moreover, monoamine oxidases are considered an important therapeutic target for neurodegenerative disorders. Among them, selective MAO-A inhibitors could be used as antidepressants and anxiolytics, and selective MAO-B inhibitors are used for treatments of Parkinson's disease and Alzheimer's disease.[72] Interestingly, many coumarin derivatives have been reported as potential inhibitors against both cholinesterases and monoamine oxidases[73]. Therefore, chromeno[3,4-*b*]pyrrol-4(3*H*)-ones could be considered as a potential approach to cholinesterase and monoamine oxidase inhibitors.

Table 2.5: Anticholinesterase activities of chromeno[3,4-*b*]pyrrol-4(3*H*)-ones

	AcetylCholinesterase activity	ButyrylCholinesterase activity
Compounds	**IC50±SEM (μM)**	**IC50±SEM (μM)**
2.6d	0.47±0.01	57.8±1.23
2.6e	11.8±0.99	82.1±2.45
2.6a	257.6±3.11	127.2±4.21
2.6f	2.87±0.56	159.1±3.11
2.6h	385.1±4.11	51.3±3.11
2.6i	0.47±0.01	208.8±2.56
2.6k	8.01±1.21	39.8±3.11
2.6q	248.7±4.89	14.9±2.16
2.6p	173.5±2.98	9.45±1.56
2.6m	308.7±3.12	34.1±1.78
2.6n	4.04±0.34	57.8±3.12
2.6l	16.8±1.56	18.4±1.89
2.6c	3.59±0.34	43.5±4.78
Donepezil	0.03 ± 0.01	6.41 ± 0.34
Neostigmine	22.2 ± 3.2	49.6 ± 6.11

As the results of anticholinesterase activity study (table 2.5), compounds **2.6d** and **2.6i** showed highest inhibitory activity against AChE with the IC_{50} value of 0.47±0.01 μM. Structurally, compound **2.6d** contains phenyl group at C2 and N1 while **2.6i** possesses phenyl group at C2 and phenethyl group at N1. Others modifications of the substituent at C2 and N1 lead to the devaluation of inhibitory activity against AchE. Notably, the presence of aliphatic substituents, methoxybenzyl at C2, or benzyl at N1 in the structure of chromeno[3,4-*b*]pyrrol-4(3*H*)-ones significantly decreased the value of IC_{50} (compounds **2.6a**, **2.6h**, **2.6m**, **2.6p**, **2.6q**). Compound **2.6i**, however, exhibits lowest inhibitory activity against BChE, with the IC_{50} value of 208.8±2.56 μM. The most active BchE inhibitor was found to be compound **2.6p** with the IC_{50} value of 9.45±1.56 μM. Furthermore, the data suggested that chromeno[3,4-*b*]pyrrol-4(3*H*)-ones displayed selective inhibitory activity against either AChE or BChE.

Table 2.6: Monoamine oxidase (A & B) activities of chromeno[3,4-*b*]pyrrol-4(3*H*)-ones

Compounds	MA0-A IC 50 μM & SEM VALUE	MAO-B IC 50 μM & SEM VALUE
2.6d	0.79±0.005	0.33 ±0.06
2.6a	41%	43%
2.6b	0.77±0.003	2.18±0.03
2.6c	2.73±0.08	0.59±0.003
2.6f	1.09±0.01	4.71±0.05
2.6h	1.28±0.04	0.21±0.0005
2.6i	26%	11%
2.6j	0.53±0.001	15%
2.6k	1.21±0.02	40%
2.6q	1.51±0.03	37%
2.6p	5.12±0.07	0.15±0.0001
2.6m	0.69±0.0004	32%
2.6n	1.06±0.06	0.32±0.0002
2.6o	0.52±0.0003	21%
Clorgyline	3.64±0.012	-
Deprenyl	-	0.007±0.001

Clorgyline were used as the standard inhibitor for monoamine oxidase A with IC_{50} value of 3.64±0.012 μM, and deprenyl for monoamine oxidase B with 0.007±0.001 μM. Compound **2.6j** and **2.6o** were found to be potential inhibitors against monoamine oxidase A with IC_{50} value of 0.53±0.001 μM and 0.52±0.0003 μM respectively, which are about 7 times stronger compared to the standard. Compound **2.6p**, with IC_{50} = 0.15±0.0001 μM, exhibits the most effective inhibitory activity against monoamine oxidase B among the tested chromeno[3,4-*b*]pyrrol-4(3*H*)-ones. There is no clear trend between structure and monoamine oxidase activities (table 2.6).

Compounds **2.6d** and **2.6i** showed similar activities against AChE, therefore these compounds were chosen for molecular docking study. Both compounds show similar interactions inside the receptor and form hydrophobic pocket with amino acid residues Trp279, Ile287, Phe330, Phe33d1, Tyr334, and Gly335. However, the results showed that compound **2.6i** established more stable conformation inside the receptor and formed additional hydrogen bonds with two water molecules. Figure 2.3 shows the docked pose of **2.6i** with AChE receptor and Figure 2.4 shows interaction in 2D.

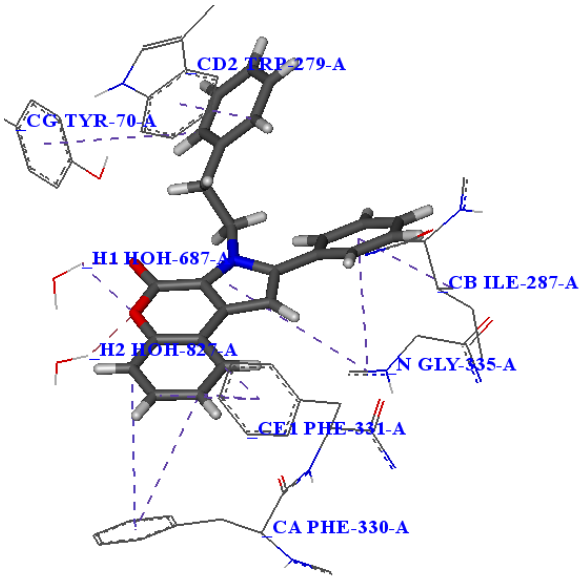


Figure 2.3: Putative binding mode of **2.6i** inside AChE receptor (PDB ID 3I6Z).
The blue dashed lines indicate hydrophobic interactions of amino acids with phenyl groups of the compound.

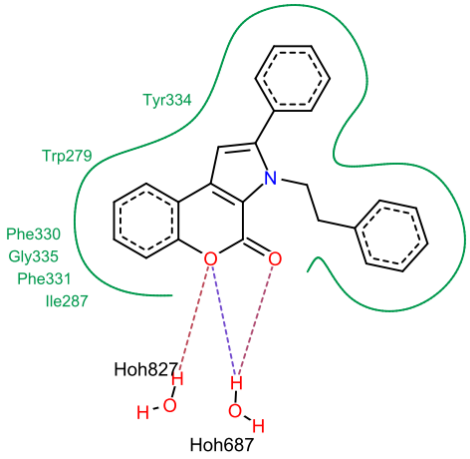


Figure 2.4: Putative binding mode of **2.6i** inside AChE receptor (PDB ID 3I6Z).
Green solid line around the compound shows the hydrophobic layer of active site and the dahed lines show hydrogen bonds with water molecule

Compound **2.6p** was docked inside the active pocket of BuChE. The molecular docking revealed that amino acid residues Gly16, Gly17, Ser198, Trp231, Leu286, Val288, Phe329, and His438 formed weak hydrophobic bonding with **2.6p** (figure 2.5). Additionally, carbonyl moiety of compound **2.6p** shows hydrogen bonding with amino group of amino acid residues Ile199, Gly116, and Gly117 (figure 2.6).

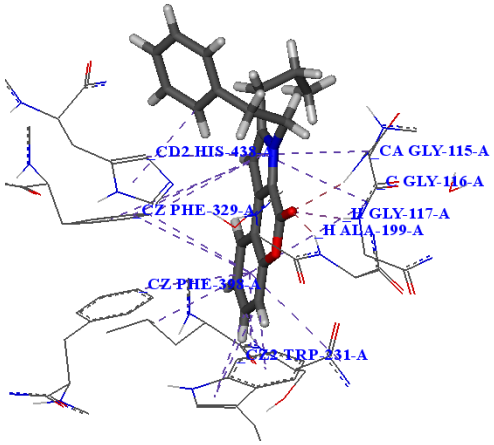


Figure 2.5: Putative binding mode of **2.6p** inside BuChE receptor (PDB ID 1P0I)
The blue dashed lines show the hydrophobic interactions of amino acid residues with phenyl groups of compound **2.6p** and the red dashed lines indicate hydrogen bonds between amino group of Gly116, Gly117, Ala199 and carbonyl group of compound **2.6p**.

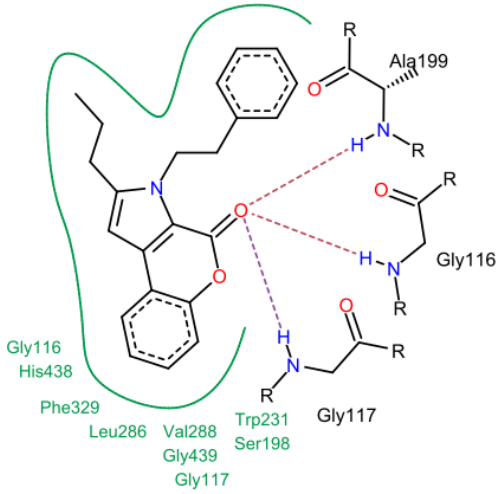


Figure 2.6: Putative binding mode of **2.6p** inside BuChE receptor (PDB ID 1P0I)
Green solid line around the compound shows the hydrophobic layer of active sites and the dahed lines depict hydrogen bonds beteween carbonyl group of compound **2.6p** with amino groups of amino acid residues

After docking study, the docked poses were further verified by HYDE assessment. The ΔG value for the compound **2.6i** was calculated as -26 KJmol^{-1} while that of the **2.6h** was only -10 KJmol^{-1}. These results also prove the experimental data, which compound **2.6i** is the best inhibitor against AChE while compound **2.6h** exhibit the least active inhibior. Similar results were found in case of BuChE. The ΔG value for the strongest compound **2.6p** is -18 KJmol^{-1} and for **2.6i** is -15 KJmol^{-1}.

2.4. Conclusion

A convenient method for the synthesis of chromeno[3,4-*b*]pyrrol-4(3*H*)-ones was successfully developed. Moreover, a series of chromeno[3,4-*b*]pyrrol-4(3*H*)-ones, which are difficult to obtained by known methods, were prepared. New synthesized chromeno[3,4-*b*]pyrrol-4(3*H*)-ones were studied regarding their inhibitory activity against cholinesterases and monoamine oxidases. Among them, compounds **2.6d** and **2.6i** were found to be potent selective inhibitors against AChE while compound **2.6p** showed the best activity as selective inhibitor against BuChE. Furthermore, chromeno[3,4-*b*]pyrrol-4(3*H*)-ones **2.6j** and **2.6o** also displayed potent inhibitory activity against monoamine oxidase A.

A part of the results of this chapter were published in:

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3. Palladium(0)-catalyzed domino C-N coupling/hydroamination/ C-H arylation reactions: Synthesis of indolo[1,2-*f*]phenanthridines, azaindolo[1,2-*f*]phenanthridines

3.1. Introduction

Fused phenanthridines are recognized as an important motif among drug-like molecules and found many applications in medicinal chemistry.[74] For example, nitidine, fagaronine, and coralyne, which are natural alkaloids containing the benzo[*c*]phenanthridine moiety, possess interesting antitumor activity and are important targets for total syntheses and biological evaluations;[75] ethidium bromide, an intercalating agent, is used as a fluorescent tag;[76] and pyrrolo[1,2-*f*]phenanthridines was found capable of inhibiting HIV (figure 3.1).[77]

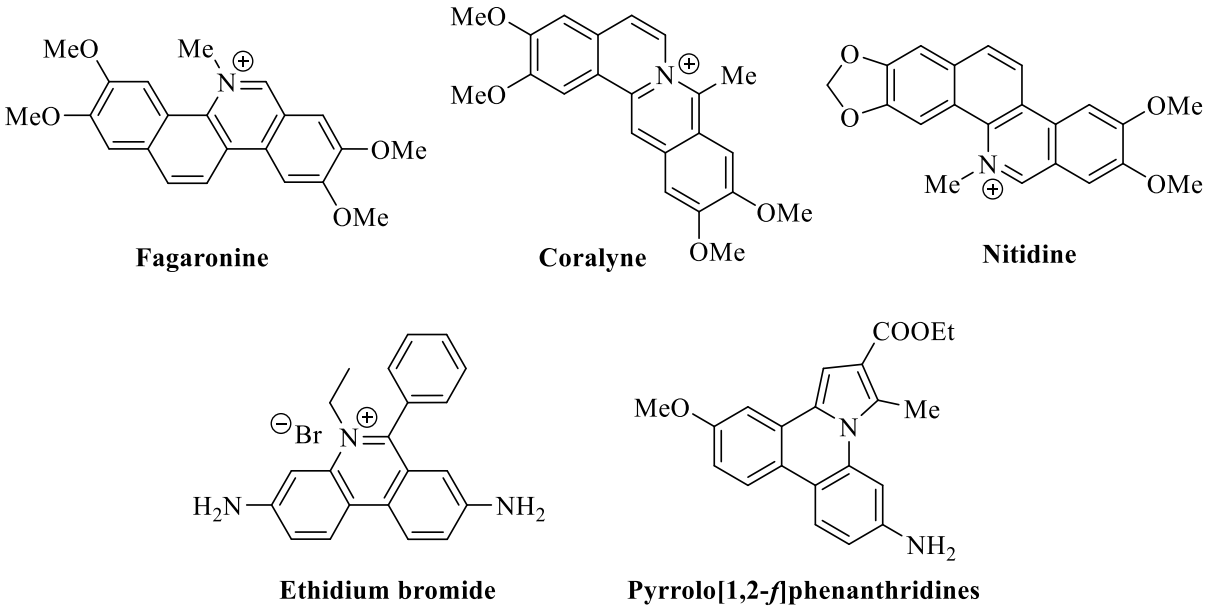


Figure 3.1: Biologically active phenanthridines

In addition to their biological activities, due to their large π-conjugated electron system and effects of heteroatom contributing to the conjugated system, fused phenanthridines are essential components for developing new semiconductors and organic light-emitting diodes (OLEDs).[78] Particularly, recent studies showed that fused phenanthridines possess interesting optical and electronic properties, in which phenanthridines fused with *N*-heterocycles are potential candidates for the development of new blue-emitting materials.[79] Furthermore, organic dyes developed from indolo[1,2-*f*]phenanthridine structure show broad and intense visible absorptions, which are promising new sensitizers for dye-sensitized solar cells (figure 3.2).[80]

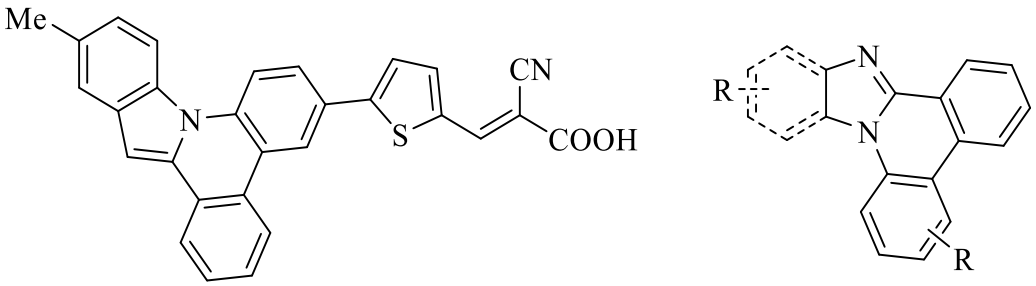
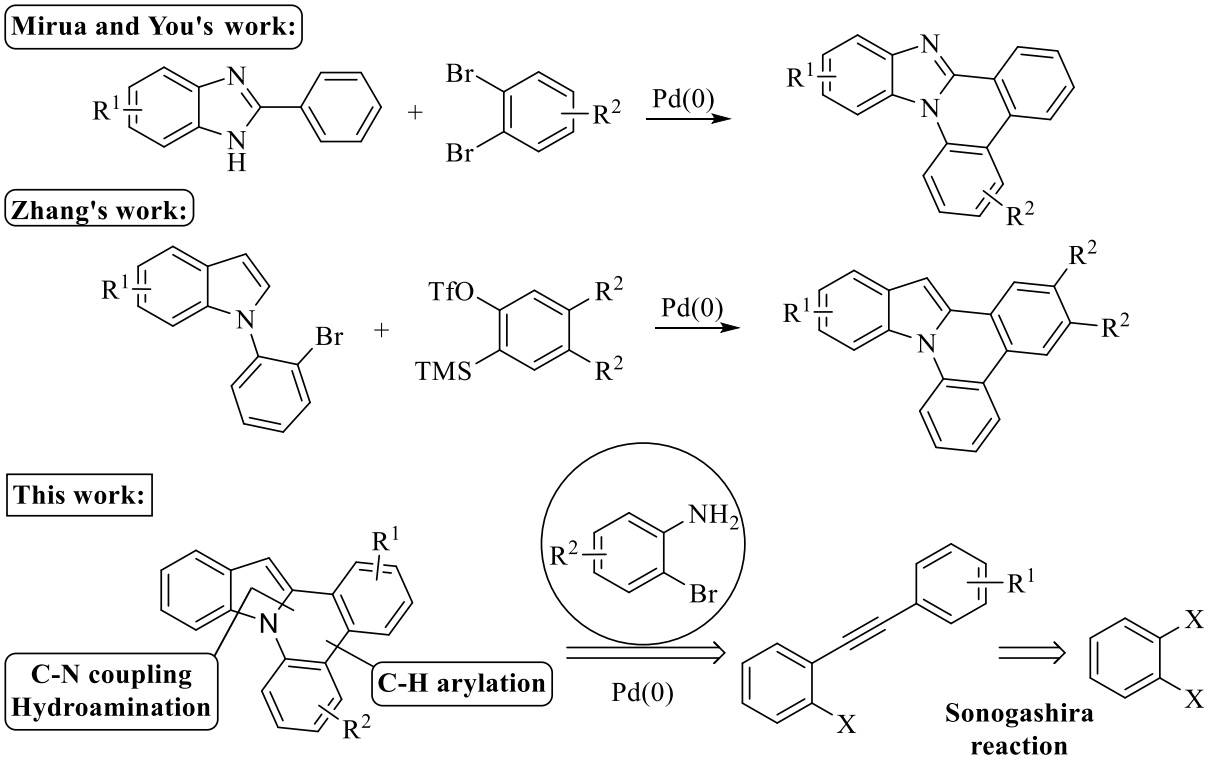


Figure 3.2: Phenanthridine derivatives with potential physical properties

Although many methods for the synthesis of phenanthridines were developed in recent years, most of them require many steps and/or harsh conditions, and even more challenging for fused phenanthridines.[81] Therefore, developing new and efficient methods is important and necessary for the development of new bioactive molecules and organic materials. In recent years, the advances in transition metal-catalyzed reactions have facilitated considerably the approach to complex structures. Among them, palladium-catalyzed domino reactions proved to be a useful tool for the synthesis of fused heterocyclic compounds with high atom economy. In 2007, Zhang and coworkers published a convenient method to synthesize indolo[1,2-*f*]phenanthridines by reaction of arynes with 1-(2-bromophenyl)-1*H*-indole in the presence of a Pd catalyst.[82] However, approaching starting materials for this method could be problematic and requires many synthetic steps. In 2012, Mirua *et al.* and later in 2013, You *et al.* independently reported an interesting Pd-catalyzed domino N–H/C–H arylation for the regioselective synthesis of *N*-heterocyclic fused phenanthridines.[83,84] These authors used readily available 2-arylindoles and 1,2-dibromobenzene as the starting materials, however, the selectivity of reactions was difficult to control, which may result in mixtures of isomers. A similar cascade process involving C-H arylations followed by an intramolecular *N*-arylation reaction to prepare benzimidazole-fused phenanthridines in moderate to good yields was published by Peng *et al.* in 2014.[85] More recently, Wang and Lv reported a one-pot tandem approach to indolo[1,2-*f*]phenanthridines employing 2-alkynylanilines and boronic acids via Cu-catalyzed C-N coupling/hydroamination and Pd-catalyzed C-H arylation.[86] Retrospectively, I believe that by combining intramolecular C-H arylation with the construction of indole scaffold, fused phenanthridines could be formed in a one-pot domino reaction. For constructing indole moiety, sequential Pd-catalyzed C-N coupling and intramolecular hydroamination of *ortho*-halogenated phenylacetylene is expected to be most suitable in this scenario.



Scheme 3.1: Domino reactions for the synthesis of fused-phenanthridines

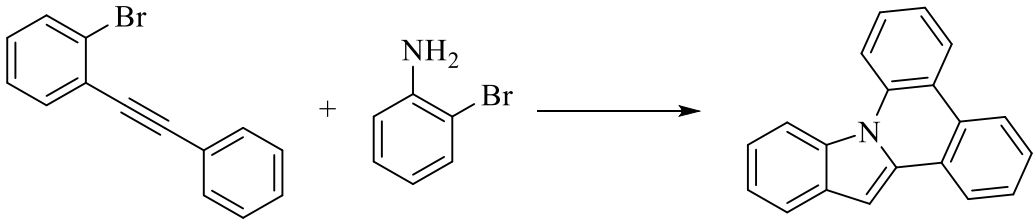
In this chapter, I wish to describe a new synthetic methodology to efficiently approach various indolo[1,2-*f*]phenathridines. The transformations proceed through three sequential steps in a one-pot reaction: C-N coupling, hydroamination, and C-H arylation reactions with employment of a single Pd catalyst. The reaction employs commercially available starting materials: dihalogenated arenes, terminal alkynes, and 2-bromoanilines or anilines.

3.2. Synthesis of indolo[1,2-*f*]phenanthridines

For studying the reaction, 1-bromo-2-(phenylethynyl)benzene **3.1a** and 2-bromoaniline **3.2a** were chosen as model substrates. Initially, the reaction was carried out in DMF at 120 °C using Cs_2CO_3 as the base in the absence of catalyst and ligand. However, the reaction did not give the desired product **3.3a**. When 10 mol% $Pd(OAc)_2$ and 20 mol% PPh_3 were introduced to the reaction mixture as the catalyst, the product was isolated in 34% yield after 24 h. To improve the yield, a series of monodentate and bidentate phosphine ligands were examined. Consequently, XantPhos (10 mol%) and $PCy_3 \cdot HBF_4$ (20 mol%) were found to be the best ligands as the reaction resulted in 75% and 74% yields of **3.3a**, respectively. For further investigation, other combinations of various palladium precursors and XantPhos were screened. No product could be isolated when $Pd_2(dba)_3$ was used, while 70% yield of the desired product was obtained when employing $Pd(PPh_3)_4$. It proved to be important to use Cs_2CO_3 as the base.

Only trace amounts of product were detected when other bases were used, such as K_2CO_3 and KO*t*Bu. Variation of solvent and temperature did not lead to improved yields (table 3.1).

Table 3.1: Optimization for the synthesis of **3.3a**



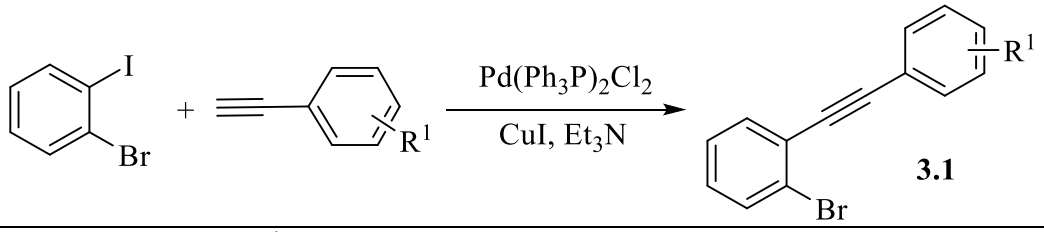
3.1a **3.2a** **3.3a**

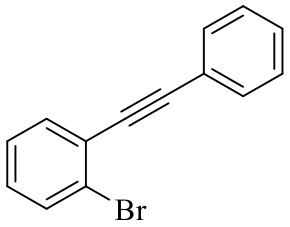
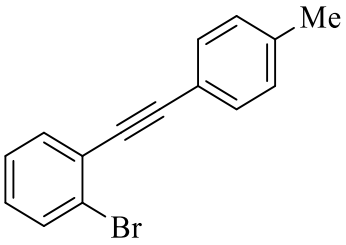
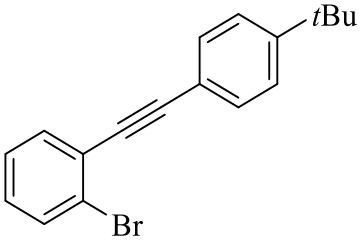
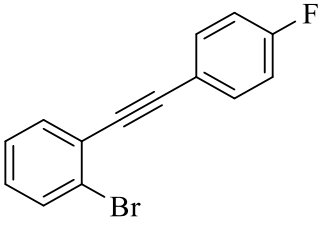
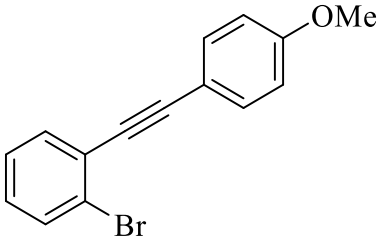
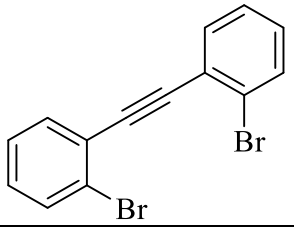
Entry	Catalyst	Ligand	Base	Yield (%)
1	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	34
2	$Pd(OAc)_2$	BINAP	Cs_2CO_3	34
3	$Pd(OAc)_2$	XantPhos	Cs_2CO_3	75
4	$Pd(OAc)_2$	DPEPhos	Cs_2CO_3	70
5	$Pd(OAc)_2$	DPPE	Cs_2CO_3	38
6	$Pd(OAc)_2$	DPPF	Cs_2CO_3	41
7	$Pd(OAc)_2$	XPhos	Cs_2CO_3	45
8	$Pd(OAc)_2$	SPhos	Cs_2CO_3	34
9	$Pd(OAc)_2$	RuPhos	Cs_2CO_3	38
10	$Pd(OAc)_2$	DavePhos	Cs_2CO_3	64
11	$Pd(OAc)_2$	$PCy_3 \cdot HBF_4$	Cs_2CO_3	74
12	$Pd(OAc)_2$	$P(tBu)_3 \cdot HBF_4$	Cs_2CO_3	5
13	$Pd(PPh_3)_4$	XantPhos	Cs_2CO_3	70
14	$Pd_2(dba)_3$	XantPhos	Cs_2CO_3	trace
15	$Pd(OAc)_2$	XantPhos	K_2CO_3	trace
16	$Pd(OAc)_2$	XantPhos	KO*t*Bu	5

Conditions: **3.1a** (0.1 mmol, 1 equiv.), **3.2a** (0.12 mmol, 1.2 equiv.), $Pd(OAc)_2$ (0.01 mmol, 10 mol%), ligand (20 mol% with monodentate ligands, 10 mol% with bidentate ligands), Cs_2CO_3 (0.3 mmol, 3 equiv.), DMF (1 mL), 120 °C, 24 h.

With the optimized conditions in hand, I extended the scope of the reaction by modifying both substrates to prepare a series of indolo[1,2-*f*]phenanthridines. First, several alkynes **3.1a-f** were synthesized by chemoselective Sonogashira coupling reactions of 2-bromo-iodobenzene with 1.1 equiv. of various phenylacetylenes, including electron-withdrawing and -donating substituents. These compounds were obtained in nearly quantitative yield when using reported procedure.[87]

Table 3.2: Synthesis of alkynes **3.1**

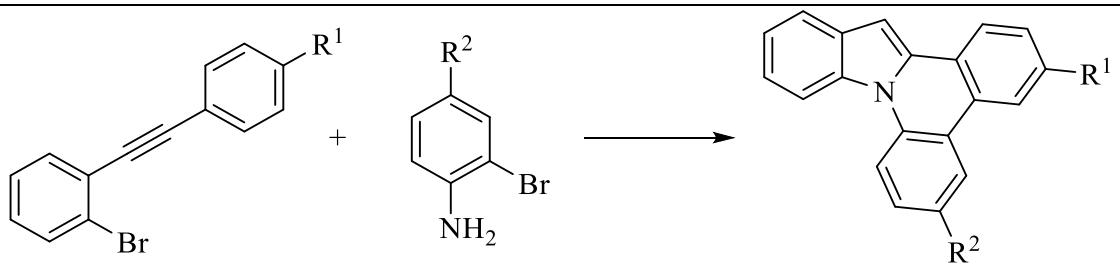


Compound	R^1	Structure	Yield (%)
3.1a	H		95
3.1b	4-Me		94
3.1c	4-*t*Bu		92
3.1d	4-F		90
3.1e	4-OMe		96
3.1f	2-Br		74

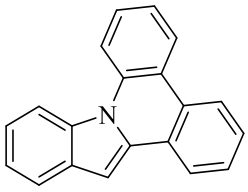
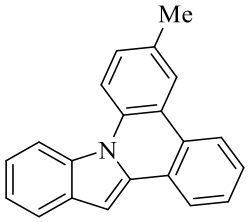
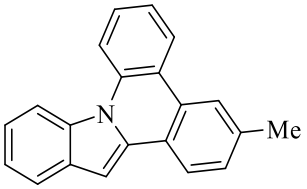
Conditions: 2-bromo-iodobenzene 1 equiv., alkynes 1.1 equiv., $Pd(PPh_3)_2Cl_2$ 2.5 mol%, CuI 10 mol%, Et_3N is used as solvent and base, 25 °C, 4 h.

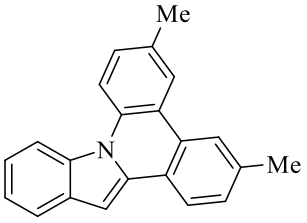
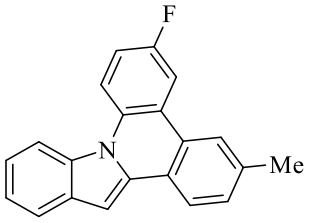
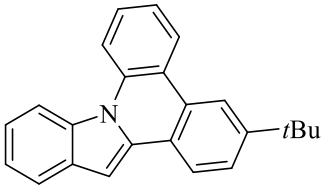
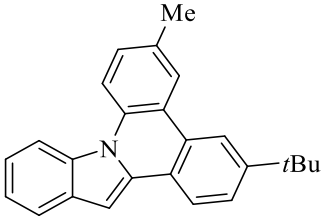
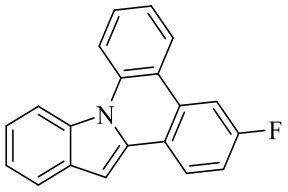
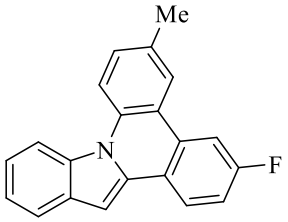
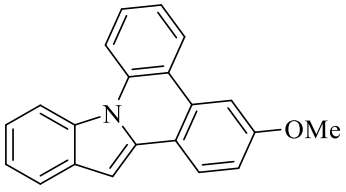
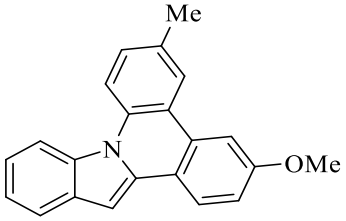
Then, reactions of **3.1a-e** with 2-bromoanilline **3.2a**, 2-bromo-4-methylaniline **3.2b**, and 2-bromo-4-fluoroaniline **3.2c** afforded various indolo[1,2-*f*]phenathridines **3.3** (Table 3.3). In general, 1-bromo-2-(phenylethynyl)benzene or 2-bromoaniline derivatives, bearing electron-donating or -withdrawing groups, afforded the corresponding products in moderate to good yields under optimized conditions. The presence of substituents located at the aryl group of the 1-bromo-2-(phenylethynyl)benzene had no pronounced effect on the yield. In contrast, the structure of the 2-bromoaniline derivative had a greater impact, but did not follow a clear trend. The best yields were obtained for **3.3h** and **3.3j**. The structure of **3.3i** was unambiguously confirmed by X-ray crystallography (figure 3.3).

Table 3.3: Synthesis of indolo[1,2-*f*]phenathridines



3.1 **3.2** **3.3**

Compound	R^1	R^2	Structure	Yield (%)[a]
3.3a	H (**3.1a**)	H (**3.2a**)		75
3.3b	H (**3.1a**)	Me (**3.2b**)		66
3.3c	Me (**3.1b**)	H (**3.2a**)		52

3.3d	Me (**3.1b**)	Me (**3.2b**)		45
3.3e	Me (**3.1b**)	F (**3.2c**)		55
3.3f	*t*Bu (**3.1c**)	H (**3.2a**)		65
3.3g	*t*Bu (**3.1c**)	Me (**3.2b**)		67
3.3h	F (**3.1d**)	H (**3.2a**)		77
3.3i	F (**3.1d**)	Me (**3.2b**)		54
3.3j	MeO (**3.1e**)	H (**3.2a**)		78
3.3k	MeO (**3.1e**)	Me (**3.2b**)		73

***Conditions*: 3.1** (0.3 mmol, 1 equiv.), **3.2** (0.36 mmol, 1.2 equiv.), $Pd(OAc)_2$ (0.03 mmol, 10 mol%), XantPhos (0.03 mmol, 10 mol%), Cs_2CO_3 (0.9 mmol, 3 equiv.), DMF (4 mL), 120 °C, 24 h.

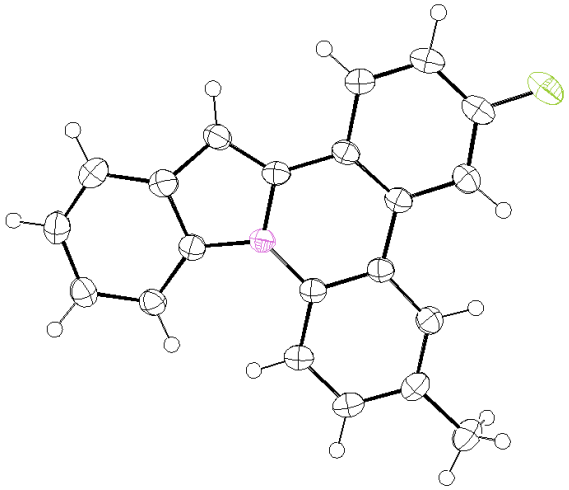
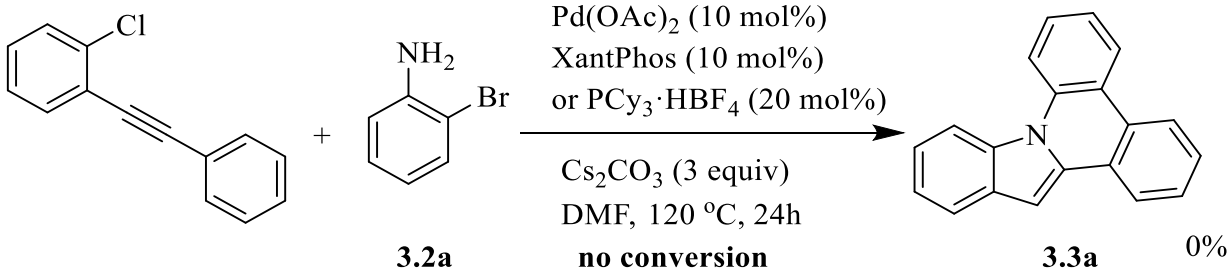


Figure 3.3: X-ray crystal structure analysis of **3.3i**

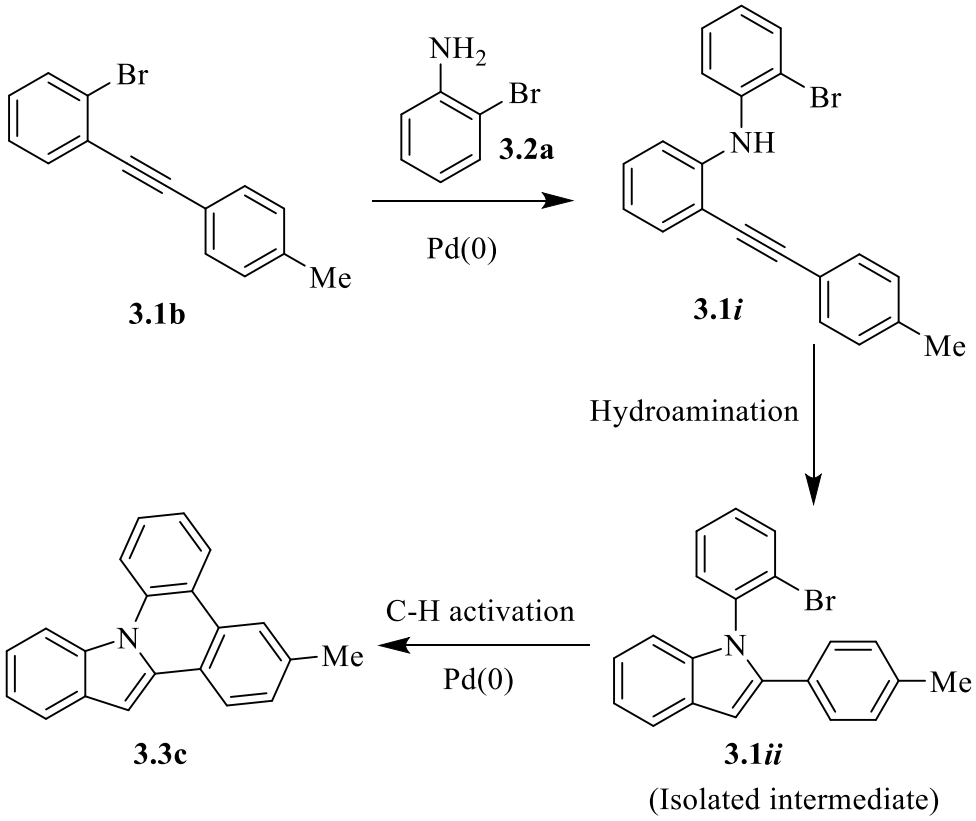
Moreover, I conducted additional experiments to study the applicability of less reactive chlorine substituents in the reaction. I realized that the bromine substituent in acetylenes **3.1** played a crucial role in the reaction, since no conversion of 1-chloro-2-(phenylethynyl)benzene was observed when reacting with 2-bromoaniline under the optimized conditions.



3.2a **no conversion** **3.3a** 0%

Scheme 3.2: Reaction of 1-chloro-2-(phenylethynyl)benzene with 2-bromoaniline

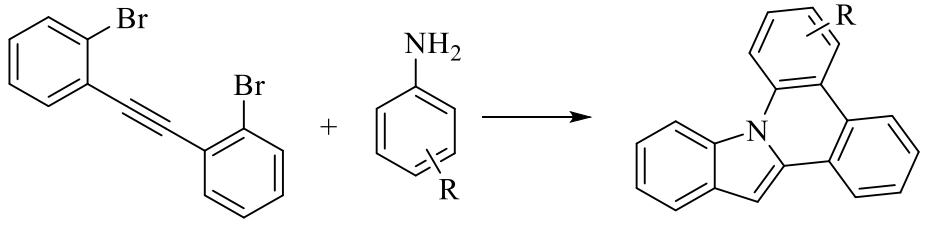
A possible mechanistic pathway of the formation of indolo[1,2-*f*]phenanthridines is proposed in Scheme 3.3. First, a Buchwald-Hartwig reaction of **3.1b** with 2-bromoaniline **3.2a** gave intermediate **3.1*i***. Intramolecular hydroamination of **3.1*i*** subsequently formed intermediate **3.1*ii*** (which could be isolated and structurally confirmed by NMR spectroscopy). Finally, an intramolecular C-H activation took place to give indolo[1,2-*f*]phenanthridine **3.3c.**



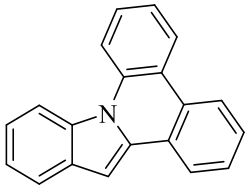
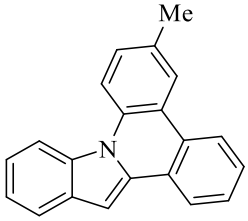
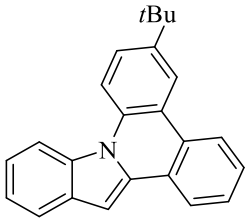
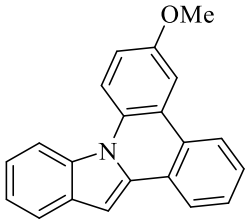
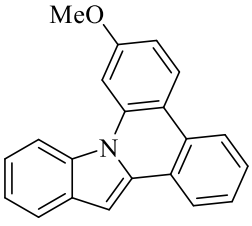
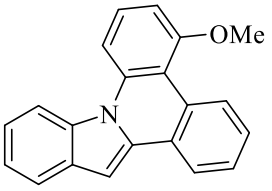
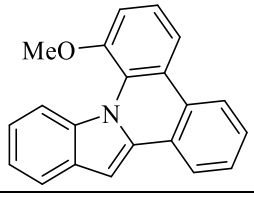
Scheme 3.3: Proposed pathway for the reaction

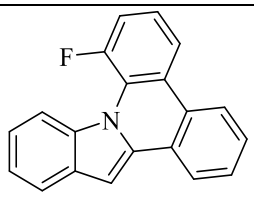
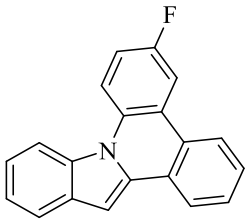
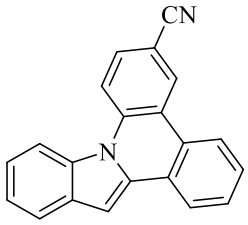
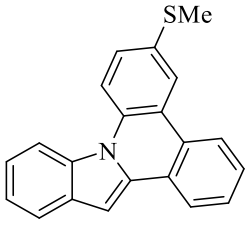
Encouraged by the successful isolation of intermediate **3.1*ii***, I considered the application of 1,2-bis(2-bromophenyl)ethyne **3.1f** as a suitable alternative precursor for the reaction. This would allow the employment of simple anilines as educts and would widely broaden the scope of the methodology. To my delight, the reaction of 1,2-bis(2-bromophenyl)ethyne **3.1f** with various anilines proceeded smoothly and produced the desired products **3.5a-j** in moderate to good yields (Table 3.4). Anilines containing a fluoro substituent gave very good results with 72% (**3.5g**) and 75% (**3.5h**) isolated yields. When employing an unsymmetrical aniline, a mixture of two inseparable isomers **3.5e1** and **3.5e2** with 1:3 ratios was formed.

Table 3.4: Reaction of 1,2-bis(2-bromophenyl)ethyne **3.1f** with amines



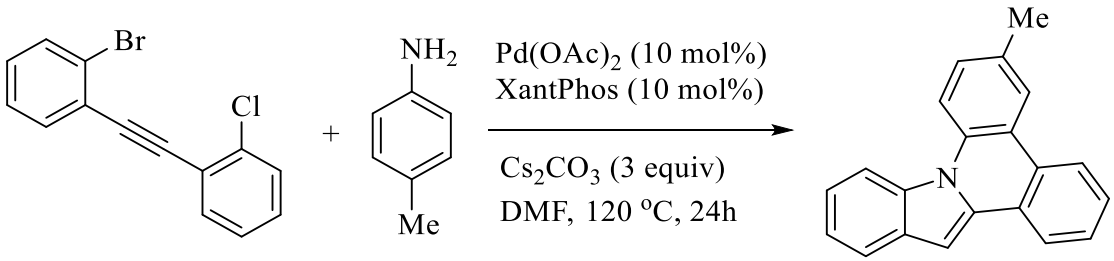
3.1f **3.4** **3.5**

Compound	R	Products	Yield (%)[a]
3.5a (3.3a)	H (**3.4a**)		52
3.5b (3.3b)	4-Me (**3.4b**)		55
3.5c	4-*t*Bu (**3.4c**)		43
3.5d	4-MeO (**3.4d**)		49
3.5e	3-MeO (**3.4e**)	 **3.5e1**  **3.5e2**	43[a]
3.5f	2-MeO (**3.4f**)		49

3.5g	2-F (**3.4g**)		72
3.5h	4-F (**3.4h**)		75
3.5i	4-CN (**3.4i**)		44
3.5j	4-MeS (**3.4j**)		56

Conditions: **3.1f** (0.3 mmol, 1equiv.), **3.4** (0.36 mmol, 1.2 equiv.), $Pd(OAc)_2$ (0.03 mmol, 10 mol%), ($PCy_3 \cdot HBF_4$ 0.06 mmol, 20 mol%), Cs_2CO_3 (0.9 mmol, 3 equiv.), DMF (4 mL), 120 °C, 24 h.
[a] inseparable mixture (ratio 1:3 determined by NMR)

It is clear that employment of unsymmetrical dibromoacetylenes would result in a selectivity issue. In order to address this problem, we investigated the reaction of 1-bromo-2-((2-chlorophenyl)ethynyl)benzene **3.1g** containing two different halides. The reaction of **3.1g** with *p*-toluidine afforded, using the optimized conditions, the desired product **3.5b** in only 14% yield. As mentioned before, no conversion takes place in the reaction of 1-chloro-2-(phenylethynyl)benzene with 2-bromoaniline under the same conditions. Therefore, the reactions were assumed to proceed starting from Buchwald Hartwig reaction at the C-Br bond, followed by hydroamination and intramolecular C-H arylation at the C-Cl bond (scheme 3.4).



3.1g **3.4b** **3.5b (14%)**

Scheme 3.4: Reaction of 1-bromo-2-((2-chlorophenyl)ethynyl)benzene with *p*-toluidine

3.3. Synthesis of azaindolo[1,2-*f*]phenanthridines

As mentioned previously, the structure obtained when phenanthridine fused with N-heterocycles, such as imidazole, benzoimidazole, indole, and pyrrole, were reported to possess remarkable optical and electronic properties. For example, phenanthridine fused with N-heterocycles, such as imidazole, benzoimidazole, indole, and pyrrole, were reported to possess remarkable optical and electronic properties.[79,83,85] Moreover, azaindoles are also considered as important core structures and have been studied for decades.[88] However, the scaffold of phenanthridine fused with azaindole is rarely reported, probably because of difficulties in synthetic approaches. To my best knowledge, only one work (patented) related to azaindolo[1,2-*f*]phenanthridines was published (figure 3.4); authors of the patent claimed that electroluminescent devices employing these compounds showed improvement in driving voltage and lifespan in comparison of using Alq_3.[89] Therefore, developing an efficient synthetic method for this scaffold is compelling for further studies of its properties.

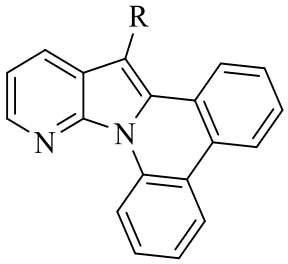
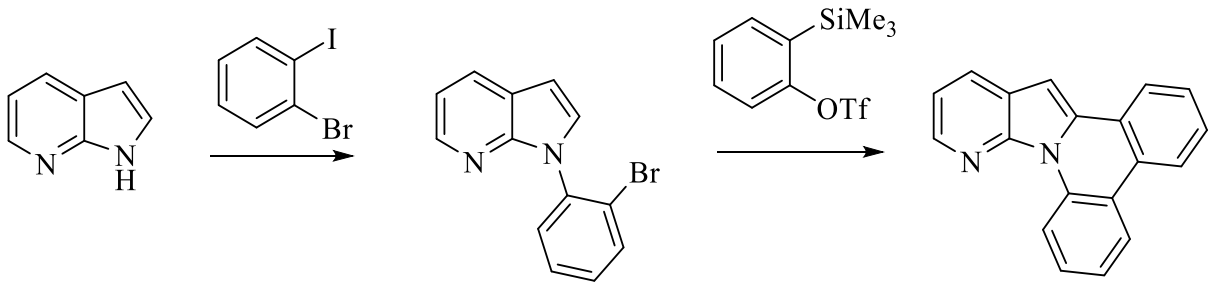


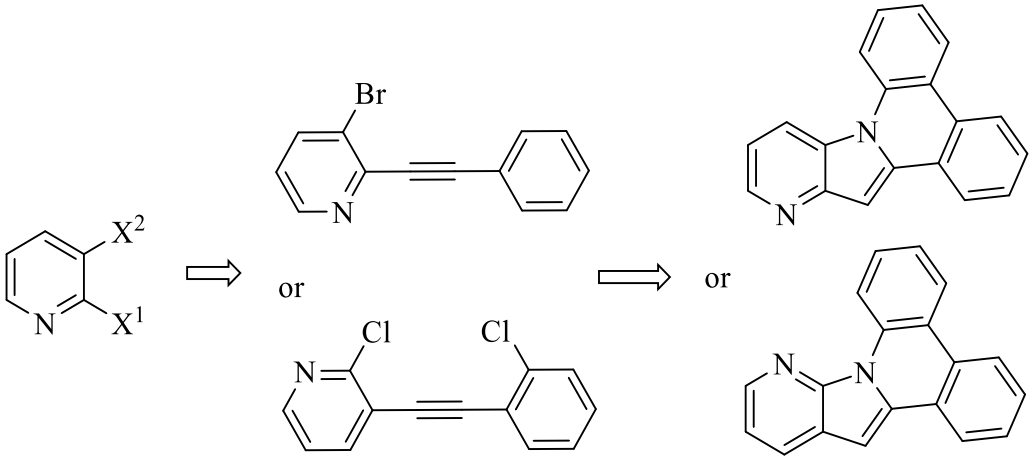
Figure 3.4: Azaindolo[1,2-*f*]phenanthridines applicable in electroluminescent devices

In the reported patent, authors synthesized azaindolo[1,2-*f*]phenanthridine scaffold starting from 7-azaindole, following by Ullmann reaction to obtain the key intermediate. This precursor was transformed to azaindolo[1,2-*f*]phenanthridine by Pd-catalyzed cascade reaction with benzyne generated *in situ* from 2-(trimethylsilyl)phenyl trifluoromethanesulfonate, which was mentioned in previous part (scheme 3.5).



Scheme 3.5: Synthesis of azaindolo[1,2-*f*]phenanthridines via *in situ* benzyme

Regarding my methodology for the synthesis of fused phenanthridines, the strategy relies on three sequential steps catalyzed by a single Pd catalyst in a one-pot reaction: C-N coupling, hydroamination and intramolecular C-H arylation. After contemplation, I realized that this strategy could be applied efficiently to synthesize phenanthridines-fused azaindole scaffolds from simple and commercially available dihalogentated pyridines. Especially by employing chemo- or regioselective of Sonogashira reaction for modifying the alkyne precursors, different scaffolds, 4- or 7-azaindolo[1,2-*f*]phenanthridines, could be obtained (scheme 3.6).

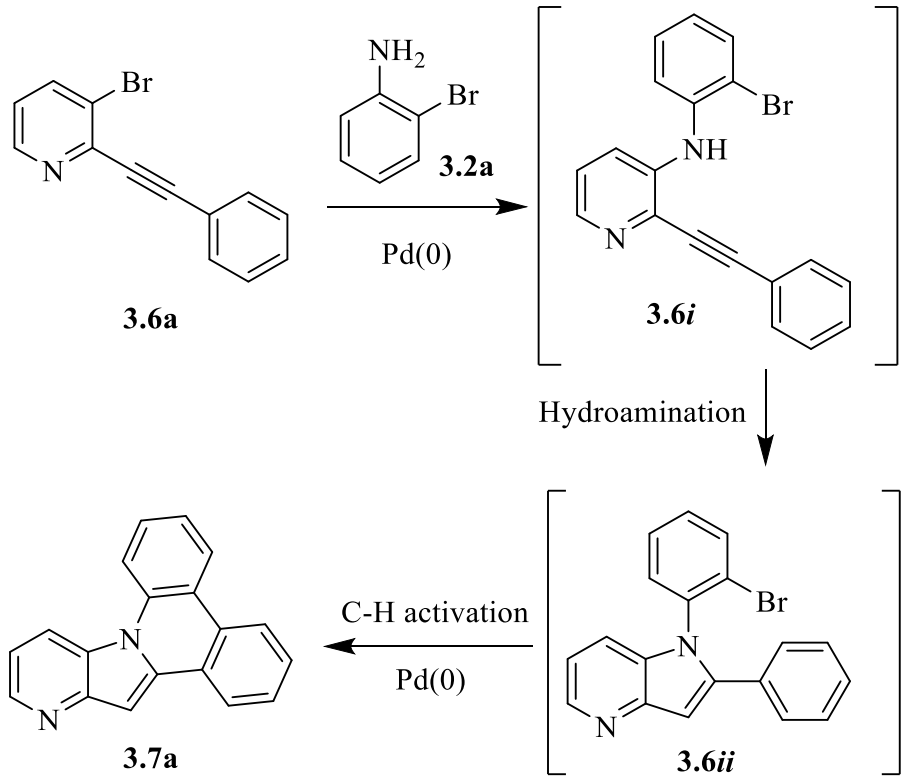


Scheme 3.6: Synthesis of azaindolo[1,2-*f*]phenanthridines

In the following section, the details will be discussed, and furthermore, the optical properties of selected synthesized compounds will be studied to justify the objective of the proposed idea.

Initially, 3-bromo-2-(phenylethynyl)pyridines **3.6a** and 2-bromoaniline were chosen as model substrates to study the reaction. No desired product was obtained after stirring the mixture of substrates and cesium carbonate in DMF at 120 °C for 24 h. At the beginning, we applied the reaction conditions from the previous reactions (table 3.3), which utilizes $Pd(OAc)_2$/XantPhos as the catalytic system. Interestingly, these conditions produced the desired product with 39% yield. Furthermore, when the reaction time was increased to 48 h, the yield of the reaction raised to 64%. Encouraged by this result, we continued to investigate other combinations of catalytic sources and ligands using the same solvent, base, and temperature

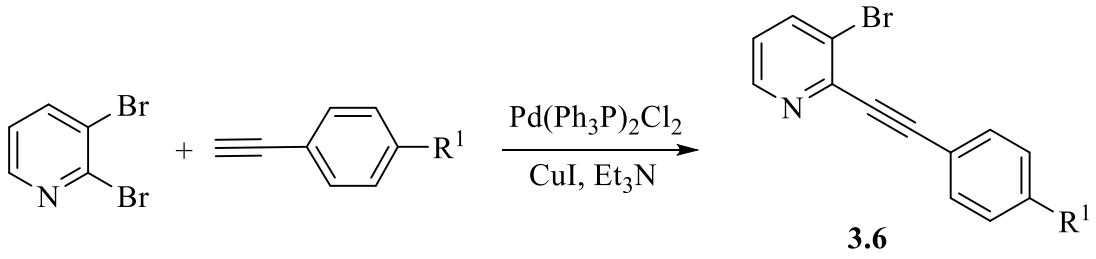
conditions. To my delight, XantPhos was the best choice of ligand so far. The combination of $Pd(PPh_3)_4$ and XantPhos gave the best result with 68% yield. Other attempts to change the solvent and base did not lead to higher yields. Notably, decreasing the reaction temperature also led to a significant decrease of yield. During the reaction, we observed the formation of intermediate **3.6*ii*** as a potential intermediate of the reaction pathway which is proposed in Scheme 3.7.



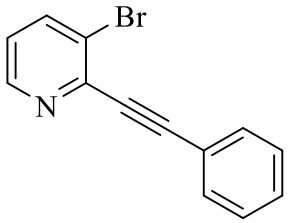
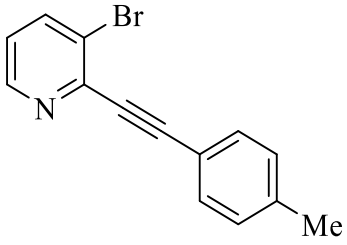
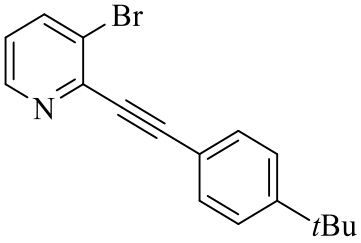
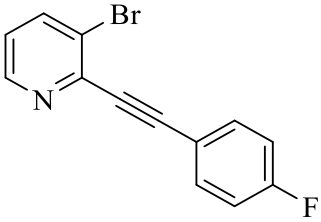
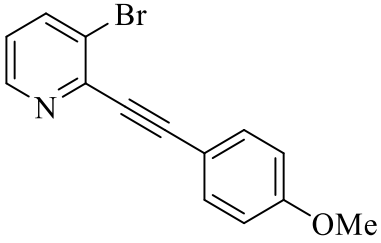
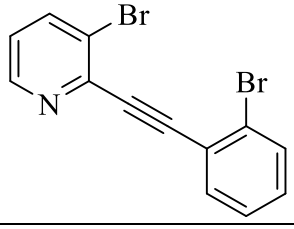
Scheme 3.7: Proposed pathway for the reaction

With the optimized conditions in hand, the scope of the reaction was extended by modifying the starting alkynes and 2-bromoanilines. Both electron-withdrawing and electron-donating substituents were introduced into both substrates. Firstly, 3-bromo-2-(alkynyl)pyridines **3.6a-3.6f** were synthesized from 2,3-dibromopyridine by selective Sonogashira reaction at its C2, affording desired compounds with good to excellent yields (table 3.5).

Table 3.5: Synthesis of 3-bromo-2-(alkynyl)pyridines



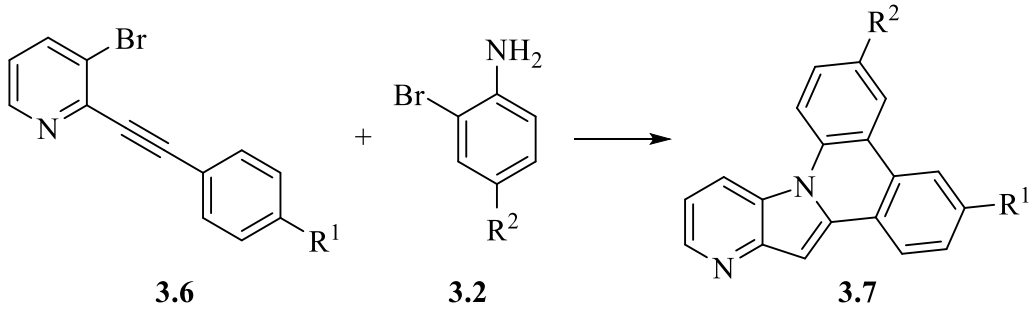
3.6

Compound	R^1	Structure	Yield (%)
3.6a	H		86
3.6b	4-Me		91
3.6c	4-*t*Bu		95
3.6d	4-F		80
3.6e	4-OMe		91
3.6f	2-Br		77

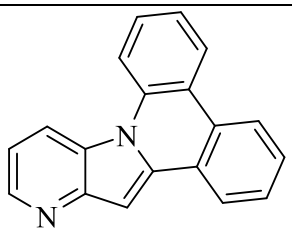
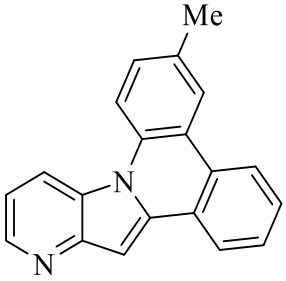
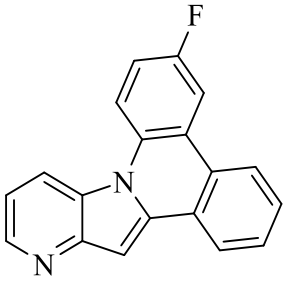
Conditions: 2,3-dibromopyridine 1 equiv., alkynes 1.1 equiv., $Pd(PPh_3)_2Cl_2$ 2.5 mol%, CuI 10 mol%, Et_3N is used as solvent and base, 25 °C, 4 h.

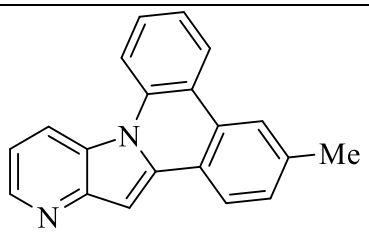
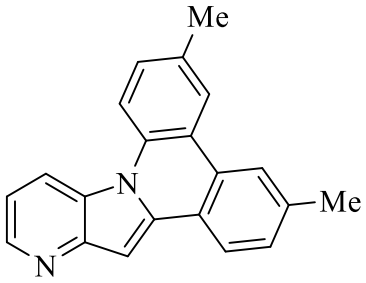
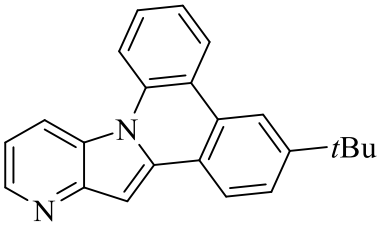
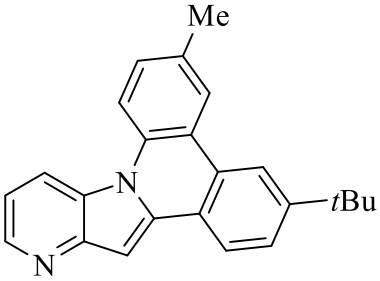
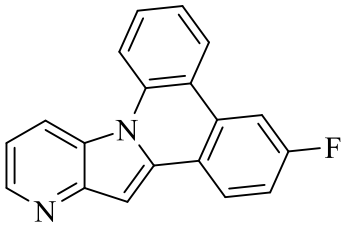
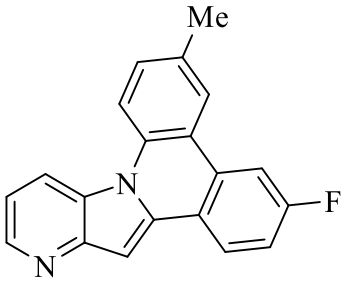
Then the domino reactions were performed with obtained 3-bromo-2-(alkynyl)pyridines and several anilines. The reaction proceeded smoothly with various starting materials under optimized conditions affording the desired products **3.7a-3.7k** in moderate to high yields. However, no apparent effect of the substituents on the yield was observed. Compound **3.7h** was obtained with the highest yield (88%) **(**Table 3.6). Furthermore, the structure of **3.7j** was independently confirmed by X-ray crystallographic analysis (figure 3.5).

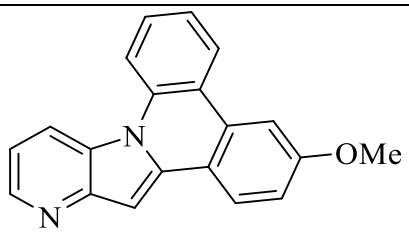
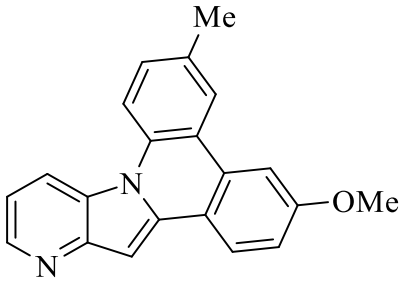
Table 3.6: Synthesis of 4-azaindolo[1,2-*f*]phenanthridines



3.6 **3.2** **3.7**

Compound	R^1	R^2	Structure	Yield (%)[a]
3.7a	H	H		68
3.7b	H	Me		64
3.7c	H	F		41

3.7d	Me	H		61
3.7e	Me	Me		72
3.7f	*t*Bu	H		69
3.7g	*t*Bu	Me		32
3.7h	F	H		88
3.7i	F	Me		79

3.7j	MeO	H		85
3.7k	MeO	Me		37

Conditions: **3.6** (0.3 mmol, 1 equiv.), **3.2** (0.36 mmol, 1.2 equiv.), $Pd(PPh_3)_4$ (0.03 mmol, 10 mol%), XantPhos (0.03 mmol, 10 mol%), Cs_2CO_3 (0.9 mmol, 3 equiv.), DMF (4 mL), 120 °C, 24 h.

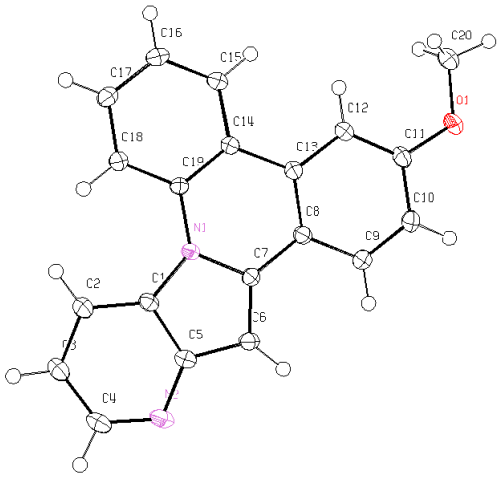
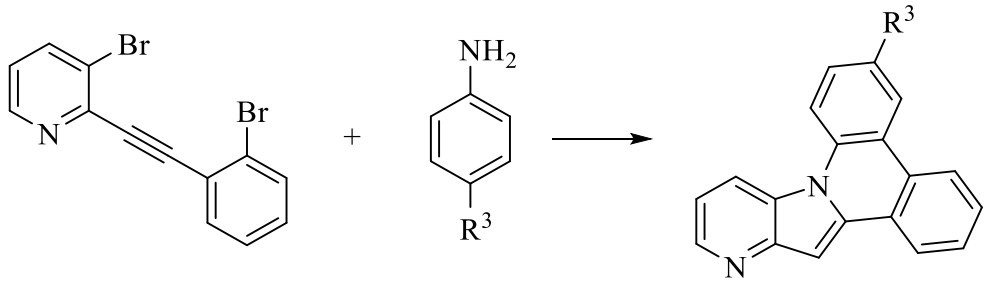


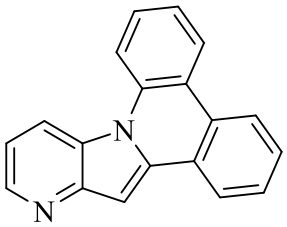
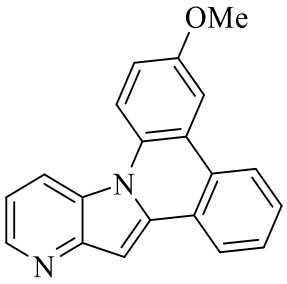
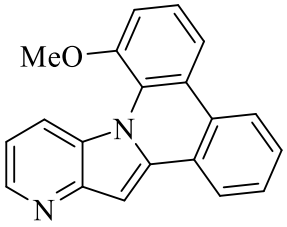
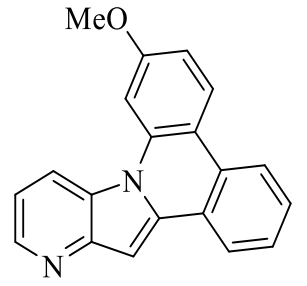
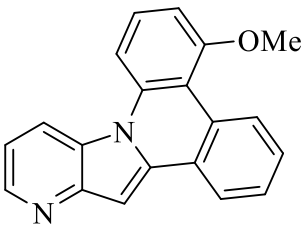
Figure 3.5: X-ray crystallographic analysis of **3.7j.**

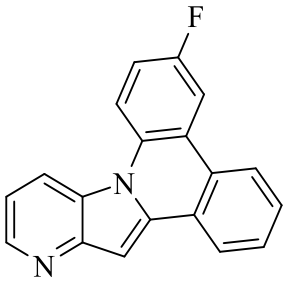
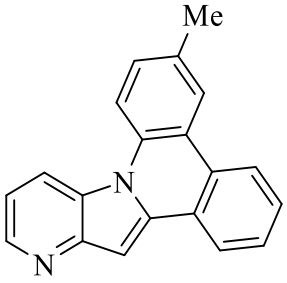
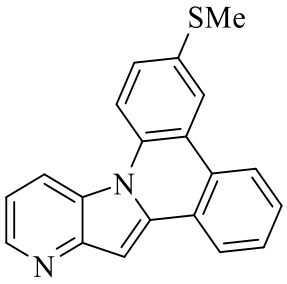
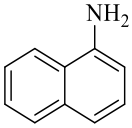
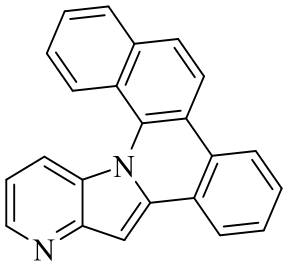
Similarly, I assumed that the position of bromine and hydrogen atom participating in the last step of the reaction could be interchangeable. With this idea in mind, reactions of **3.6f** with various amines were investigated to broaden the scope of this strategy (table 3.7).

Table 3.7: Synthesis of 4-azaindolo[1,2-*f*]phenanthridines



3.6f **3.4** **3.8**

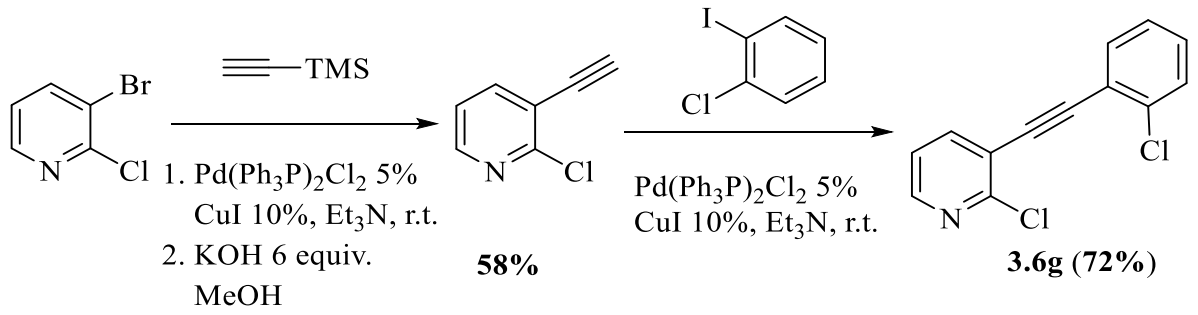
Compound	R^3	Structure	Yield (%)
3.8a (3.7a)	H **(3.4a)**		87
3.8b	4-MeO **(3.4d)**		51
3.8c	2-MeO **(3.4f)**		60
3.8d	3-MeO **(3.4e)**	 	65 (mixture)

3.8e (3.7c)	4-F **(3.4g)**		76
3.8f (3.7b)	4-CH_3 **(3.4b)**		65
3.8g	4-SMe **(3.4j)**		81
3.8h	 **(3.4k)**		42

Conditions: **3.6f** (0.3 mmol), **3.4** (0.36 mmol), $Pd(PPh_3)_4$ (0.03 mmol), XantPhos (0.03 mmol), Cs_2CO_3 (0.9 mmol), DMF (4 mL), 120 °C, 24 h.

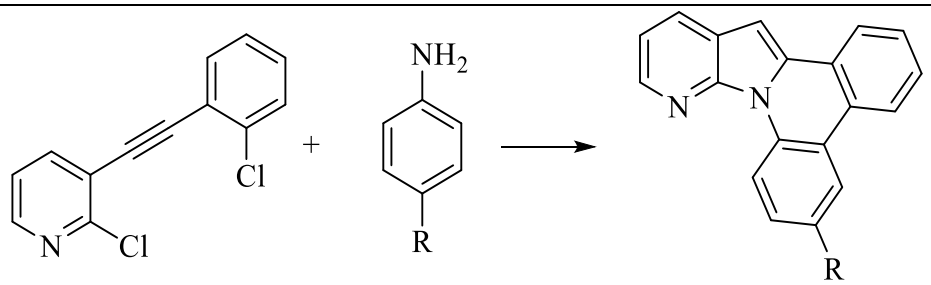
To my delight, the reaction proceeded without any problem when the same conditions as in the previous reaction were applied, affording desired products in moderate to high yields. Interestingly, compounds **3.7a** (**3.8a**), **3.7b** (**3.8f**), **3.7c** (**3.8e**) could be synthesized by this method with higher yield. Besides, other modifications on the aniline ring gave lower yields compared to 2-bromoanline. However, the limitation of this method is the selectivity when meta-substituted amines are used, such as 3-methoxyaniline **3.4e**. In this case, using 3-methoxyaniline resulted in a mixture of two products, which were not separable by column chromatography.

Additionally, the selectivity of the Sonogashira reaction on halogenated pyridines gives us the possibility to deliver a higher diversity of products by customizing the starting material. To demonstrate this, the selective Sonogashira mono-coupling reaction of 1-chloro-2-ethynylbenzene on 3-bromo-2-chloropyridine was performed to afford alkyne **3.6g**. The coupling reaction of 3-bromo-2-chloropyridine is controlled by the chemoselectivity of bromide at position 3 versus the chloride at position 2, compared to 2,3-dibromopyridine in which reactions at position 2 are more favored. Subsequently, alkyne **3.6g** produced various 7-azaindolo[1,2-*f*]phenanthridines **3.9a-3.9c** under optimized conditions as shown in table 3.8. Noteworthy, the C^2-Cl of **3.6g** (of pyridine ring) is more reactive than of 1-chloro-2-(phenylethynyl)benzene for the first step of the domino reaction (Buchwald-Hartwig reaction), as 1-chloro-2-(phenylethynyl)benzene showed no conversion when applied conditions to perform the domino reaction (scheme 3.2).

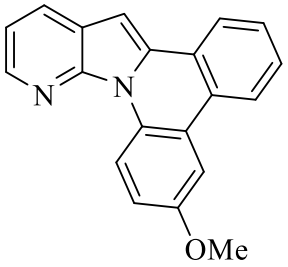


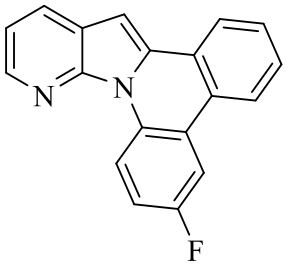
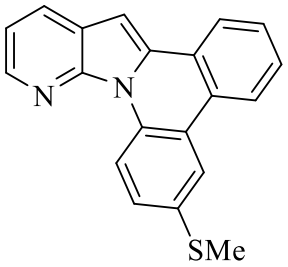
Scheme 3.8: Synthesis of **3.6g**

Table 3.8: Synthesis of 7-azaindolo[1,2-*f*]phenanthridines



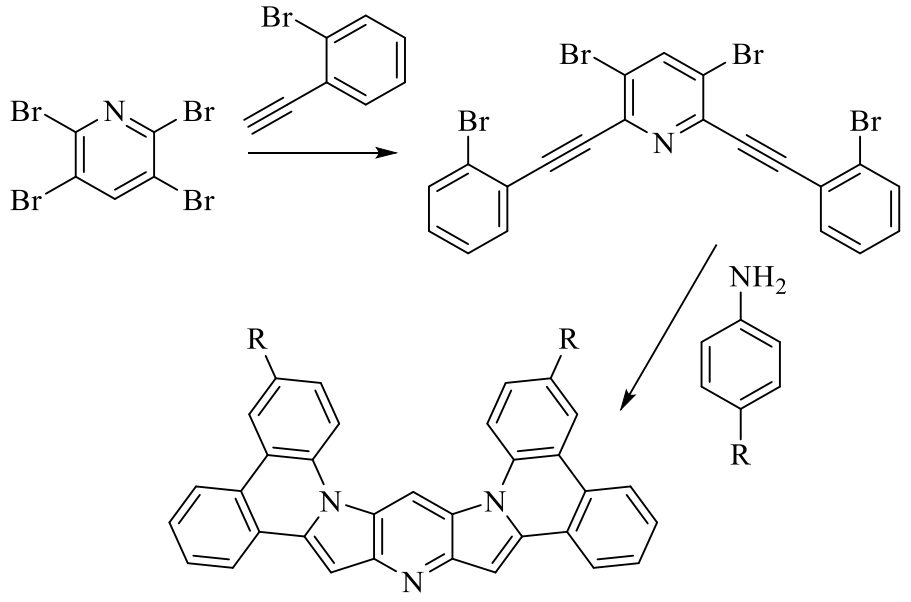
3.6g **3.4** **3.9**

Compound	R	Structure	Yield (%)[a]
3.9a	4-MeO (**3.4d**)		34

3.9b	4-F (**3.4g**)		51
3.9c	4-SMe (**3.4j**)		36

Conditions: **3.6g** (0.3 mmol, 1 equiv.), **3.4** (0.36 mmol, 1.2 equiv.), $Pd(PPh_3)_4$ (0.03 mmol, 10 mol%), XantPhos (0.03 mmol, 10 mol%), Cs_2CO_3 (0.9 mmol, 3 equiv.), DMF (4 mL), 120 °C, 24 h. (temperature and reaction time were not optimized)

To explore larger conjugated systems, I considered structure **3.10** (scheme 3.9) as the target of the domino reaction. Then, 2,3,5,6-tetrabromopyridine was utilized as the starting material, affording product of selective two-fold Sonogashira reaction at 2 and 6 positions as the set-up for the domino reaction. Unfortunately, the reaction resulted in an inseparable mixture.



3.10
Inseparable mixture

Scheme 3.9: Two-fold domino reaction

3.4. Absorption and fluorescence properties of azaindolo[1,2-*f*]phenanthridines

The optical properties of all synthesized compounds were studied by UV/Vis and fluorescence spectroscopy in CH_2Cl_2 at 25 °C as summarized in table 3.9. The UV/Vis spectra show an absorption band in the range of 270-300 nm and several weaker bands in the range of 300-400 nm (figure 3.6). In general, introducing electron-donor groups, such as a methyl or methoxy group, at the core structure **3.7a** causes a slight red shift of the absorption bands. A stronger redshift was observed for compound **3.8h** by extending the conjugated system of the core structure. Changing the position of the nitrogen atom in the azaindole moiety (compounds **3.9a**, **3.9b**, **3.9c**) caused also a shift to longer wavelengths. The similar trend was also observed in the emission spectra.

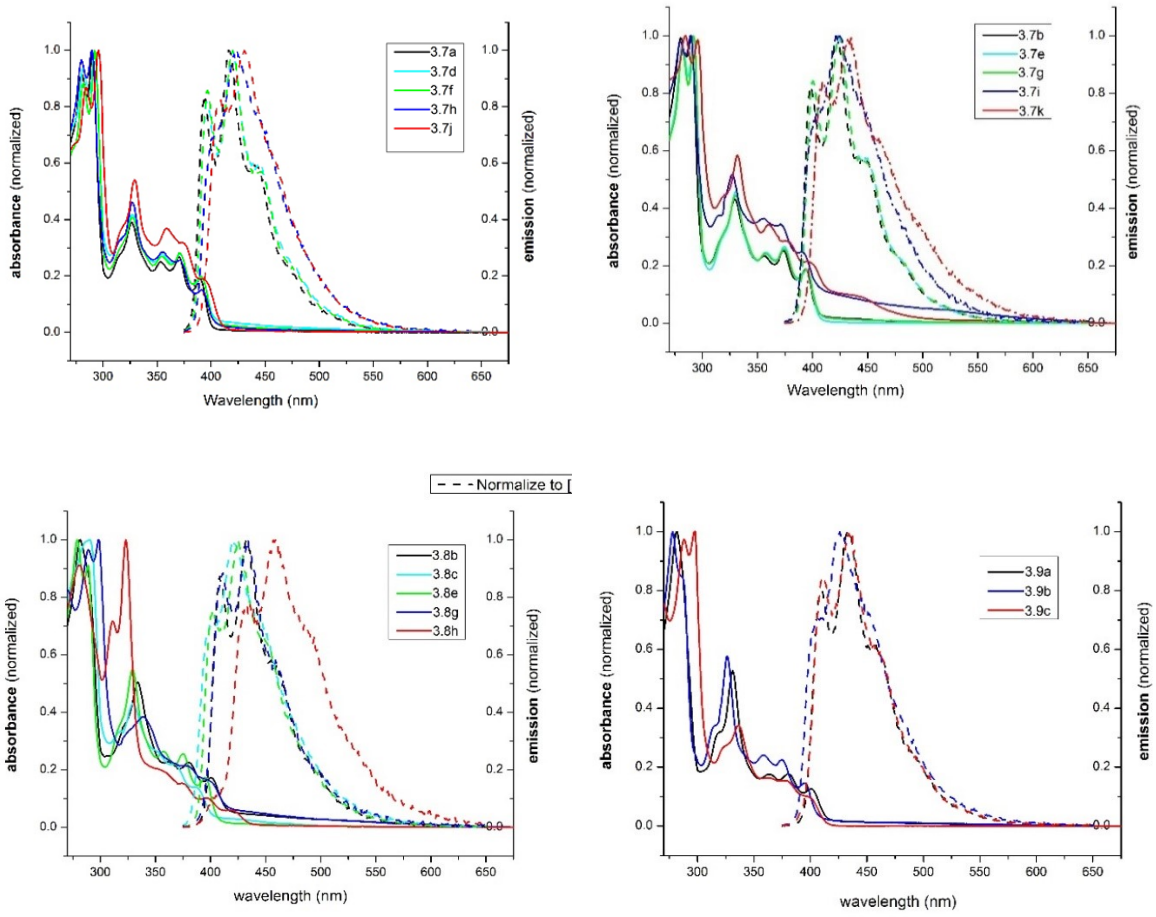


Figure 3.6: Normalized absorption and corrected emission spectra of azaindolo[1,2-*f*]phenanthridines in CH_2Cl_2.

Table 3.9: Absorption and emission spectroscopic data of azaindolo[1,2-*f*]phenanthridines

Cp	λ_{abs1}	Log $\varepsilon(\lambda_{abs1})$	λ_{abs2} (nm)	Log $\varepsilon(\lambda_{abs2})$	λ_{abs3} (nm)	Log $\varepsilon(\lambda_{abs3})$	λ_{abs4} (nm)	Log $\varepsilon(\lambda_{abs4})$	λ_{abs5} (nm)	Log $\varepsilon(\lambda_{abs5})$	λ_{em} max (nm)	Φ_{fluo} %
3.7a	290	6.347	326	5.937	354	5.744	370	5.777	390	5.623	416	65
3.7d	292	6.598	328	6.251	355	6.098	371	6.100	391	5.978	420	42
3.7f	292	6.729	327	6.349	354	6.178	371	6.196	390	6.054	420	53
3.7h	290	6.614	327	6.296	355	6.105	371	6.065	391	5.872	424	28
3.7j	296	6.554	329	6.287	359	6.121	373	6.059	391	5.836	431	47
3.7b	290	6.576	329	6.214	356	5.953	374	5.984	394	5.860	421	52
3.7e	292	6.647	330	6.308	357	6.039	374	6.072	394	5.916	424	56
3.7g	292	6.649	330	6.301	375	6.041	374	6.069	394	5.929	425	55
3.7i	289	6.469	327	6.233	356	6.122	371	6.105	390	6.011	424	14
3.7k	296	6.338	332	6.115	360	5.893	375	5.819	396	5.702	435	32
3.8b	282	6.503	334	6.234	361	5.947	380	5.946	400	5.858	432	28
3.8c	290	6.645	330	6.288	-	-	368	6.010	385	5.832	420	28
3.8e	289	6.581	329	6.363	357	6.049	375	6.036	395	5.871	425	38
3.8g	289	6.567	338	6.203	-	-	375	5.994	-	-	434	12
3.8h	281	6.646	-	-	374	5.897	396	5.735	418	5.530	459	19
3.9a	282	6.785	331	6.060	364	6.060	380	6.063	400	5.930	433	40
3.9b	278	6.649	326	6.416	358	6.056	375	6.027	395	5.858	426	30
3.9c	288	6.845	337	6.337	363	6.018	376	5.993	400	5.785	436	26

Fluorescence spectra of the compounds were measured in CH_2Cl_2 exciting them at 360 nm. The spectra show maximal emission in the range of 416 nm to 469 nm. Emission quantum yields were determined using a solution of quinine hemisulfate salt monohydrate in 0.05 M H_2SO_4 ($\Phi = 0.52$) as a reference standard.[90] Among the synthesized compounds, 4-azaindolo[1,2-*f*]phenanthridine **3.7a**, which contains no substituent, possesses the highest quantum yield of 65%. In addition, 7-azaindolo[1,2-*f*]phenanthridine **3.9a** also exhibit a good quantum yield of 40%. Noteworthy, the quantum yield of indolo[1,2-*f*]phenanthridine was reported to be only 21%.[83] Therefore, introducing one more nitrogen atom to the scaffold of indolo[1,2-*f*]phenanthridine to obtain azaindolo[1,2-*f*]phenanthridines gives a much better result. However, introducing both electron-donating and electron-withdrawing groups to the core structure leads to decreased quantum yields. The poorest quantum yield of 12% was observed in compound **3.8g** which contains a methylthio group.

3.5. Unsuccessful results

Attempt to total synthesis of arnoamine C, D, and their derivatives

Recently, the search for new pharmaceuticals from the marine environment has resulted in the isolation of a large number of alkaloids. In 2013, arnoamine C and D, which contain a pentacyclic unit, were isolated from Cystodytes violatinctus and showed interesting anticancer activities. IC_{50} values of arnoamine D are less than 10 μM in the presence of HCT116, SW480,

and A375 cancer cell lines.[91] Derivatives of Arnoamine C & D would have interesting bioactivities for applications in medicinal chemistry.

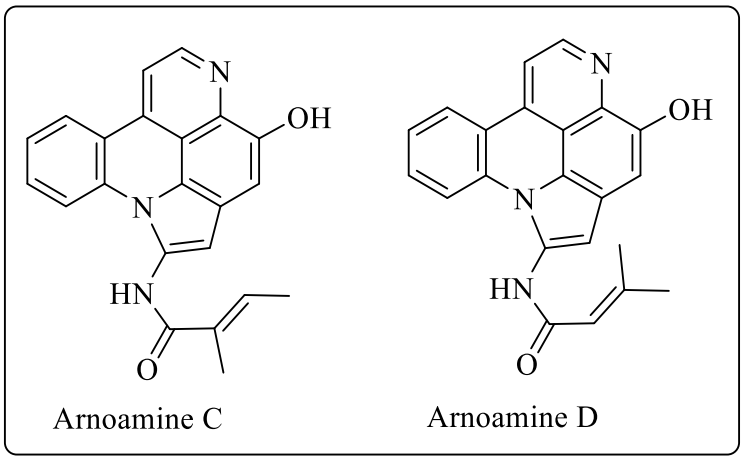
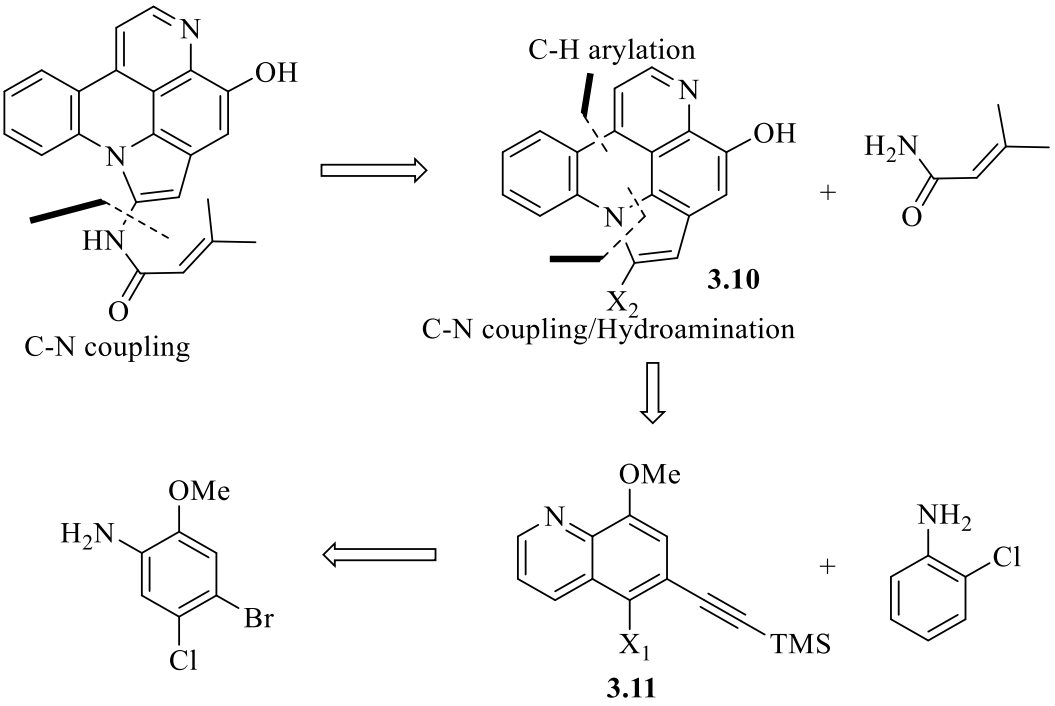


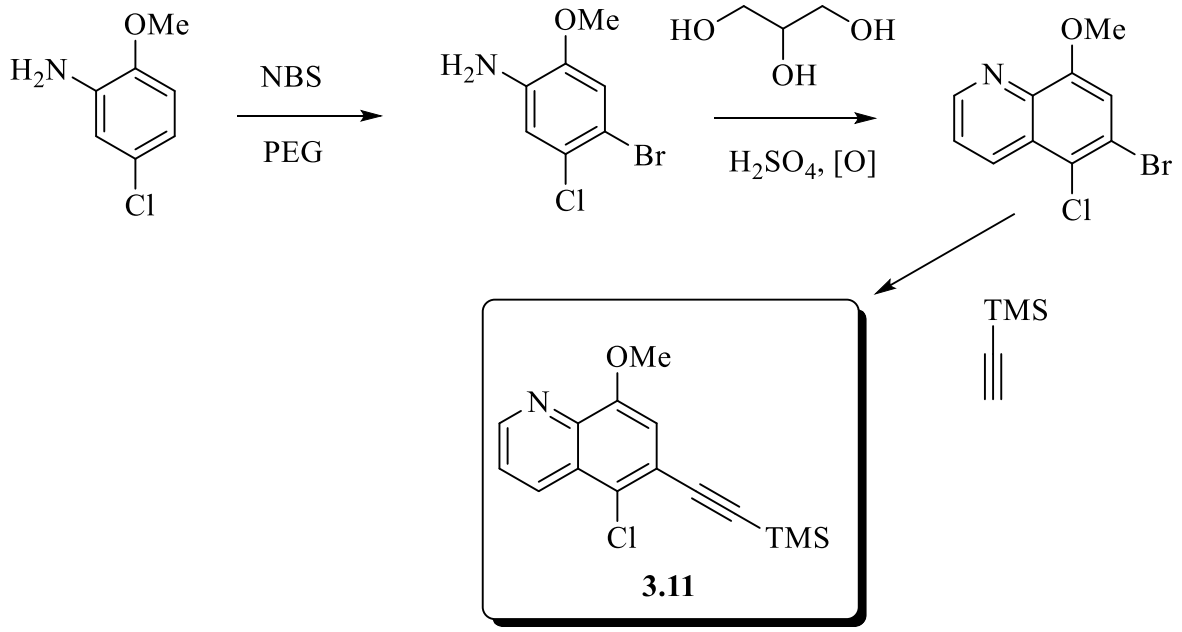
Figure 3.7: Arnoamine C & D

Based on the same strategy described in scheme 3.1, the total synthesis of Arnoamine C & D and their derivatives could be synthesized using three-step domino reaction (scheme 3.11).



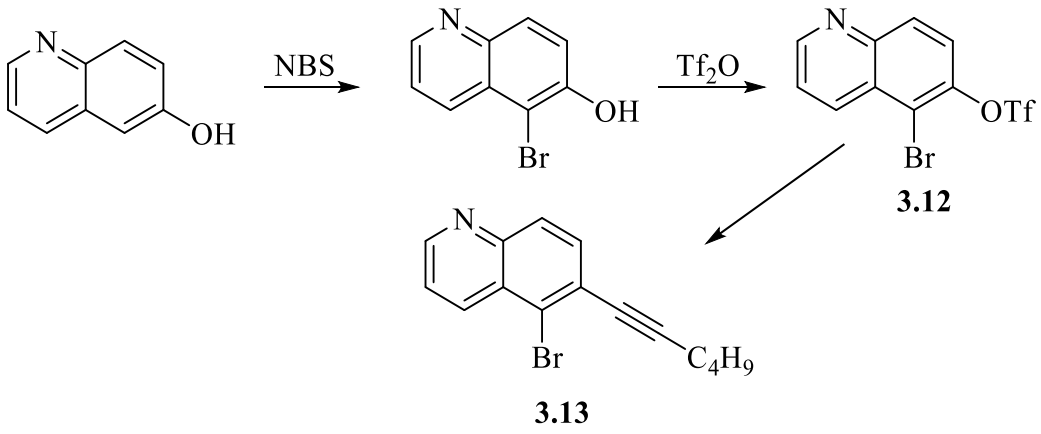
Scheme 3.10: Retrosynthesis analysis of Arnoamines

The starting material **3.11** can be synthesized from 5-chloro-2-methoxyaniline via 3 steps in scheme 3.11.[92]



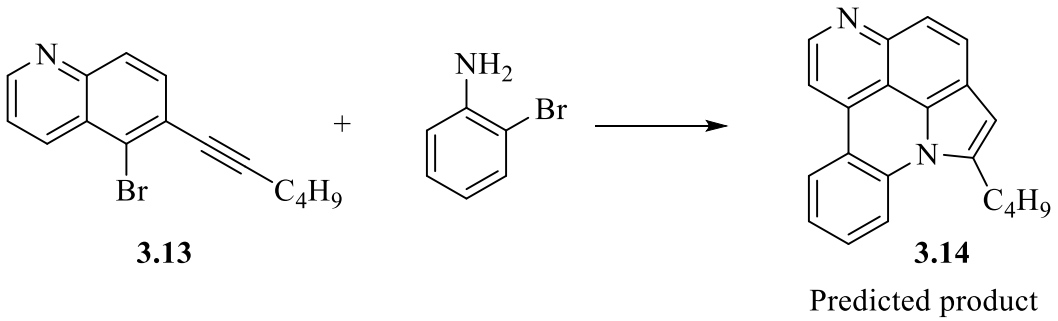
Scheme 3.11: Proposed Synthesis of starting material

However, the precursor **3.11** failed to convert to corresponding desired compound **3.10**. I assumed that chlorine might be not reactive enough for the reaction; therefor, another starting material containing bromine was employed. For this purpose, 6-hydroxyquinoline was used as the starting point, following by bromination with NBS and triflation to obtain 5-bromo-6-trifluoromethanesulfonatequinoline **3.12**. Selective Sonogashira at the C-OTf of quinoline **3.12** was performed successfully, affording precursor **3.13** for the domino reaction.



Scheme 3.12: Alternative starting material **3.13**

With the initial screening, the formation of desired product was observed together with the intermediate by GC/MS. But unfortunately, the desired product **3.14** was not separable as the pure product.



3.13 **3.14**

Predicted product

Scheme 3.13: Domino reaction of **3.13**

3.6. Conclusion

In conclusion, two Pd-catalyzed three-step tandem reactions comprising of the three sequential reactions: C-N coupling, hydroamination and C-H arylation reaction were developed. These methods offer a straightforward synthesis of indolo[1,2-*f*]phenanthridines under mild conditions with good yields, which are interesting for further applications in the synthesis of new organic materials and bioactive molecules. In addition, a series of new azaindolo[1,2-*f*]phenanthridines were synthesized conveniently by this strategy. The starting materials were easily accessible by regioselective Sonogashira cross-coupling reaction, which lead to diverse final products. The absorption and fluorescence properties of all products were studied. This class of compounds shows promising photophysical properties, in particular, high quantum yields. Furthermore, other new aromatic polyheterocycles are being explored by the developed synthetic method.

The results of this chapter were published in:

T. N. Ngo, P. Ehlers, T. T. Dang, A. Villinger, P. Langer, *Org. Biomol. Chem.* **2015**, *13*, 3321–3330. ***Highlighted in Synfacts S001815SF***.

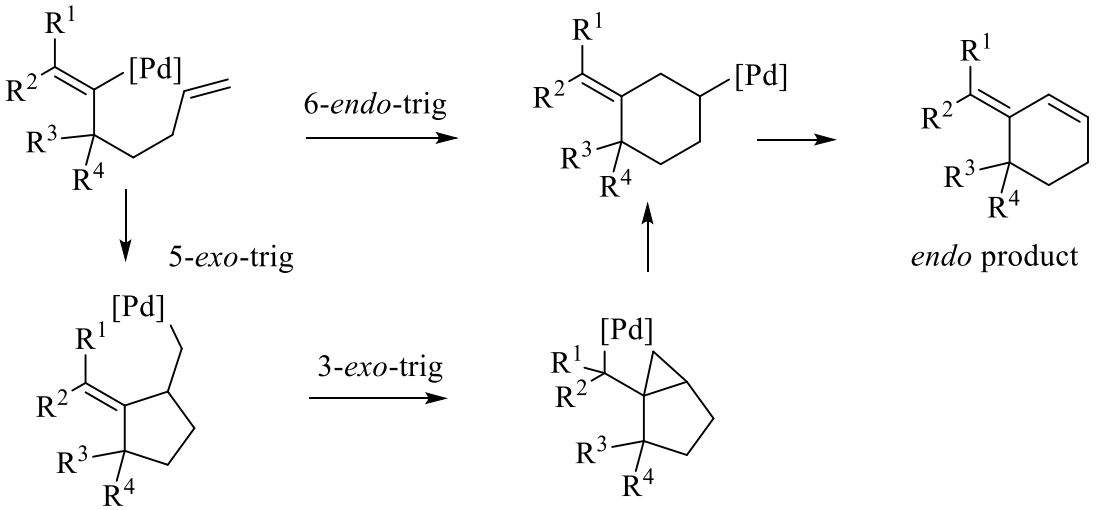
and

T. N. Ngo, F. Janert, P. Ehlers, D. H. Hoang, T. T. Dang, A. Villinger, S. Lochbrunner, P. Langer, *Org. Biomol. Chem.* **2016**, *14*, 1293–1301.

4. Regioselective synthesis of naphtho-fused heterocycles *via* palladium(0)-catalyzed tandem reaction of *N*-tosylhydrazones

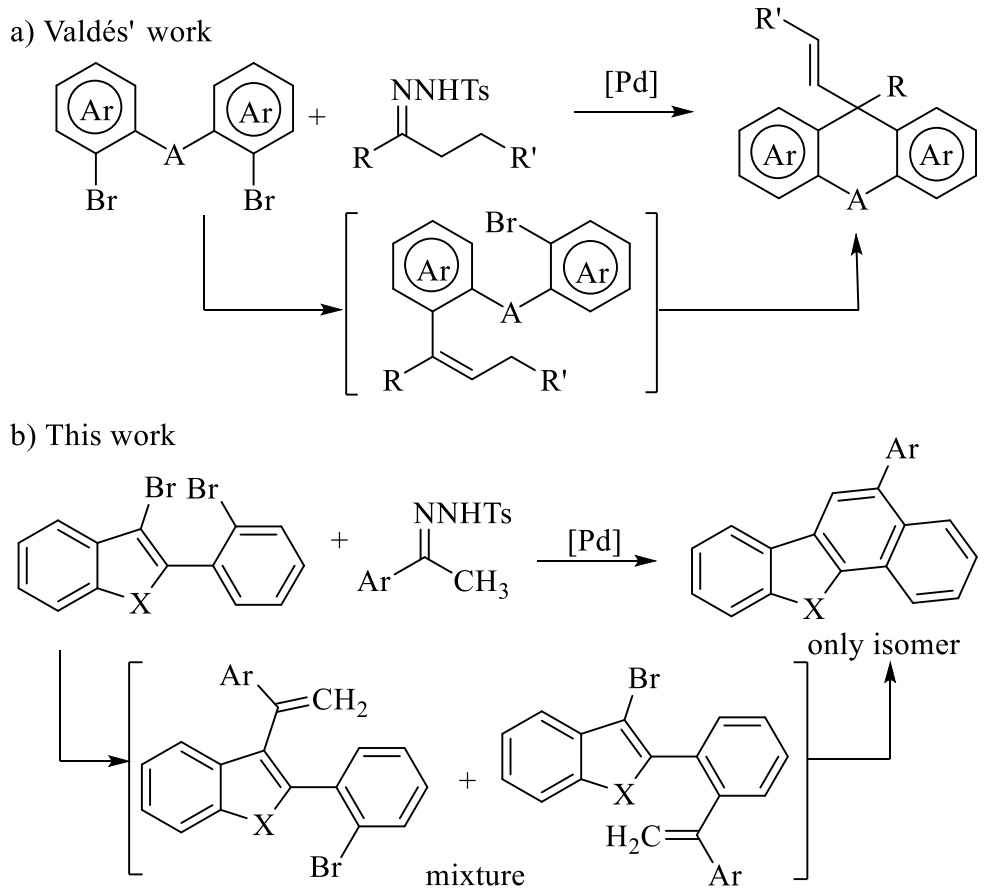
4.1. Introduction

Since its first discovery, independently by Mizoroki and Heck, Heck-Mizoroki reaction is among the most useful synthetic tools due to its high chemoselectivity, mild reaction conditions, and cheap reaction reagents.[93] Especially, domino processes involving intramolecular Heck-Mizoroki reaction have been known as one of the most powerful methods to produce polycarbocyclic or polyheterocyclic compounds with a variety of ring sizes. The active alkyl intermediate palladium complexes, formed by insertion of double bond to Pd(II) complex, can participate in sequential intra- or intermolecular processes before the *β*-hydride elimination step[94]. For example, the active intermediate alkyl palladium complex could react with another double bond in the molecule to afford fused bicyclic compounds.[95] Moreover, regioselectivity in intramolecular Heck reaction has also attracted a lot of attention. Generally, intramolecular Heck reactions give *exo*-trig cyclization products, however, several reactions formed 6-*endo*-trig instead of 5-*exo*-trig cyclized products.[96] In some cases, the 6-membered ring might be the result of a sequence of 5-*exo*-trig, then 3-*exo*-trig cyclization, finally ring opening of cyclopropane (Scheme 4.1). If the *β*-hydride elimination occurs before the ring opening process, the cyclopropane ring is still retained in the product as the evidence for this mechanism.[97] Although many studies regarding this process have been achieved, studying the behavior of palladium on the variety of substrates is still compelling for insightful understanding.



Scheme 4.1: Pathways of 6-*endo*-trig and 5-*exo*-trig cyclizations

Recently, the utility of easily accessible *N*-tosylhydrazones as the coupling partner for metal-catalyzed cross-coupling reactions has attracted growing attention.[28–31,98] As discussed earlier in chapter 1, the method relies on the insertion of carbene species, generated in situ from *N*-tosylhydrazones, to Pd(II) complexes. In 2007, the group of Barluenga developed palladium-catalyzed cross coupling reactions of *N*-tosylhydrazones and aryl halides, efficiently affording polysubstituted olefins.[30] Furthermore, the presence of the double bond in obtained olefins attracts a sequential intramolecular Heck cyclization. To exemplify, Valdés *et. al.* reported a palladium-catalyzed autotandem process which involves cross-coupling of *N*-tosylhydrazones with 2,2′-dibromobiphenyls followed by a 5-*exo*-trig Heck-type cyclization, final *β*-hydride elimination step to give the formation of various polycyclic compounds (Scheme 4.2a).[99]



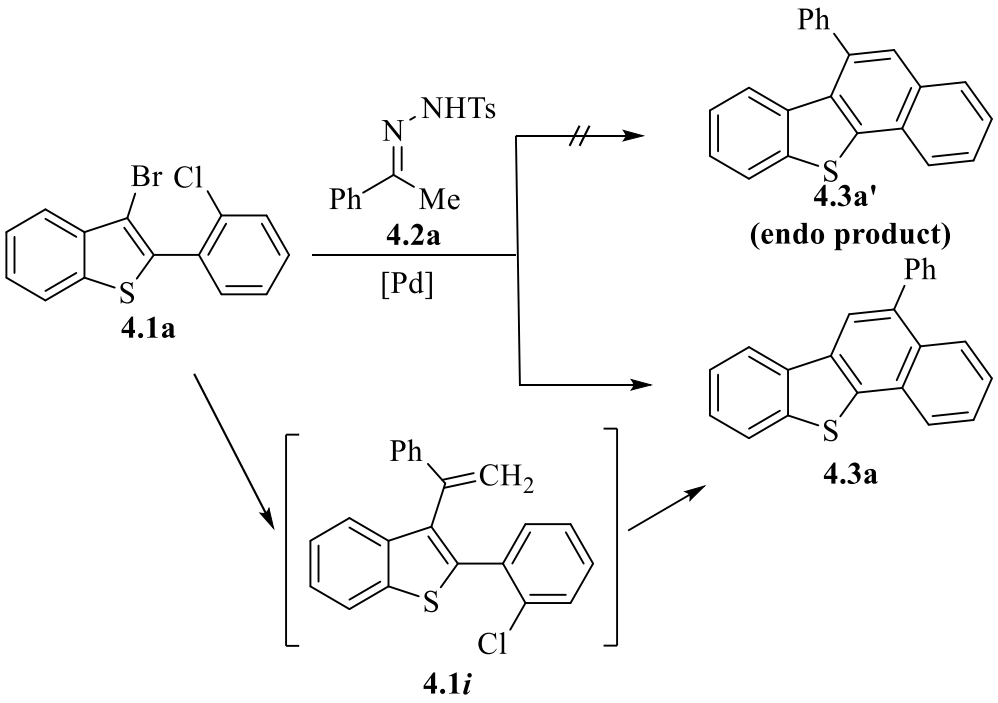
Scheme 4.2: Pd-catalyzed cyclization of dibrominated compounds with hydrazones

From this perspective, I wish to report a novel tandem process started from the cross-coupling reaction of *N*-tosylhydrazones with dibromide compounds, then followed by a sequence of intramolecular 5-*exo*-trig, 3-*exo*-trig cyclization, ring opening, *β*-hydride elimination in the presence of a single palladium catalyst to give 6-*endo*-trig cyclization products (scheme 4.2b). The obtained fused heterocycles, heterotetracenes and

heteropentacene, with large π-extended conjugated aromatic system are important in both materials science and medicinal chemistry.[100] To the best of my knowledge, only few tandem procedures to access these fused systems were developed to date.[101]

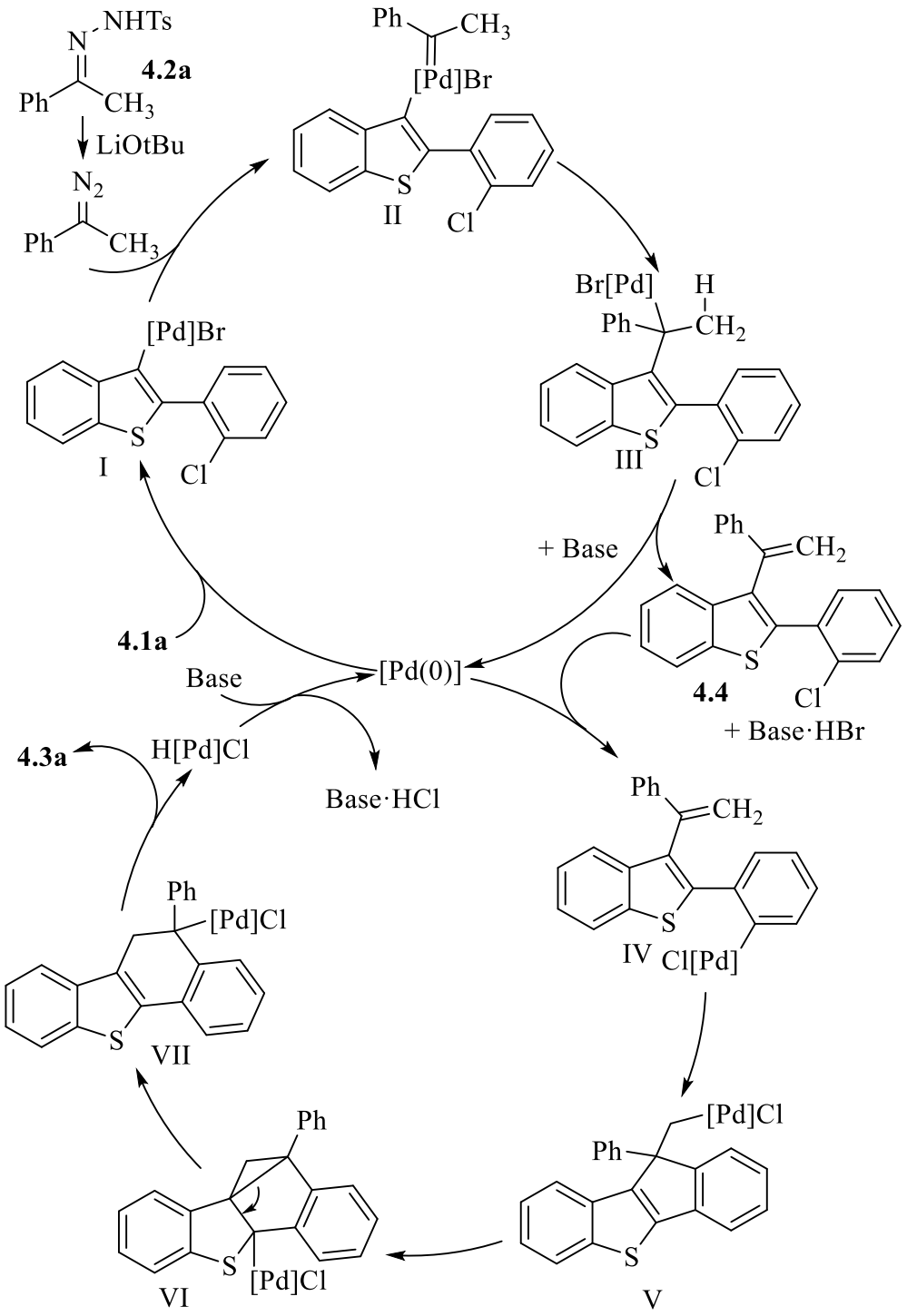
4.2. Synthesis of naphtho-fused heterocycles

For the initial investigation, 3-bromo-2-(2'-chlorophenyl)benzo[*b*]thiophene (**4.1a**) and acetophenone *N*-tosylhydrazone (**4.2a**) were chosen as model substrates (Scheme 4.3). Firstly, I utilized $Pd_2(dba)_3$ and XPhos as the catalytic system and LiO*t*Bu as the base, which are known as standard conditions for the cross-coupling reaction of *N*-tosylhydrazones and aryl halides. Two similar reactions at 90 °C in dioxane as the solvent were performed under argon. One reaction was stopped after 2 hours, and the intermediate as the product of the first coupling was isolated. The structure of the intermediate **4.1*i*** was confirmed by NMR and mass spectra as the new terminal double bond was formed and the chlorine still remained in the molecule. The remaining reaction was continued and the reaction temperature was raised to 100 ºC. After 4 h, complete conversion of **4.1a** and formation of only one product with 72% yield were observed. Surprisingly, the product was proved to be regioisomer **4.3a** by X-ray crystallographic analysis, which is different from the 6-*endo*-trig cyclization **4.3a'**.

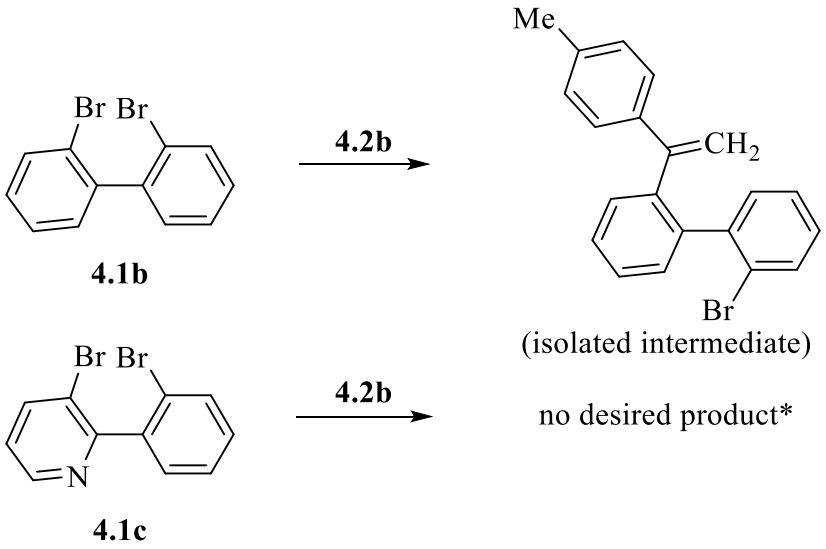


Scheme 4.3: Tandem reaction of 3-bromo-2-(2'-chlorophenyl)benzo[*b*]thiophene **4.1a** with *N*-tosylhydrazone of acetophenone **4.2a**
Conditions: **4.1a** (0.2 mmol, 1 equiv.), **4.2a** (0.3 mmol, 1.5 equiv.), $Pd_2(dba)_3$ 2.5 mol%, XPhos 10 mol%, LiO*t*Bu (0.8 mmol, 4 equiv.), dioxane (4 mL).

On the basis of these experimental results in the combination with reported literature on domino palladium-catalyzed processes as well as Barluenga's and Valdés' reports of *N*-tosylhydrazones and aryl halides, I postulate that the mechanism of the reaction followed a sequence of intramolecular 5-*exo*-trig, 3-*exo*-trig cyclization, ring opening, and finally *β*-hydride elimination. The proposed mechanism is described in Scheme 4.4. The catalytic cycle is believed to initiate by the first oxidative addition of C-Br bond of **4.1a** with palladium catalyst to form an active Pd-complex (**I**). This complex reacts with the carbene generated from *N*-Tosylhydrazone **4.2a** to give new palladium active species (**III**) *via* intermediate complex (**II**). The reductive elimination of complex (**III**) regenerates palladium(0) species and an intermediate (**4.4**), which was isolated. The second oxidative addition of intermediate (**4.4**) with palladium catalyst results in formation of a new active palladium complex (**IV**). The intramolecular cyclization of this palladium species (**IV**) *via* 5-*exo*-trig, 3-*exo*-trig cyclization, and then ring opening of cyclopropane lead to the more stable palladium complex (**VII**). A second reductive elimination of palladium complex (**VII**) releases the cyclized product (**4.3a**) and H[Pd]Cl, which reacts with base to reproduce palladium(0) catalyst (Schem 4.4).



Scheme 4.4: Proposed mechanism of Pd-catalyzed cyclization of dibrominated compounds with hydrazones.



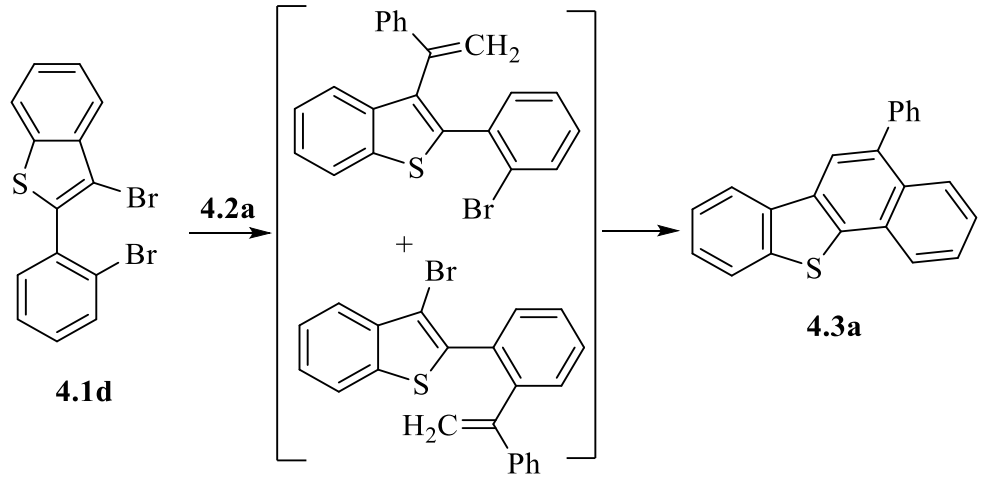
Scheme 4.5: Tandem reaction of 2,2′-dibromobiphenyl **4.1b** and 3-bromo-2-(2-bromophenyl)pyridine **4.1c**.

Reaction conditions: **1** (0.2 mmol), **4.2a** (0.3 mmol, 1.5 equiv.), $Pd_2(dba)_3$ 2.5 mol%, XPhos 10 mol%, Li*O*t*Bu (0.8 mmol, 4 equiv.), dioxane 4 mL, 110 °C 24 h.* inseparable mixture

In addition, the reaction 2,2′-dibromobiphenyl (**4.1b**) and *N*-tosylhydrazone of 4'-methylacetophenone (**4.2b)** was carried out under the same conditions (Scheme 4.5). It is worth to mention again that the tandem reaction of 2,2′-dibromobiphenyl and *N*-tosylhydrazone of cyclic ketones underwent *β*-hydride elimination after the 5-*exo*-trig cyclization to afford 5-membered ring spiro compounds. In this work, the absence of *β*-hydrogens promoted 3-*exo*-trig cyclization to the double bond of benzothiophene which is not fully conjugated in the aromatic system. However, in the case of 2,2′-dibromobiphenyl, the alkyl palladium complex was not able to perform 3-*exo*-trig cyclization to the stable conjugated aromatic system of benzene. Therefore, only the uncyclized product was detected after 24 h. The same result was observed with 3-bromo-2-(2-bromophenyl)pyridine. These results also confirmed the hypothesis about the mechanism of the reaction.

In order to improve the yield of the desired products, I utilized 3-bromo-2-(2-bromophenyl)benzo[*b*]thiophene (**4.1d**) as the starting material instead of 3-bromo-2-(2'-chlorophenyl)benzo[*b*]thiophene (**4.1a**). The reaction was performed under the same conditions at 90 °C. Surprisingly, the reaction completed after 4 h producing only **4.3a** with 83% yield. Then, other combinations of $Pd(OAc)_2$, $Pd_2(dba)_3$ and different ligands were examined, however, no significant improvement of yield was observed. Therefore, the combination of $Pd_2(dba)_3$ and XPhos proved to be the best so far. Increasing the amount of $Pd_2(dba)_3$ to 5 mol% and XPhos to 20% increased the yield to 85%, so it was not reasonable to use more amount of catalyst. As I reviewed the literature, almost of the publications related to

the cross-coupling of *N*-tosylhydrazones employed the conditions with LiO*t*Bu as the base and dioxane as the solvent, so the combination of LiO*t*Bu and dioxane is believed to be important for the first cross-coupling of *N*-tosylhydrazones. Moreover, the reaction was additionally carried out in toluene but resulted in a complicated mixture, without the possibility to isolate the pure compound. The reaction was also tested at 60 °C, 90 °C, and 110 °C. At 60 °C, after 4h, I detected mainly the intermediates. At 110 °C, the reaction completed after 2 hours, but more spots on the TLC were observed, one of them overlapped with the spot of the product, leading to the difficulty in isolating the pure product, so I found that carrying out the reaction at 90 °C was most suitable for this purpose. Interestingly, the formation of two intermediates was observed in this case, because the first coupling of *N*-tosylhydrazone with **4.1d** could undergo at either C-Br bond (Scheme 4.6). The two intermediates gave the same palladium complex after the 5-*exo*-trig cyclization (similar to complex **V**), thus, only one product was formed. Besides, double Heck reaction of **4.1d** with styrene utilizing above conditions as well as conditions reported by Blacklock *et. al*. produced a complicated mixture without the formation of **4.3a**.[102] Therefore, the cross-coupling reaction of *N*-tosylhydrazone was proved to be superior in this tandem reaction.

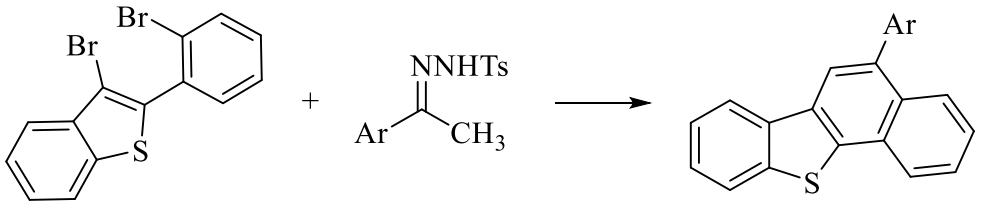


Scheme 4.6: Tandem reaction of 3-bromo-2-(2-bromophenyl)benzo[*b*]thiophene **4.1d** and *N*-tosylhydrazones.

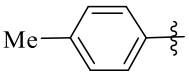
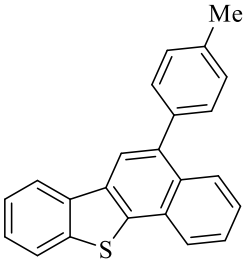
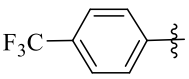
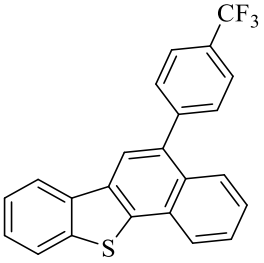
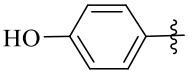
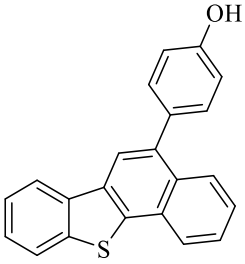
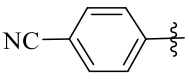
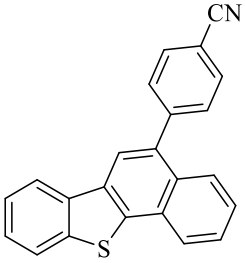
Encouraged by these results, I examined the scope and limitation of the tandem reaction by varying the substrates (table 4.1). Firstly, the tandem reactions of various *N*-tosylhydrazones were performed with 3-bromo-2-(2'-bromophenyl)benzo[*b*]thiophene **4.1d**. To my delight, the optimized conditions were applicable for numerous *N*-tosylhydrazones of substituted acetophenones. Both electron-donating and electron-withdrawing groups on *N*-tosylhydrozones resulted in only one isomer from good to excellent yields. *N*-tosylhydrazone of 4'-methoxyacetophenone gave the best yield of 95% (**4.3i**) while the trifluoromethyl substituent

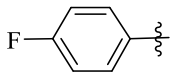
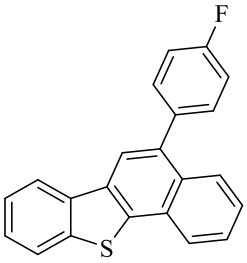
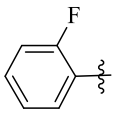
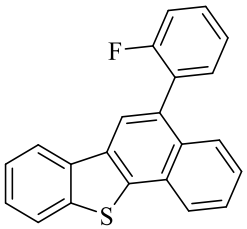
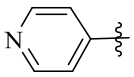
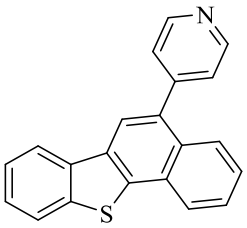
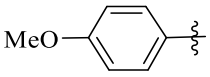
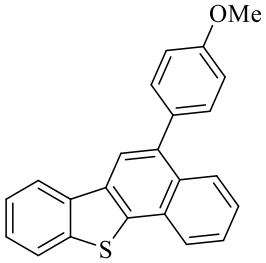
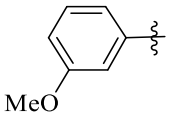
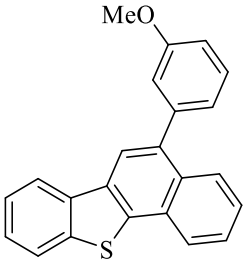
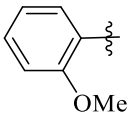
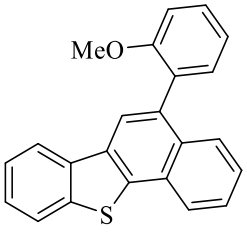
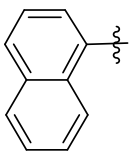
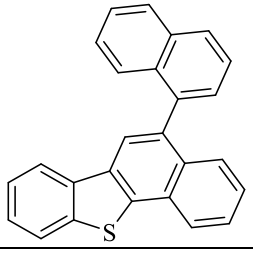
on acetophenone gave the poorest yield with 53% (**4.3c**). There is no predictable effect of substituents on acetophenones moiety on yields of the reaction. The reaction conditions are tolerable with several substituents such as unprotected hydroxyl (**4.3d**) or cyano groups (**4.3e**). *N*-tosylhydrazone derived from hetero-aromatic acetophenone such as 4-acetylpyridine also gave the desired product under the reaction conditions (**4.3h**). Interestingly, a heteropentacene (**4.3o)** could be successfully prepared with 34% yield in the employment of reaction conditions with corresponding 3,3'-dibromo-2,2'-bibenzo[*b*]thiophene. Unfortunately, the reaction of *N*-tosylhydrazone of 1,2-diphenylethan-1-one with **4.1d** resulted in an inseparable mixture.

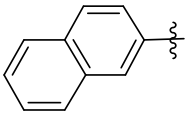
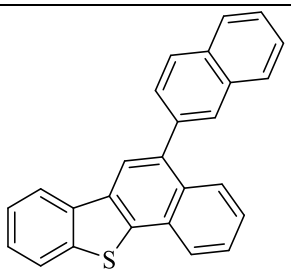
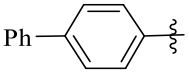
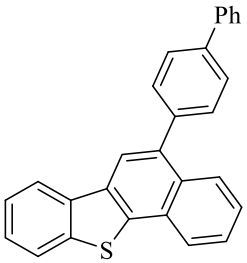
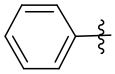
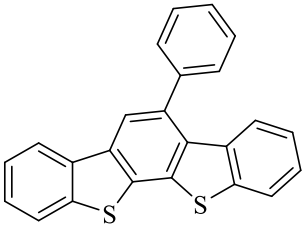
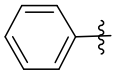
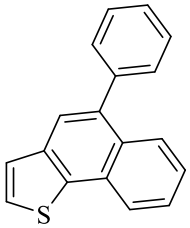
Table 4.1: Synthesis of benzo[*b*]naphtho[2,1-*d*]thiophenes



4.1d **4.2** **4.3**

Compound	Ar	Structure	Yield (%)
4.3b			90
4.3c			53
4.3d			81
4.3e			68

4.3f			89
4.3g			75
4.3h			56
4.3i			95
4.3j			80
4.3k			71
4.3l			65

4.3m			67
4.3n			63
4.3o			34*
4.3p			0**

Conditions: **4.1d** (0.2 mmol), **4.2** (0.3 mmol, 1.5 equiv.), $Pd_2(dba)_3$ 2.5 mol%, XPhos 10 mol%, LiO*t*Bu (0.8 mmol, 4 equiv.), dioxane 4 mL, 90 °C, 4 h.
*) 3,3'-dibromo-2,2'-bibenzo[*b*]thiophene was used instead of **4.1d**.
) 3-bromo-2-(2-bromophenyl)thiophene was used instead of **4.1d, a mixture of uncyclized intermediates was obtained instead of **4.3p**.

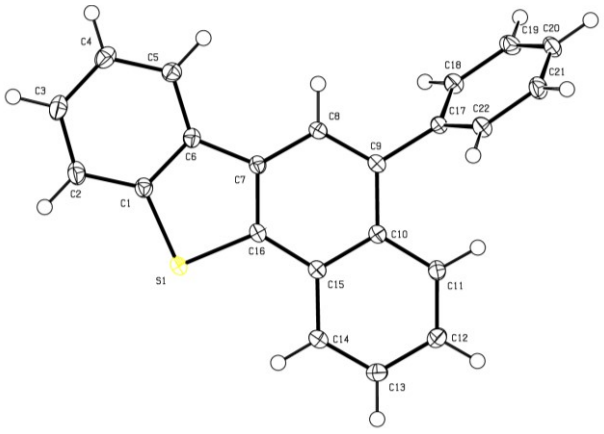


Figure 4.1: The structure of **4.3a** determined by X-ray crystallographic analysis

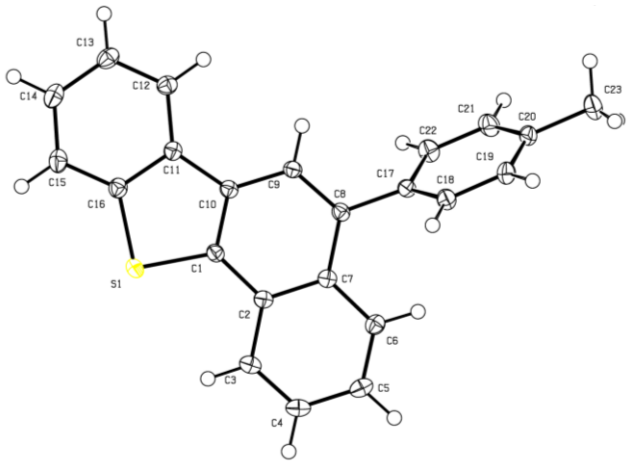
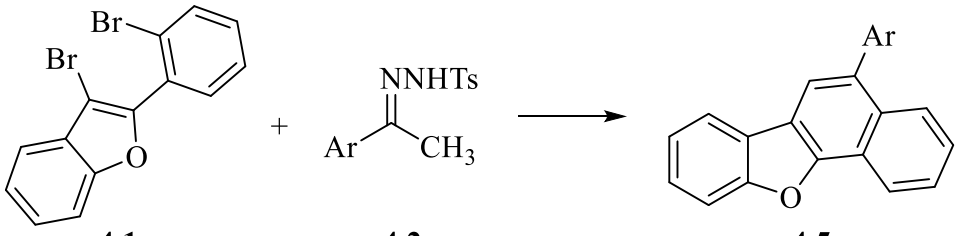


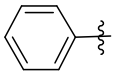
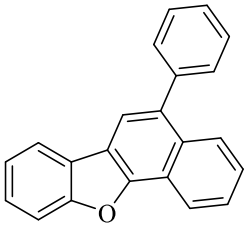
Figure 4.2: The structure of **4.3b** determined by X-ray crystallographic analysis

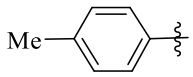
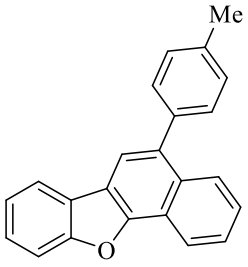
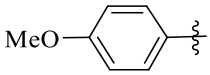
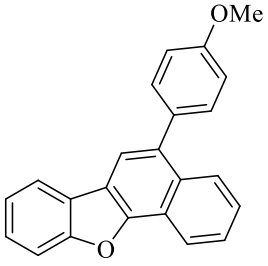
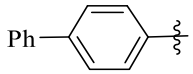
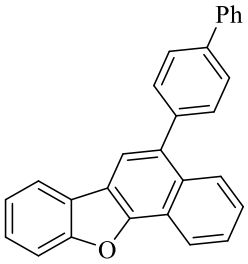
In order to further explore the scope of reaction, I studied the reaction with other dibromide derivatives from different heterocycles. The reaction gave good yields and regioselectivity when applied for 3-bromo-2-(2-bromophenyl)benzofuran **4.1e**. The reaction was assumed following the proposed mechanism for 3-bromo-2-(2'-bromophenyl)benzo[*b*]thiophene, forming similar isomer (table 4.2). Higher temperature and longer reaction time were required when 3-bromo-2-(2-bromophenyl)-1-methyl-1*H*-indole **4.1f** was employed as the precursor, producing benzo[*a*]carbazole derivatives in relatively lower yields (table 4.3).

Table 4.2: Synthesis of naphtho[1,2-*b*]benzofurans



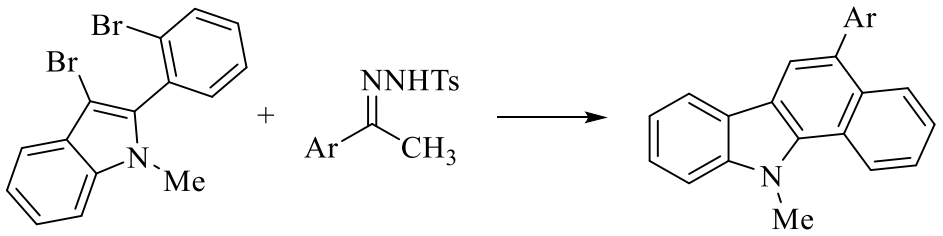
4.1e **4.2** **4.5**

Compound	Ar	Structure	Yield (%)
4.5a			60

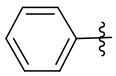
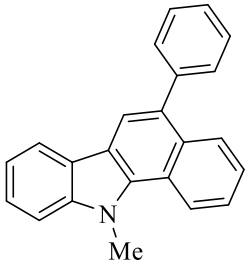
4.5b			45
4.5c			77
4.5d			41

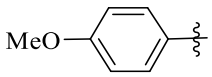
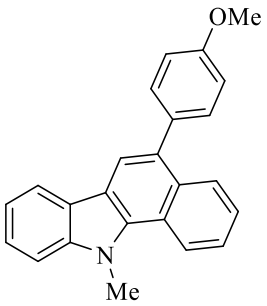
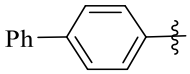
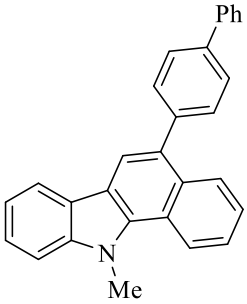
Reaction conditions: **4.1e** (0.2 mmol)**, 4.2** (0.3 mmol, 1.5 equiv.), $Pd_2(dba)_3$ 2.5 mol%, XPhos 10 mol%, LiO*t*Bu (0.8 mmol, 4 equiv.), dioxane 4 mL, 90 °C, 4 h.

Table 4.3: Synthesis of benzo[*a*]carbazoles



4.1f **4.2** **4.6**

Compounds	Ar	Structure	Yield
4.6a			31

4.6b			45
4.6c			39

Reaction conditions: **4.1f** (0.2 mmol), **4.2** (0.3 mmol, 1.5 equiv.), $Pd_2(dba)_3$ 2.5 mol%, XPhos 10 mol%, LiO*t*Bu (0.8 mmol, 4 equiv.), dioxane 4 mL, 100 °C, 12 h.

4.3. Conclusion

In conclusion, I have developed a tandem reaction for regioselective synthesis of a range of π-extended polyheterocyclic aromatic compounds. The reaction can be applied to numerous substrates with the tolerance of various functional groups. Products of the reaction, heterotetracenes and a heteropentacene, are interesting targets to explore potential applications in materials science as well as medicinal chemistry. This strategy could be applied in the synthesis of advanced functional materials containing larger π-extended heteroacene compounds.

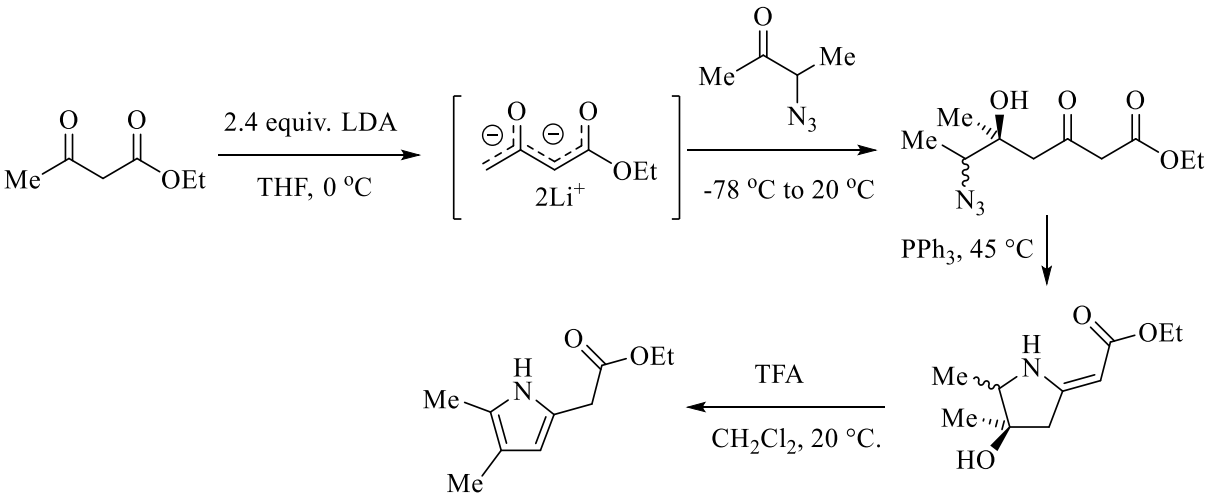
The results of this chapter were published in:

T. N. Ngo, T. T. Dang, A. Villinger, P. Langer, *Adv. Synth. Catal.* **2016**, *358*, 1328–1336.

5. Efficient one-pot synthesis of 5-perfluoroalkylpyrazoles by cyclization of hydrazone dianions

5.1. Introduction

Dianions, contained two negative charges, are known for versatility in cyclization reactions with dielectrophiles to form rings with various size. The group of Prof. Langer has developed several domino or one-pot cyclization reactions based on 1,1-, 1,2-, 1,3-, and 1,4-dianions, affording important core structures ranging from three- to six-membered rings. These concepts can apply to synthesize heterocycles, for example, the regioselective synthesis of functionalized pyrroles by one-pot cyclocondensation of 1,3-dicarbonyl dianions with α-azidoketones. Due to dianions are highly reactive, reactions with dielectrophiles can result in elimination, polymerization, decomposition, and formation of open chained products. An important discovery to overcome the drawback of dianions is the employment of electroneutral dianions, or masked dianions, which are activated when reacting with Lewis acid. The idea was well demonstrated by using 1,3-bis-silyl enol ethers as masked dianions in cyclization reactions with dielectrophiles.[103]



Scheme 5.1: One-pot cyclocondensation of 1,3-dicarbonyl dianions with α-azidoketones

Fluorinated organic compounds have become essential in the development of agrochemicals, and more importantly, in pharmaceuticals.[104] Recently, the number of approved drugs or drug candidates containing fluorine is increasing noticeably, contributing about 25% compounds in pharmaceuticals. In fact, three of ten best-selling drugs contain at least one fluorine: rosuvastatin used for the treatment of high cholesterol and prevent cardiovascular disease,[105] sofosbuvir, and ledipasvir used for the treatment of hepatitis C infection.[106] The high electronegativity combining with its small size makes fluorine

extremely low polarizability, resulting in drastic changes in physicochemical properties of fluoroorganic compounds, most importantly enhancing thermal stability and lipophilicity, thus, increasing bioavailability. In addition, fluorine has the size similar to hydrogen, however, could act as a hydrogen bond acceptor, benefiting the molecules with similar geometry to those of hydrogen but completely different interactions.[107]

Moreover, nitrogen-containing heterocycles constitute a large part of biologically active compounds. Among them, pyrazole moiety is widely recognized, presenting in many leading drugs,[108] such as Zometapine[109] and Viagra[110] and in agrochemicals, such as Tolfenpyrad and Fenpyroximate.[111] Recently, the progression of synthetic fluorination methods leads to the discovery of a pyramid of fluorinated pyrazoles with remarkable biological activities.[112] For example, many important drugs and agrochemicals, such as Celecoxib (antiarthritic),[113] Mavacoxib (antiarthritic),[114] Razaxaban (anticoagulant),[115] Fluazolate (herbicide),[116] Penthiopyrad (fungicide)[117] are derived from trifluoromethylated and perfluoroalkylated pyrazoles. Therefore, developing new efficient methods for the synthesis of fluorinated heterocycles, particularly fluorinated pyrazoles, is still in demand.

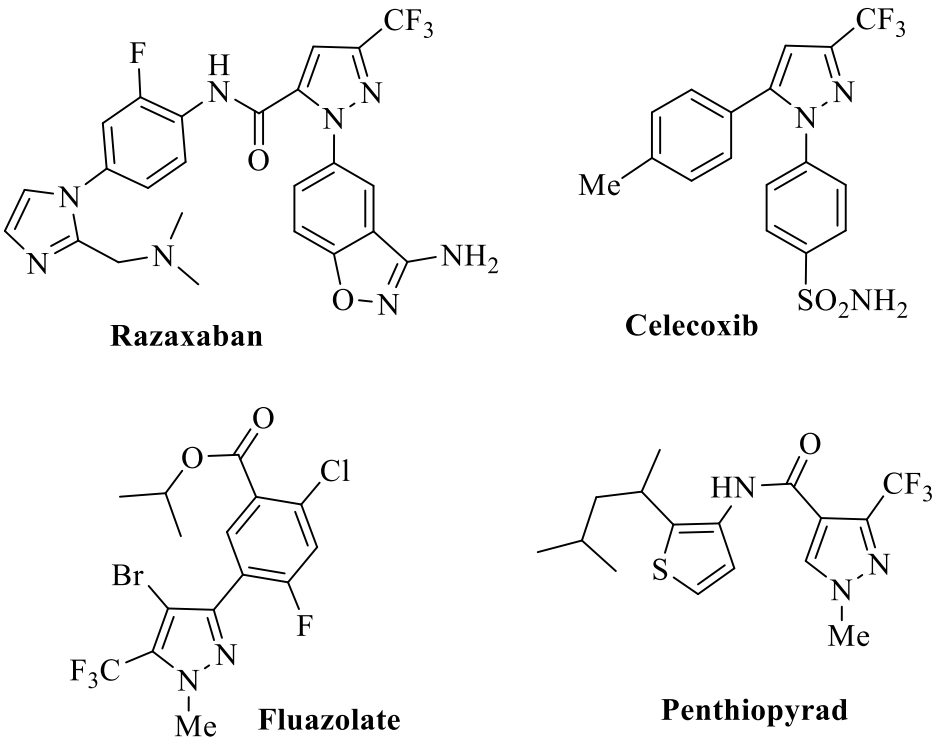
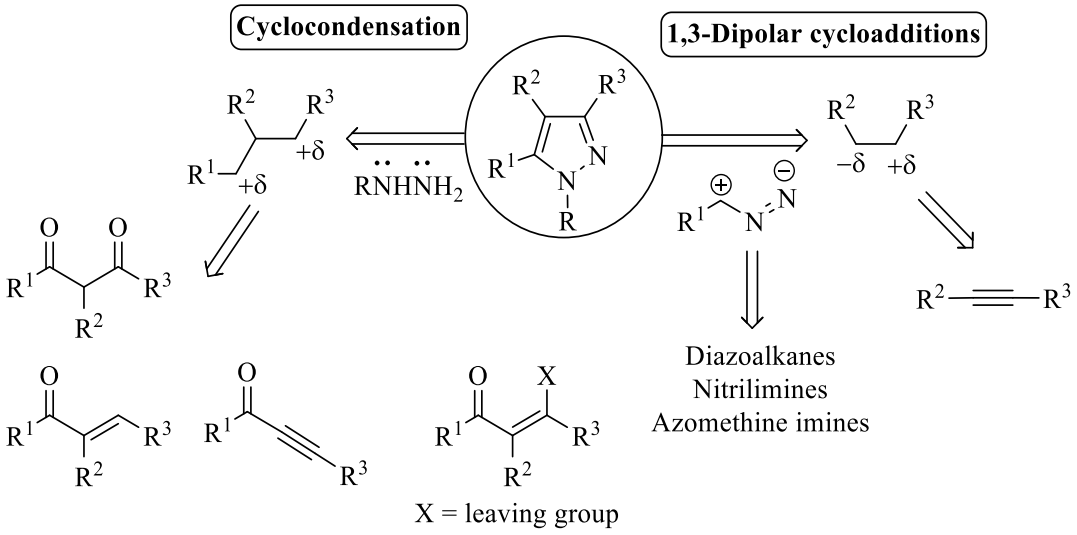


Figure 5.1: Drugs and agrochemicals containing trifluoromethylated pyrazoles

There are two strategies to introduce florine to a structrue: direct fluorination or synthesis from pre-fluorinated building blocks. Although direct fluorination is flourishing and gaining significance with the rapid development of transition metal-catalyzed reactions, the strategy

involving fluorine-containing intermediates is still efficient in various scenarios. Based on developed synthetic methods for specific class of heterocycles, which are already proved their efficiency, fluorine or fluorinated groups, such as trifluoromethyl or perfluoroalkyl, are embedded in molecules of the precursors.

Particularly, conventional methods for the synthesis of pyrazoles are based on the cyclocondensation of hydrazine with 1,3-dielectrophiles, such as 1,3-dicarbonyl or *α,β*-unsaturated carbonyl compounds.[118] Another approach is 1,3-dipolar cycloadditions of an alkyne with various 1,3-dipoles, such as diazoalkanes, nitrilimines, or azomethine imines.[119]

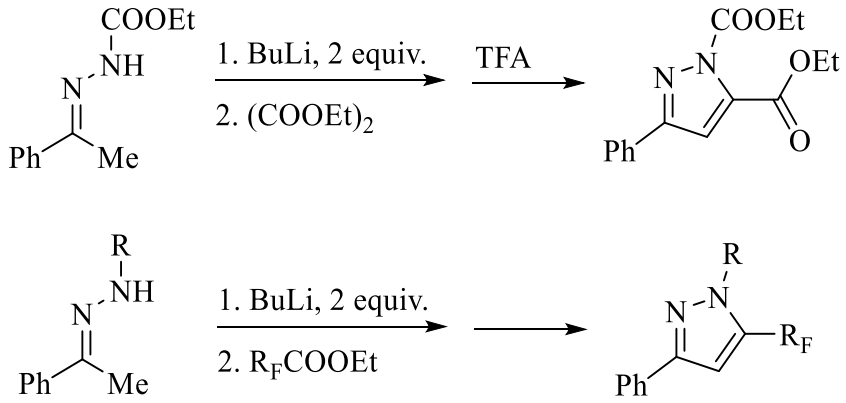


Scheme 5.2: Synthesis of pyrazoles

Trifluoromethylated pyrazoles have been prepared by cyclocondensation of trifluoromethyl-1,3-diketones with phenylhydrazine, however, mixtures of regioisomers were formed.[120] In order to discover more efficient approaches for the synthesis of trifluoromethylated pyrazoles, several research groups have focused on the development of new methods to address the issue of regioselectivity. Frizzo *et al.* reported a useful method for the synthesis of 5-trifluoromethylpyrazoles based on the condensation of 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones with phenyl-hydrazine using the ionic liquid [BMIM][BF_4] as the solvent. In general, this method gave very good yields of 5-trifluoromethylpyrazoles, but for some derivatives, regioisomeric mixtures were still obtained.[121] Recently, some useful methods have been developed to overcome this problem, e.g., the use of fluorinated alcohols (TFE and HFIP) in the cyclocondensation of trifluoromethyl-1,3-diketones with phenylhydrazine or the employment of 4-trifluoromethyl-sydnones as starting materials in the cycloaddition reaction with alkynes.[122] In early 2014, Mykhailiuk and coworkers reported an interesting approach to the synthesis of

3-trifluoromethylpyrazoles in very good yields based on the [3+2] cycloaddition of CF_3CHN_2 with alkynes.[123] Very recently, a new method for the synthesis of 3-trifluoromethylpyrazoles was described via trifluoromethylation/cyclization of *α,β*-alkynic hydrazone with hypervalent iodine reagent.[124]

In addition, another interesting approach is the cyclization of hydrazone dianions with esters. Hauser and co-workers were the first to report the synthesis of 5-substituted pyrazoles by cyclization of hydrazone 1,4-dianions with esters. The same strategy was applied by the group of Prof. Langer to prepare pyrazole-5-carboxylates and pyrazole-1,5-dicarboxylates.[125] I believe that this method could be employed to prepare regioselectively 5-perfluoroalkylpyrazoles (scheme 5.3).



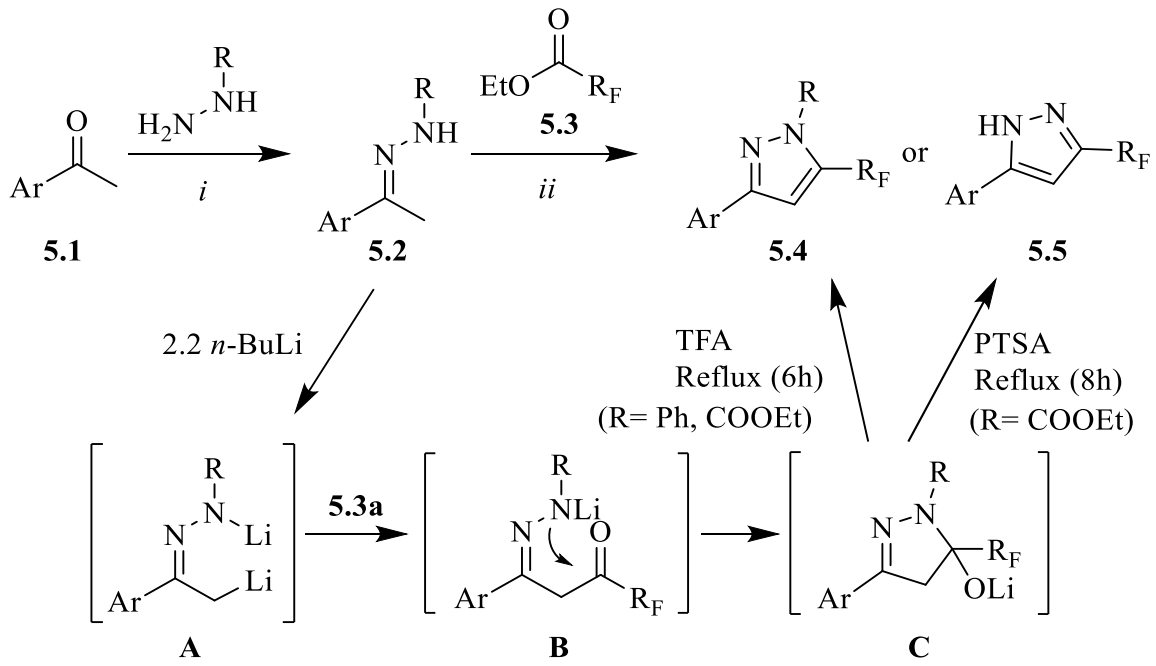
Scheme 5.3: Synthesis of pyrazoles by cyclization of hydrazone 1,4-dianions

In this chapter, a convenient and efficient method for the synthesis 5-trifluoromethyl- and 5-perfluoroalkylpyrazoles by one-pot cyclization of hydrazone 1,4-dianions with fluorinated esters is being described. In addition, the activity of the pyrazoles prepared as inhibitors of human tissue-nonspecific alkaline phosphatase (h-TNAP) and human intestinal alkaline phosphatase (h-IAP) are being discussed. Furthermore, the effects of these molecules were also tested on two other human ectonucleotidases, ecto-nucleotide pyrophosphatase/ phosphodiesterase-1 (h-NPP1) and h-NPP3.

5.2. Synthesis of perfluoroalkylated pyrazoles

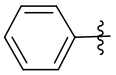
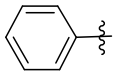
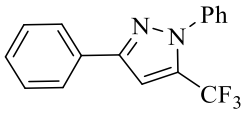
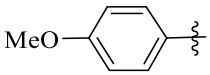
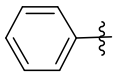
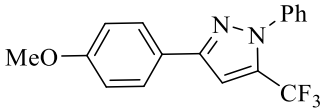
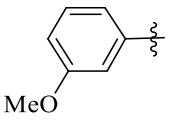
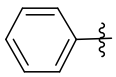
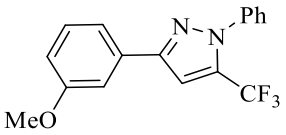
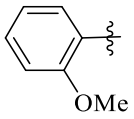
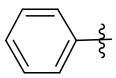
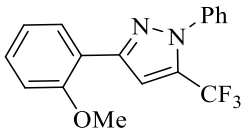
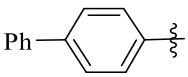
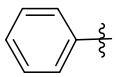
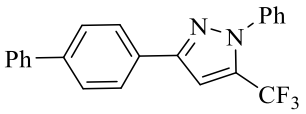
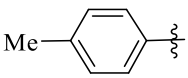
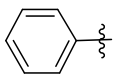
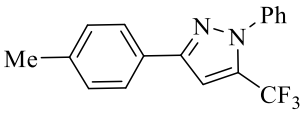
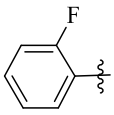
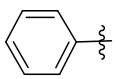
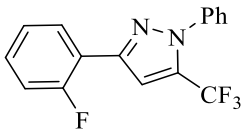
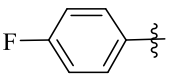
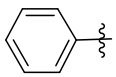
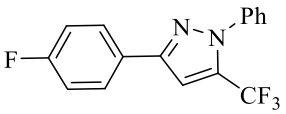
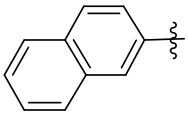
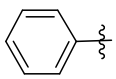
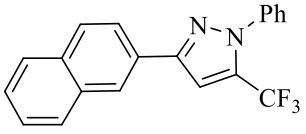
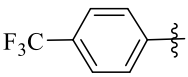
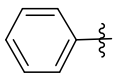
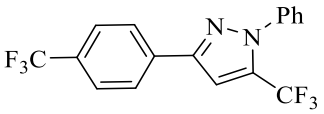
Hydrazones **5.2** were prepared by condensation of ketones **5.1** with hydrazine derivatives. This reaction proceeded under solvent free ('green') conditions at room temperature and is catalyzed by acetic acid and provided nearly quantitative yields of hydrazones. Then, **5.2** were converted to their dianions by treatment with 2 equivalents of *n*-BuLi in THF at -78 °C. Subsequently, ethyl perfluorocarboxylates **5.3** were added to the reaction mixture. After warming to ambient temperature, either trifluoroacetic acid (TFA) or *p*-toluenesulfonic acid

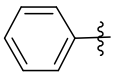
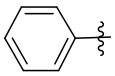
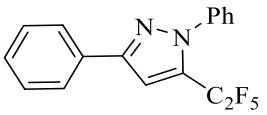
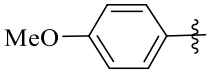
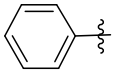
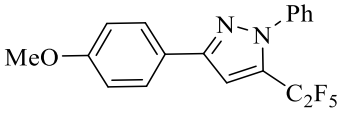
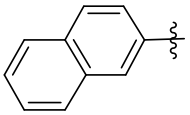
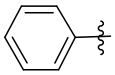
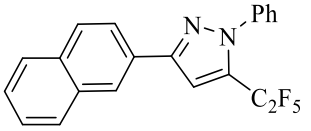
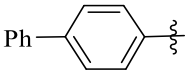
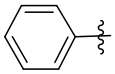
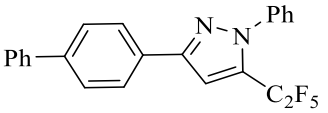
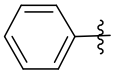
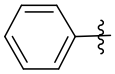
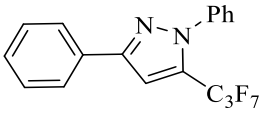
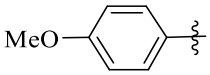
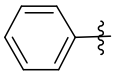
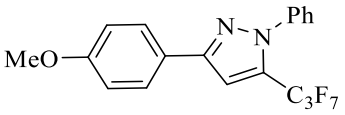
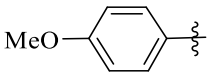
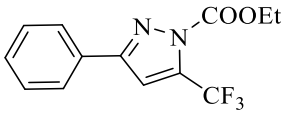
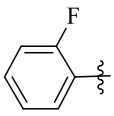
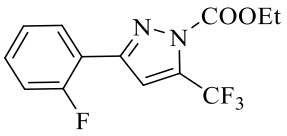
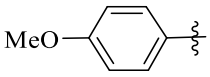
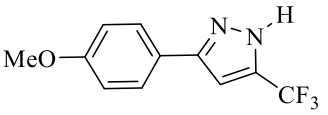
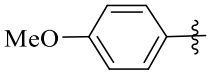
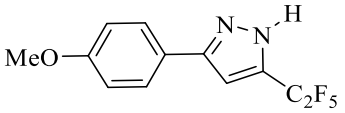
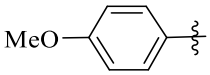
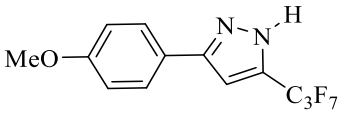
(PTSA) was added to the reaction mixture to give perfluoroalkylated pyrazoles **5.4** or **5.5**, respectively (Scheme 5.4 & table 5.1). The formation of the product proceeds by the attack of the carbon of dianion **A** onto **5.3** to give intermediate **B**, cyclization by the attack of the nitrogen atom onto the carbonyl group to give intermediate **C**, and subsequent acid-mediated dehydration. Treatment of intermediate **C** with TFA under reflux in dioxane allowed 5-perfluoromethylated pyrazoles **5.4** in good to excellent isolated yields. On the other hand, treatment of intermediate **C** with PTSA (reflux, toluene) gave the *N*-deprotected 3-perfluoromethylpyrazoles **5.5**. This could be explained by the fact that PTSA is a stronger acid than TFA. The carbamate protecting group was removed when PTSA was used but remained intact when TFA was used. It is noteworthy that the synthesis of compound **5.4f** could be scaled up to gram quantities. Starting with 10 mmol of **5.1f**, product **5.4f** was isolated in 88% yield (2.67 g).

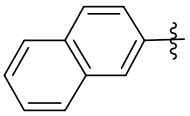
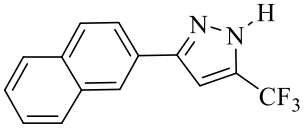
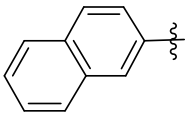
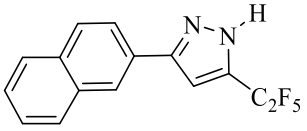
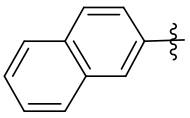
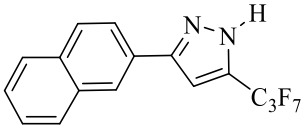
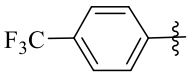
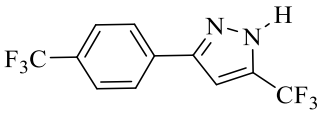
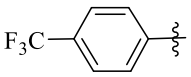
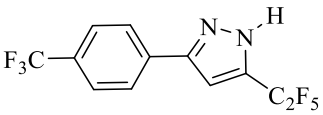
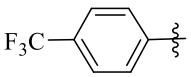
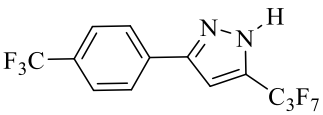


Scheme 5.4: Synthesis of pyrazoles **5.4** and **5.5**
Conditions: i, neat, acetic acid (catalytic amount, 3 drops), 20 °C; *ii*, 1) 2.2 equiv. *n*-BuLi, THF, -78 °C to 20 °C. 2) 1.5 equiv. **5.3a**, -78 °C to 20 °C. 3) TFA, reflux 2h (or PTSA, reflux, 8h).

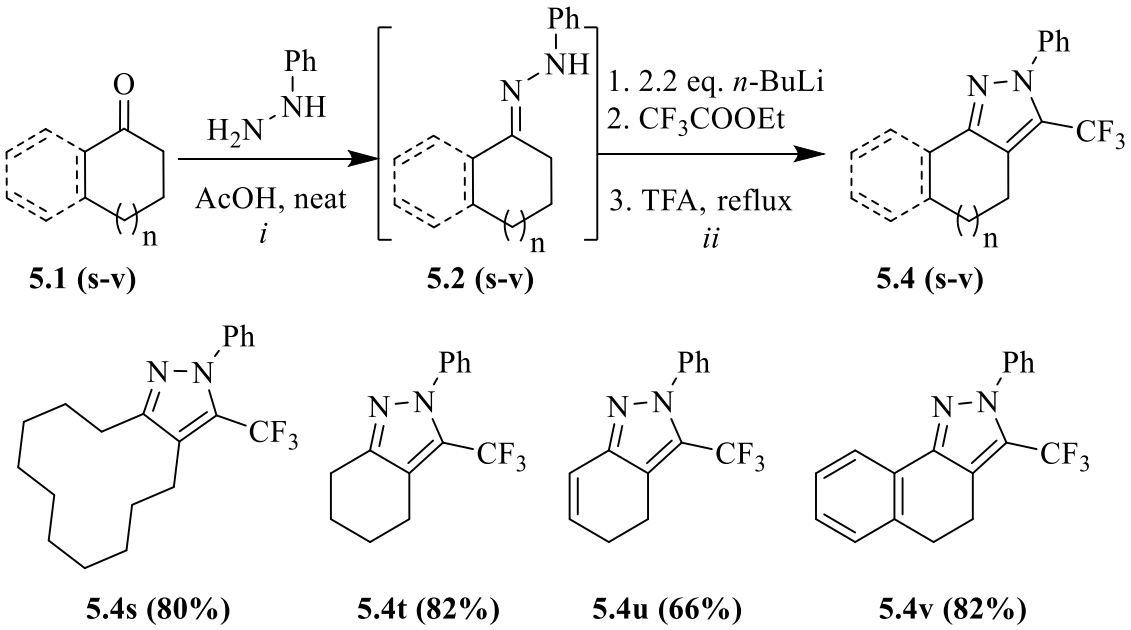
Table 5.1: Synthesis of pyrazoles **5.4** and **5.5**

Compound	Ar	R	R_F	Structure	Yield (%)
5.4a			CF_3		89
5.4b			CF_3		79
5.4c			CF_3		81
5.4d			CF_3		61
5.4e			CF_3		74
5.4f			CF_3		87
5.4g			CF_3		90
5.4h			CF_3		82
5.4i			CF_3		78
5.4j			CF_3		64

5.4k			C_2F_5		95
5.4l			C_2F_5		91
5.4m			C_2F_5		93
5.4n			C_2F_5		85
5.4o			C_3F_7		83
5.4p			C_3F_7		76
5.4q		CO_2Et	CF_3		57
5.4r		CO_2Et	CF_3		65
5.5a		H	CF_3		51
5.5b		H	C_2F_5		56
5.5c		H	C_3F_7		57

5.5d		H	CF_3		78
5.5e		H	C_2F_5		86
5.5f		H	C_3F_7		64
5.5g		H	CF_3		75
5.5h		H	C_2F_5		74
5.5i		H	C_3F_7		67

The cyclization of the dianion of the hydrazone of cyclododecanone **5.2s** with ethyl 2,2,2-trifluoroacetate afforded the annulated trifluoromethylated pyrazole **5.4s** in 80% yield (Scheme 5.5). The cyclizations of the hydrazones of cyclohexanone **5.2t**, cyclohex-2-en-1-one **5.2u** and tetralone **5.2v** afforded the corresponding products **5.4t-v**.



Scheme 5.5: Synthesis of **5.4s-v**
Conditions:i, neat, acetic acid (catalytic amount, 3 drops), 20 °C; *ii*, 1) 2.2 equiv. *n*-BuLi, THF, -78 °C to 20 °C. 2) 1.5 equiv. **5.3a**, -78 °C to 20 °C. 3) TFA, reflux 2h.

Recently, it has been reported that trifluoromethylated indazole **D**[32] represents a highly selective ligand for the estrogen receptor *β*. Trifluoromethylated indazole **E**[33] is a useful agent for the treatment of obesity and diabetes (Figure 5.2). Therefore, it would be interesting to prepare trifluoromethylated indazoles starting from ring-fused pyrazoles.

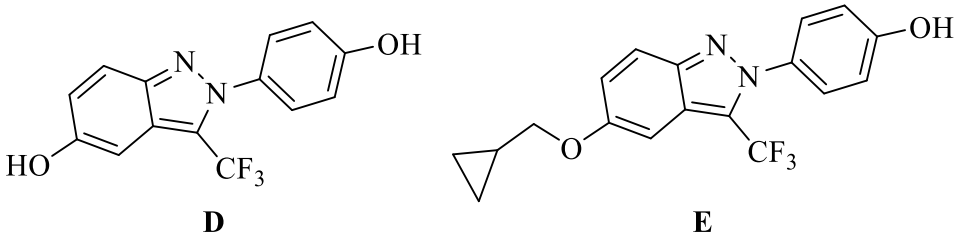
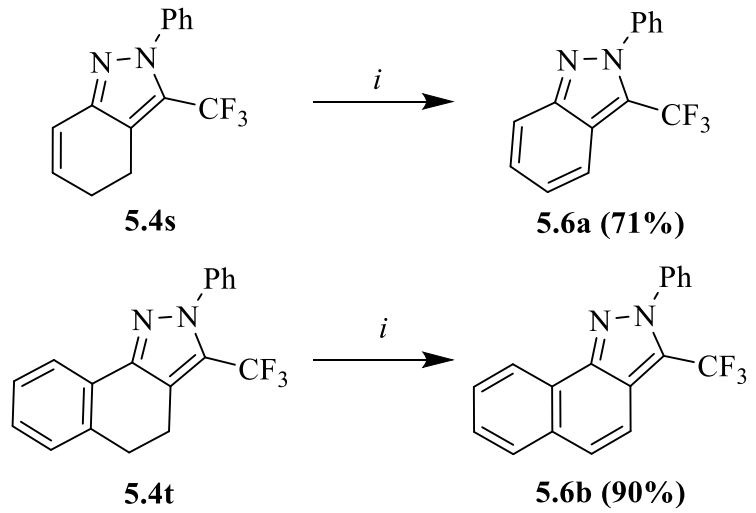


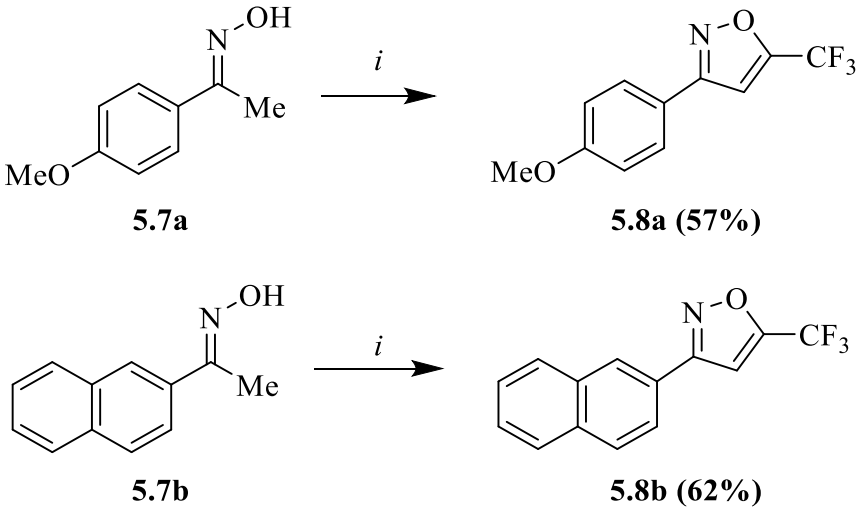
Figure 5.2: Bioactive trifluoromethylated indazoles **D** and **E**

The dehydrogenation of pyrazoles **5.4s** and **5.4t** with DDQ afforded the desired indazoles **5.6a** and **5.6b** in high yields, respectively. These experiments show that this methodology can be successfully applied also for the synthesis of trifluorinated indazoles (scheme 5.6).



Scheme 5.6: Synthesis of **5.6a** and **5.6b**
Conditions:i, 2.0 equiv. DDQ, toluene, reflux, 3 h.

The cyclization of the dianions of oximes **5.7a, b** with ethyl trifluoroacetate and subsequent treatment with TFA (reflux, 8h) afforded 5-trifluoromethylated isoxazoles **5.8a** and **5.8b** in 57% and 62% isolated yields, respectively.



Scheme 5.7: Synthesis of isoxazoles **5.8a, b**
Conditions:i, 1) 2.2 equiv. *n*-BuLi, THF, -78 °C to 20 °C. 2) 1.5 equiv. CF_3COOEt, -78 °C to 20 °C. 3) TFA, reflux 2h.

5.3. Alkaline phosphatase and nucleotide pyrophosphatase activity and SAR

Intestinal alkaline phosphatase (IAP) is believed to play an important role in detoxification of bacterial endotoxin, dephosphorylation of triphosphorylated and diphosphorylated nucleotides, regulation of the intestinal microbiome, and regulation of intestinal lipid absorption.[126] However, overexpression of IAP might have a connection with some inflammatory bowel diseases such as Crohn's disease.[127] On the other hand, tissue

non-specific alkaline phosphatases (TNAP), which participate in the maintenance of the PPi level in the body, share significant homology with IAP.[128] Therefore, selective inhibitors against IAP would be potential therapeutic agents. Interestingly, pyrazole derivatives were observed having inhibitory activity against alkaline phosphatases.[129] In this context, embedding fluorine atoms in pyrazole molecules is promising to the discovery of potential inhibitors for APs. In addition, nucleotide pyrophosphatase/phosphodiesterases (NPPs), which affect a number of processes like bone mineralization, cell proliferation, motility, and digestion, are also important therapeutic targets and it is worth to examine the inhibitory activity of fluorinated pyrazoles against them.[130]

All the fluorinated pyrazole derivatives were tested for human recombinant APs and NPPs and they were found to be selective inhibitors of APs in comparison to NPPs. Against h-NPP1 and h-NPP3, these compounds exhibited low response of inhibition. The data obtained showed that all the values were below 50%. Compound **5.4i** was found to be the potent inhibitor of h-TNAP having IC_{50} value of IC_{50} ±SEM = 0.45±0.01 μM. It can be suggested that the activity of this compound might be due to the presence of a phenyl and a trifluoromethyl group at the parent pyrazole ring. When the activity of this compound was compared with the other derivatives containing naphthalene ring attached to parent pyrazole it was clearly observed that compound having phenyl and side chain with less carbon atom, has more impact on activity against h-TNAP. When the number of carbon and fluorine increased the activity of the compound was decreased as it was reflected in activity values of **5.4m**, **5.5d**, **5.5e,** and **5.5f**. Levamisole was used as a standard inhibitor against h-TNAP. Other compounds inhibited h-TNAP with IC_{50} values in the range of IC_{50} ±SEM = 0.449±0.001 to 50.3±3.28 μM. Compound **5.4n** exhibited the most potent inhibition of h-IAP with an IC_{50}value of IC_{50} ±SEM= 0.65±0.04 μM [sic] which is over 120 folds more efficient than the known standard inhibitor L-phenylalanine. The comprehensive study of the compound structure was justified by comparing with L-phenylalanine (known reference standard) which contain only one phenyl ring. This confirmed that the presence of biphenyl group on the pyrazole ring might be responsible for its high activity against h-IAP. On the other hand, when this compound was compared with **5.4e** containing biphenyl ring with the different carbon side chain it was observed that with a reduced number of carbon atoms in the side chain, the activity of compound was decreased against h-IAP. Other pyrazole derivatives displayed h-IAP inhibition activity in the range IC_{50} ±SEM = 0.647±0.04 to 7.36±0.25 μM. The above-mentioned data showed that most pyrazole derivatives were better inhibitors of h-IAP than of h-TNAP.

Table 5.2: Alkaline phosphatase AP (h-TNAP & h-IAP) and NPP (h-NPP1 & h-NPP3) inhibition in presence of the synthesized compounds

No.	h-TNAP	h-IAP	h-NPP1	h-NPP3
	IC_{50} [a] (μM)±SEM	IC_{50} [a](μM)±SEM	(%inhibition)[b]	(%inhibition)[b]
5.4a	9.52±1.53	1.49±0.38	18.9%	12.5%
5.4b	11.1±1.06	1.22±0.22	23.4%	27.6%
5.4c	10.46±.65	1.63±0.41	21.2%	22.6%
5.4d	26.6±2.56	2.31±0.13	1.65%	4.87%
5.4e	3.23±0.48	1.41±0.05	12.4%	13.5%
5.4f	1.48±0.72	3.52±0.98	7.98%	19.8%
5.4g	2.59±0.38	5.78±0.74	13.8%	6.87%
5.4h	10.1±1.72	1.62±0.23	4.89%	2.76%
5.4i	0.45±0.01	4.46±0.78	23.2%	2.87%
5.4j	3.11±0.84	2.37±0.79	6.98%	1.09%
5.4k	2.11±0.28	5.12±0.84	34.5%	24.8%
5.4l	5.01±0.79	3.71±0.37	2.89%	4.67%
5.4m	1.35±0.06	2.19±0.05	38.4%	14.6%
5.4n	48.6±3.22	0.65±0.04	6.98%	9.87%
5.4o	50.3±3.28	1.35±0.14	28.2%	12.7%
5.4p	25.9±1.38	7.11±0.98	11.5%	17.8%
5.5a	11.6±1.28	7.36±0.25	3.08%	6.08%
5.5b	13.1±0.63	10.5±1.02	14.8%	18.9%
5.5c	4.34±0.03	2.91±0.35	39.1%	34.6%
5.5d	8.09±1.28	1.95±0.26	22.4%	18.7%
5.5e	13.9±1.08	4.47±0.97	6.87%	7.98%
5.5f	12.9±1.38	2.23±0.32	15.9%	10.8%
5.5g	1.62±0.11	2.39±0.36	19.3%	14.7%
5.5h	47.1±3.11	2.57±0.77	25.6%	29.8%
5.5i	2.04±0.17	1.96±0.33	28.2%	31.2%
5.6b	21.2±1.78	6.03±0.75	27.6%	12.6%
5.6a	17.2±0.89	5.84±0.37	12.8%	16.7%
Levamisole	19.21±0.001			
L-Phenylalanine	-------	80.21±0.001		

Values are expressed as mean ± SEM of n = 3. [a]The IC_{50} is the concentration at which 50% of the enzyme activity is inhibited. [b]The % inhibition of the enzyme activity caused by 0.1

5.4. Conclusion

In conclusion, I have demonstrated that a series of 5-trifluoromethylated and 5-perfluoroalkylated pyrazoles, including deprotected derivatives, could be efficiently and selectively synthesized by one-pot cyclization of hydrazone dianions with ethyl perfluorocarboxylates. In addition, two trifluoromethylated indazoles were prepared from the corresponding bicyclic hydrazones. The cyclization of oxime dianions afforded

trifluoromethyl-substituted isoxazoles. All the compounds were selective inhibitors of APs with little effect on h-NPP1 and h-NPP3. In addition, the data showed that most of the compounds presented here inhibited h-IAP more efficiently than h-TNAP. Therefore these compounds appear as selective inhibitors of h-IAP.The results reported herein are of considerable interest for further applications in medicinal chemistry.

The results of this chapter were published in:

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APPENDIX

Methods for compound characterization and analysis

Melting Points

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

Nuclear Magnetic Reasonance Spectroscopy (NMR)

Bruker: AM 250, (62.9 MHz); Bruker: ARX 300, (75.4 MHz), Bruker: ARX 500, (125 MHz). The chemical shifts are given in parts per million (ppm). Coupling constants are given in Hz.

References for ^{1}H NMR: TMS ($\delta = 0.00$) or residual deuterated solvent ($CDCl_3$ ($\delta = 7.26$), C_6D_6 ($\delta = 7.16$), $(CD_3)_2CO$ ($\delta = 2.05$), $(CD_3)_2SO$ ($\delta = 2.50$)), for ^{13}C NMR TMS ($\delta = 0.00$) or residual deuterated solvent ($CDCl_3$ ($\delta = 77.16$), C_6D_6 ($\delta = 128.06$), $(CD_3)_2CO$ ($\delta = 29.84$; 206.26), $(CD_3)_2SO$ ($\delta = 39.52$)) were taken as internal standard. The splitting pattern was characterized by s: singlet, d: doublet, t: triplet, q: quartet, quin: quintet, sex: sextet, m: multiplet. More complicate coupling peaks are represented by combinations of the respective symbol. For example, dt indicate to doublet of triplet. Distortionless enhancement polarization transfer (DEPT) spectra were taken to determine the types of carbon signals.

Mass Spectroscopy (MS)

AMD MS40, Varian MAT CH 7, MAT 731 (EI, 70 eV), Intecta AMD 402 (EI, 70 eV, and CI).

High Resolution Mass Spectroscopy (HRMS)

Finnigan MAT 95 or Varian MAT 311; Bruker FT CIR, AMD 402 (AMD Intectra).

Infrared Spectroscopy (IR)

Bruker IFS 66 (FT IR), Nicolet 205 FT IR; Nicolet Protege 460, Nicolet 360 Smart Orbit (ATR); KBr, KAP, Nujol, and ATR; Peaks were characterized with abbreviation: w = weak, m = medium, s = strong, br = broad.

X-ray Crystal Structure Analysis

Bruker X8Apex diffractometer with CCD camera (Mo Kαradiation and graphite monochromator, λ=0.71073 Å). The structures were solved by direct methods andrefined by full-matrix least-squares procedures on F_2 with the SHELXTL software package.

UV/Vis spectroscopy

Lambda 5 (Perkin Elmer) and Analytic Jena Specord 50 UV/VIS spectrometer in acetonitril.

Fluorescence spectroscopy

Fluoromax4P-0759D-0311-FM. The samples were dissolved in dichloromethane. The quinine hemisulfate salt monohydrate in 0.05M H_2SO_4 which has a fluorescence yield of 0.52, was used as the standard for the fluorescent quantum yield determination.

Thin Layer Chromatography (TLC)

Merck Silica 60 F254 on aluminum foil from Macherey-Nagel. Detection under UV light at 254 nm and/or 365 nm of wavelength and visualize by dipping in TLC stains solution including conc. H_2SO_4/vaniline, Cerium-ammonium-molybdate (CAM), ceric sulfate and Dragendorff reagent.

Column chromatography

Column chromatography was performed over Merck silica gel (63-200 μM) as normal column and (40-63 μM) as flash column. All the solvent were distilled prior to use.

Biological protocols

The biotests were performed by Sundas Sarwar, Syeda Abida Ejaz, and Syeda Mahwish Bakht in the group of Dr. Jamshed Iqbal, Centre for Advanced Drug Research, COMSATS Institute of Information Technology, Abbottabad, Pakistan.

Cell Transfection with Human APs and NPPs

COS-7 cells were transfected with plasmids expressing human APs (TNAP & IAP) or human NPPs ((NPP-1) or (NPP-3)) in 10-cm plates, by using Lipofectamine. The confluent cells were incubated for 5 h at 37 °C in DMEM/F-12 in the absence of fetal bovine serum and

with 6 µg of plasmid DNA and 24 μL of Lipofectamine reagent. The same volume of DMEM/F-12 containing 20% FBS was added to stop the transfection and cells were harvested 48–72 h later.

Preparation of membrane fractions

The transfected cells were washed three times at 4 °C, with Tris–saline buffer, collected by scraping in the harvesting buffer (95 mM NaCl, 0.1 mM PMSF, and 45 mM Tris buffer, pH 7.5) and washed twice by centrifugation at 300×*g* for 5 min at 4 °C. Subsequently, cells were resuspended in the harvesting buffer containing 10 µg/mL aprotinin and sonicated. Nuclear and cellular debris were discarded by 10 min centrifugation (300×*g* at 4 °C). Glycerol was added to the resulting supernatant at a final concentration of 7.5%.
Samples were kept at -80 °C until used. Protein concentration was estimated using Bradford microplate assay and bovine serum albumin was used as a standard.

Protocol of Cholinesterase inhibition assay

For the determination of cholinesterase inhibition, electric eel and horse serum were used as sources of AChE and BChE, respectively. AChE and BChE inhibition was measured in vitro by the Ellman's spectrophotometric method with slight modification. The reaction started by mixing 20 µL assay buffer, 10 µL of test compound and 10 µL of enzymes (0.5 and 3.4 U/mg of AChE or BChE, respectively). Then the reaction mixture was incubated for 10 min at 25 °C. At the end of the pre/incubation period, 10 µL of 1 mM acetylthiocholine iodide or butyrylthiocholine chloride were added to the respective AChE or BChE enzyme solution and 50 µL of 0.5 mM, 5,5'/Dithiobis/2/Nitrobenzoic Acid (DTNB) was added as coloring reagent. The mixtures were incubated for 15 min at 25 °C. The formation of enzymatic product was determined by the variation in absorbance measured at 405 nm with a microplate reader (Bio/Tek ELx800TM, Instruments Inc., Winooski, VT, USA). In this bioactivity assay, the standard drugs, neostigmine and donepezil were used. The buffer for enzyme dilution comprised of 50 mM Tris/HCl containing 0.1% (w/v) BSA (pH 8). To remove the effect of DMSO on enzymes, a blank assay was performed without any enzyme and accounted as non/enzymatic reaction. The analysis of each concentration was done in triplicate and the IC50 values were calculated with the linear regression parameters. The computer program used for this purpose is GraphPad Prism 5.0 (San Diego, CA, USA).

Protocol of Monoamine oxidase inhibition assay

Monoamine oxidase inhibitory activities of the synthesized compounds were evaluated using standard protocol. Assays were performed in 200 µL final volume in 96 well plate. Rat liver mitochondria were pretreated for 15 min at room temperature with an aqueous solution of clorgyline (30 nM) or deprenyl (300 nM) to irreversibly block MAO/A or MAO/B activity, respectively. Test compounds (2 µL), dissolved in DMSO (100%), were added to 90 µL of mitochondrial preparation (25.0 µg of protein for rat MAO/A and 5.0 µg protein for rat MAO/B) and were incubated for 30 min prior to the addition of 90 µL of freshly prepared Amplex Red fluorogenic substrate. The Amplex Red reagent were used as follows, for a 96 well plate, 1.0 mg of Amplex Red, dissolved in 200 μL of DMSO (100%) and 100 µL of reconstituted horseradish peroxidase (HRP 200 U/mL) stock solution (kit vial + 1.0 mL of 50 mM sodium phosphate buffer) was added to 9700 µL of sodium phosphate buffer (250 mM, pH 7.4). The enzymatic reaction was started by the addition of 20 µL/well of an aqueous solution of the substrate p/ tyramine (300 μM final concentration). Deprenyl and clorgyline (each in a final concentration of 1.0 μM) were used to determine non MAO/B and non/MAO/A enzyme activity, respectively. Fluorescence measurements were performed over 45 min and the concentration response curves of clorgyline and deprenyl served as positive controls for the rat MAO/A and rat MAO/B assay, respectively.

Protocol of Alkaline Phosphatase Assay (h-TNAP & h-IAP)

A chemiluminescent substrate, CDP-star, was used for the determination of activity of h-TNAP and h-IAP. The conditions for the assay were optimized with the slight modifications in the previously used spectrophotometric method. The assay buffer was composed of 2.5 mM $MgCl_2$, 0.05 mM $ZnCl_2$ and 8 M DEA (pH 9.8). Initial screening was performed at a concentration of 0.2 mM of the tested compounds. The total volume of 50 μL contained 10 µL of tested compound (0.2 mM with final DMSO 1% (v/v)), 20 μL of h-TNAP (46 ng of protein from COS cell lysate in assay buffer) or of h-IAP (57 ng protein in assay buffer). The mixture was pre-incubated for 5-7 minutes at 37 °C and luminescence was measured as pre-read using microplate reader (BioTek FLx800, Instruments, Inc. USA). Then, 20 μL of CDP-star (final concentration of 110 μM) was added to initiate the reaction and the assay mixture was incubated for 15 min more at 37 °C. The change in the luminescence was measured as after-read. The activity of each compound was compared with total activity control (without any inhibitor). Levamisole (2 mM per well) and L-phenylalanine (4 mM per well) were used as a positive control for the inhibition of h-TNAP and h-IAP, respectively. For the compounds which exhibited over 50% inhibition of either h-TNAP activity or h-IAP activity, full concentration

inhibition curves were produced to evaluate IC_{50} values. For this purpose, 6 to 8 serial dilutions of each compound were prepared in assay buffer and their dose response curves were obtained by assaying each inhibitor concentration against both ALPs using the above mentioned reaction conditions. All experiments were repeated three times in triplicate. The Cheng Prusoff equation was used to calculate the IC_{50} values, determined by the non-linear curve fitting program PRISM 5.0 (GraphPad, San Diego, California, USA).

Protocol of Nucleotide pyrophosphatase (h-NPP-1 & h-NPP-3) activity

The conditions for the assay were optimized with the slight modifications in the previously used spectrophotometric method. The reaction was carried out in the assay buffer which contained 5 mM $MgCl_2$, 0.1 mM $ZnCl_2$, 50% glycerol and 50 mM tris-hydrochloride (pH: 9.5). Initial screening was performed at a concentration of 0.1 mM of the tested compounds. The total volume of 100 μL contained 70 μL of the assay buffer, 10 μL of tested compound (0.1 mM with final DMSO 1% (v/v)) and 10 µL of h-NPP-1 (27 ng of protein from COS cell lysate in assay buffer) or 10 µL of h-NPP-3 (25 mg of protein from COS cell lysate in assay buffer). The mixture was pre-incubated for 10 minutes at 37 °C and absorbance was measured at 405 nm as pre-read using microplate reader (BioTek FLx800, Instruments, Inc. USA). The reaction was then initiated by the addition of 10 μL of p-Nph-5-TMP substrate at a final concentration of 0.5 mM and the reaction mixture was incubated for 30 more min at 37 °C. The change in the absorbance was measured as after-read. The activity of each compound was compared with the reaction in absence of synthesized compounds/inhibitors. The compounds which exhibited over 50% inhibition of either the h-NPP-1 activity or h-NPP-3 activity were further evaluated for determination of IC_{50} values. For this purpose, their dose response curves were obtained by assaying each inhibitor concentration against both NPPs using the above mentioned reaction conditions. All experiments were repeated three times in triplicate. The Cheng Prusoff equation was used to calculate the IC_{50} values, determined by the non-linear curve fitting program PRISM 5.0 (GraphPad, San Diego, California, USA).

Preparation of receptor and ligands

Prior to docking procedures, the receptor crystalline structures were downloaded from RCSB Protein Data Bank. As no good resolution template was present for eeAChE, the crystal structure of Torpedo *californica* AChE (PDB ID 3I6Z) with resolution of 2.19 Å and Human BuChE (PDB ID 1P0I) of human BuChE with resolution of 2.0 Å were downloaded. Receptors for docking studies were prepared by using Load or Prepare Utility of LeadIT v2.1.8 from

BioSolveIT GmbH, Germany. The active site of the receptor was defined by selecting amino acid residue in 7.5 Å radius around reference ligands i.e. Galantamine (G6X) in AChE receptor and Butanoic acid (BUA) in BuChE.

Ligands: Chemical structures of the ligands were drawn using ACD/ChemSketch v14.1, and 3D optimized. Using ANTECHAMBER, Gasteiger charges were added. Ligand structures were then subjected to energy minimization using default values in Chimera v1.10.0[4] and saved as mol2 files.

Molecular docking

Molecular docking was performed by Syed Jawad Ali Shah in the group of Dr. Jamshed Iqbal, Centre for Advanced Drug Research, COMSATS Institute of Information Technology, Abbottabad, Pakistan.

Molecular docking was carried out using FlexX utility of LeadIT v2.1.8 from BioSolveIT GmbH, Germany. The binding site was defined as stated above. Water, amino acid residues and small molecules were handled automatically by the software. Compounds were protonated as in aqueous solution. Top ranking 30 poses were kept and further used for HYDE Assessment.

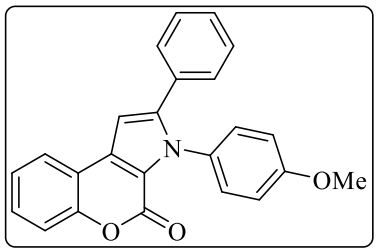
Hyde assessment and visual affinity

Top ranking docked poses were then subjected to HYDE assessment of LeadIT v.2.1.8 to determine the Binding Free Energy (binding affinity). HYDE is based on two parameters. One is hydrogen bonding and the second one is dehydration term i.e. $\Delta G^{i}_{HYDE} = \Sigma\ \Delta G^{i}_{Dehydration} + \Sigma\ \Delta G^{i}_{H\text{-}bond}$

General procedure for the synthesis of pyrrolocoumarins

Compound **2.4** (0.3 mmol), aniline **2.5** (0.36 mmol, 1.2 equiv), $Pd(OAc)_2$ (0.03 mmol, 10% mol), SPhos (0.06 mmol, 20% mol), CuI (20% mol), and Cs_2CO_3 (2.5 equiv. 0.9 mmol) were placed in a dried pressure tube equipped with a septum. The reaction was back-filled with argon three times. Then dry and degassed DMF (4 mL) was added under argon and the septum was replaced with a Teflon cap. The reaction mixture was allowed to stir at 80 °C for 4 h. Then the reaction mixture was cooled to room temperature and was filtered through a pad of Celite. The Celite pad was washed three times with ethyl acetate (3x20 mL). The filtrate was dried under reduced pressure, and the product **2.6** was obtained after flash chromatography on a silica gel column.

3-(4-Methoxyphenyl)-2-phenylchromeno[3,4-*b*]pyrrol-4(3*H*)-one 2.6a



White solid, 64% (70.5 mg). M.p.: 197–199 °C.

IR (ATR, cm^{-1}): 3068.7 (w), 2971.0 (w), 2840.9 (w), 1720.8 (s), 1608.6 (m), 1512.0 (s), 1464.4 (s), 1356.6 (m), 1249.1 (m), 1168.0 (s), 1065.4 (s), 973.8 (s), 831.2 (m), 755.7 (s), 693.9 (s), 553.3 (s).

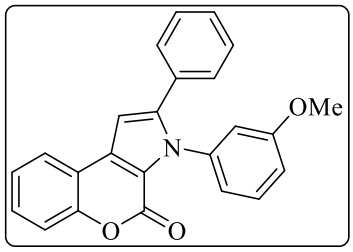
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 – 7.79 (m, 1H, CH_{Ar}), 7.40 (dd, ^3J = 4.9, ^4J = 1.4 Hz, 2H, CH_{Ar}), 7.34 – 7.15 (m, 8H, CH_{Ar}), 6.95 – 6.84 (m, 3H, CH_{Ar}), 3.83 (s, 3H, OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5 (*C*-OCH_3), 154.2 (C=O), 151.6, 145.5, 131.2, 130.5, 130.3 (C_{Ar}), 129.3 ($2CH_{Ar}$), 129.0 ($2CH_{Ar}$), 128.2 ($3CH_{Ar}$), 127.9, 123.8, 122.8 (CH_{Ar}), 118.3, 117.7 (C_{Ar}), 116.9 (C_{Ar}), 113.7 ($2CH_{Ar}$), 102.9 (CH_{Ar}), 55.3 (OCH_3).

MS (EI,70 eV): m/z (%) = 367 (M+, 100), 278 (5), 205 (10), 176 (9), 133 (5), 77 (4).

HRMS (EI, 70 eV): calcd for $C_{24}H_{16}O_3N_1$ ($[M]^+$): 367.12029, found: 367.11931.

3-(3-Methoxyphenyl)-2-phenylchromeno[3,4-*b*]pyrrol-4(3*H*)-one 2.6b



Yellowish solid, 47% (51.7 mg). M.p.: 182–183 °C.

IR (ATR, cm^{-1}): 3116.2 (w), 3063.7 (w), 2951.1 (w), 2849.3 (w), 1710.4 (s), 1598.8 (m), 1487.0 (m), 1463.4 (s), 1356.2 (m), 1213.5 (s), 1111.8 (m), 1031.5 (s), 989.4 (m), 954.4 (m), 850.0 (m), 762.4 (s), 693.9 (s), 647.1 (m).

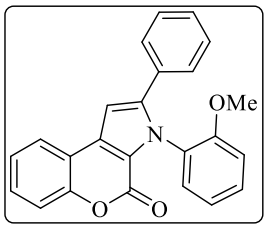
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, ^3J = 7.6 Hz, 1H, CH_{Ar}), 7.47 – 7.36 (m, 2H, CH_{Ar}), 7.36 – 7.17 (m, 7H, CH_{Ar}), 7.06 – 6.74 (m, 4H, CH_{Ar}), 3.74 (s, 3H, OCH_3).

^{13}C NMR (63 MHz, $CDCl_3$) δ 159.7 (*C*-OCH_3), 154.0 (C=O), 151.6, 145.3, 138.4, 131.1, 130.7 (C_{Ar}), 129.3 (CH_{Ar}), 129.2 (2 CH_{Ar}), 128.6 (CH_{Ar}), 128.5 (2 CH_{Ar}), 128.3, 124.2, 123.2, 121.1 (CH_{Ar}), 118.1, 117.7 (C_{Ar}), 117.3, 114.8, 114.5, 103.5 (CH_{Ar}), 55.6 (OCH_3)

MS (EI,70 eV): m/z (%) = 367 (M+, 100), 278 (5), 205 (7), 176 (9), 92 (4), 77 (4).

HRMS (EI, 70 eV): calcd for $C_{24}H_{16}O_3N_1$ ($[M]^+$): 367.12029, found: 367.11972.

3-(2-Methoxyphenyl)-2-phenylchromeno[3,4-*b*]pyrrol-4(3*H*)-one 2.6c



Yellowish solid, 61% (67.2 mg). M.p.: 162–163 °C.

IR (ATR, cm^{-1}): 3067.7 (w), 2923.1 (w), 2843.0 (w), 1717.9 (s), 1598.9 (w), 1503.0 (m), 1465.0 (s), 1279.3 (m), 1220.4 (m), 1162.0 (m), 1108.9 (m), 1060.3 (m), 969.9 (s), 896.1 (m), 756.1 (s), 700.5 (s), 655.3 (m), 549.6 (m).

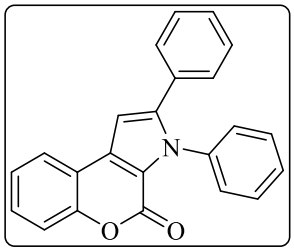
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 – 7.73 (m, 1H, CH_{Ar}), 7.43 – 7.35 (m, 3H, CH_{Ar}), 7.34 – 7.21 (m, 6H, CH_{Ar}), 7.16 (dd, ^3J = 7.7, ^4J = 1.7 Hz, 1H, CH_{Ar}), 7.02 – 6.88 (m, 3H, CH_{Ar}), 3.68 (s, 3H, OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8 (*C*-OCH_3), 154.0 (C=O), 151.6, 145.5, 131.3, 130.4 (C_{Ar}), 130.4 (CH_{Ar}), 129.8 (CH_{Ar}), 128.8 ($2CH_{Ar}$), 128.5 (CH_{Ar}), 128.3 (2 CH_{Ar}), 128.0 (CH_{Ar}), 126.8 (C_{Ar}), 124.0, 123.1, 120.5 (CH_{Ar}), 118.4, 117.9 (C_{Ar}), 117.2, 112.0, 102.9 (CH_{Ar}), 55.8 (OCH_3).

MS (EI,70 eV): m/z (%) = 367 (M+, 100), 336 (35), 261 (25), 205 (5), 176 (10), 139 (9), 77 (6).

HRMS (EI, 70 eV): calcd for $C_{24}H_{16}O_3N_1$ ($[M]^+$): 367.12029, found: 367.11965.

2,3-Diphenylchromeno[3,4-*b*]pyrrol-4(3*H*)-one 2.6d



White solid, 52% (52.6 mg). M.p.: 215–216 °C.

IR (ATR, cm^{-1}): 3051.9 (w), 2922.3 (w), 2849.8 (w), 1714.0 (s), 1590.1 (w), 1495.0 (m), 1468.7 (m), 1390.6 (m), 1352.7 (m), 1224.1 (m), 1165.9 (m), 1110.5 (m), 1063.1 (s), 760.2 (s), 690.5 (s), 558.7 (m).

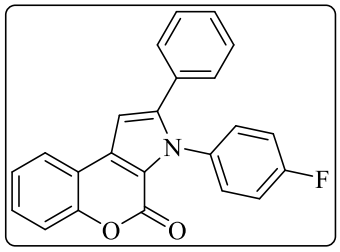
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 – 7.75 (m, 1H, CH_{Ar}), 7.51 – 7.13 (m, 13H, CH_{Ar}), 6.95 (s, 1H, CH_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1 (C=O), 151.6, 145.4, 137.5, 131.1, 130.7 (C_{Ar}), 129.3 ($2CH_{Ar}$), 128.7 (2 CH_{Ar}), 128.7 (CH_{Ar}), 128.7 (2 CH_{Ar}), 128.5 (CH_{Ar}), 128.5 (2 CH_{Ar}), 128.3, 124.2, 123.12 (CH_{Ar}), 118.1, 117.7 (C_{Ar}), 117.2, 103.5 (CH_{Ar}).

MS (EI,70 eV): m/z (%) = 337 (M+, 100), 307 (5), 291 (13), 278 (5), 205 (12), 176 (10), 146 (8), 77 (11).

HRMS (+ESI, 180 eV): calcd for $C_{23}H_{15}O_2N_1$ ($[M+H]^+$): 338.11773, found: 338.11756.

3-(4-Fluorophenyl)-2-phenylchromeno[3,4-*b*]pyrrol-4(3*H*)-one 2.6e



Yellowish solid, 41% (43.7 mg). M.p.: 226–227 °C.

IR (ATR, cm^{-1}): 3412.0 (w), 3096.6 (w), 3069.1 (w), 1710.4 (w), 1609.2 (w), 1507.4 (s), 1467.2 (m), 1355.7 (m), 1220.4 (s), 1117.2 (m), 1064.2 (m), 977.5 (m), 845.3 (m), 756.7 (s), 695.1 (m), 553.3 (s).

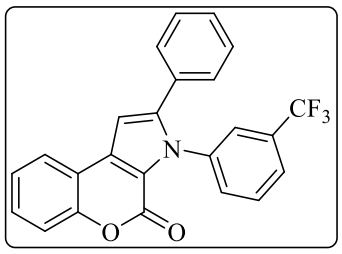
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (dt, ^{3}J = 7.6, ^{4}J = 1.1 Hz, 1H, CH_{Ar}), 7.41 (dd, ^{3}J = 4.7, ^{4}J = 1.0 Hz, 2H, CH_{Ar}), 7.38 – 7.15 (m, 8H, CH_{Ar}), 7.13 – 7.02 (m, 2H, CH_{Ar}), 6.93 (s, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$) δ -112.40.

^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4 (d, ^{1}J = 248.7 Hz, CF), 154.2 (C=O), 151.6, 145.5, 133.5 (d, ^{4}J = 3.3 Hz), 130.9, 130.8 (C_{Ar}), 130.4 (d, ^{3}J = 8.8 Hz, 2 CH_{Ar}), 129.3 (2 CH_{Ar}), 128.7 (CH_{Ar}), 128.6 (2 CH_{Ar}), 128.4, 124.3, 123.2 (CH_{Ar}), 118.2, 117.6 (C_{Ar}), 117.3 (CH_{Ar}), 115.8 (d, ^{2}J = 23.0 Hz, 2 CH_{Ar}), 103.6 (CH_{Ar}).

MS (EI,70 eV): m/z (%) = 355 (M+, 100), 309 (11), 224 (6), 205 (8), 176 (9), 155 (5), 95 (7). 77 (2).

2-Phenyl-3-(3-(trifluoromethyl)phenyl)chromeno[3,4-*b*]pyrrol-4(3*H*)-one 2.6f



Yellowish solid, 35% (42.5 mg). M.p.: 191–192 °C.

IR (ATR, cm^{-1}): 3059.1 (w), 2922.3 (w), 2851.1 (w), 1713.6 (s), 1612.3 (w), 1498.5 (w), 1463.6 (m), 1401.8 (w), 1330.0 (s), 1251.2 (w), 1166.3 (m), 1125.0 (s), 1064.6 (s), 987.7 (m), 818.9 (m), 765.3 (s), 698.6 (s), 654.4 (m), 550.0 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 – 7.78 (m, 1H, CH_{Ar}), 7.70 – 7.60 (m, 1H, CH_{Ar}), 7.58 – 7.45 (m, 3H, CH_{Ar}), 7.45 – 7.38 (m, 2H, CH_{Ar})), 7.38 – 7.22 (m, 4H, CH_{Ar}), 7.22 – 7.12 (m, 2H, CH_{Ar}), 6.96 (s, 1H, CH_{Ar}).

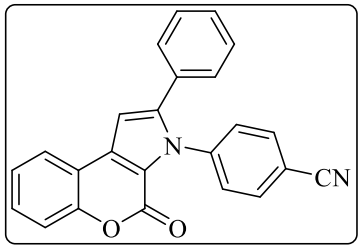
^{19}F NMR (282 MHz, $CDCl_3$) δ -62.73.

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1 (C=O), 151.6, 145.5, 137.8 (C_{Ar}), 132.1(CH_{Ar}), 131.2 (C_{Ar}), 131.2 (q, ^{2}J = 33.1 Hz, C_{Ar}-CF_3), 130.5 (C_{Ar}), 129.4 (2 CH_{Ar}), 129.3 (CH_{Ar}), 128.9 (CH_{Ar}), 128.7 (2 CH_{Ar}), 128.6, 125.8 (q, ^{3}J = 3.8 Hz), 125.4 (q, ^{3}J = 3.6 Hz), 124.3, 123.9 (CH_{Ar}), 123.58 (q, ^{1}J = 270.2 Hz, CF_3), 118.0, 117.4 (C_{Ar}), 117.3, 104.1 (CH_{Ar}).

MS (EI,70 eV): m/z (%) = 405 (M+, 100), 384 (36), 274 (4), 205 (11), 176 (9), 145 (7), 75 (3).

HRMS (EI, 70 eV): calcd for $C_{24}H_{14}F_3O_2N_1$ ($[M]^+$): 405.09711, found: 405.09668.

4-(4-Oxo-2-phenylchromeno[3,4-*b*]pyrrol-3(4*H*)-yl)benzonitrile 2.6g



Yellow solid, 40% (43.3 mg). M.p.: 233–234 °C.

IR (ATR, cm^{-1}): 3096.1 (w), 3067,6 (w), 3046.2 (w), 2241.8 (w), 2232.5 (w), 1719.4 (m), 1704.5 (s), 1600.6 (w), 1507.9 (m), 1466.4 (m), 1399.7 (m), 1355.2 (w), 1223.5 (w), 1065.2 (m), 977.7 (m), 854.4 (m), 756.5 (s), 696.4 (m), 566.9 (m).

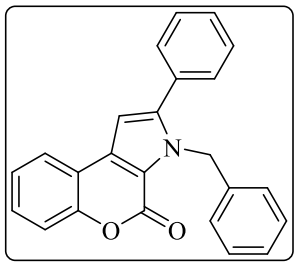
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 – 7.78 (m, 1H, CH_{Ar}), 7.72 – 7.63 (m, 2H, CH_{Ar}), 7.46 – 7.27 (m, 8H, CH_{Ar}), 7.16 (dd, ^3J = 7.8, ^4J = 1.7 Hz, 2H, CH_{Ar}), 6.97 (s, 1H, CH_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1 (C=O), 151.6, 145.3, 141.2 (C_{Ar}), 132.6 (2 CH_{Ar}), 131.7, 130.3 (C_{Ar}), 129.7 (2 CH_{Ar}), 129.3 (2 CH_{Ar}), 129.1 (CH_{Ar}), 128.8 (3 CH_{Ar}), 124.5, 123.3 (CH_{Ar}), 117.9 (C_{Ar}), 117.4 (CH_{Ar}), 117.3, 112.5 (C_{Ar}), 104.5 (CH_{Ar}). (one signal could not be detected)

MS (EI,70 eV): m/z (%) = 362 (M+, 100), 316 (12), 277 (1), 230 (4), 203 (6), 176 (8), 152 (6), 75 (4).

HRMS (EI, 70 eV): calcd for $C_{24}H_{14}O_2N_2$ ($[M]^+$): 362.10498, found: 362.10398.

3-Benzyl-2-phenylchromeno[3,4-*b*]pyrrol-4(3*H*)-one 2.6h



Yellowish solid, 82% (86.3 mg). M.p.: 199–201 °C.

IR (ATR, cm^{-1}): 3130.8 (w), 3025.7 (w), 2962.9 (w), 2850.9 (w), 1702.9 (s), 1496.5 (m), 1427.0 (m), 1257.1 (m), 1202.5 (m), 1010.3 (m), 963.0 (m), 892.9 (m), 813.5 (m), 751.8 (s), 727.5 (s), 689.9 (s), 648.6 (m), 584.0 (m).

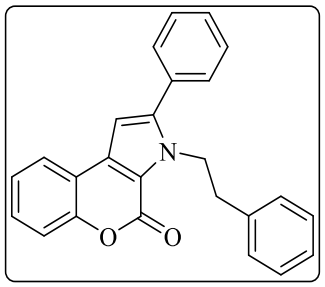
^{1}H NMR (250 MHz, $CDCl_3$) δ 7.79 (dd, ^3J = 7.0, ^4J = 1.0 Hz, 1H, CH_{Ar}), 7.50 – 7.35 (m, 7H, CH_{Ar}), 7.35 – 7.15 (m, 4H, CH_{Ar}), 6.93 (dd, ^3J = 7.2, ^4J = 2.3 Hz, 2H, CH_{Ar}), 6.77 (s, 1H, CH_{Ar}), 5.77 (s, 2H, CH_2).

^{13}C NMR (63 MHz, $CDCl_3$) δ 154.9 (C=O), 151.4, 145.9, 138.1, 131.2, 130.4 (C_{Ar}), 129.5 (2 CH_{Ar}), 129.1 (CH_{Ar}), 128.7 (2 CH_{Ar}), 128.5 (2 CH_{Ar}), 127.9 (CH_{Ar}), 127.3 (CH_{Ar}), 126.4 (2CH_{Ar}), 124.1, 122.9 (CH_{Ar}), 117.7 (C_{Ar}), 117.1, 103.3 (CH_{Ar}), 49.1 (CH_2) (One signal could not be detected).

MS (EI,70 eV): m/z (%) = 351 (M+, 76), 334 (4), 260 (4), 232 (7), 203 (5), 176 (6), 157 (3), 91 (100), 65 (10).

HRMS (EI, 70 eV): calcd for $C_{24}H_{17}O_2N_1$ ($[M]^+$): 351.12538, found: 351.12528.

3-Phenethyl-2-phenylchromeno[3,4-*b*]pyrrol-4(3*H*)-one 2.6i



Yellowish solid, 76% (83.2 mg). M.p.: 185–186 °C.

IR (ATR, cm^{-1}): 3064.6 (w), 3025.6 (w), 2924.7 (w), 2860.8 (w), 1703.1 (s), 1603.2 (w), 1504.7 (w), 1465.5 (m), 1356.5 (m), 1198.2 (m), 1110.2 (m), 1070.7 (m), 953.6 (m), 757.1 (s), 693.8 (s), 652.7 (m).

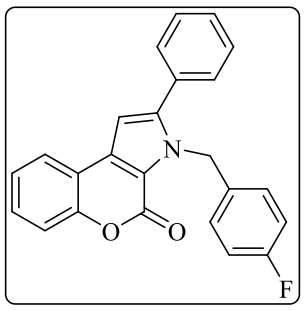
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (dd, ^3J = 7.7, ^4J = 1.3 Hz, 1H, CH_{Ar}), 7.53 – 7.33 (m, 5H, CH_{Ar}), 7.34 – 7.20 (m, 3H, CH_{Ar}), 7.21 – 7.08 (m, 3H, CH_{Ar}), 6.99 – 6.82 (m, 2H, CH_{Ar}), 6.62 (s, 1H, CH_{Ar}), 4.66 (dd, ^3J = 8.2, ^3J = 6.8 Hz, 2H, NC*H*$_2$CH$_2$), 3.10 – 2.96 (m, 2H, NCH$_2$C*H*$_2$).

^{13}C NMR (63 MHz, $CDCl_3$) δ 155.5 (C=O), 151.8, 146.2, 138.2, 131.6, 130.7 (C_{Ar}), 129.8 (2 CH_{Ar} , 129.3 (CH_{Ar}), 129.3 (2 CH_{Ar}), 129.0 (2 CH_{Ar}), 128.8 (2 CH_{Ar}), 128.3, 126.9, 124.5, 123.4 (CH_{Ar}), 118.2 (C_{Ar}), 117.5 (CH_{Ar}), 116.9 (C_{Ar}), 103.2 (CH_{Ar}), 47.9 (N*C*H$_2$CH$_2$), 38.5 (NCH$_2$*C*H$_2$).

MS (EI,70 eV): m/z (%) = 365 (M+, 41), 274 (44), 261 (100), 244 (4), 230 (16), 202 (14), 152 (3), 91 (6), 65 (3).

HRMS (EI, 70 eV): calcd for $C_{25}H_{19}O_2N_1$ ($[M]^+$): 365.14103, found: 365.14097.

3-(4-Fluorobenzyl)-2-phenylchromeno[3,4-*b*]pyrrol-4(3*H*)-one 2.6j



Yellowish solid, 61% (67.5 mg). M.p.: 211–212 °C.

IR (ATR, cm^{-1}): 3114.5 (w), 3054.4 (w), 2943.7 (w), 1703.7 (s), 1604.6 (w), 1506.2 (s), 1465.1 (s), 1381.6 (w), 1295.3 (m), 1208.2 (s), 1113.9 (s), 1040.5 (s), 949.6 (m), 894.5 (m), 765.2 (s), 698.2 (s), 651.5 (m), 538.4 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 – 7.75 (m, 1H, CH_{Ar}), 7.49 – 7.43 (m, 3H, CH_{Ar}), 7.43 – 7.34 (m, 4H, CH_{Ar}), 7.33 – 7.27 (m, 1H, CH_{Ar}), 6.90 – 6.86 (m, 4H, CH_{Ar}), 6.76 (s, 1H, CH_{Ar}), 5.73 (s, 2H, CH_2).

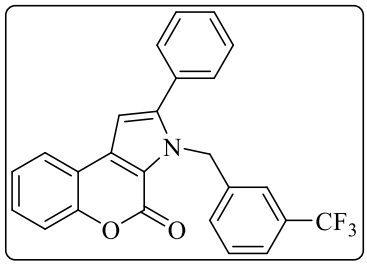
^{19}F NMR (282 MHz, $CDCl_3$) δ -115.07.

^{13}C NMR (63 MHz, $CDCl_3$) δ 162.2 (d, ^1J = 245.7 Hz, CF), 155.2 (C=O), 151.6, 146.0, 133.9 (d, ^4J = 3.2 Hz), 131.2, 130.7 (C_{Ar}), 129.6 (2 CH_{Ar}), 129.4 (CH_{Ar}), 128.9 (2 CH_{Ar}), 128.48 (d, ^3J = 8.1 Hz, 2 CH_{Ar}), 128.2, 124.3, 123.1 (CH_{Ar}), 117.8 (C_{Ar}), 117.3 (CH_{Ar}), 117.1 (C_{Ar}), 115.6 (d, ^2J = 21.6 Hz, 2 CH_{Ar}), 103.6 (CH_{Ar}), 48.5 (CH_2).

MS (EI,70 eV): m/z (%) = 369 (M+, 70), 260 (4), 232 (6), 203 (4), 176 (5), 109 (100), 83 (7).

HRMS (EI, 70 eV): calcd for $C_{24}H_{16}F_1O_2N_1$ ($[M]^+$): 369.11596, found: 369.11563.

2-Phenyl-3-(3-(trifluoromethyl)benzyl)chromeno[3,4-*b*]pyrrol-4(3*H*)-one 2.6k



Yellow solid, 46% (57.8 mg). M.p.: 153–154 °C.

IR (ATR, cm^{-1}): 3119.1 (w), 3067.1 (w), 2981.0 (w), 2851.0 (w), 1707.7 (s), 1504.7 (m), 1427.7 (m), 1325.6 (s), 1202.7 (m), 1118.5 (s), 1071.8 (m), 1037.2 (m), 1016.3 (m), 894.9 (m), 817.7 (m), 759.4 (s), 694.5 (s), 653.9 (s), 557.3 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 – 7.70 (m, 1H, CH_{Ar}), 7.54 – 7.27 (m, 10H, CH_{Ar}), 7.17 (d, ^3J = 7.8 Hz, 1H, CH_{Ar}), 7.09 (s, 1H, CH_{Ar}), 6.78 (s, 1H, CH_{Ar}), 5.81 (s, 2H, CH_2).

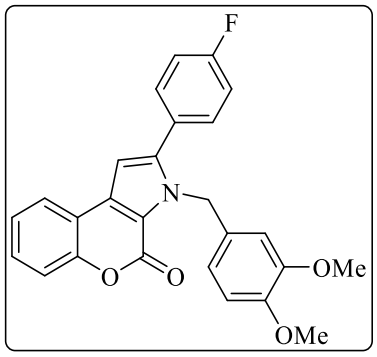
^{19}F NMR (282 MHz, $CDCl_3$) δ -62.70.

^{13}C NMR (63 MHz, $CDCl_3$) δ 155.3 (C=O), 151.6, 146.1, 139.1, 131.0 (C_{Ar}), 130.9 (q, ^2J = 32.5 Hz, *C*-CF_3), 130.8 (C_{Ar}), 130.2 (CH_{Ar}), 129.6 (2 CH_{Ar}), 129.6, 129.3 (CH_{Ar}), 129.1 (2 CH_{Ar}), 128.3 (CH_{Ar}), 124.5 (q, ^3J = 8.1 Hz, CH_{Ar}), 124.4 (CH_{Ar}), 123.8 (q, ^1J = 273 Hz, CF_3), 123.7 (q, ^3J = 7.7 Hz, CH_{Ar}), 123.2 (CH_{Ar}), 117.8 (C_{Ar}), 117.3 (CH_{Ar}), 177.1 (C_{Ar}), 103.8 (CH_{Ar}), 48.7 (CH_2).

MS (EI,70 eV): m/z (%) = 419 (M+, 100), 398 (13), 274 (9), 260 (27), 232 (27), 203 (10), 176 (11), 159 (37), 109 (12), 75 (4).

HRMS (EI, 70 eV): calcd for $C_{25}H_{16}F_3O_2N_1$ ($[M]^+$): 419.11276, found: 419.11272.

3-(3,4-Dimethoxybenzyl)-2-(4-fluorophenyl)chromeno[3,4-*b*]pyrrol-4(3*H*)-one 2.6l



Yellowish solid, 57% (73.4 mg). M.p.: 231–231 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 – 7.73 (m, 1H, CH_{Ar}), 7.45 – 7.33 (m, 4H, CH_{Ar}), 7.33 – 7.25 (m, 1H, CH_{Ar}), 7.23 – 7.09 (m, 2H, CH_{Ar}), 6.72 (s, 1H. CH_{HAr}), 6.67 (d, ^3J = 8.3 Hz, 1H, CH_{Ar}), 6.53 (d, ^4J = 2.0 Hz, 1H, CH_{Ar}), 6.43 (dd, ^3J = 8.2, ^4J = 2.0 Hz, 1H, CH_{Ar}), 5.67 (s, 2H, CH_2), 3.79 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3).

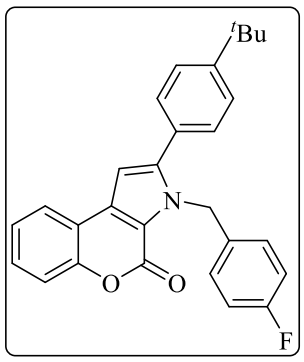
^{19}F NMR (282 MHz, $CDCl_3$) δ -111.39.

^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3 (d, ^1J = 250.0 Hz, CF), 155.2 (C=O), 151.5, 149.0, 148.5, 144.8 (C_{Ar}), 131.6 (d, ^3J = 8.3 Hz, 2CH_{Ar}), 130.6 (CH_{Ar}), 130.5 (C_{Ar}), 127.5 (d, ^4J = 3.5 Hz, C_{Ar}), 124.3, 123.1, 119.2 (CH_{Ar}), 117.8 (C_{Ar}), 117.2 (CH_{Ar}), 117.1 (C_{Ar}), 116.1 (d, ^2J = 21.7 Hz, 2CH_{Ar}), 111.3, 110.3, 103.6 (CH_{Ar}), 55.9, 55.9 (OCH_3), 48.8 (CH_2).

MS (EI,70 eV): m/z (%) = 429 (M+, 18), 151 (100), 107 (7), 78 (3).

HRMS (EI, 70 eV): calcd for $C_{26}H_{20}F_1O_4N_1$ ($[M]^+$): 429.13709, found: 429.13713.

2-(4-(*Tert*-butyl)phenyl)-3-(4-fluorobenzyl)chromeno[3,4-*b*]pyrrol-4(3*H*)-one 2.6m



Yellowish solid, 47% (60.0 mg). M.p.: 187–188 °C.

IR (ATR, cm^{-1}): 3074.1 (w), 2961.9 (w), 2866.9 (w), 1720.6 (s), 1605.8 (m), 1508.8 (m), 1475.7 (m), 1358.2 (m), 1219.9 (m), 1156.6 (m), 1083.2 (m), 1032.4 (m), 970.7 (m), 765.3 (s), 652.1 (m), 575.9 (m), 526.5 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 – 7.70 (m, 1H, CH_{Ar}), 7.51 – 7.43 (m, 2H, CH_{Ar}), 7.43 – 7.36 (m, 2H, CH_{Ar}), 7.36 – 7.27 (m, 3H, CH_{Ar}), 6.95 – 6.84 (m, 4H, CH_{Ar}), 6.75 (s, 1H, CH_{HAr}), 5.73 (s, 2H, CH_2), 1.37 (s, 9H, $C(CH_3)_3$).

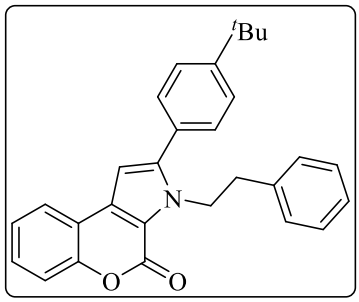
^{19}F NMR (282 MHz, $CDCl_3$) δ -115.21.

^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1 (d, ^1J = 245.6 Hz, CF), 155.1 (C=O), 152.7, 151.6, 146.2, 134.1 (d, ^4J = 3.2 Hz, C_{Ar}), 130.7 (C_{Ar}), 129.3 ($2CH_{Ar}$), 128.4 (d, ^3J = 8.1 Hz, $2CH_{Ar}$), 128.2 (C_{Ar}), 128.1 (CH_{Ar}), 125.9 ($2CH_{Ar}$), 124.2, 123.1 (CH_{Ar}), 117.8 (C_{Ar}), 117.2 (CH_{Ar}), 116.9 (C_{Ar}), 115.51 (d, ^2J = 21.5 Hz, $2CH_{Ar}$), 103.4 (CH_{Ar}), 48.6 (CH_2), 34.9 ($C(CH_3)_3$), 31.4 (3C, $C(CH_3)_3$).

MS (EI,70 eV): m/z (%) = 425 (M+, 94), 410 (21), 301 (26), 273 (6), 109 (100), 83 (6).

HRMS (EI, 70 eV): calcd for $C_{28}H_{24}F_1O_2N_1$ ($[M]^+$): 425.17856, found: 425.1782.

2-(4-(*Tert*-butyl)phenyl)-3-phenethylchromeno[3,4-*b*]pyrrol-4(3*H*)-one 2.6n



Yellowish solid, 65% (82.1 mg). M.p.: 168–169 °C.

IR (ATR, cm^{-1}): 3030.4 (w), 2962.0 (w), 2921.1 (w), 2847.9 (w), 1704.6 (s), 1514.5 (w), 1490.3 (m), 1452.8 (m), 1398.2 (m), 1284.0 (m), 1070.4 (m), 1014.0 (m), 942.9 (w), 764.3 (s), 700.6 (s), 659.3 (m), 576.7 (m), 532.6 (w).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 – 7.73 (m, 1H, CH_{Ar}), 7.50 – 7.33 (m, 4H, CH_{Ar}), 7.33 – 7.11 (m, 6H, CH_{Ar}), 7.02 – 6.93 (m, 2H, CH_{Ar}), 6.62 (s, 1H, CH_{HAr}), 4.79 – 4.59 (m, 2H, NCH_2CH_2), 3.12 – 2.76 (m, 2H, NCH_2CH_2), 1.40 (s, 9H, $C(CH_3)_3$).

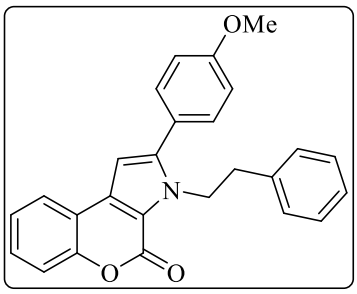
^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2 (C=O), 152.3, 151.6, 145.9, 138.0, 130.4 (C_{Ar}), 129.3 ($2CH_{Ar}$), 129.0 ($2CH_{Ar}$), 128.5 ($2CH_{Ar}$), 128.3 (C_{Ar}), 127.9, 126.6 (CH_{Ar}), 125.7 ($2CH_{Ar}$),

124.1, 123.1 (CH_{Ar}), 117.9 (C_{Ar}), 117.2 (CH_{Ar}), 116.5 (C_{Ar}), 102.7 (CH_{Ar}), 47.6 (NCH_2CH_2), 38.3 (NCH_2CH_2), 34.9 ($C(CH_3)_3$), 31.4 (3C, $C(CH_3)_3$).

MS (EI,70 eV): m/z (%) = 421 (M+, 75), 317 (77), 302 (84), 274 (100), 230 (7), 202 (8), 105 (9), 77 (9), 57 (36), 41 (10).

HRMS (EI, 70 eV): calcd for $C_{29}H_{27}O_2N_1$ ($[M]^+$): 421.20363, found: 421.20335.

2-(4-methoxyphenyl)-3-phenethylchromeno[3,4-*b*]pyrrol-4(3*H*)-one 2o



Yellowish solid, 69% (81.8 mg). M.p.: 194–195 °C

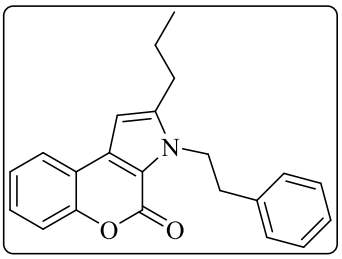
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (dd, ^3J = 7.7, ^4J = 1.2 Hz, 1H, CH_{Ar}), 7.48 – 7.33 (m, 2H, CH_{Ar}), 7.29 (dd, ^3J = 7.6, ^4J = 1.7 Hz, 1H, CH_{Ar}), 7.22 – 7.10 (m, 5H, CH_{Ar}), 7.01 – 6.88 (m, 4H, CH_{Ar}), 6.57 (s, 1H, CH_{Ar}), 4.84 – 4.35 (m, 2H, NCH_2CH_2), 3.88 (s, 3H, OCH_3), 3.11 – 2.94 (m, 2H, NCH_2CH_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2 (*C*-OCH_3), 155.2 (C=O), 151.6, 145.8, 138.0 (C_{Ar}), 130.8 ($2CH_{Ar}$), 130.4 (C_{Ar}), 129.1 ($2CH_{Ar}$), 128.6 ($2CH_{Ar}$), 127.9, 126.6, 124.1 (CH_{Ar}), 123.5 (C_{Ar}), 123.1 (CH_{Ar}), 117.9 (C_{Ar}), 117.0 (CH_{Ar}), 116.4 (C_{Ar}), 114.2 ($2CH_{Ar}$), 102.7 (CH_{Ar}), 55.5 (OCH_3), 47.56 (N CH_2CH_2), 38.2 (N CH_2CH_2).

MS (EI,70 eV): m/z (%) = 395 (M+, 57), 304 (56), 291 (100), 276 (24), 217 (12), 190 (6), 91 (6), 77 (8).

HRMS (EI, 70 eV): calcd for $C_{26}H_{21}O_3N_1$ ($[M]^+$): 395.15160, found: 395.15141.

3-Phenethyl-2-propylchromeno[3,4-*b*]pyrrol-4(3*H*)-one 2.6p



Yellowish oil, 62% (61.6 mg).

IR (ATR, cm^{-1}): 3124.1 (w), 3024.2 (w), 2959.5 (w), 2873.7 (w), 1710.7 (s), 1593.8 (w), 1491.6 (m), 1434.0 (m), 1362.3 (m), 1285.2 (m), 1208.0 (m), 1153.9 (w), 1062.2 (m), 1015.2 (m), 965.1 (m), 895.0 (m), 793.0 (m), 763.1 (s), 748.8 (s), 697.5 (s), 657.1 (m), 575.2 (m), 531.7 (m).

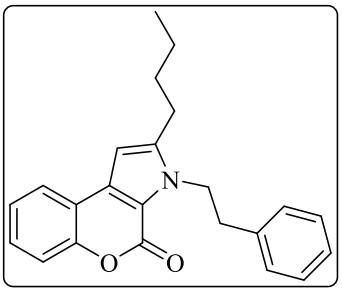
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 – 7.64 (m, 1H, CH_{Ar}), 7.43 – 7.32 (m, 2H, CH_{Ar}), 7.31 – 7.21 (m, 4H, CH_{Ar}), 7.15 – 7.08 (m, 2H, CH_{Ar}), 6.40 (s, 1H, CH_{Ar}), 4.67 – 4.50 (m, 2H), 3.21 – 3.03 (m, 2H), 2.38 – 2.24 (m, 2H), 1.74 – 1.55 (m, 2H, CH_2), 0.96 (t, ^3J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (63 MHz, $CDCl_3$) δ 155.0 (C=O), 151.5, 146.3, 138.3, 130.2 (C_{Ar}), 129.2 ($2CH_{Ar}$), 128.7 ($2CH_{Ar}$), 127.7, 126.8, 124.0, 123.0 (CH_{Ar}), 118.1 (C_{Ar}), 117.2 (CH_{Ar}), 115.5 (C_{Ar}), 100.2 (CH_{Ar}), 47.1 (N*C*H_2CH_2), 38.2 (NCH_2*C*H_2), 28.3, 21.62 (CH_2), 14.1 (CH_3).

MS (EI,70 eV): m/z (%) = 331 (M+, 74), 240 (100), 227 (42), 212 (17), 198 (39), 181 (5), 115 (9), 91 (12), 77 (12), 65 (5).

HRMS (EI, 70 eV): calcd for $C_{22}H_{21}O_2N_1$ ($[M]^+$): 331.15668, found: 331.15666.

2-Butyl-3-phenethylchromeno[3,4-*b*]pyrrol-4(3*H*)-one 2.6q



Yellowish oil, 65% (67.2 mg).

IR (ATR, cm^{-1}): 3118.7 (w), 3025.9 (w), 2959.3 (w), 2864.4 (w), 1703.8 (s), 1612.7 (w), 1507.5 (w), 1477.5 (m), 1428.2 (m), 1358.6 (m), 1301.0 (w), 1202.2 (m), 1037.0 (m), 956.3 (w), 829.0 (m), 751.2 (s), 697.4 (m), 570.3 (m).

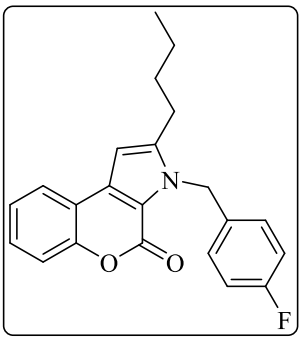
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (dd, ^3J = 7.6, ^4J = 1.3 Hz, 1H, CH_{Ar}), 7.43 – 7.31 (m, 2H, CH_{Ar}), 7.31 – 7.21 (m, 4H, CH_{Ar}), 7.16 – 7.07 (m, 2H, CH_{Ar}), 6.39 (s, 1H, CH_{Ar}), 4.70 – 4.49 (m, 2H, CH_2), 3.10 (t, ^3J = 7.3 Hz, 2H, CH_2), 2.48 – 2.22 (m, 2H, CH_2), 1.73 – 1.48 (m, 2H, CH_2), 1.43 – 1.25 (m, 2H, CH_2), 0.93 (t, ^3J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9 (C=O), 151.4, 146.4, 138.2, 130.1 (C_{Ar}), 129.1 ($2CH_{Ar}$), 128.6 ($2CH_{Ar}$), 127.6, 126.7, 123.9, 122.9 (CH_{Ar}), 117.9 (C_{Ar}), 117.0 (CH_{Ar}), 115.3 (C_{Ar}), 100.1 (CH_{Ar}), 46.9 (N*C*H_2CH_2), 38.1 (NCH_2*C*H_2), 30.3, 25.8, 22.5 (CH_2), 13.9 (CH_3).

MS (EI,70 eV): m/z (%) = 345 (M+, 57), 316 (8), 254 (20), 241 (6), 212 (100), 199 (59), 167 (9), 105 (9), 91 (12), 77 (11).

HRMS (EI, 70 eV): calcd for $C_{23}H_{23}O_2N_1$ ($[M]^+$): 345.17233, found: 345.17210.

2-Butyl-3-(4-fluorobenzyl)chromeno[3,4-*b*]pyrrol-4(3*H*)-one 2.6r



Yellowish oil, 51% (53.4 mg).

IR (ATR, cm^{-1}): 3069.6 (w), 2957.3 (w), 2926.6 (w), 2855.0 (w), 1706.5 (s), 1603.4 (w), 1495.9 (m), 1432.4 (m), 1392.2 (m), 1314.5 (w), 1221.8 (m), 1159.4 (m), 1072.8 (m), 977.5 (m), 895.2 (m), 839.8 (m), 808.7 (m), 767.3 (s), 733.5 (m), 659.8 (m), 551.5 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 – 7.71 (m, 1H, CH_{Ar}), 7.43 – 7.32 (m, 2H, CH_{Ar}), 7.32 – 7.23 (m, 1H, CH_{Ar}), 7.10 – 6.81 (m, 4H, CH_{Ar}), 6.54 (s, 1H, CH_{HAr}), 5.73

(s, 2H, CH_2), 2.67 – 2.55 (m, 2H, CH_2), 1.74 – 1.59 (m, 2H, CH_2), 1.40 (m, 2H, CH_2), 0.92 (t, ^3J = 7.3 Hz, 3H, CH_3).

^{19}F NMR (282 MHz, $CDCl_3$) δ -115.08.

^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1 (d, ^1J = 244.5 Hz, CF), 155.0 (C=O), 151.3, 146.5 (C_{Ar}), 133.3 (d, ^4J = 3.3 Hz, C_{Ar}), 130.2 (C_{Ar}), 128.1 (d, ^3J = 7.5 Hz, 2CH_{Ar}), 127.8 (C_{Ar}), 124.0, 122.9 (CH_{Ar}), 117.8 (C_{Ar}), 117.1, 115.9 (CH_{Ar}), 115.7 (d, ^2J = 21.7 Hz, 2CH_{Ar}), 101.0 (CH_{Ar}), 47.6 (N*C*H_2), 30.3, 26.3, 22.4 (CH_2), 13.8 (CH_3).

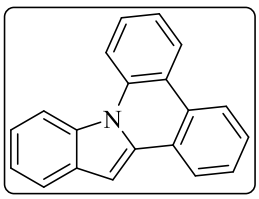
MS (EI,70 eV): m/z (%) = 349 (M+, 32), 320 (11), 307 (29), 24 (7), 224 (3), 198 (10), 109 (100), 83 (8), 63 (2).

HRMS (EI, 70 eV): calcd for $C_{22}H_{20}F_1O_2N_1$ ($[M]^+$): 349.14726, found: 349.14690.

General procedure for synthesis of Indolo[1,2-*f*]phenanthridines

1-Bromo-2-(phenylethynyl)benzene **3.1** (0.3 mmol), 2-bromoaniline **3.2** (0.33 mmol), $Pd(OAc)_2$ (0.03 mmol, 10%), XantPhos (0.03 mmol, 10%), and Cs_2CO_3 (0.9 mmol) were placed in a dried pressure tube equipped with a septum. The reaction vessel was back-filled with argon three times. Then dried and degassed DMF (4 mL) was added under argon and the septum was replaced with a Teflon cap. The reaction mixture was allowed to stir at 120 °C for 24 h. Then the reaction mixture was cooled to room temperature and was filtered through a pad of Celite. The filtrate was dried under reduced pressure, and the product **3.3** was obtained after flash chromatography on a silica gel column with heptane.

Indolo[1,2-*f*]phenanthridine 3.3a:



Yellowish solid, 75% (60.1 mg). M.p.: 150–151 °C.

IR (ATR, cm^{-1}): 3054.8 (w), 1938.2 (w), 1594.9 (w), 1562.1 (w), 1550.6 (w), 1485 (m), 1452.2 (m), 1434.9 (s), 1355.8 (m), 1334.6 (s), 1251.6 (m), 1199.6 (m), 1107.0 (m), 1041.4 (w), 956.6 (w), 788.8 (w), 754.1 (m), 742.5 (s), 711.6 (m), 613.3 (m), 574.7 (m).

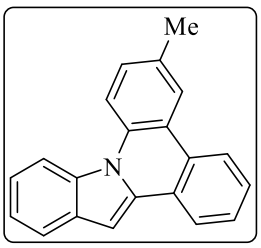
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (dd, ^3J = 8.5, ^4J = 0.8 Hz, 1H, CH_{Ar}), 8.45 – 8.35 (m, 1H, CH_{Ar}), 8.32 (dd, ^3J = 8.1, ^4J = 1.4 Hz, 1H, CH_{Ar}), 8.27 – 8.18 (m, 1H, CH_{Ar}), 8.18 – 8.09 (m, 1H, CH_{Ar}), 7.90 – 7.80 (m, 1H, CH_{Ar}), 7.63 – 7.52 (m, 1H, CH_{Ar}), 7.53 – 7.44 (m, 2H, CH_{Ar}), 7.44 – 7.31 (m, 3H, CH_{Ar}), 7.26 (s, 1H, CH_{Ar}).

^{13}C NMR (63 MHz, $CDCl_3$) δ 136.3, 135.5, 134.2, 130.6 (C_{Ar}), 129.0, 128.5, 128.1 (CH_{Ar}), 127.1, 126.4 (C_{Ar}), 124.4, 124.3, 123.3, 122.7 (CH_{Ar}), 122.4 (C_{Ar}), 122.3, 122.1, 121.3, 116.6, 114.5, 96.5 (CH_{Ar}).

MS (EI,70 eV): m/z (%) = 267 (M+, 100), 239(8), 134(11), 120(4), 106(3).

HRMS (EI, 70 eV): calcd for $C_{20}H_{13}N_1$ ($[M]^+$): 267.10425, found: 267.10431.

6-Methylindolo[1,2-*f*]phenanthridine 3.3b:



Yellowish solid, 66% (55.6 mg). M.p.: 170–171 °C.

IR (ATR, cm^{-1}): 3120.4 (w), 3043.3 (w), 2914.1 (w), 1930.0 (w), 1593.0 (m), 1562.1 (m), 1550.6 (m), 1488.8 (m), 1446.4 (s), 1355.8 (s), 1332.6 (m), 1251.6 (m), 1195.7 (m), 1112.8 (m), 1043.4 (m), 958.5 (m), 788.8 (s), 754.1 (m), 736.7 (s), 713.6 (m), 615.2 (m), 578.6 (m).

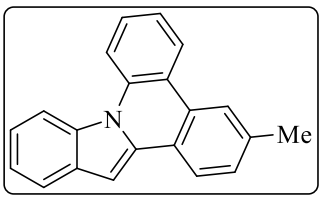
^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.46 (d, ^3J = 8.6 Hz, 1H, CH_{Ar}), 8.38 (d, ^3J = Hz, 1H, CH_{Ar}), 8.32 – 8.24 (m, 1H, CH_{Ar}), 8.22 – 8.13 (m, 2H, CH_{Ar}), 7.88 – 7.79 (m, 1H, CH_{Ar}), 7.57 – 7.48 (m, 2H, CH_{Ar}), 7.47 – 7.42 (m, 1H, CH_{Ar}), 7.42 – 7.30 (m, 2H, CH_{Ar}), 7.29 (d, ^4J = 0.7 Hz, 1H, CH_{Ar}), 2.53 (s, 3H, CH_3).

^{13}C NMR (63 MHz, CD_2Cl_2) δ 135.7, 134.4, 134.4, 133.3, 130.8 (C_{Ar}), 130.3, 128.8, 128.5 (CH_{Ar}), 127.5, 126.7 (C_{Ar}), 124.9, 124.7, 123.0, 122.5 (CH_{Ar}), 122.5 (C_{Ar}), 122.2, 121.5, 116.7, 114.7, 96.4 (CH_{Ar}), 21.4 (CH_3).

MS (EI,70 eV): m/z (%) = 281 (M+, 100), 252(3), 139(12).

HRMS (+ESI): calcd for $C_{21}H_{16}N_1$ ($[M+H]^+$): 282.12773, found: 282.12775.

3-Methylindolo[1,2-*f*]phenanthridine 3.3c:



Yellowish solid, 52% (43.8 mg). M.p.: 135–136 °C.

IR (ATR, cm^{-1}): 3114.6 (w), 3043.3 (w), 2912.1 (w), 2854.3 (w), 1907.3 (m), 1598.8 (m), 1564.1 (w), 1556.3 (w), 1494.6 (w), 1440.6 (s), 1351.9 (s), 1340.4 (m), 1253.6 (m), 1199.6 (w), 1112.8 (w), 1035.6 (m), 958.5 (m), 781.1 (m), 757.9 (s), 740.6 (s), 713.6 (s), 615.2 (m), 578.6 (m), 532.3 (s).

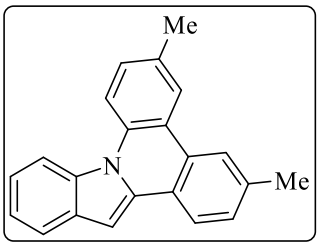
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (dd, ^3J = 8.5, ^4J = 0.9 Hz, 1H, CH_{Ar}), 8.43 – 8.30 (m, 2H, CH_{Ar}), 8.08 – 8.01 (m, 2H, CH_{Ar}), 7.88 – 7.80 (m, 1H, CH_{Ar}), 7.64 – 7.53 (m, 1H, CH_{Ar}), 7.44 – 7.30 (m, 4H, CH_{Ar}), 7.22 (s, 1H, CH_{Ar}), 2.53 (s, 3H, CH_3).

^{13}C NMR (63 MHz, $CDCl_3$) δ 137.8, 136.3, 135.7, 134.0, 130.7 (C_{Ar}), 129.7, 128.8 (CH_{Ar}), 127.0 (C_{Ar}), 124.3, 124.1 (CH_{Ar}), 123.9 (C_{Ar}), 123.1, 122.7 (CH_{Ar}), 122.3 (C_{Ar}), 121.9, 121.9, 121.1, 116.5, 114.3, 95.6 (CH_{Ar}), 22.0 (CH_3).

MS (EI,70 eV): m/z (%) = 281 (M^+, 100), 252 (3), 139 (10), 126 (4).

HRMS (EI, 70 eV): calcd for $C_{21}H_{15}N_1$ ($[M]^+$): 281.11990, found: 281.12033.

3,6-Dimethylindolo[1,2-*f*]phenanthridine 3.3d:



Yellowish solid, 45% (39.8 mg). M.p.: 185–186 °C.

IR (ATR, cm^{-1}): 3106.9 (w), 3054.8 (w), 2912.1 (w), 2850.4 (w), 2725.1 (w), 1917.0 (w), 1729.9 (w), 1598.8 (m), 1562.1 (m), 1498.5 (w), 1444.5 (s), 1350.0 (s), 1251.6 (m), 1201.5 (s), 1112.8 (m), 1033.7 (m), 960.4 (m), 867.9 (m), 823.5 (s), 784.9 (s), 756.0 (s), 736.7 (s), 713.6 (s), 655.7 (s), 613.3 (m), 574.7 (m), 538.1 (s).

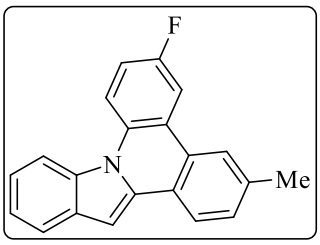
^{1}H NMR (250 MHz, $CDCl_3$) δ 8.40 (d, ^3J = 8.6 Hz, 1H, CH_{Ar}), 8.37 – 8.29 (m, 1H, CH_{Ar}), 8.07 (d, ^4J = 1.2 Hz, 1H, CH_{Ar}), 8.04 – 7.95 (m, 2H, CH_{Ar}), 7.87 – 7.77 (m, 1H, CH_{Ar}), 7.42 – 7.24 (m, 4H, CH_{Ar}), 7.18 (s, 1H, CH_{Ar}), 2.51 (s, 3H, CH_3), 2.50 (s, 3H, CH_3).

^{13}C NMR (63 MHz, $CDCl_3$) δ 137.7, 135.6, 134.1, 133.8, 132.4, 130.5 (C_{Ar}), 129.5, 129.5 (CH_{Ar}), 126.9 (C_{Ar}), 124.3, 124.3 (CH_{Ar}), 123.9 (C_{Ar}), 122.6 (CH_{Ar}), 122.1 (C_{Ar}), 121.7, 121.6, 120.9, 116.3, 114.2, 95.3 (CH_{Ar}), 22.0 (CH_3), 21.3 (CH_3).

MS (EI,70 eV): m/z (%) = 295 (M^+, 100), 278 (13), 139 (9).

HRMS (EI, 70 eV): calcd for $C_{22}H_{17}N_1$ ($[M]^+$): 295.13555, found: 295.13567.

6-Fluoro-3-methylindolo[1,2-*f*]phenanthridine 3.3e:



Yellowish solid, 55% (49.3 mg). M.p.: 165–166°C.

IR (ATR, cm^{-1}): 3106.9 (w), 3049.1 (w), 2917.9 (w), 2856.2 (w), 2736.6 (w), 1917.0 (w), 1729.9 (w), 1606.5 (w), 1567.9 (m), 1496.6 (m), 1448.4 (m), 1429.1 (s), 1353.9 (m), 1276.7 (m), 1249.7 (m), 1203.4 (m), 1172.6 (s), 1116.6 (m), 1068.4 (m), 1041.4 (m), 960.4 (m), 948.9 (m), 867.9 (s), 823.5 (s), 788.8 (s), 754.1 (m), 734.8 (s), 713.6 (m), 655.7 (m), 611.4 (m), 572.8 (m), 536.1 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (dd, ^3J = 9.2, ^4J = 4.9 Hz, 1H, CH_{Ar}), 8.26 (dd, ^3J = 6.5, ^4J = 2.6 Hz, 1H, CH_{Ar}), 7.96 (d, ^3J = 8.1 Hz, 1H, CH_{Ar}), 7.89 (dd, ^3J = 10.2, ^4J = 2.9 Hz, 1H,

CH_{Ar}), 7.86 – 7.73 (m, 2H, CH_{Ar}), 7.43 – 7.27 (m, 3H, CH_{Ar}), 7.27 – 7.10 (m, 1H, CH_{Ar}), 2.49 (s, 3H, CH_3) (signal of one H could not be detected).

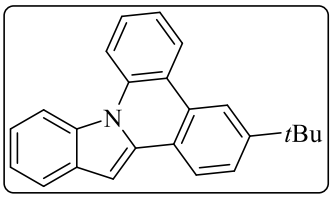
^{19}F NMR (282 MHz, $CDCl_3$) δ -119.57.

^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7 (d, ^1J = 241.8 Hz, CF), 137.9, 135.2, 133.7 (C_{Ar}), 132.6 (d, ^4J = 2.2 Hz, C_{Ar}), 130.4 (C_{Ar}), 130.3 (CH_{Ar}), 126.1 (d, ^4J = 2.5 Hz, C_{Ar}), 124.3 (CH_{Ar}), 124.2 (d, ^3J = 7.6 Hz, C_{Ar}), 124.1 (C_{Ar}), 122.8, 122.1, 121.9, 121.2 (CH_{Ar}), 117.7 (d, ^4J = 8.2 Hz), 115.5 (d, ^2J = 23.0 Hz, CH_{Ar}), 113.8 (CH_{Ar}), 110.2 (d, ^2J = 23.8 Hz, CH_{Ar}), 95.7 (CH_{Ar}), 21.9 (CH_3).

MS (EI,70 eV): m/z (%) = 299 (M^+, 100), 270 (3), 148 (6).

HRMS (EI, 70 eV): calcd for $C_{21}H_{14}N_1F_1$ ($[M]^+$): 299.11048, found: 299.11053.

3-(*Tert*-butyl)indolo[1,2-*f*]phenanthridine 3.3f:



Yellowish solid, 65% (63.0 mg). M.p.: 151–152 °C.

IR (ATR, cm^{-1}): 3122.3 (w), 3043.3 (w), 2950.7 (w), 2863.9 (w), 2742.4 (w), 2331.6 (w), 1917.0 (w), 1731.8 (w), 1606.5 (w), 1562.1 (w), 1490.8 (w), 1448.4 (s), 1440.6 (s), 1417.5 (s), 1348.1 (s), 1276.7 (m), 1259.4 (m), 1197.6 (m), 1172.6 (m), 1112.8 (m), 1072.3 (m), 1053.0 (m), 1020.2 (m), 958.5 (w), 875.6 (m), 831.2 (m), 788.8 (m), 754.1 (s), 734.8 (s), 723.2 (m), 661.5 (m), 611.4 (m), 588.2 (m), 541.9 (m).

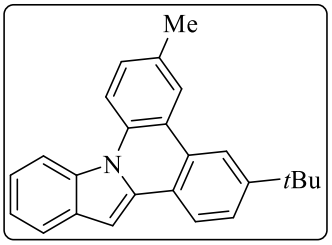
^1H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, ^3J = 8.4 Hz, 1H, CH_{Ar}), 8.41 – 8.31 (m, 2H, CH_{Ar}), 8.25 (d, ^4J = 1.7 Hz, 1H, CH_{Ar}), 8.06 (d, ^3J = 8.4 Hz, 1H, CH_{Ar}), 7.86 – 7.76 (m, 1H, CH_{Ar}), 7.61 – 7.47 (m, 2H, CH_{Ar}), 7.41 – 7.28 (m, 3H, CH_{Ar}), 1.45 (s, 9H, $C(CH_3)_3$). (signal of one H could not be detected).

^{13}C NMR (63 MHz, $CDCl_3$) δ 136.2, 135.4, 133.9, 130.6, 130.5 (C_{Ar}), 128.6 (CH_{Ar}), 126.5 (C_{Ar}), 126.2, 124.1, 123.9 (CH_{Ar}), 123.8 (C_{Ar}), 123.0 (CH_{Ar}), 122.5 (C_{Ar}), 121.8, 121.8, 120.9, 118.6, 116.5, 114.3, 95.7 (CH_{Ar}), 35.2 ($C(CH_3)_3$), 31.4 (3C, $C(CH_3)_3$).

MS (EI,70 eV): m/z (%) = 323 (M^+,100), 308 (70), 293 (34), 267 (13), 140 (23).

HRMS (EI, 70 eV): calcd for $C_{24}H_{21}N_1$ ($[M]^+$): 323.16685, found: 323.16687.

3-(*Tert*-butyl)-6-methylindolo[1,2-*f*]phenanthridine 3.3g:



Yellowish solid, 67% (67.7 mg). M.p.: 195–196 °C.

IR (ATR, cm^{-1}): 3124.3 (w), 3049.1 (w), 2950.7 (w), 2863.9 (w), 2732.8 (w), 2331.6 (w), 1913.1 (w), 1731.8, 1606.5 (w), 1564.1 (m), 1488.8 (m), 1446.4 (s), 1421.4 (s), 1351.9 (s), 1280.6 (m), 1261.3 (m), 1195.7 (m), 1114.7 (m), 1066.5 (m), 1045.3 (w), 1024.1 (w), 788.8 (s), 757.9 (s), 736.7 (m), 611.4 (m), 588.2 (m), 555.4 (s).

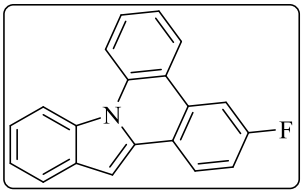
^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.46 (d, ^{3}J = 8.5 Hz, 1H, CH_{Ar}), 8.38 (d, ^{3}J = 8.2 Hz, 1H, CH_{Ar}), 8.30 (d, ^{4}J = 1.7 Hz, 1H, CH_{Ar}), 8.22 (s, 1H, CH_{Ar}), 8.11 (d, ^{3}J = 8.4 Hz, 1H, CH_{Ar}), 7.83 (dd, ^{3}J = 6.8, ^{4}J = 1.9 Hz, 1H, CH_{Ar}), 7.61 (dd, ^{3}J = 8.4, ^{4}J = 1.8 Hz, 1H, CH_{Ar}), 7.49 – 7.28 (m, 3H, CH_{Ar}), 7.24 (s, 1H, CH_{Ar}), 2.55 (s, 3H, CH_3), 1.49 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (63 MHz, CD_2Cl_2) δ 151.6, 135.9, 134.5, 134.3, 133.2, 130.9 (C_{Ar}), 130.1 (CH_{Ar}), 127.0 (C_{Ar}), 126.7, 124.7, 124.5 (CH_{Ar}), 124.2, 122.8 (C_{Ar}), 122.2, 122.1, 121.4, 119.3, 116.8, 114.7, 95.8 (CH_{Ar}), 35.6 (*C*-$(CH_3)_3$), 31.7 (3C, C-(*C*$H_3)_3$), 21.4 (CH_3).

MS (EI,70 eV): m/z (%) = 337 (M^+, 100), 322 (59), 307 (32), 278 (10), 161 (5), 147 (17).

HRMS (EI, 70 eV): calcd for $C_{25}H_{23}N_1$ ($[M]^+$): 337.1825, found: 337.18270.

3-Fluoroindolo[1,2-*f*]phenanthridine 3.3h:



Yellowish solid, 77% (65.8 mg). M.p.: 129–130 °C.

IR (ATR, cm^{-1}): 3054.8 (w), 2952.6 (w), 2850.4 (w), 2734.7 (w), 2331.6 (w), 1928.6 (w), 1884.2 (w), 1731.8 (w), 1602.6 (m), 1558.3 (m), 1490.8 (m), 1440.6 (s), 1350.0 (s), 1280.6 (m), 1272.9 (m), 1195.7 (m), 1120.5 (m), 887.1 (w), 835.1 (m), 777.2 (m), 754.1 (m), 736.7 (s), 729.0 (s), 651.9 (m), 597.9 (m), 555.4 (m), 534.2 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 – 8.31 (m, 1H, CH_{Ar}), 8.26 – 8.17 (m, 1H, CH_{Ar}), 8.00 (dd, ^{3}J = 8.1, ^{4}J = 1.3 Hz, 1H, CH_{Ar}), 7.90 (dd, ^{3}J = 8.8, ^{4}J = 5.7 Hz, 1H, CH_{Ar}), 7.75 – 7.62 (m, 2H, CH_{Ar}), 7.51 – 7.39 (m, 1H, CH_{Ar}), 7.33 – 7.13 (m, 3H, CH_{Ar}), 7.12 – 7.01 (m, 1H, CH_{Ar}), 7.00 (s, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$) δ -112.61.

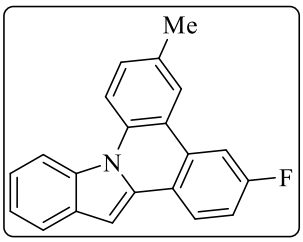
^{13}C NMR (63 MHz, $CDCl_3$) δ 162.5 (d, ^{1}J = 246.4 Hz, CF), 136.2, 134.6, 133.7, 130.3 (C_{Ar}), 129.4 (CH_{Ar}), 128.9 (d, ^{3}J = 8.2 Hz, C_{Ar}), 126.2 (d, ^{3}J = 8.7 Hz, CH_{Ar}), 124.1, 123.0 (CH_{Ar}), 122.5 (d, ^{4}J = 2.5 Hz, C_{Ar}), 122.0, 121.89 (CH_{Ar}), 121.2 (d, ^{4}J = 3.1 Hz, C_{Ar}), 120.9, 116.3

(CH_{Ar}), 116.1 (d, ^{2}J = 23.0 Hz, CH_{Ar}), 114.2 (CH_{Ar}), 108.4 (d, ^{2}J = 23.2 Hz), 95.8 (d, ^{6}J = 1.5 Hz, CH_{Ar}).

MS (EI,70 eV): m/z (%) = 285 (M^{+}, 100), 257 (7), 143 (10).

HRMS (EI, 70 eV): calcd for $C_{20}H_{12}N_1F_1$ ($[M]^{+}$): 285.09483, found: 285.09458.

3-Fluoro-6-methylindolo[1,2-*f*]phenanthridine 3.3i:



Yellowish solid, 54% (48.4 mg). M.p.: 203–204 °C.

IR (ATR, cm^{-1}): 3108.8 (w), 3051.0 (w), 2917.9 (w), 2850.4 (w), 2732.8 (w), 2325.8 (w), 1928.6 (w), 1895.8 (w), 1731.8 (w), 1614.2 (m), 1554.4 (m), 1486.9 (m), 1438.7 (m), 1350.0 (m), 1280.6 (m), 1274.8(m), 1189.9, 1120.5, 1076.1, 1041.4, 1024.1, 960.4, 900.6, 844.7(m), 784.9 (s), 736.7 (s), 653.8 (m), 632.6 (m), 615.2 (m), 607.5 (m), 574.7(m), 530.4 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 – 8.21 (m, 2H, CH_{Ar}), 8.01 (dd, ^{3}J = 8.8, ^{4}J = 5.7 Hz, 1H, CH_{Ar}), 7.87 (s, 1H, CH_{Ar}), 7.84 – 7.64 (m, 2H, CH_{Ar}), 7.43 – 7.28 (m, 3H, CH_{Ar}), 7.21 – 6.99 (m, 2H, CH_{Ar}), 2.46 (s, 3H, CH_3).

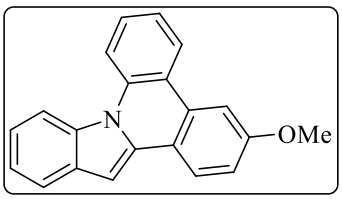
^{19}F NMR (282 MHz, $CDCl_3$) δ -112.82.

^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6 (d, ^{1}J = 246.2 Hz, CF), 134.6, 134.2, 133.8, 132.6 (C_{Ar}), 130.4 (CH_{Ar}), 129.0 (d, ^{3}J = 8.2 Hz, C_{Ar}), 126.3 (d, ^{3}J = 8.7 Hz, CH_{Ar}), 124.5 (CH_{Ar}), 122.7 (d, ^{4}J = 2.4 Hz, C_{Ar}), 122.0, 121.8 (CH_{Ar}), 121.2 (d, ^{4}J = 3.0 Hz, C_{Ar}), 121.1, 116.3 (CH_{Ar}), 116.1 (d, ^{2}J = 22.7 Hz, CH_{Ar}) (one signal of the doublet is overlapped with the signal at 116.3), 114.2 (CH_{Ar}), 108.5 (d, ^{2}J = 23.3 Hz, CH_{Ar}), 95.6 (CH_{Ar}), 21.2 (CH_3) (signal of one C_{Ar} could not be detected).

MS (EI,70 eV): m/z (%) = 299 (M^{+}, 100), 149 (8).

HRMS (EI, 70 eV): calcd for $C_{21}H_{14}N_1F_1$ ($[M]^{+}$): 299.11048, found: 299.10984.

3-Methoxyindolo[1,2-*f*]phenanthridine 3.3j:



Yellowish solid, 78% (69.5 mg). M.p.: 143–144 °C.

IR (ATR, cm^{-1}): 3108.8 (w), 3043.3 (w), 2919.8 (w), 2850.4 (w), 2732.8 (w), 2323.9 (w), 2057.8 (w), 1918.9 (w), 1891.9 (w), 1731.8 (w), 1610.3 (m), 1558.3 (m), 1492.7 (s), 1427.1 (s), 1348.1 (m), 1286.4 (m), 1199.6 (m), 1120.5 (m), 1078.1 (m), 1037.6 (m), 1024.1 (m), 958.5 (m), 910.3 (m), 835.1 (m), 777.2 (m), 740.6 (s), 653.8 (m), 638.4 (m), 607.5 (m), 565.1 (m), 538.1.

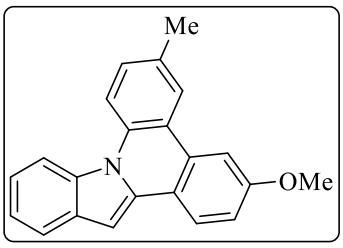
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (dd, ^{3}J = 8.5, ^{4}J = 0.9 Hz, 1H, CH_{Ar}), 8.37 – 8.28 (m, 1H, CH_{Ar}), 8.18 (dd, ^{3}J = 8.1, ^{4}J = 1.4 Hz, 1H, CH_{Ar}), 7.97 (d, ^{3}J = 8.8 Hz, 1H, CH_{Ar}), 7.84 – 7.73 (m, 1H, CH_{Ar}), 7.60 – 7.49 (m, 2H, CH_{Ar}), 7.41 – 7.27 (m, 3H, CH_{Ar}), 7.03 (dd, ^{3}J = 8.8, ^{4}J = 2.5 Hz, 1H, CH_{Ar}), 3.92 (s, 3H, OCH_3). (Signal of one H could not be detected).

^{13}C NMR (63 MHz, $CDCl_3$) δ 159.5 (*C*-OCH_3), 136.3, 135.6, 133.8, 130.8 (C_{Ar}), 128.9 (CH_{Ar}), 128.4 (C_{Ar}), 125.8, 124.0, 122.9 (CH_{Ar}), 121.9 (C_{Ar}), 121.8, 121.6, 120.8 (CH_{Ar}), 119.8 (C_{Ar}), 116.4, 116.1, 114.2, 105.8, 94.7 (CH_{Ar}), 55.5 (OCH_3).

MS (EI, 70 eV): m/z (%) = 297 (M^+, 100), 282 (19), 254 (56), 226 (4), 149 (12), 126 (12).

HRMS (EI, 70 eV): calcd for $C_{21}H_{15}N_1O_1$ ($[M]^+$): 297.11482, found: 297.11474.

3-Methoxy-6-methylindolo[1,2-*f*]phenanthridine 3.3k:



Yellowish solid, 73% (68.1 mg). M.p.: 188–189 °C.

IR (ATR, cm^{-1}): 3108.8 (w), 3045.2 (w), 2910.2 (w), 2840.8 (w), 2725.1 (w), 2325.8 (w), 2055.8 (w), 1918.9 (w), 1888.1 (w), 1731.8 (w), 1608.4 (m), 1556.3 (m), 1488.8 (m), 1431.0 (m), 1350.0 (m), 1286.4 (m), 1201.5 (m), 1130.1 (m), 1072.3 (m), 1037.6 (m), 1024.1 (m), 958.5 (m), 919.9 (m), 838.9 (m), 781.1 (s), 736.7 (s), 655.7 (m), 609.4 (m), 565.1 (m), 547.7 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 – 8.21 (m, 2H), 8.06 – 7.91 (m, 2H), 7.86 – 7.72 (m, 1H), 7.57 (d, ^{4}J = 2.3 Hz, 1H), 7.43 – 7.28 (m, 3H), 7.04 (dd, ^{3}J = 8.8, ^{4}J = 2.4 Hz, 2H), 3.94 (s, 3H, OCH_3), 2.47 (s, 3H, CH_3).

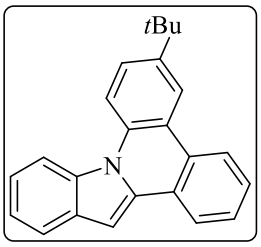
^{13}C NMR (63 MHz, $CDCl_3$) δ 159.5 (*C*-OCH_3), 135.5, 134.2, 133.7, 132.3, 130.6 (C_{Ar}), 129.8 (CH_{Ar}), 128.4 (C_{Ar}), 125.9, 124.3 (CH_{Ar}), 121.8 (C_{Ar}), 121.6, 121.4, 120.7 (CH_{Ar}), 119.9 (C_{Ar}), 116.3, 116.1, 114.2, 105.7, 94.4 (CH_{Ar}), 55.6 (OCH_3), 21.2 (CH_3).

MS (EI, 70 eV): m/z (%) = 311 (M^+, 100), 296 (13), 268 (42), 156 (10), 133 (10).

HRMS (EI, 70 eV): calcd for $C_{22}H_{17}N_1O_1$ ($[M]^+$): 311.13047, found: 311.13016.

For compounds **3.5c**, **3.5d**, **3.5h**, **3.5i**, **3.6j**, **3.5g**, **3.5f**, 20% of $PCy_3 \cdot HBF_4$ was used instead of XantPhos.

6-(*Tert*-butyl)indolo[1,2-*f*]phenanthridine 3.5c:



Yellowish solid, 43% (41.7 mg). M.p.: 146–168 °C.

IR (ATR, cm^{-1}): 3065.8 (w), 3043.2 (w), 2955.5 (w), 2898.7 (w), 2859.4 (w), 1953.0 (w), 1921.3 (w), 1881.4 (w), 1593.0 (m), 1552.4 (m), 1487.5 (m), 1448.4 (s), 1408.1 (w), 1357.5 (m), 1255.0 (m), 1228.8 (m), 1206.2 (m), 1120.3 (m), 1019.2 (m), 945.7 (m), 877.9 (m), 802.3 (m), 755.3 (s), 732.5 (s), 624.4 (m), 526.5 (m).

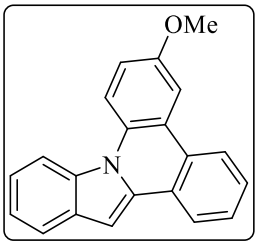
^{1}H NMR (250 MHz, Acetone) δ 8.62 (d, ^{3}J = 8.8 Hz, 1H, CH_{Ar}), 8.57 – 8.47 (m, 3H, CH_{Ar}), 8.33 – 8.24 (m, 1H, CH_{Ar}), 7.84 (dd, ^{3}J = 7.1, ^{4}J = 1.5 Hz, 1H, CH_{Ar}), 7.76 (dd, ^{3}J = 8.8, ^{4}J = 2.3 Hz, 1H, CH_{Ar}), 7.64 – 7.49 (m, 2H, CH_{Ar}), 7.48 – 7.25 (m, 3H, CH_{Ar}), 1.48 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (63 MHz, Acetone) δ 147.0, 135.9, 134.8, 134.7, 131.4 (C_{Ar}), 129.3, 129.1 (CH_{Ar}), 128.1 (C_{Ar}), 127.5 (CH_{Ar}), 127.1 (C_{Ar}), 125.3, 123.8, 123.1, 122.7 (CH_{Ar}), 122.5 (C_{Ar}), 122.0, 121.8, 117.1, 115.2, 97.2 (CH_{Ar}), 35.4 (3C, $C(CH_3)_3$), 31.8 ($C(CH_3)_3$).

MS (EI, 70 eV): m/z (%) = 323 (M^+, 100), 308 (90), 293 (28), 267 (16), 239 (3), 140 (22).

HRMS (EI, 70 eV): calcd for $C_{24}H_{21}N_1$ ($[M]^+$): 323.16685, found: 323.16686.

6-Methoxyindolo[1,2-*f*]phenanthridine 3.5d:



Yellowish solid, 49% (43.7 mg). M.p.: 154–155 °C.

IR (ATR, cm^{-1}): 3105.0 (w), 3043.3 (w), 2910.2 (w), 2836.9 (w), 2325.8 (w), 2053.9 (w), 1917.0 (w), 1890.0 (w), 1731.8 (w), 1620.0 (w), 1562.1 (m), 1488.8 (m), 1438.7 (m), 1357.7(m), 1288.3 (m), 1197.6 (m), 1130.1 (m), 1070.4 (m), 1041.4 (m), 1026.0 (m), 958.5 (m), 919.9 (m), 838.9 (m), 790.7 (S), 734.8 (S), 655.7 (m), 607.5 (m), 563.1(m).

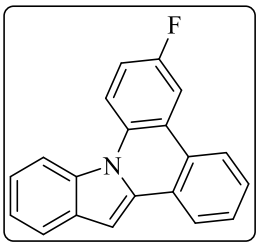
^{1}H NMR (250 MHz, CD_2Cl_2) δ 8.38 (d, ^{3}J = 9.2 Hz, 1H, CH_{Ar}), 8.23 (d, ^{3}J = 8.4 Hz, 1H, CH_{Ar}), 8.15 (dd, ^{3}J = 6.2, ^{4}J = 3.1 Hz, 1H, CH_{Ar}), 8.10 – 7.93 (m, 1H, CH_{Ar}), 7.74 (d, ^{4}J = 2.8 Hz, 1H, CH_{Ar}), 7.70 – 7.57 (m, 1H, CH_{Ar}), 7.46 – 7.26 (m, 2H, CH_{Ar}), 7.27 – 6.95 (m, 4H, CH_{Ar}), 3.80 (s, 3H, OCH_3).

^{13}C NMR (63 MHz, CD_2Cl_2) δ 156.2 (C-OCH_3), 135.3, 134.1, 130.7, 130.6 (C_{Ar}), 129.0, 128.4 (CH_{Ar}), 127.2, 126.8 (C_{Ar}), 124.7 (CH_{Ar}), 123.8 (C_{Ar}), 123.3, 122.5, 121.9, 121.5, 118.0, 115.8, 114.4, 108.9, 96.3 (CH_{Ar}), 55.7 (OCH_3).

MS (EI,70 eV): m/z (%) = 297 (M^+, 100), 282 (25), 254 (53), 226 (5), 148 (11), 127 (14).

HRMS (EI, 70 eV): calcd for $C_{21}H_{15}N_1O_1$ ($[M]^+$): 297.13047, found: 297.13000.

6-Fluoroindolo[1,2-*f*]phenanthridine 3.5h:



Yellowish solid, 75% (64.1 mg). M.p.: 169–170 °C.

IR (ATR, cm^{-1}): 3049.1 (w), 2140.7 (w), 1918.9 (w), 1729.9 (w), 1621.9 (w), 1567.9 (m), 1488.8 (m), 1448.4 (s), 1357.7 (m), 1276.7 (m), 1247.8 (m), 1197.6 (m), 1180.3 (s), 1139.8 (m), 1066.5 (m), 1041.4 (m), 1024.1 (m), 960.4 (m), 921.9 (m), 838.9 (m), 796.5 (s), 734.8 (s), 659.6 (m), 611.4 (m), 565.1(m).

^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.39 (dd, ^{3}J = 9.2, ^{4}J = 4.9 Hz, 1H, CH_{Ar}), 8.29 – 8.18 (m, 1H, CH_{Ar}), 8.13 – 7.97 (m, 2H, CH_{Ar}), 7.89 (dd, ^{3}J = 10.3, ^{4}J = 2.9 Hz, 1H, CH_{Ar}), 7.85 – 7.75 (m, 1H, CH_{Ar}), 7.54 – 7.41 (m, 2H, CH_{Ar}), 7.41 – 7.30 (m, 2H, CH_{Ar}), 7.30 – 7.20 (m, 1H, CH_{Ar}), 7.19 (s, 1H, CH_{Ar}).

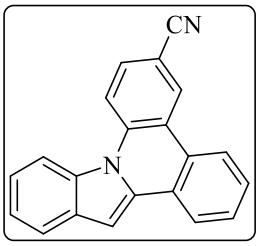
^{19}F NMR (282 MHz, CD_2Cl_2) δ -120.10.

^{13}C NMR (63 MHz, CD_2Cl_2) δ 159.2 (d, ^{1}J = 241.2 Hz, CF), 135.3, 134.2, 132.9 (d, ^{4}J = 2.2 Hz), 130.7 (C_{Ar}), 129.4, 128.5 (CH_{Ar}), 126.8, 126.5 (d, ^{4}J = 2.5 Hz, C_{Ar}), 124.6 (CH_{Ar}), 124.5 (d, ^{3}J = 7.7 Hz, C_{Ar}), 123.1, 122.8, 122.4, 121.7 (CH_{Ar}), 118.2 (d, ^{3}J = 8.2 Hz, CH_{Ar}), 116.0 (d, ^{2}J = 23.1 Hz, CH_{Ar}), 114.3 (CH_{Ar}), 110.6 (d, ^{2}J = 23.9 Hz, CH_{Ar}), 96.8 (CH_{Ar}).

MS (EI, 70 eV): m/z (%) = 285 (M^+, 100), 257 (8), 143 (10), 128 (4).

HRMS (EI, 70 eV): calcd for $C_{20}H_{12}N_1F_1$ ($[M]^+$): 285.09483, found: 285.09477.

Indolo[1,2-*f*]phenanthridine-6-carbonitrile 3.5i:



Yellowish solid, 44% (38.5 mg). M.p.: 217–218 °C.

IR (ATR, cm^{-1}): 3068.3 (w), 2221.7 (m), 1593.0 (m), 1556.3 (m), 1490.8 (m), 1446.4 (s), 1409.8 (m), 1353.9 (m), 1288.3 (m), 1251.6 (m), 1207.3 (m), 1182.2 (w), 1145.6 (w), 1068.4 (w), 1045.3 (w), 1024.1 (w), 958.5 (w), 919.9 (w), 877.5 (m), 833.1 (m), 798.4 (s), 734.8 (s), 657.6 (m), 611.4 (m), 565.1 (m).

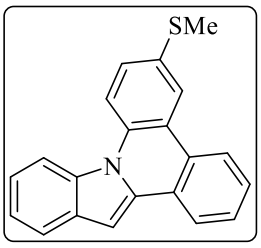
^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.45 (d, ^{4}J = 1.8 Hz, 1H, CH_{Ar}), 8.42 (d, ^{3}J = 8.8 Hz, 1H, CH_{Ar}), 8.20 (dd, ^{3}J = 6.4, ^{4}J = 2.5 Hz, 1H, CH_{Ar}), 8.14 – 7.97 (m, 2H, CH_{Ar}), 7.85 – 7.77 (m, 1H, CH_{Ar}), 7.73 (dd, ^{3}J = 8.8, ^{4}J = 1.9 Hz, 1H, CH_{Ar}), 7.59 – 7.45 (m, 2H, CH_{Ar}), 7.45 – 7.32 (m, 2H, CH_{Ar}), 7.22 (s, 1H, CH_{Ar}).

^{13}C NMR (63 MHz, CD_2Cl_2) δ 138.9, 135.4, 134.5 (C_{Ar}), 132.3 (CH_{Ar}), 131.2 (C_{Ar}), 129.9, 128.9, 128.8 (CH_{Ar}), 126.7, 125.5 (C_{Ar}), 124.7, 123.5, 123.3 (CH_{Ar}), 123.2 (C_{Ar}), 122.9, 121.9 (CH_{Ar}), 119.4 (CN), 117.2, 114.8 (CH_{Ar}), 106.9 (C_{Ar}), 98.4 (CH_{Ar}).

MS (EI,70 eV): m/z (%) = 292 (M^+, 100), 264 (10), 146 (8), 132 (9), 118 (3).

HRMS (EI, 70 eV): calcd for $C_{21}H_{12}N_2$ ($[M]^+$): 292.0995, found: 292.09960.

6-(Methylthio)indolo[1,2-*f*]phenanthridine 3.5j:



Yellowish solid, 56% (52.6 mg). M.p.: 143–144 °C.

IR (ATR, cm^{-1}): 3043.3 (w), 2917.9 (w), 1915.1 (w), 1591.1 (w), 1546.7 (m), 1490.8 (m), 1448.4 (s), 1398.2 (m), 1353.9 (m), 1288.3 (m), 1253.6(m), 1203.4 (w), 1188.0 (m), 1164.9 (m), 1114.7 (m), 1024.1 (w), 954.6 (m), 916.1 (w), 864.0 (w), 790.7 (s), 734.8 (s), 613.3 (m), 582.4 (m).

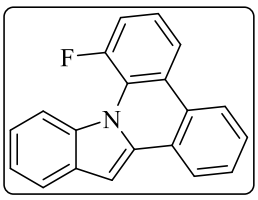
^{1}H NMR (250 MHz, CD_2Cl_2) δ 8.38 (d, ^3J = 8.8 Hz, 1H, CH_{Ar}), 8.24 (d, ^3J = 8.2 Hz, 1H, CH_{Ar}), 8.20 – 8.09 (m, 2H, CH_{Ar}), 8.09 – 7.98 (m, 1H, CH_{Ar}), 7.79 – 7.63 (m, 1H, CH_{Ar}), 7.50 – 7.33 (m, 3H, CH_{Ar}), 7.33 – 7.20 (m, 2H, CH_{Ar}), 7.18 (s, 1H, CH_{Ar}), 2.51 (s, 3H, SCH_3).

^{13}C NMR (63 MHz, CD_2Cl_2) δ 135.3, 134.2, 134.2, 133.3, 130.8 (C_{Ar}), 129.0, 128.4, 128.3 (CH_{Ar}), 126.7, 126.7 (C_{Ar}), 124.6 (CH_{Ar}), 123.2 (C_{Ar}), 123.1, 123.0, 122.6, 122.2, 121.5, 117.4, 114.6, 96.8 (CH_{Ar}), 16.7 (SCH_3).

MS (EI,70 eV): m/z (%) = 313 (M^+, 100), 298 (47), 265 (12), 254 (25), 156 (9), 132 (5).

HRMS (EI, 70 eV): calcd for $C_{21}H_{15}N_1S_1$ ($[M]^+$): 313.09197, found: 313.09196.

8-Fluoroindolo[1,2-*f*]phenanthridine 3.5g:



Yellowish solid, 72% (61.6 mg). M.p.: 115–116 °C.

IR (ATR, cm^{-1}): 3041.3 (w), 2923.7 (w), 1901.6 (w), 1604.6 (w), 1552.5 (w), 1494.6 (w), 1475.3 (m), 1442.6 (s), 1436.8 (m), 1346.1 (m), 1288.3 (m), 1251.6 (m), 1213.1 (m), 1184.1 (m), 1134.0 (m), 1074.2 (w), 1018.3 (w), 954.6 (w), 912.2 (m), 781.1 (m), 759.9 (s), 736.7 (s), 551.6 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 – 8.02 (m, 3H, CH_{Ar}), 8.02 – 7.87 (m, 1H, CH_{Ar}), 7.85 – 7.74 (m, 1H, CH_{Ar}), 7.59 – 7.41 (m, 2H, CH_{Ar}), 7.41 – 7.27 (m, 5H, CH_{Ar}).

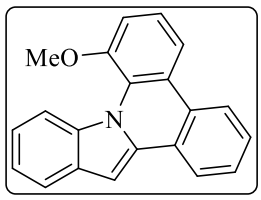
^{19}F NMR (282 MHz, $CDCl_3$) δ -111.04.

^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3 (d, ^1J = 249.6 Hz, CF), 135.6 (d, ^4J = 1.2 Hz), 135.5, 130.1 (C_{Ar}), 129.0, 127.9 (CH_{Ar}), 126.8, 126.5 (d, ^4J = 2.7 Hz), 126.2 (d, ^4J = 3.0 Hz, C_{Ar}), 124.0 (CH_{Ar}), 123.9 (d, ^3J = 8.5 Hz, CH_{Ar}), 123.2 (d, ^3J = 11.1 Hz, C_{Ar}), 123.0, 122.0 (CH_{Ar}), 121.7 (d, ^4J = 4.1 Hz, CH_{Ar}), 120.5 (CH_{Ar}), 119.5 (d, ^4J = 2.9 Hz, CH_{Ar}), 116.0 (d, ^2J = 22.3 Hz, CH_{Ar}), 115.8 (d, ^2J = 26.6 Hz, CH_{Ar}), 98.0 (CH_{Ar}).

MS (EI, 70 eV): m/z (%) = 285 (M^+, 100), 264 (12), 142 (9).

HRMS (EI, 70 eV): calcd for $C_{20}H_{12}N_1F_1$ ($[M]^+$): 285.09483, found: 285.09470.

8-Methoxyindolo[1,2-*f*]phenanthridine 3.5f:



Yellowish oil, 49% (43.7 mg).

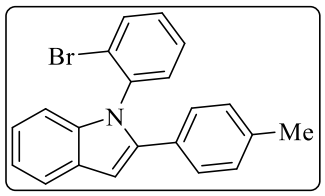
^{1}H NMR (250 MHz, Acetone) δ 8.39 – 8.31 (m, 1H, CH_{Ar}), 8.25 (dd, ^3J = 6.4, ^4J = 2.6 Hz, 1H, CH_{Ar}), 8.05 (d, ^3J = 7.9 Hz, 1H, CH_{Ar}), 7.80 – 7.68 (m, 2H, CH_{Ar}), 7.56 – 7.48 (m, 2H, CH_{Ar}), 7.40 (m, 2H, CH_{Ar}), 7.35 – 7.21 (m, 3H, CH_{Ar}), 3.95 (d, ^3J = 5.1 Hz, 3H).

^{13}C NMR (63 MHz, Acetone) δ 150.7 (*C*-OCH_3), 137.2, 136.6, 130.8 (C_{Ar}), 129.6, 128.8 (CH_{Ar}), 127.9, 127.6, 126.2 (C_{Ar}), 125.6 (CH_{Ar}), 125.0 (C_{Ar}), 124.7, 124.1, 122.0, 121.4, 120.9, 118.3, 116.9, 112.8, 98.3 (CH_{Ar}), 55.8 (O*C*H_3).

MS (EI,70 eV): m/z (%) = 297 (M^+,100), 282 (56), 252 (13), 141 (12), 126 (10), 113 (4).

HRMS (EI, 70 eV): calcd for $C_{21}H_{15}N_1O_1$ ($[M]^+$): 297.11482, found: 297.11451.

1-(2-Bromophenyl)-2-(*p*-tolyl)-1*H*-indole 3.1*ii*



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 – 7.56 (m, 2H, CH_{Ar}), 7.30 – 7.03 (m, 7H, CH_{Ar}), 6.95 (d, ^3J = 8.0 Hz, 2H, CH_{Ar}), 6.90 – 6.83 (m, 1H, CH_{Ar}), 6.71 (d, ^4J = 0.7 Hz, 1H, CH_{Ar}), 2.20 (s, 3H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.5, 138.9, 138.4, 137.4 (C_{Ar}), 133.8, 131.5, 129.8 (CH_{Ar}), 129.7 (C_{Ar}), 129.1 (2 CH_{Ar}), 128.5 (C_{Ar}), 128.5 (2CH_{Ar}), 128.5 (CH_{Ar}), 124.2 (C_{Ar}), 122.3, 120.9, 120.6, 111.0, 103.1 (CH_{Ar}), 21.3 (CH_3).

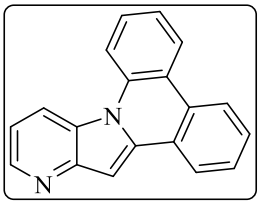
MS (EI, 70 eV): m/z (%) = 361 (M^+,100), 281 (51), 267 (74), 190 (5), 165 (6), 133 (50).

HRMS (EI, 70 eV): calcd for $C_{21}H_{16}N_1Br_1$ ($[M]^+$): 361.04606, found: 361.04591.

General procedure for synthesis of azaindolo[1,2-*f*]phenanthridines

3-bromo-2-(phenylethynyl)pyridine **3.6** (0.3 mmol), 2-bromoaniline **3.2** (1.1 equiv., 0.33 mmol), $Pd(PPh_3)_4$ (10 mol%, 0.03 mmol,), XantPhos (10 mol%, 0.03 mmol), and Cs_2CO_3 (3 equiv., 0.9 mmol) were placed in a dried pressure tube equipped with a septum. The reaction was back-filled with argon three times. Then dried and degassed DMF (4 mL) was added under argon and the septum was replaced with a Teflon cap. The reaction mixture was allowed to stir at 120 °C for 24 h. Then the reaction mixture was cooled to room temperature and was filtered through a pad of Celite. The filtrate was dried under reduced pressure, and the product **3.7** was obtained after flash chromatography on a silica gel column with ethyl acetate.

Pyrido[2',3':4,5]pyrrolo[1,2-*f*]phenanthridine 3.7a



Yellowish solid, 86% (69.1 mg). M.p.: 144–145 °C.

IR (ATR, cm^{-1}): = 3123 (w), 3099 (w), 3062 (w), 3034 (w), 1887 (w), 1598 (m), 1580 (w), 1556 (s), 1503 (w), 1488 (w), 1479 (m), 1453 (m), 1440 (s), 1414 (s), 1401 (w), 1378 (m), 1356 (m), 1325 (w), 1311 (w), 1303 (w), 1279 (m), 1236 (m), 1186 (m), 1138 (w), 1127 (w), 1110 (w), 1073 (w), 1051 (w), 1042 (w), 973 (w), 954 (w), 943 (w), 923 (w), 908 (w), 877 (w), 862 (w), 833 (w), 805 (w), 774 (w), 745 (s), 731 (w), 708 (m), 666 (w), 640 (w), 617 (m), 608 (w), 584 (w), 574 (w), 556 (w), 537 (w).

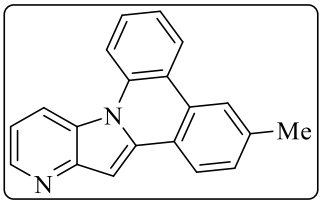
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.62 (dd, ^3J = 4.6, ^4J = 1.0 Hz, 1H, CH_{Ar}), 8.50 (d, ^3J = 8.6 Hz, 1H, CH_{Ar}), 8.35 – 8.17 (m, 2H, CH_{Ar}), 8.17 – 7.90 (m, 2H, CH_{Ar}), 7.53 – 7.43 (m, 3H, CH_{Ar}), 7.39 – 7.09 (m, 3H, CH_{Ar}).

^{13}C NMR (63 MHz, $CDCl_3$) δ = 147.6 (C_{Ar}), 144.9 (CH_{Ar}), 138.3, 135.2 (C_{Ar}), 129.0, 128.9, 128.5 (CH_{Ar}), 127.0, 126.9, 125.1 (C_{Ar}), 124.9, 124.3, 123.7, 122.4 (CH_{Ar}), 121.9 (C_{Ar}), 121.3, 116.2, 116.0, 96.8 (CH_{Ar}).

MS (EI, 70 eV): m/z(%) = 268 (M^+, 100), 240 (7), 214 (3), 134 (10), 120 (13), 106 (5).

HRMS (EI): Calculated for $C_{19}H_{12}N_2$ (M^+): 268.09950, found: 268.09952.

3-Methylpyrido[2',3':4,5]pyrrolo[1,2-*f*]phenanthridine 3.7d



Yellowish solid, 61% (51.6 mg). M.p.:162–164 °C.

IR(ATR, cm^{-1}): = 3120 (w), 3093 (w), 3061 (w), 3032 (w), 2917 (w), 2851 (w), 1914 (w), 1883 (w), 1613 (w), 1598 (m), 1575 (w), 1557 (m), 1550 (w), 1493 (w), 1481 (w), 1444 (s), 1414 (s), 1375

(m), 1349 (m), 1306 (m), 1283 (m), 1238 (m), 1208 (w), 1189 (m), 1164 (w), 1149 (w), 1127 (w), 1115 (w), 1079 (m), 1039 (m), 956 (m), 943 (w), 923 (m), 913 (w), 903 (w), 873 (m), 834 (w), 810 (s), 772 (m), 755 (s), 734 (s), 714 (w), 660 (w), 651 (w), 623 (m), 610 (m), 578 (s), 545 (w), 532 (s).

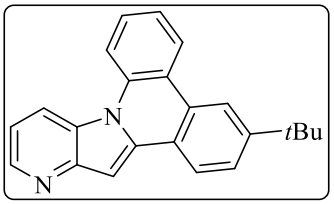
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.72 – 8.54 (m, 1H, CH_{Ar}), 8.50 – 8.36 (m, 1H, CH_{Ar}), 8.19 (dd, ^{3}J = 10.5, ^{3}J = 5.7 Hz, 2H, CH_{Ar}), 7.95 – 7.78 (m, 2H, CH_{Ar}), 7.54 – 7.36 (m, 1H, CH_{Ar}), 7.34 – 7.09 (m, 4H, CH_{Ar}), 2.45 (s, 3H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 147.9 (C_{Ar}), 144.8 (CH_{Ar}), 138.8, 138.5, 135.3 (C_{Ar}), 129.7, 128.8 (CH_{Ar}), 126.8 (C_{Ar}), 124.8, 124.1, 123.5 (CH_{Ar}), 122.6 (C_{Ar}), 122.5 (CH_{Ar}), 121.9 (C_{Ar}), 121.0, 115.9, 115.8, 96.1 (CH_{Ar}), 22.0 (CH_3). (one signal of C tertiary could not be detected).

MS (EI, 70 eV): m/z(%) = 282 (M^+, 100), 266 (4), 140 (10), 128 (2), 126 (5).

HR-MS (EI): calculated for $C_{20}H_{14}N_2$ (M^+): 282.11515, found: 282.11477.

3-(*Tert*-butyl)pyrido[2',3':4,5]pyrrolo[1,2-*f*]phenanthridine 8f



Yellowish solid, 69% (67.1 mg). M.p.: 176–178 °C.

IR (ATR, cm^{-1}): = 3060 (w), 3025 (w), 2947 (m), 2902 (w), 2860 (w), 1931 (w), 1884 (w), 1732 (w), 1615 (w), 1598 (m), 1578 (w), 1557 (m), 1504 (w), 1494 (m), 1479 (w), 1463 (w), 1443 (s), 1413 (s), 1392 (w), 1357 (w), 1348 (m), 1303 (w), 1275 (m), 1265 (m), 1242 (w), 1205 (w), 1187 (m), 1162 (w), 28 1151 (w), 1127 (w), 1115 (w), 1097 (w), 1070 (w), 1053 (w), 1039 (w), 1021 (w), 970 (w), 956 (m), 925 (w), 913 (w), 875 (m), 832 (w), 813 (m), 788 (s), 769 (m), 756 (s), 738 (s), 710 (w), 657 (w), 648 (w), 623 (s), 608 (w), 584 (m), 542 (s).

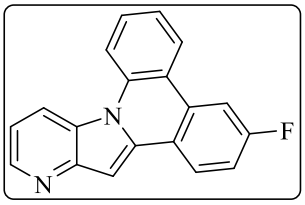
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.63 (d, ^{4}J = 4.1 Hz, 1H, CH_{Ar}), 8.53 (d, ^{3}J = 8.6 Hz, 1H, CH_{Ar}), 8.41 – 8.29 (m, 2H, CH_{Ar}), 8.24 (d, ^{4}J = 1.7 Hz, 1H, CH_{Ar}), 8.10 (d, ^{3}J = 8.4 Hz, 1H, CH_{Ar}), 7.64 – 7.48 (m, 2H, CH_{Ar}), 7.42 – 7.32 (m, 2H, CH_{Ar}), 7.22 (dd, ^{3}J = 8.5, ^{4}J = 4.6 Hz, 1H, CH_{Ar}), 1.47 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.1, 148.0 (C_{Ar}), 144.9 (CH_{Ar}), 138.5, 135.5 (C_{Ar}), 128.9 (CH_{Ar}), 127.0, 126.6 (C_{Ar}), 126.5, 124.9, 124.2, 123.6 (CH_{Ar}), 122.8, 122.4 (C_{Ar}), 121.1, 118.7, 116.1, 116.0, 96.3 (CH_{Ar}), 35.4 ($C(CH_3)_3$), 31.4 (3C, $C(CH_3)_3$).

MS (EI, 70 eV): m/z(%) = 324 (M^+, 100), 309 (98), 294 (28), 290 (4), 281 (12), 268 (15), 240 (4), 154 (4), 146 (4), 140 (24), 132 (6), 126 (4), 41 (3), 39 (3).

HR-MS (EI): calculated for $C_{23}H_{20}N_2$ (M^+): 324.16210, found: 324.16196.

3-Fluoropyrido[2',3':4,5]pyrrolo[1,2-*f*]phenanthridine 3.7h



Yellowish solid, 88% (75.5 mg). M.p.: 213–215 °C.

IR (ATR, cm^{-1}): = 3059 (w), 3035 (w), 1616 (m), 1603 (m), 1580 (w), 1558 (m), 1551 (m), 1489 (m), 1443 (s), 1416 (s), 1379 (w), 1349 (m), 1331 (w), 1304 (w), 1272 (m), 1245 (w), 1236 (w), 1180 (s), 1135 (w), 1128 (w), 1106 (w), 1072 (w), 1054 (w), 1032 (w), 957 (m), 933 (w), 915 (w), 892 (m), 854 (w), 819 (w), 810 (m), 784 (w), 763 (s), 755 (m), 733 (s), 706 (w), 652 (m), 631 (m), 621 (m), 606 (w), 599 (m), 583 (w), 545 (w), 533 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.61 (d, ^{4}J = 3.6 Hz, 1H, CH_{Ar}), 8.41 (d, ^{3}J = 8.6 Hz, 1H, CH_{Ar}), 8.23 – 8.11 (m, 1H, CH_{Ar}), 8.02 (dd, ^{3}J = 8.1, ^{4}J = 1.3 Hz, 1H, CH_{Ar}), 7.95 (dd, ^{3}J = 8.8, ^{3}J = 5.7 Hz, 1H, CH_{Ar}), 7.66 (dd, ^{3}J = 10.6, ^{4}J = 2.5 Hz, 1H, CH_{Ar}), 7.55 – 7.45 (m, 1H, CH_{Ar}), 7.32 – 7.23 (m, 2H, CH_{Ar}), 7.23 – 7.08 (m, 3H, CH_{Ar}).

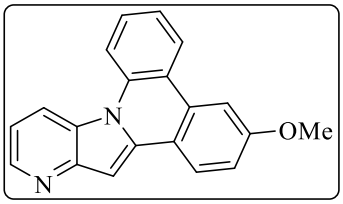
^{19}F NMR (63 MHz, CDCl3) δ = 110.77 Hz.

^{13}C NMR (63 MHz, $CDCl_3$) δ = 163.1 (d, ^{1}J = 248.2 Hz, CF), 147.7 (C_{Ar}), 145.1 (CH_{Ar}), 137.5, 135.5 (C_{Ar}), 129.7 (CH_{Ar}), 129.1 (d, ^{3}J = 8.4 Hz, C_{Ar}), 127.2 (d, ^{3}J = 8.9 Hz, CH_{Ar}), 126.8 (C_{Ar}), 124.4, 123.7 (CH_{Ar}), 121.5 (d, ^{4}J = 2.5 Hz, C_{Ar}), 121.1 (CH_{Ar}), 121.1 (C_{Ar}), 116.5 (d, ^{2}J = 23.2 Hz, CH_{Ar}), 116.2, 116.0 (CH_{Ar}), 108.5 (d, ^{2}J = 23.4 Hz, CH_{Ar}), 96.5 (d, ^{6}J = 1.3 Hz, CH_{Ar}).

MS (EI, 70 eV): m/z(%) = 286 (M^+, 100), 258 (7), 232 (3), 195 (2), 143 (10), 129 (11), 115 (3).

HR-MS (EI): calculated for $C_{19}H_{11}N_2F_1$ (M^+): 286.09008, found: 286.08980.

3-Methoxypyrido[2',3':4,5]pyrrolo[1,2-*f*]phenanthridine 3.7j



Yellowish solid, 85% (76.0 mg). M.p.: 200–201 °C.

IR (ATR, cm^{-1}): = 3089 (w), 3032 (w), 2999 (w), 2958 (w), 2930 (w), 2908 (w), 2831 (w), 1609 (s), 1601 (s), 1550 (s), 1493 (s), 1450 (s), 1438 (w), 1428 (w), 1414 (s), 1379 (w), 1347 (m), 1334 (w), 1303 (w), 1278 (s), 1244 (w), 1219 (s), 1190 (m), 1181 (w), 1141 (w), 1130 (w), 1111 (w), 1079 (w), 1073 (w), 1056 (w), 1041 (w), 1033 (w), 1021 (m), 980 (w), 971 (w), 956 (m), 912 (w), 905 (w), 883 (w), 872 (w), 865 (w), 830 (m), 823 (w), 813 (s), 785 (w), 766 (s), 753 (s), 736 (s), 705 (w), 656 (m), 634 (m), 623 (m), 607 (s), 584 (m), 555 (m), 539 (m).

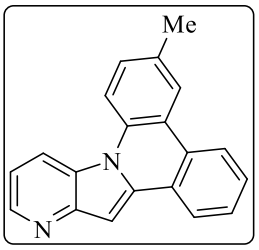
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.49 (d, ^{4}J = 4.2 Hz, 1H, CH_{Ar}), 8.31 (d, ^{3}J = 8.5 Hz, 1H, CH_{Ar}), 8.08 (d, ^{3}J = 8.1 Hz, 1H, CH_{Ar}), 7.98 (dd, ^{3}J = 8.1, ^{4}J = 1.0 Hz, 1H, CH_{Ar}), 7.79 (d,

^{3}J = 8.8 Hz, 1H, CH_{Ar}), 7.44 – 7.29 (m, 2H, CH_{Ar}), 7.22 – 7.12 (m, 1H, CH_{Ar}), 7.07 (dd, ^{3}J = 8.5, ^{4}J = 4.6 Hz, 1H, CH_{Ar}), 7.02 (s, 1H, CH_{Ar}), 6.90 (dd, ^{3}J = 8.8, ^{4}J = 2.4 Hz, 1H, CH_{Ar}), 3.79 (s, 3H, OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 160.2 (C_{Ar}-OCH_3), 148.0 (C_{Ar}), 144.7 (CH_{Ar}), 138.6, 135.5 (C_{Ar}), 129.1 (CH_{Ar}), 128.5, 126.8 (C_{Ar}), 126.6, 124.2, 123.5 (CH_{Ar}), 121.7 (C_{Ar}), 120.9 (CH_{Ar}), 118.6 (C_{Ar}), 116.3, 116.0, 115.6, 105.6, 95.2 (CH_{Ar}), 55.5 (OCH_3).

MS (EI, 70 eV): m/z(%) = 298 (M^+, 100), 283 (20), 255 (63), 227 (7), 149 (9), 127 (4), 113 (5), 99 (3). HR-MS (EI): calculated for $C_{20}H_{14}N_2O_1$ (M^+): 298.11006, found: 298.10998.

6-Methylpyrido[2',3':4,5]pyrrolo[1,2-*f*]phenanthridine 3.7b



Yellow solid, 64% (54.1 mg). M.p.: 184–186 °C.

IR (ATR, cm^{-1}): = 3124 (w), 3069 (w), 3036 (w), 2954 (w), 2916 (m), 2850 (m), 2746 (w), 1942 (w), 1900 (w), 1877 (w), 1860 (w), 1823 (w), 1795 (w), 1600 (m), 1577 (w), 1569 (m), 1553 (s), 1524 (w), 1496 (m), 1450 (s), 1416 (s), 1387 (w), 1372 (w), 1354 (m), 1324 (w), 1310 (w), 1300 (w), 1279 (m), 1236 (w), 1193 (w), 1182 (m), 1165 (w), 1145 (w), 1124 (m), 1116 (m), 1066 (w), 1042 (w), 999 (w), 972 (w), 955 (m), 937 (w), 910 (m), 883 (w), 866 (m), 853 (m), 828 (w), 801 (m), 790 (s), 772 (m), 748 (s), 730 (w), 720 (w), 710 (w), 694 (w), 660 (w), 643 (m), 620 (w), 576 (s), 540 (m).

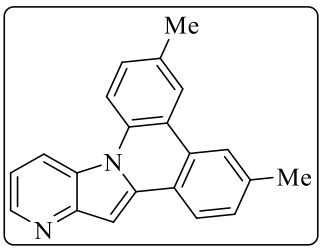
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.60 (s, 1H, CH_{Ar}), 8.39 (d, ^{3}J = 8.5 Hz, 1H, CH_{Ar}), 8.13 – 7.95 (m, 3H, CH_{Ar}), 7.91 (s, 1H, CH_{Ar}), 7.54 – 7.35 (m, 2H, CH_{Ar}), 7.30 (s, 1H, CH_{Ar}), 7.19 (d, ^{3}J = 7.0 Hz, 2H, CH_{Ar}), 2.39 (s, 3H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 147.2 (C_{Ar}), 144.4 (CH_{Ar}), 139.9, 138.3, 133.1, 133.0 (C_{Ar}), 129.8, 128.8, 128.3 (CH_{Ar}), 127.0, 125.0 (C_{Ar}), 125.0, 124.4, 122.4 (CH_{Ar}), 121.7 (C_{Ar}), 121.3, 116.0, 115.7, 96.2 (CH_{Ar}), 21.2 (CH_3).

MS (EI, 70 eV): m/z(%) = 282 (M^+, 100), 266 (4), 252 (3), 140 (16), 126 (5), 113 (2), 100 (2).

HRMS (EI): calculated for $C_{20}H_{14}N_2$ (M^+): 282.11515, found: 282.11484.

3,6-Dimethylpyrido[2',3':4,5]pyrrolo[1,2-*f*]phenanthridine 3.7e



Yellowish solid, 72% (63.9 mg). M.p.: 208–210 °C.

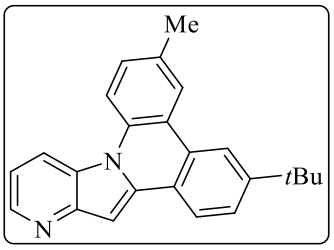
IR (ATR, cm^{-1}): = 3154 (w), 3115 (w), 3097 (w), 3056 (w), 3025 (w), 3004 (w), 2952 (w), 2917 (m), 2851 (w), 1920 (w), 1898 (w), 1854 (w), 1613 (w), 1601 (m), 1569 (w), 1549 (s), 1491 (m), 1481 (w), 1434 (w), 1416 (s), 1373 (w), 1352 (w), 1300 (w), 1281 (m), 1262 (w), 1237 (m), 1205 (w), 1192 (m), 1152 (w), 1121 (w), 1099 (w), 1069 (w), 1041 (m), 957 (m), 929 (w), 906 (w), 877 (m), 867 (w), 817 (w), 806 (s), 784 (s), 754 (s), 741 (w), 716 (w), 694 (w), 660 (m), 629 (w), 622 (w), 590 (m), 578 (m), 560 (w), 533 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.59 (s, 1H, CH_{Ar}), 8.36 (d, ^{3}J = 8.5 Hz, 1H, CH_{Ar}), 7.98 (d, ^{3}J = 8.5 Hz, 1H, CH_{Ar}), 7.88 (d, ^{3}J = 8.3 Hz, 2H, CH_{Ar}), 7.79 (s, 1H, CH_{Ar}), 7.35 – 6.87 (m, 4H, CH_{Ar}), 2.45 (s, 3H, CH_3), 2.38 (s, 3H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 147.7 (C_{Ar}), 144.6 (CH_{Ar}), 138.6, 138.4, 133.1, 132.8 (C_{Ar}), 129.6, 129.5 (CH_{Ar}), 126.8, 126.7 (C_{Ar}), 124.8, 124.2 (CH_{Ar}), 122.6 (C_{Ar}), 122.4 (CH_{Ar}), 121.7 (C_{Ar}), 120.9 (CH_{Ar}), 115.6 (2 CH_{Ar}), 95.6 (CH_{Ar}), 22.0 (CH_3), 21.2 (CH_3).

MS (EI, 70 eV): m/z(%) = 296 (M^+, 100), 279 (11), 266 (2), 148 (6), 147 (3), 146 (3), 140 (7), 126 (2). HR-MS (EI): calculated for $C_{21}H_{16}N_2$ ($[M+1]^{+1}$): 297.13862, found: 297.13882.

3-(*Tert*-butyl)-6-methylpyrido[2',3':4,5]pyrrolo[1,2-*f*]phenanthridine 3.7g



Yellow solid, 32% (32.4 mg). M.p. 197–199 °C.

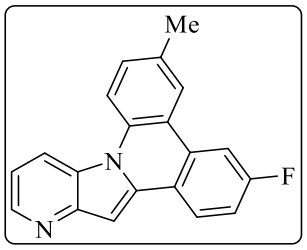
IR (ATR, cm^{-1}): = 3033 (w), 2956 (m), 2914 (w), 2864 (w), 1615 (w), 1600 (w), 1569 (w), 1556 (m), 1548 (m), 1489 (w), 1482 (w), 1460 (w), 1444 (w), 1427 (w), 1414 (s), 1391 (w), 1379 (w), 1357 (m), 1353 (m), 1301 (w), 1280 (m), 1263 (m), 1240 (w), 1202 (w), 1187 (w), 1159 (w), 1131 (w), 1121 (w), 1067 (w), 1045 (w), 958 (m), 941 (w), 925 (w), 904 (w), 880 (m), 865 (w), 830 (m), 811 (w), 786 (s), 774 (s), 757 (s), 736 (w), 722 (m), 666 (w), 656 (w), 634 (w), 620 (w), 611 (w), 578 (m), 552 (s), 533 (w).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.67 – 8.56 (m, 1H, CH_{Ar}), 8.49 (d, ^{3}J = 8.5 Hz, 1H, CH_{Ar}), 8.23 – 8.07 (m, 4H, CH_{Ar}), 7.63 – 7.57 (m, 1H, CH_{Ar}), 7.36 – 7.29 (m, 2H, CH_{Ar}), 7.20 (dd, ^{3}J = 8.5 Hz, ^{4}J = 4.5 Hz, 1H, CH_{Ar}), 2.51 (s, 3H, CH_3), 1.48 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.0, 147.9 (C_{Ar}), 144.8 (CH_{Ar}), 138.4, 133.4, 133.1 (C_{Ar}), 129.8 (CH_{Ar}), 126.7 (C_{Ar}), 126.3, 125.0, 124.3 (CH_{Ar}), 122.9, 122.3 (C_{Ar}), 121.0, 118.6, 116.0, 115.8, 96.0 (CH_{Ar}), 35.4 ($C(CH_3)_3$), 31.5 (CH_3), 21.3 (3C, $C(CH_3)_3$) (one signal of C_{Ar} could not be detected).

MS (EI, 70 eV): m/z(%) = 338 (M^+, 100), 323 (85), 308 (29), 295 (9), 282 (11) , 266 (3), 161 (7), 153 (4), 152 (3), 147 (23), 140 (8), 139 (5), 133 (4), 41 (5), 39 (4). HR-MS (EI): calculated for $C_{24}H_{22}N_2$ (M^+): 338.17775, found: 338.17773.

3-Fluoro-6-methylpyrido[2',3':4,5]pyrrolo[1,2-*f*]phenanthridine 3.7i



Yellow solid, 79% (80.1 mg). M.p.: 233–235 °C.

IR (ATR, cm^{-1}): = 3033 (w), 2956 (m), 2914 (w), 2864 (w), 1615 (w), 1600 (w), 1569 (w), 1556 (m), 1548 (m), 1489 (w), 1482 (w), 1460 (w), 1444 (w), 1427 (w), 1414 (s), 1391 (w), 1379 (w), 1357 (m), 1353 (m), 1301 (w), 1280 (m), 1263 (m), 1240 (w), 1202 (w), 1187 (w), 1159 (w), 1131 (w), 1121 (w), 1067 (w), 1045 (w), 958 (m), 941 (w), 925 (w), 904 (w), 880 (m), 865 (w), 830 (m), 811 (w), 786 (s), 774 (s), 757 (s), 736 (w), 722 (m), 666 (w), 656 (w), 634 (w), 620 (w), 611 (w), 578 (m), 552 (s), 533 (w).

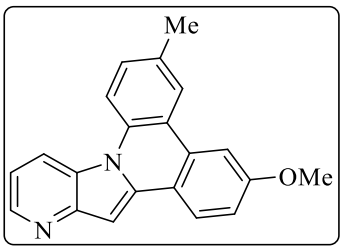
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.68 (s, 1H, CH_{Ar}), 8.45 (d, ^3J = 8.5 Hz, 1H, CH_{Ar}), 8.11 – 8.01 (m, 2H, CH_{Ar}), 7.84 (s, 1H, CH_{Ar}), 7.76 – 7.69 (m, 1H, CH_{Ar}), 7.35 – 7.22 (m, 3H, CH_{Ar}), 7.19 (dd, ^3J = 8.4 Hz, ^4J = 2.3 Hz, 1H, CH_{Ar}), 2.48 (s, 3H, CH_3).

^{19}F NMR (63 MHz, $CDCl_3$) δ = 110.92.

^{13}C NMR (63 MHz, $CDCl_3$) δ = 163.1 (d, ^1J = 247.9 Hz, CF), 147.5 (C_{Ar}), 144.9 (CH_{Ar}), 137.5, 133.3, 133.3 (C_{Ar}), 130.5 (CH_{Ar}), 129.1 (d, ^3J = 8.4 Hz, C_{Ar}), 127.2 (d, ^3J = 8.9 Hz, CH_{Ar}), 124.6 (CH_{Ar}), 121.6 (d, ^4J = 2.4 Hz, C_{Ar}), 121.0 (CH_{Ar}), 120.9 (d, ^4J = 3.0 Hz, C_{Ar}), 116.4 (d, ^2J = 23.2 Hz, CH_{Ar}), 116.0, 115.8 (CH_{Ar}), 108.5 (d, ^2J = 23.4 Hz, CH_{Ar}), 96.1 (CH_{Ar}), 21.2 (CH_3). (Signal of one C_{Ar} could not be detected).

MS (EI, 70 eV): m/z(%) = 338 (M^+, 100), 323 (85), 308 (29), 295 (9), 282 (11), 266 (3), 161 (7), 153 (4), 147 (23), 140 (8), 139 (5), 133 (4), 41 (5), 39 (4). HR-MS (EI): calculated for $C_{20}H_{13}F_1N_2$ (M^+): 338.17775, found: 338.17773.

3-Methoxy-6-methylpyrido[2',3':4,5]pyrrolo[1,2-*f*]phenanthridine 3.7k



Yellow solid, 37% (34.6 mg). M.p.: 183–185 °C.

IR (ATR, cm^{-1}): = 3094 (w), 3029 (w), 3005 (w), 2916 (w), 2839 (w), 2054 (m), 1722 (w), 1610 (s), 1572 (w), 1546 (s), 1493 (s), 1467 (w), 1452 (w), 1432 (w), 1418 (s), 1378 (w), 1353 (w), 1333 (w), 1300 (w), 1282 (s), 1243 (w), 1223 (s), 1194 (m), 1188 (m), 1152 (w), 1125 (w), 1074 (w), 1028 (s), 959 (m), 936 (w), 906 (w), 860 (w), 833 (m), 819 (m),

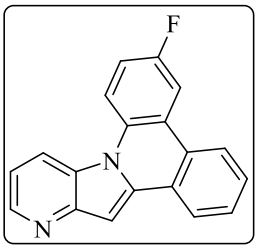
803 (w), 782 (s), 773 (m), 751 (s), 710 (w), 682 (w), 668 (w), 633 (m), 621 (w), 587 (w), 579 (w), 545 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.57 (s, 1H, CH_{Ar}), 8.47 (d, ^{3}J = 8.5 Hz, 1H, CH_{Ar}), 8.12 (d, ^{3}J = 8.5 Hz, 1H, CH_{Ar}), 7.99 (d, ^{3}J = 8.8 Hz, 1H, CH_{Ar}), 7.93 (s, 1H, CH_{Ar}), 7.53 (d, ^{4}J = 2.4 Hz, 1H, CH_{Ar}), 7.31 (dd, ^{3}J = 8.5, ^{4}J = 1.1 Hz, 1H, CH_{Ar}), 7.24 – 7.13 (m, 2H, CH_{Ar}), 7.07 (dd, ^{3}J = 8.8, ^{4}J = 2.4 Hz, 1H, CH_{Ar}), 3.95 (s, 3H, OCH_3), 2.46 (s, 3H, CH_3).

^{13}C NMR (63 MHz, $CDCl_3$) δ = 160.5 (*C*-OCH_3), 147.2 (C_{Ar}), 143.7 (CH_{Ar}), 139.1, 133.3 (C_{Ar}), 130.2 (CH_{Ar}), 128.8, 127.0 (C_{Ar}), 126.9, 124.5 (CH_{Ar}), 121.7 (C_{Ar}), 121.4 (CH_{Ar}), 118.6 (C_{Ar}), 116.4, 115.9, 115.4, 105.8, 94.5 (CH_{Ar}), 55.7 (OCH_3), 21.3 (CH_3). (one signal of C_{Ar} could not be detected).

MS (EI, 70 eV): m/z(%) = 312 (M^+, 100), 297 (16), 269 (53), 253 (4), 239 (2), 156 (10), 134 (7), 121 (3), 120 (3), 107 (2). HR-MS (EI): calculated for $C_{21}H_{16}N_2O_1$ (M^+): 312.12571, found: 312.12596.

6-Fluoropyrido[2',3':4,5]pyrrolo[1,2-*f*]phenanthridine 3.7c (3.8e)



Yellow solid, 41% (35.2 mg). M.p.: 220–221 °C.

IR (ATR, cm^{-1}): = 3131.1 (w), 3056.8 (w), 3031.7 (w), 2920.8 (w), 2850.5 (w), 1942.2 (w), 1889.7 (w), 1573.4 (m), 1557.6 (s), 1496.3 (m), 1452.2 (m), 1420.5 (s), 1280.2 (m), 1243.7 (m), 1201.1 (m), 1174.1 (m), 1137.7 (m), 1108.0 (w), 1168.8 (m), 957.1 (m), 909.6 (m), 856.1 (m), 806.8 (m), 782.8 (m), 746.5 (s), 577.9 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.65 (d, ^{4}J = 4.0 Hz, 1H, CH_{Ar}), 8.44 (d, ^{3}J = 8.6 Hz, 1H, CH_{Ar}), 8.23 (dd, ^{3}J = 9.2, ^{4}J = 4.8 Hz, 1H, CH_{Ar}), 8.16 – 8.07 (m, 1H, CH_{Ar}), 8.07 – 8.00 (m, 1H, CH_{Ar}), 7.90 (dd, ^{3}J = 10.0, ^{4}J = 2.8 Hz, 1H, CH_{Ar}), 7.60 – 7.47 (m, 2H, CH_{Ar}), 7.36 (s, 1H, CH_{Ar}), 7.28 – 7.16 (m, 2H, CH_{Ar}).

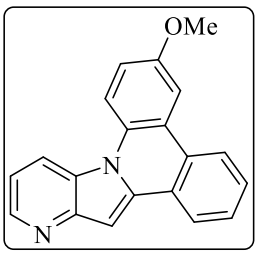
^{19}F NMR (282 MHz, $CDCl_3$) δ -118.20.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.0 (d, ^{1}J = 243.3 Hz, CF), 147.7 (C_{Ar}), 145.3 (CH_{Ar}), 137.9, 131.8 (d, ^{4}J = 2.1 Hz, C_{Ar}), 129.3, 129.0 (CH_{Ar}), 126.8 (C_{Ar}), 126.2 (d, ^{4}J = 2.5 Hz, C_{Ar}), 125.6 (C_{Ar}), 125.1 (CH_{Ar}), 124.0 (d, ^{3}J = 7.7 Hz, C_{Ar}), 122.7, 120.7 (CH_{Ar}), 117.5 (d, ^{3}J = 8.1 Hz, CH_{Ar}), 116.5 (CH_{Ar}), 116.1 (d, ^{2}J = 23.2 Hz, CH_{Ar}), 110.6 (d, ^{2}J = 23.9 Hz, CH_{Ar}), 97.1 (CH_{Ar}).

MS (EI, 70 eV): m/z(%) = 286 (M^+, 100), 258 (7), 232 (5), 208 (2), 195 (3), 168 (3), 143 (6), 128 (3), 99 (2), 87 (2), 75 (2), 62 (5), 51 (3), 39 (3).

HR-MS (EI): calculated for $C_{19}H_{11}N_2F_1$ (M^+): 286.09008, found: 286.09014

6-Methoxypyrido[2',3':4,5]pyrrolo[1,2-*f*]phenanthridine 3.8b



Yellowish solid, 51% (45.6 mg). M.p.: 156–157 °C.

IR (ATR, cm^{-1}): = 3133.5 (w), 3055.6 (w), 2919.6 (w), 2849.1 (w), 1957.7 (w), 1925.7 (w), 1900.2 (w), 1726.6 (w), 1616.8 (m), 1606.1 (m), 1569.7 (m), 1552.5 (s), 1500.3 (m), 1453.4 (m), 1419.4 (s), 1350.4 (m), 1218.9 (m), 1185.5 (m), 1138.4 (m), 1018.3 (m), 956.6 (m), 850.5 (m), 789.6 (m), 755.3 (s), 694.9 (m), 583.2 (m).

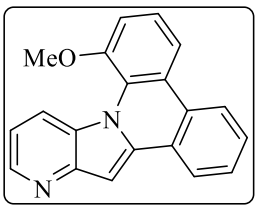
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.61 (d, ^4J = 4.0 Hz, 1H, CH_{Ar}), 8.41 (d, ^3J = 8.6 Hz, 1H, CH_{Ar}), 8.13 (d, ^3J = 9.2 Hz, 1H, CH_{Ar}), 8.10 – 8.00 (m, 2H, CH_{Ar}), 7.64 (d, ^4J = 2.8 Hz, 1H, CH_{Ar}), 7.53 – 7.39 (m, 2H, CH_{Ar}), 7.32 (s, 1H, CH_{Ar}), 7.19 (dd, ^3J = 8.6, ^4J = 4.6 Hz, 1H, CH_{Ar}), 7.03 (dd, ^3J = 9.1, ^4J = 2.9 Hz, 1H, CH_{Ar}), 3.89 (s, 3H, OCH_3).

^{13}C NMR (63 MHz, $CDCl_3$) δ = 155.7, 147.4 (C_{Ar}), 144.7 (CH_{Ar}), 137.9, 129.7 (C_{Ar}), 128.8, 128.6 (CH_{Ar}), 126.8, 126.7, 125.4 (C_{Ar}), 125.1 (CH_{Ar}), 123.3(C_{Ar}), 122.5, 120.8, 117.1, 116.0, 115.3, 108.4, 96.3 (CH_{Ar}), 55.7 (OCH_3).

MS (EI, 70 eV): m/z(%) = 298 (M^+, 100), 283 (37), 255 (70), 227 (11). 200 (5), 174 (4), 149 (8), 127 (7), 114 (11), 100 (5), 87 (7), 75 (4), 63 (4), 51 (4), 39 (6).

HR-MS (EI): calculated for $C_{20}H_{14}N_2O_1$ (M^+): 298.11006, found: 298.10977.

8-Methoxypyrido[2',3':4,5]pyrrolo[1,2-*f*]phenanthridine 3.8c



Yellow oil, 60% (53.6 mg).

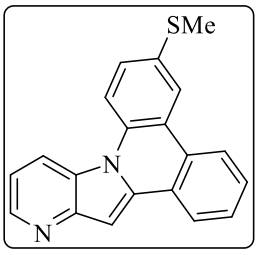
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.59 (dd, ^3J = 4.5, ^4J = 0.9 Hz, 1H, CH_{Ar}), 8.25 – 8.12 (m, 2H, CH_{Ar}), 8.10 – 8.03 (m, 1H, CH_{Ar}), 7.94 (dd, ^3J = 8.1, ^5J = 0.9 Hz, 1H, CH_{Ar}), 7.65 – 7.45 (m, 3H, CH_{Ar}), 7.39 (t, ^3J = 8.1 Hz, 1H, CH_{Ar}), 7.22 – 7.07 (m, 2H, CH_{Ar}), 3.90 (s, 3H, OMe).

^{13}C NMR (63 MHz, $CDCl_3$) δ = 149.5, 146.9 (C_{Ar}), 144.4 (CH_{Ar}), 139.1, 129.9 (C_{Ar}), 128.9, 128.8 (CH_{Ar}), 127.3, 125.9, 125.4 (C_{Ar}), 124.9 ($2CH_{Ar}$), 124.7 (CH_{Ar}), 124.1 (C_{Ar}), 123.1, 116.4, 115.0, 112.1, 97.6 (CH_{Ar}), 55.9 (OCH_3).

MS (EI, 70 eV): m/z(%) = 298 (M^+, 100), 283 (83), 253 (13), 227 (7), 201 (4), 175 (2), 142 (10), 127 (6), 114 (7), 100 (7).

HRMS (EI): calculated for $C_{20}H_{14}N_2O_1$ (M^+): 298.11006, found: 298.11014.

6-(Methylthio)pyrido[2',3':4,5]pyrrolo[1,2-*f*]phenanthridine 3.8g



Yellow solid, 81% (77.2 mg). M.p.: 172–173 °C.

IR (ATR, cm^{-1}): = 3031.8 (w), 3001.0 (w), 2958.0 (w), 2917.4 (w), 2849.2 (w), 1597.0 (w), 1646.3 (m), 1488.3 (w), 1449.2 (m), 1413.4 (s), 1354.0 (m), 1278.7 (m), 1189.0 (m), 1115.3 (w), 955.0 (m), 855.7 (w), 789.8 (s), 750.4 (s), 580.6 (m).

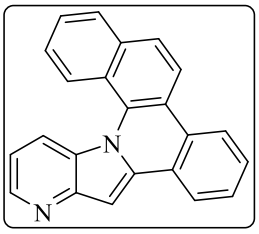
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.61 (s, 1H, CH_{Ar}), 8.42 (d, ^3J = 8.5 Hz, 1H, CH_{Ar}), 8.17 – 7.97 (m, 4H, CH_{Ar}), 7.57 – 7.42 (m, 2H, CH_{Ar}), 7.35 (dd, ^3J = 8.8, ^4J = 2.1 Hz, 1H, CH_{Ar}), 7.31 (s, 1H, CH_{Ar}), 7.22 (dd, ^3J = 8.5, ^4J = 4.6 Hz, 1H, CH_{Ar}), 2.57 (s, 3H, SCH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 147.2 (C_{Ar}), 144.6 (CH_{Ar}), 138.2, 133.5, 133.0 (C_{Ar}), 129.0, 128.8, 127.9 (CH_{Ar}), 126.4, 125.2 (C_{Ar}), 125.1, 122.8 (CH_{Ar}), 122.6 (C_{Ar}), 122.4, 121.3, 116.5, 116.2, 96.7 (CH_{Ar}), 16.8 (SCH_3). (one signal of C_{Ar} could not be detected).

MS (EI, 70 eV): m/z(%) = 314 (M^+, 100), 299 (52), 266 (9), 255 (28), 227 (4), 157 (13), 127 (6), 113 (3), 100 (2).

HRMS (EI): calculated for $C_{20}H_{14}N_2S_1$ (M^+): 314.08722, found: 314.08694.

Benzo[*c*]pyrido[2',3':4,5]pyrrolo[1,2-*f*]phenanthridine 3.8h



Yellow solid, 42% (40.1 mg). M.p.: 231–232 °C.

IR (ATR, cm^{-1}): = 3096.6 (w), 2958.7 (w), 2850.5 (w), 1954.5 (w), 1915.3 (w), 1808.3, 1713.7 (w), 1621.8 (w), 1576.9 (m), 1543.0 (m), 1416.8 (s), 1389.4 (m), 1274.8 (m), 1029.8 (m), 807 (m), 752.5 (s), 611.2 (m), 566.6 (m).

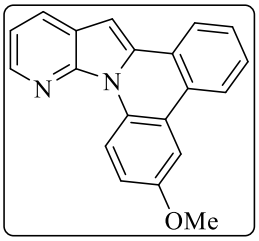
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.64 (d, ^4J = 4.0 Hz, 1H, CH_{Ar}), 8.34 – 8.11 (m, 4H, CH_{Ar}), 7.96 – 7.84 (m, 2H, CH_{Ar}), 7.79 (d, ^3J = 8.7 Hz, 1H, CH_{Ar}), 7.60 – 7.47 (m, 3H, CH_{Ar}), 7.45 (d, ^5J = 0.6 Hz, 1H, CH_{Ar}), 7.43 – 7.34 (m, 1H, CH_{Ar}), 7.03 (dd, ^3J = 8.5, ^4J = 4.5 Hz, 1H, CH_{Ar}).

^{13}C NMR (63 MHz, $CDCl_3$) δ = 147.6 (C_{Ar}), 145.4 (CH_{Ar}), 139.8, 134.1, 129.9, 129.2 (C_{Ar}), 129.0, 128.7, 128.3 (CH_{Ar}), 127.6 (C_{Ar}), 127.2 (CH_{Ar}), 125.9 (C_{Ar}), 125.2, 124.7, 124.6, 124.3 (CH_{Ar}), 123.7 (C_{Ar}), 123.0, 122.1 (CH_{Ar}), 121.0 (C_{Ar}), 120.5, 114.0, 97.7 (CH_{Ar}).

MS (EI, 70 eV): m/z(%) = 318 (M^+, 100), 291 (12), 237 (2), 159 (41), 144 (23), 131 (9), 105 (2), 87 (1).

HRMS (EI): calculated for $C_{23}H_{14}N_2$ (M^+): 318.11515, found: 318.11507.

6-Methoxypyrido[3',2':4,5]pyrrolo[1,2-*f*]phenanthridine 3.9a



Yellowish solid, 34% (30.4 mg). M.p.: 186–187 °C.

IR (ATR, cm^{-1}): = 3104.4 (w), 2997.7 (w), 2930.7 (w), 2830.5 (w), 2089.0 (w), 1892.9 (w), 1713.5 (w), 1620.3 (w), 1563.3 (m), 1543.8 (s), 1499.5 (m), 1453.9 (m), 1407.9 (m), 1327 (m), 1293.2 (m), 1215.2 (m), 1075.3 (m), 1042.8 (m), 1016.0 (m), 945.9 (w), 855.2 (m), 792.4 (m), 758.9 (m), 729.0 (m), 607.9 (m), 566.3 (m).

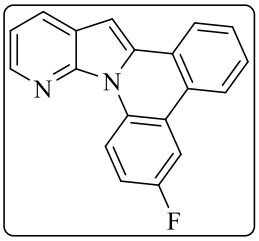
^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.15 (d, ^3J = 9.3 Hz, 1H, CH_{Ar}), 8.50 (dd, ^4J = 4.6, ^4J = 1.6 Hz, 1H, CH_{Ar}), 8.24 – 7.97 (m, 3H, CH_{Ar}), 7.72 (d, ^4J = 2.8 Hz, 1H, CH_{Ar}), 7.57 – 7.39 (m, 2H, CH_{Ar}), 7.34 – 7.16 (m, 2H, CH_{Ar}), 7.08 (s, 1H, CH_{Ar}), 3.95 (s, 3H, OCH_3).

^{13}C NMR (63 MHz, $CDCl_3$) δ = 155.8 (*C*-OCH_3), 146.9 (C_{Ar}), 141.8 (CH_{Ar}), 134.6, 129.9 (C_{Ar}), 128.4, 128.3, 128.2 (CH_{Ar}), 127.4, 125.8 (C_{Ar}), 124.3, 122.8 (CH_{Ar}), 122.7, 122.1 (C_{Ar}), 120.4, 117.5, 115.5, 107.5, 92.4 (CH_{Ar}), 55.7 (OCH_3).

MS (EI, 70 eV): m/z(%) = 298 (M^+, 100), 283 (34), 255 (61), 227 (7), 201 (3), 175 (2), 149 (15), 127 (16), 113 (4), 100 (5).

HRMS (EI): calculated for $C_{20}H_{14}N_2O_1$ (M^+): 298.11066, found: 298.11047

6-Fluoropyrido[3',2':4,5]pyrrolo[1,2-*f*]phenanthridine 3.9b



Yellowish solid, 51% (43.8 mg). M.p.: 201–202 °C.

IR (ATR, cm^{-1}): = 3122.0 (w), 3054.0 (w), 1920.0 (w), 1884.2 (w), 1798.7 (w), 1661.0 (w), 1620.4 (w), 1567.0 (m), 1497.6 (m), 1454.6 (m), 1409.4 (m), 1329.7 (m), 1267.7 (m), 1174.5 (m), 1141.0 (m), 892.5 (m), 824.2 (m), 752.8 (m), 724.4 (m), 662.7 (w), 593.9 (m), 566.3 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.26 (dd, ^3J = 9.3, ^3J = 5.5 Hz, 1H, CH_{Ar}), 8.50 (dd, ^4J = 4.5, ^4J = 1.3 Hz, 1H, CH_{Ar}), 8.25 – 8.03 (m, 3H, CH_{Ar}), 7.91 (dd, ^3J = 10.3, ^4J = 2.7 Hz, 1H, CH_{Ar}), 7.52 (dd, ^3J = 6.0, ^4J = 3.3 Hz, 2H, CH_{Ar}), 7.41 – 7.26 (m, 2H, CH_{Ar}), 7.11 (s, 1H, CH_{Ar}).

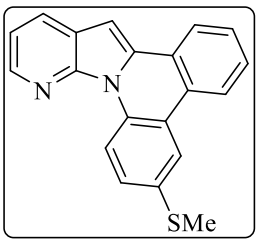
^{19}F NMR (282 MHz, $CDCl_3$) δ = -118.48.

^{13}C NMR (63 MHz, $CDCl_3$) δ = 159.3 (d, ^1J = 242.1 Hz, CF), 142.1 (CH_{Ar}), 134.6, 131.9, 130.4 (C_{Ar}), 128.9, 128.7, 128.4 (CH_{Ar}), 126.8 (d, ^4J = 1.9 Hz, C_{Ar}), 125.8 (C_{Ar}), 124.3 (CH_{Ar}), 123.4 (d, ^3J = 7.6 Hz, C_{Ar}), 122.9 (CH_{Ar}), 122.2 (C_{Ar}), 121.0 (d, ^3J = 7.8 Hz, CH_{Ar}), 117.9 (CH_{Ar}), 116.4 (d, ^2J = 22.4 Hz, CH_{Ar}), 109.3 (d, ^2J = 24.0 Hz, CH_{Ar}), 93.0 (CH_{Ar}).

MS (EI, 70 eV): m/z(%) = 286 (M^+, 100), 258 (10), 232 (3), 143 (17), 129 (4), 115 (3).

HRMS (EI): calculated for $C_{19}H_{11}N_2F_1$ (M^+): 286.09008, found: 286.08990.

6-(Methylthio)pyrido[3',2':4,5]pyrrolo[1,2-*f*]phenanthridine 3.9c



Yellow solid, 36% (33.9 mg). M.p.: 168–169 °C.

IR (ATR, cm^{-1}): = 3107.2 (w), 3037.2 (w), 2918.0 (w), 2849.6 (w), 2731.2 (w), 2520.1 8w), 2387.1 (w), 2116.4 (w), 1959.0 (w), 1916.1 (w), 1724.9 (w), 1595.9 (m), 1541.6 (m), 1453.3 (s), 1405.6 (s), 1323.5 (m), 1103.3 (m), 955.8 (m), 818.2 (m), 793.9 (s), 758.7 (s), 730.2 (s), 646.5 (m), 585.3 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.14 (d, ^3J = 8.9 Hz, 1H, CH_{Ar}), 8.49 (dd, ^4J = 4.6, ^4J = 1.7 Hz, 1H, CH_{Ar}), 8.27 – 8.11 (m, 2H, CH_{Ar}), 8.10 – 7.99 (m, 2H, CH_{Ar}), 7.57 – 7.41 (m, 3H, CH_{Ar}), 7.26 (dd, ^3J = 7.9, ^4J = 4.7 Hz, 1H, CH_{Ar}), 7.06 (s, 1H, CH_{Ar}), 2.61 (s, 3H, SCH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 147.1 (C_{Ar}), 142.0 (CH_{Ar}), 134.7, 133.4, 132.9 (C_{Ar}), 128.5 (2 CH_{Ar}), 128.4, 128.2 (CH_{Ar}), 127.0, 125.7 (C_{Ar}), 124.2, 122.7 (CH_{Ar}), 122.3 (C_{Ar}), 122.2 (CH_{Ar}), 122.0 (C_{Ar}), 119.8, 117.7, 93.0 (CH_{Ar}), 17.2 (SCH_3).

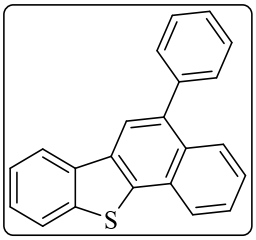
MS (EI, 70 eV): m/z(%) = 314 (M^+, 100), 299 (59), 266 (7), 255 (29), 227 (3), 201 (1), 157 (14), 133 (5), 113 (2).

HRMS (EI): calculated for $C_{20}H_{14}N_2S_1$ (M^+): 314.08722, found: 314.08645.

General procedure for domino reaction of dibromide compounds and *N*-tosylhydrazones

Dibromide compound **4.1** (0.2 mmol), *N*-tosylhydrazone **4.2** (1.5 equiv., 0.3 mmol), $Pd_2(dba)_3$ (2.5 mol%, 4.6 mg, 0.005 mmol), XPhos (10 mol%, 9.6 mg, 0.01 mmol), and LiO*t*Bu (4 equiv. 64 mg, 0.8 mmol) were placed in a dried pressure tube equipped with a septum. The reaction vessel was back-filled with argon three times. Then dried and degassed dioxane (4 mL) was added to the reaction mixture under argon and the septum was replaced with a Teflon cap. The reaction mixture was stirred at 20 °C for 15 mins and then at 90 °C for 4 hours. After cooling to room temperature, water (10 mL) and ethyl acetate (10 mL) were added and the organic layer was separated. The aqueous layer was extracted three times with ethyl acetate (3x10 mL). Combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was chromatographed (silica gel, heptane) to obtain the pure product.

5-Phenylbenzo[*b*]naphtho[2,1-*d*]thiophene 4.3a



White solid, 83% (52 mg). M.p.: 196–197 °C.

IR (ATR, cm^{-1}): 3041.6 (w), 1950.5 (w), 1893.8 (w), 1802.3 (w), 1745.3 (w), 1432.7 (w), 1339.2 (w), 1247.1 (w), 1155.1 (w), 1071.7 (w), 873.6 (m), 744.8 (s), 697.5 (s).

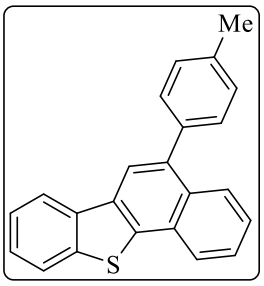
^{1}H NMR (250 MHz, $CDCl_3$) δ 8.27 – 8.15 (m, 2H, CH_{Ar}), 8.13 (s, 1H, CH_{Ar}), 8.06 – 7.92 (m, 2H, CH_{Ar}), 7.71 – 7.44 (m, 9H, CH_{Ar}).

^{13}C NMR (63 MHz, $CDCl_3$) δ 140.9, 139.4, 138.2, 137.0, 136.8, 132.3, 131.1 (C_{Ar}), 130.5 (2 CH_{Ar}), 129.3 (C_{Ar}), 128.5 (2CH_{Ar}), 127.6 (2CH_{Ar}), 126.8, 126.5, 126.4, 124.9, 124.8, 123.1, 121.8, 120.7 (CH_{Ar}).

MS (EI, 70 eV): m/z (%) = 310 (M^+, 100), 276 (4), 154 (28), 131 (7), 118 (4).

HRMS (EI): Calculated for $C_{22}H_{14}S_1$ (M^+): 310.08107, found: 310.08151.

5-(*p*-Tolyl)benzo[*b*]naphtho[2,1-*d*]thiophene 4.3b



White solid, 90% (58 mg). M.p.: 143–144 °C.

IR (ATR, cm^{-1}): 3043.5 (w), 2919.8 (w), 2860.6 (w), 2726.5 (w), 1895.5 (w), 1512.0 (w), 1433.0 (w), 1339.7 (w), 1107.1 (w), 875.8 (m), 819.9 (m), 747.0 (s), 607.2 (m).

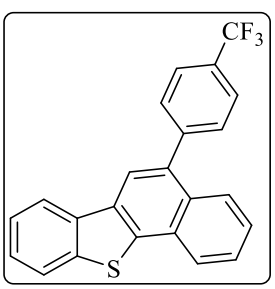
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 – 8.16 (m, 2H, CH_{Ar}), 8.13 (s, 1H, CH_{Ar}), 8.07 – 8.02 (m, 1H, CH_{Ar}), 8.02 – 7.95 (m, 1H, CH_{Ar}), 7.68 – 7.60 (m, 1H, CH_{Ar}), 7.56 – 7.46 (m, 5H, CH_{Ar}), 7.38 (d, ^3J = 7.8 Hz, 2H, CH_{Ar}), 2.52 (s, 3H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4, 138.1, 138.0, 137.3, 136.8, 132.3, 131.2 (C_{Ar}), 130.3 (2CH_{Ar}), 129.3 (C_{Ar}), 129.2 (2CH_{Ar}), 127.6, 126.7, 126.4, 126.3, 124.9, 124.7, 123.1, 121.7, 120.7 (CH_{Ar}), 21.4 (CH_3) (signal of one tertiary carbon is overlapped).

MS (EI, 70 eV): m/z (%) = 324 (M^+, 100), 308 (36), 154 (10), 125 (2), 39 (7).

HRMS (EI): Calculated for $C_{23}H_{16}S_1$ (M^+): 324.09672, found: 324.09641.

5-(4-(Trifluoromethyl)phenyl)benzo[*b*]naphtho[2,1-*d*]thiophene 4.3c



Yellowish solid, 53% (40 mg). M.p.: 167–169 °C.

IR (ATR, cm^{-1}): 3066.7 (w), 2922.7 (w), 2851.0 (w), 1923.3 (w), 1724.8 (w), 1614.7 (m), 1435.9 (m), 1319.7 (s), 1159.9 (s), 1102.4 (s), 1063.7 (s), 841.6 (m), 749.9 (s), 632.4 (m).

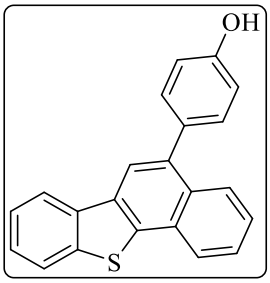
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 – 8.15 (m, 2H, CH_{Ar}), 8.11 – 8.07 (m, 1H, CH_{Ar}), 8.04 – 7.95 (m, 1H, CH_{Ar}), 7.89 (dd, ^{3}J = 7.2, ^{3}J = 6.8 Hz, 1H, CH_{Ar}), 7.85 – 7.77 (m, 2H, CH_{Ar}), 7.75 – 7.61 (m, 3H, CH_{Ar}), 7.61 – 7.46 (m, 3H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$) δ -62.62.

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 139.4, 137.8, 136.6, 136.5, 132.2 (C_{Ar}), 130.8 ($2CH_{Ar}$), 130.6 (C_{Ar}), 129.8 (q, ^{2}J = 32.5 Hz, *C*-CF_3), 129.3 (C_{Ar}), 127.1, 127.0, 126.8, 126.6 (CH_{Ar}), 125.5 (q, ^{3}J = 3.8 Hz, $2CH_{Ar}$), 125.1, 124.9 (CH_{Ar}), 124.5 (q, ^{1}J = 272.0 Hz, CF_3), 123.2, 121.7, 120.9 (CH_{Ar}).

HRMS (EI): Calculated for $C_{23}H_{13}F_3S_1$ (M^+): 378.06848, found: 378.06817.

4-(Benzo[*b*]naphtho[2,1-*d*]thiophen-5-yl)phenol 4.3d



White solid, 81% (53 mg). M.p.: 195–197 °C.

IR (ATR, cm^{-1}): 3534.5 (w), 3163.9 (w, br), 3040.1 (w), 2924.4 (w), 1888.9 (w), 1592.8 (m), 1506.0 (m), 1433.2 (m), 1339.9 (m), 1226.1 (s), 991.2 (m), 832.1 (s), 748.9 (s), 607.3 (m).

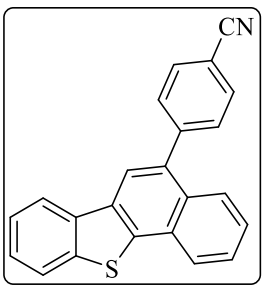
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 – 8.15 (m, 2H, CH_{Ar}), 8.09 (s, 1H, CH_{Ar}), 8.04 – 7.92 (m, 2H, CH_{Ar}), 7.69 – 7.58 (m, 1H, CH_{Ar}), 7.56 – 7.41 (m, 5H, CH_{Ar}), 7.08 – 6.96 (m, 2H, CH_{Ar}), 4.90 (s, br, 1H, OH).

^{13}C NMR (63 MHz, $CDCl_3$) δ 155.2, 139.4, 137.7, 136.8, 136.8, 133.5, 132.3 (C_{Ar}), 131.7 ($2CH_{Ar}$), 131.4, 129.3 (C_{Ar}), 127.6, 126.8, 126.5, 126.4, 125.0, 124.7, 123.1, 121.8, 120.7 (CH_{Ar}), 115.4 ($2CH_{Ar}$).

MS (EI, 70 eV): m/z (%) = 326 (M^+, 100), 308 (9), 295 (17), 271 (4), 224 (2), 148 (18), 135 (6).

HRMS (EI): Calculated for $C_{22}H_{14}O_1S_1$ (M^+): 326.07599, found: 326.07548.

4-(Benzo[*b*]naphtho[2,1-*d*]thiophen-5-yl)benzonitrile 4.3e



White solid, 68% (46 mg). M.p.: 215–216 °C.

IR (ATR, cm^{-1}): 3405.7 (w), 3046.0 (w), 3014.7 (w), 2223.6 (m), 1938.8 (w), 1602.3 (m), 1508.3 (m), 1341.4 (m), 989.5 (m), 836.7 (m), 747.0 (s), 720.4 (m), 614.1 (m), 573.9 (m).

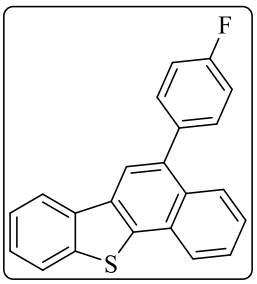
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 – 8.15 (m, 2H, CH_{Ar}), 8.07 (s, 1H, CH_{Ar}), 8.03 – 7.94 (m, 1H, CH_{Ar}), 7.92 – 7.78 (m, 3H, CH_{Ar}), 7.75 – 7.60 (m, 3H, CH_{Ar}), 7.60 – 7.45 (m, 3H, CH_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 145.7, 139.2, 138.0, 136.4, 135.9 (C_{Ar}), 132.2 ($2CH_{Ar}$), 132.0 (C_{Ar}), 131.0 ($2CH_{Ar}$), 130.1, 129.2 (C_{Ar}), 127.1, 126.9, 126.6, 126.5, 125.1, 124.8, 123.0, 121.6, 120.7 (CH_{Ar}), 118.9 (CN), 111.3 (C_{Ar}).

MS (EI, 70 eV): m/z (%) = 335 (M^+, 100), 167 (15), 153 (14), 131 (9).

HRMS (EI): Calculated for $C_{23}H_{13}N_1S_1$ (M^+): 335.07632, found: 335.07571.

5-(4-Fluorophenyl)benzo[*b*]naphtho[2,1-*d*]thiophene 4.3f



Yellowish solid, 89% (58 mg). M.p.: 176–177 °C.

IR (ATR, cm^{-1}): 3063.9 (w), 2926.3 (w), 1889.9 (w), 1667.1 (w), 1597.5 (m), 1504.2 (m), 1434.1 (m), 1215.5 (m), 1153.0 (m), 1089.1 (m), 876.9 (m), 835.6 (m), 749.0 (s), 605.1 (m).

^{1}H NMR (250 MHz, $CDCl_3$) δ 8.28 – 8.14 (m, 2H, CH_{Ar}), 8.08 (s, 1H, CH_{Ar}), 8.03 – 7.88 (m, 2H, CH_{Ar}), 7.71 – 7.58 (m, 1H, CH_{Ar}), 7.58 – 7.46 (m, 5H, CH_{Ar}), 7.33 – 7.17 (m, 2H, CH_{Ar}).

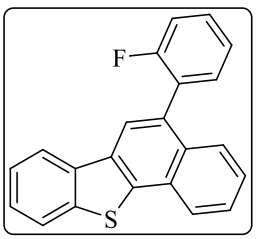
^{19}F NMR (235 MHz, $CDCl_3$) δ -115.13.

^{13}C NMR (63 MHz, $CDCl_3$) δ 162.5 (d, ^{1}J = 246.5 Hz, CF), 139.4, 137.2, 137.0 (C_{Ar}), 136.8 (d, ^{4}J = 3.4 Hz, C_{Ar}), 136.7, 132.2 (C_{Ar}), 132.0 (d, ^{3}J = 8.0 Hz, $2CH_{Ar}$), 131.1, 129.3 (C_{Ar}), 127.3, 126.9, 126.6, 126.5, 125.0, 124.8, 123.1, 121.7, 120.8, 115.5 (d, ^{2}J = 21.3 Hz, $2CH_{Ar}$).

MS (EI, 70 eV): m/z (%) = 328 (M^+, 100), 163 (23), 154 (10), 140 (8).

HRMS (EI): Calculated for $C_{22}H_{13}F_1S_1$ (M^+): 328.07165, found: 328.07113.

5-(2-Fluorophenyl)benzo[*b*]naphtho[2,1-*d*]thiophene 4.3g



Yellowish solid, 75% (49 mg). M.p.: 193–194 °C.

IR (ATR, cm^{-1}): 3054.6 (w), 1693.9 (w), 1575.4 (w), 1488.7 (m), 1449.4 (w), 1339.4 (w), 1247.6 (w), 1210.9 (w), 1095.3 (w), 887.4 (m), 746.9 (s), 725.7 (m), 611.8 (m).

^{1}H NMR (250 MHz, $CDCl_3$) δ 8.25 – 8.17 (m, 2H, CH_{Ar}), 8.15 (s, 1H, CH_{Ar}), 8.03 – 7.94 (m, 1H, CH_{Ar}), 7.82 – 7.74 (m, 1H, CH_{Ar}), 7.69 – 7.60 (m, 1H, CH_{Ar}), 7.57 – 7.45 (m, 5H, CH_{Ar}), 7.38 – 7.22 (m, 2H, CH_{Ar}).

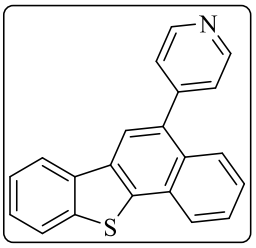
^{19}F NMR (235 MHz, $CDCl_3$) δ -113.51.

^{13}C NMR (63 MHz, $CDCl_3$) δ 160.5 (d, ^1J = 246.7 Hz, CF), 139.3, 137.8, 136.7 (C_{Ar}), 132.8 (d, ^4J = 3.4 Hz, CH_{Ar}), 132.2, 131.7, 131.1 (C_{Ar}), 129.8 (d, ^3J = 8.0 Hz, CH_{Ar}), 129.2, 128.2 (d, ^2J = 16.3 Hz, C_{Ar}), 127.3 (d, ^4J = 1.2 Hz, CH_{Ar}), 126.9, 126.7, 126.5, 125.0, 124.8 (CH_{Ar}), 124.4 (d, ^3J = 3.6 Hz, CH_{Ar}), 123.1, 121.8, 121.6, 115.9 (d, ^2J = 22.2 Hz, CH_{Ar}).

MS (EI, 70 eV): m/z (%) = 328 (M^+, 100), 163 (23), 154 (11), 131(5).

HRMS (EI): Calculated for $C_{22}H_{13}F_1S_1$ (M^+): 328.07165, found: 328.07116.

4-(Benzo[*b*]naphtho[2,1-*d*]thiophen-5-yl)pyridine 4.3h



White solid, 56% (35 mg). M.p.: 170–171 °C.

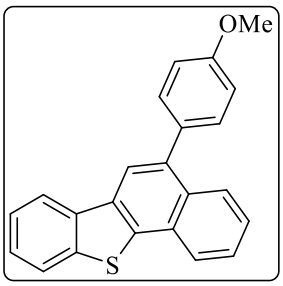
IR (ATR, cm^{-1}): 3066.6 (w), 3022.5 (w), 2922.7 (w), 1935.3 (w), 1693.5 (w), 1591.4 (m), 1402.2 (m), 1340.3 (w), 1062.1 (w), 988.3 (w), 823.4 (m), 749.2 (s), 726.3 (s), 617.4 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (s, br, 2H, CH_{Ar}), 8.26 – 8.16 (m, 2H, CH_{Ar}), 8.10 (s, 1H, CH_{Ar}), 8.03 – 7.96 (m, 1H, CH_{Ar}), 7.93 (d, ^3J = 8.2 Hz, 1H, CH_{Ar}), 7.73 – 7.43 (m, 6H, CH_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 149.6, 139.3, 138.4, 136.5, 135.1, 132.2, 129.9, 129.4 (C_{Ar}), 127.3, 127.1, 126.7, 126.7, 125.2, 124.9, 123.2, 121.7, 120.7 (CH_{Ar}). (signals of 4CH_{Ar} could not be detected).

MS (EI, 70 eV): m/z (%) = 311 (M^+, 100), 282 (12), 155 (23), 141 (14), 107 (4). HRMS (EI): Calculated for $C_{21}H_{13}N_1S_1$ (M^+): 311.07632, found: 311.07582.

5-(4-Methoxyphenyl)benzo[*b*]naphtho[2,1-*d*]thiophene 4.3i



White solid, 95% (65 mg). M.p.: 178–179 °C.

IR (ATR, cm^{-1}): 3043.2 (w), 2947.3 (w), 2832.6 (w), 1604.6 (m), 1509.9 (m), 1432.5 (m), 1290.1 (w), 1240.1 (m), 1168.9 (m), 1031.0 (m), 875.6 (m), 829.8 (m), 751.5 (s), 723.4 (,), 606.7 (m). 551.1 (m).

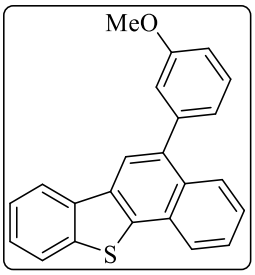
^{1}H NMR (250 MHz, $CDCl_3$) δ 8.25 – 8.15 (m, 2H, CH_{Ar}), 8.11 (s, 1H, CH_{Ar}), 8.06 – 7.93 (m, 2H, CH_{Ar}), 7.69 – 7.58 (m, 1H, CH_{Ar}), 7.58 – 7.44 (m, 5H, CH_{Ar}), 7.16 – 7.05 (m, 2H, CH_{Ar}), 3.94 (s, 3H, OCH_3).

^{13}C NMR (63 MHz, $CDCl_3$) δ 159.2, 139.4, 137.8, 136.8, 136.7, 133.2, 132.3 (C_{Ar}), 131.5 (2CH_{Ar}), 131.4, 129.3 (C_{Ar}), 127.6, 126.7, 126.4, 126.4, 124.9, 124.7, 123.1, 121.7, 120.7 (CH_{Ar}), 113.9 (2CH_{Ar}), 55.5 (OCH_3).

MS (EI, 70 eV): m/z (%) = 340 (M^+, 100), 325 (26), 295 (36), 269 (3), 148 (26), 135 (9).

HRMS (EI): Calculated for $C_{23}H_{16}O_1S_1$ (M^+): 340.09164, found: 340.09158.

5-(3-Methoxyphenyl)benzo[*b*]naphtho[2,1-*d*]thiophene 4.3j



White solid, 80% (55 mg). M.p.: 138–139 °C.

IR (ATR, cm^{-1}): 3047.3 (w), 2960.5 (w), 2831.0 (w), 1705.6 (w), 1582,9 (m), 1485.3 (m), 1459.4 (m), 1255.7 (m), 1214.0 (m), 1077.1 (m), 1034.1 (m), 952,2 (m), 789.8 (s), 748.3 (s), 649.4 (m), 570.3 (m).

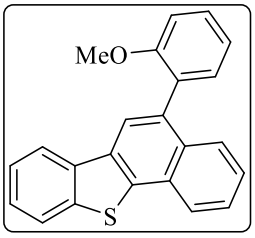
^{1}H NMR (250 MHz, $CDCl_3$) δ 8.26 – 8.16 (m, 2H, CH_{Ar}), 8.14 (s, 1H, CH_{Ar}), 8.07 – 7.90 (m, 2H, CH_{Ar}), 7.68-7.59 (m, 1H, CH_{Ar}), 7.58 – 7.41 (m, 4H, CH_{Ar}), 7.22 – 7.10 (m, 2H, CH_{Ar}), 7.09-7.00 (m, 1H, CH_{Ar}), 3.90 (s, 3H, OCH_3).

^{13}C NMR (63 MHz, $CDCl_3$) δ 159.7, 142.3, 139.4, 138.0, 137.1, 136.8, 132.2, 131.1 (C_{Ar}), 129.5 (CH_{Ar}), 129.3 (C_{Ar}), 127.6, 126.8, 126.5, 126.4, 124.9, 124.8, 123.1, 123.0, 121.8, 120.6, 116.1, 113.1 (CH_{Ar}), 55.5 (OCH_3).

MS (EI, 70 eV): m/z (%) = 340 (M^+, 100), 325 (3), 308 (10), 295 (33), 148 (22), 135 (8).

HRMS (EI): Calculated for $C_{23}H_{16}O_1S_1$ (M^+): 340.09164, found: 340.09152.

5-(2-Methoxyphenyl)benzo[*b*]naphtho[2,1-*d*]thiophene 4.3k



White solid, 71% (48 mg). M.p.: 216–218 °C.

IR (ATR, cm^{-1}): 3064.5 (w), 2952.0 (w), 2834.7 (w), 1578.4 (w), 1491.1 (m), 1461.4 (m), 1432.8 (m), 1339.4 (w), 1289.0 (m), 1241.1 (m), 1111.2 (m), 1024.2 (m), 875.4 (m), 746.2 (s), 724.4 (m), 614.1 (m), 551.5 (m).

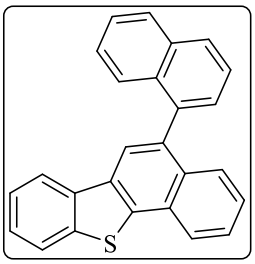
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 – 8.14 (m, 2H, CH_{Ar}), 8.12 (s, 1H, CH_{Ar}), 8.02 – 7.93 (m, 1H, CH_{Ar}), 7.69 (d, ^3J = 8.4 Hz, 1H, CH_{Ar}), 7.64-7.56 (m, 1H, CH_{Ar}), 7.55 – 7.43 (m, 4H, CH_{Ar}), 7.40 (dd, ^3J = 7.4, ^4J = 1.7 Hz, 1H, CH_{Ar}), 7.19 – 7.05 (m, 2H, CH_{Ar}), 3.72 (s, 3H, OCH_3).

^{13}C NMR (63 MHz, $CDCl_3$) δ 157.6, 139.3, 137.1, 136.9, 134.9, 132.4 (C_{Ar}), 132.3 (CH_{Ar}), 131.6, 129.7 (C_{Ar}), 129.4 (CH_{Ar}), 129.0 (C_{Ar}), 127.9, 126.6, 126.3, 126.2, 124.8, 124.6, 123.1, 121.8, 121.1, 120.9, 111.2 (CH_{Ar}), 55.7 (OCH_3).

MS (EI, 70 eV): m/z (%) = 340 (M^+, 100), 324 (21), 308 (5), 297 (28), 265 (4), 148 (21), 135 (9).

HRMS (EI): Calculated for $C_{23}H_{16}O_1S_1$ (M^+): 340.09164, found: 340.09157.

5-(Naphthalen-1-yl)benzo[*b*]naphtho[2,1-*d*]thiophene 4.3l



White solid, 65% (47 mg). M.p.: 217–218 °C

IR (ATR, cm^{-1}): 3043.8 (w), 2952.5 (w), 2850.6 (w), 1921.1 (w), 1506.2 (w), 1432.7 (m), 1235.3 (w), 1102.5 (w), 1018.6 (m), 879.7 (m), 798.7 (m), 772.9 (s), 748.4 (s), 725.4 (s), 698.6 (m), 600.2 (m), 578.3 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 – 8.23 (m, 1H, CH_{Ar}), 8.21 (s, 1H, CH_{Ar}), 8.19 – 8.10 (m, 1H, CH_{Ar}), 8.07 – 7.92 (m, 3H, CH_{Ar}), 7.70 – 7.56 (m, 3H, CH_{Ar}), 7.55 – 7.43 (m, 5H, CH_{Ar}), 7.43 – 7.27 (m, 2H, CH_{Ar}).

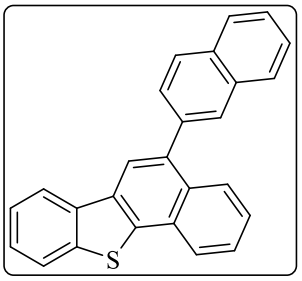
^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4, 138.5, 137.3, 136.8, 136.3, 133.7, 133.2, 132.4, 132.2, 129.1 (C_{Ar}), 128.4, 128.3, 128.3, 128.0, 126.9, 126.8, 126.5, 126.5, 126.3, 126.1, 125.6, 124.9, 124.8, 123.2, 121.8, 121.7 (CH_{Ar}).

MS (EI, 70 eV): m/z (%) = 360 (M^+, 100), 179 (46), 120 (3).

HRMS (EI): Calculated for $C_{26}H_{16}S_1$ (M^+): 360.09672, found: 360.09677.

5-(Naphthalen-2-yl)benzo[*b*]naphtho[2,1-*d*]thiophene 4.3m

White solid, 67% (48 mg). M.p.: 190–192 °C.



IR (ATR, cm^{-1}): 3036.6 (w), 2919.9 (w), 2849.9 (w), 1920.8 (w), 1704.2 (w), 1596.4 (w), 1434.9 (w), 1240.1 (w), 962.3 (m), 858.5 (m), 815.7 (m), 747.2 (s), 726.9 (s), 669.6 (m), 627.2 (m).

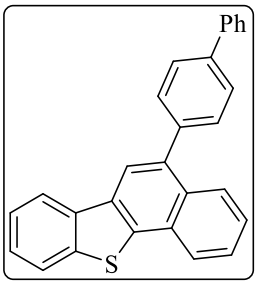
^{1}H NMR (250 MHz, $CDCl_3$) δ 8.27 – 8.16 (m, 3H, CH_{Ar}), 8.09 – 7.91 (m, 6H, CH_{Ar}), 7.75 – 7.47 (m, 7H, CH_{Ar}).

^{13}C NMR (63 MHz, $CDCl_3$) δ 139.4, 138.5, 138.1, 137.2, 136.8, 133.6, 132.8, 132.4, 131.3, 129.4 (C_{Ar}), 129.1, 128.8, 128.2, 127.9, 127.9, 127.6, 126.9 (CH_{Ar}), 126.6 ($2CH_{Ar}$), 126.5, 126.3, 125.0, 124.8, 123.1, 121.8, 121.1 (CH_{Ar}).

MS (EI, 70 eV): m/z (%) = 360 (M^+, 100), 179 (43), 143 (4).

HRMS (EI): Calculated for $C_{26}H_{16}S_1$ (M^+): 360.09672, found: 360.09575.

5-([1,1'-Biphenyl]-4-yl)benzo[*b*]naphtho[2,1-*d*]thiophene 4.3n



White solid, 63% (49 mg). M.p.: 190–192 °C.

IR (ATR, cm^{-1}): 3031.2 (w), 1599.4 (w), 1487.9 (w), 1433.1 (w), 1339.8 (w), 1235.3 (w), 990.0 (w), 888.3 (w), 842.8 (m), 747.0 (s), 724.2 (s), 693.0 (m), 645.3 (m), 579.8 (m).

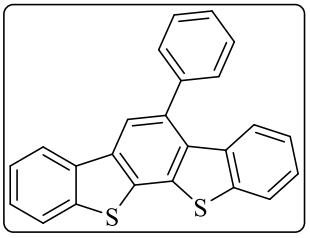
^{1}H NMR (250 MHz, $CDCl_3$) δ 8.27 – 8.18 (m, 2H, CH_{Ar}), 8.17 (s, 1H, CH_{Ar}), 8.13 – 8.06 (m, 1H, CH_{Ar}), 8.04 – 7.95 (m, 1H, CH_{Ar}), 7.84 – 7.60 (m, 7H, CH_{Ar}), 7.60 – 7.46 (m, 5H, CH_{Ar}), 7.46 – 7.37 (m, 1H, CH_{Ar}).

^{13}C NMR (63 MHz, $CDCl_3$) δ 140.9, 140.5, 139.9, 139.4, 137.7, 137.1, 136.8, 132.3, 131.1 (C_{Ar}), 130.9 ($2CH_{Ar}$), 129.4 (C_{Ar}), 129.0 ($2CH_{Ar}$), 127.6, 127.6 (CH_{Ar}), 127.3 ($2CH_{Ar}$), 127.2 ($2CH_{Ar}$), 126.9, 126.6, 126.4, 125.0, 124.8, 123.1, 121.8, 120.8 (CH_{Ar}).

MS (EI, 70 eV): m/z (%) = 386 (M^+, 100), 308 (20), 193 (10), 154 (6), 77 (5).

HRMS (EI): Calculated for $C_{28}H_{18}S_1$ (M^+): 386.11237, found: 386.11180.

6-Phenylbenzo[*b*]benzo[4,5]thio[3,2-*g*]benzothiophene 4.3o



Yellow, 34% (25 mg). M.p.: 230–231 °C.

IR (ATR, cm^{-1}): 3054.1 (w), 3025.7 (w), 2920.0 (w), 2849.8 (w), 1942.8 (w), 1905.1 (w), 1820.8 (w), 1788.0 (w), 1750.0 (w), 1693.4 (w), 1600.7 (w), 1435.4 (w), 1405.1 (m), 1330.9 (m), 1231.1(m), 1157.7 (m), 1111.9 (m), 876.9 (m), 755.7 (s), 728.2 (s), 699.6 (s), 646.1 (m), 568.9 (m).

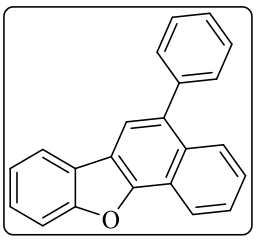
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 – 8.12 (m, 1H, CH_{Ar}), 8.02 (s, 1H, CH_{Ar}), 7.97 – 7.91 (m, 1H, CH_{Ar}), 7.91 – 7.86 (m, 1H, CH_{Ar}), 7.60 – 7.54 (m, 5H, CH_{Ar}), 7.53 – 7.44 (m, 2H, CH_{Ar}), 7.42 – 7.33 (m, 1H, CH_{Ar}), 7.20 – 7.07 (m, 2H, CH_{Ar}).

^{13}C NMR (63 MHz, $CDCl_3$) δ 141.5, 139.7, 139.4, 136.5, 136.2, 136.1, 133.8, 133.7, 132.4, 132.0 (C_{Ar}), 129.6 ($2CH_{Ar}$), 128.9 ($2CH_{Ar}$), 128.1, 127.0, 126.3, 125.1, 125.0, 124.4, 123.2, 123.0, 122.2, 120.4 (CH_{Ar}).

MS (EI, 70 eV): m/z (%) = 366 (M^+, 100), 332 (5), 182 (30), 160 (6), 121 (2).

HR-MS(+ESI): calculated for $C_{24}H_{15}S_2$ (M+H)+: 367.06097, found: 367.06144.

5-Phenylnaphtho[1,2-*b*]benzofuran 4.5a



White solid, 60% (35 mg). M.p.: 119–120 °C.

IR (ATR, cm^{-1}): 3030.2 (w), 2922.0 (w), 2850.8 (w), 1892.7 (w), 1576.1 (w), 1493.1 (w), 1457.9 (m), 1440.5 (m), 1403.5 (m), 1355.6 (m), 1235.5 (m), 1192.5 (m), 1171.9 (m), 1048.3 (m), 883.3 (m), 787.1 (m), 769.4 (m), 741.9 (s), 697.9 (s), 603.0 (m), 582.5 (m).

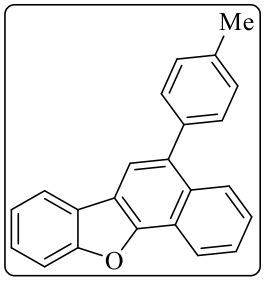
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (dd, ^3J = 8.2, ^5J = 0.5 Hz, 1H, CH_{Ar}), 8.00 (d, ^3J = 8.2 Hz, 2H, CH_{Ar}), 7.96 (s, 1H, CH_{Ar}), 7.75 (d, ^3J = 8.2 Hz, 1H, CH_{Ar}), 7.71-7.63 (m, 1H, CH_{Ar}), 7.61 – 7.37 (m, 8H, CH_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 151.8, 141.1, 136.2, 131.6 (C_{Ar}), 130.5 ($2CH_{Ar}$), 128.5 ($2CH_{Ar}$), 127.4, 127.2, 126.5, 126.5, 126.3 (CH_{Ar}), 125.2 (C_{Ar}), 123.2 (CH_{Ar}), 121.7 (C_{Ar}), 121.3, 120.4, 119.5, 118.8 (C_{Ar}), 112.0 (CH_{Ar}).

MS (EI, 70 eV): m/z (%) = 294 (M^+, 100), 263 (15), 239 (4), 146 (8), 132 (15), 119 (10).

HRMS (EI): Calculated for $C_{22}H_{14}O_1$ (M^+): 294.10392, found: 294.10358.

5-(*p*-Tolyl)naphtho[1,2-*b*]benzofuran 4.5b



White solid, 45% (28 mg). M.p.: 173–174 °C.

IR (ATR, cm^{-1}): 3025.9 (w), 2917.4 (w), 2863.5 (w), 2731.7 (w), 1930.0 (w), 1814.0 (w), 1634.2 (w), 1577.5 (w), 1459.1 (m), 1351.9 (m), 1236.6 (w), 1195.9 (m), 1049.3 (m), 822.6 (m), 766.1 (m), 739.8 (s), 601.2 (m).

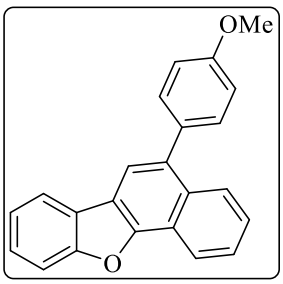
^{1}H NMR (250 MHz, $CDCl_3$) δ 8.58 – 8.49 (m, 1H, CH_{Ar}), 8.08 – 7.97 (m, 2H, CH_{Ar}), 7.95 (s, 1H, CH_{Ar}), 7.81 – 7.60 (m, 2H, CH_{Ar}), 7.58 – 7.30 (m, 7H, CH_{Ar}), 2.51 (s, 3H, CH_3).

^{13}C NMR (63 MHz, $CDCl_3$) δ 156.3, 151.7, 138.2, 137.1, 136.1, 131.7 (C_{Ar}), 130.4 ($2CH_{Ar}$), 129.2 ($2CH_{Ar}$), 127.3, 126.4, 126.4, 126.2 (CH_{Ar}), 125.3 (C_{Ar}), 123.1 (CH_{Ar}), 121.7 (C_{Ar}), 121.2, 120.4, 119.4 (CH_{Ar}), 118.8 (C_{Ar}), 112.0 (CH_{Ar}), 21.4 (CH_3).

MS (EI, 70 eV): m/z (%) = 308 (M^+, 100), 292 (10), 279 (6), 263 (5), 250 (5), 207 (10), 187 (4), 154 (8), 132 (11).

HRMS (EI): Calculated for $C_{23}H_{16}O_1$ (M^+): 308.11957, found: 308.11961.

5-(4-Methoxyphenyl)naphtho[1,2-*b*]benzofuran 4.5c



White solid, 77% (50 mg). M.p.: 168–169 °C.

IR (ATR, cm^{-1}): 3019.8 (w), 2958.7 (w), 2906.4 (w), 2542.6 (w), 2351.3 (w), 2051.5 (w), 1923.9 (w), 1605.3 (m), 1509.4 (m), 1460.4 (m), 1355.7 (m), 1238.0 (m), 1104.2 (m), 1031.5 (m), 827.2 (m), 768.5 (m), 745.5 (s), 686.4 (m), 601.3 (m), 555.4 (m).

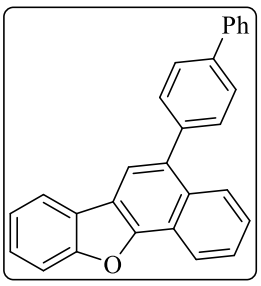
^{1}H NMR (250 MHz, $CDCl_3$) δ 8.58 – 8.47 (m, 1H, CH_{Ar}), 8.06 – 7.97 (m, 2H, CH_{Ar}), 7.94 (s, 1H), 7.79 – 7.60 (m, 2H, CH_{Ar}), 7.60 – 7.34 (m, 5H, CH_{Ar}), 7.17 – 7.00 (m, 2H, CH_{Ar}), 3.93 (s, 3H, OCH_3).

^{13}C NMR (63 MHz, $CDCl_3$) δ 159.1 (*C*-OCH_3), 156.3, 151.7, 135.8, 133.4, 131.8 (C_{Ar}), 131.6 ($2CH_{Ar}$), 127.2, 126.4, 126.4, 126.2 (CH_{Ar}), 125.3 (C_{Ar}), 123.1 (CH_{Ar}), 121.7 (C_{Ar}), 121.2, 120.4, 119.4 (CH_{Ar}), 118.8 (C_{Ar}), 113.9 ($2CH_{Ar}$), 112.0 (CH_{Ar}), 55.5 (OCH_3).

MS (EI, 70 eV): m/z (%) = 324 (M^+, 100), 309 (31), 279 (21), 252 (17), 226 (5), 162 (8), 140 (7), 113 (10).

HRMS (EI): Calculated for $C_{23}H_{16}O_2$ (M^+): 324.11448, found: 324.11403.

5-([1,1'-Biphenyl]-4-yl)naphtho[1,2-*b*]benzofuran 4.5d



White solid, 41% (30 mg). M.p.: 187–188 °C.

IR (ATR, cm^{-1}): 3029.6 (w), 2922.4 (w), 2850.5 (w), 1927.1 (w), 1580.5 (w), 1487.1 (m), 1440.6 (m), 1352.2 (m), 1236.5 (w), 1177.3 (m), 1049.4 (m), 838.7 (m), 763.6 (m), 741.9 (s), 692.7 (s), 606.2 (m), 587.4 (m).

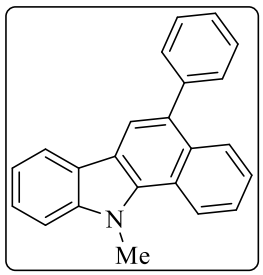
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 – 8.53 (m, 1H, CH_{Ar}), 8.09 (d, ^3J = 8.5 Hz, 1H, CH_{Ar}), 8.05 – 7.97 (m, 2H, CH_{Ar}), 7.82 – 7.70 (m, 5H, CH_{Ar}), 7.70 – 7.62 (m, 3H, CH_{Ar}), 7.59 – 7.47 (m, 4H, CH_{Ar}), 7.47 – 7.36 (m, 2H, CH_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 151.9, 141.0, 140.3, 140.1, 135.7, 131.6 (C_{Ar}), 130.9 ($2CH_{Ar}$), 129.0 ($2CH_{Ar}$), 127.5 (CH_{Ar}), 127.3 ($2CH_{Ar}$), 127.2 ($3CH_{Ar}$), 126.6, 126.5, 126.3 (CH_{Ar}), 125.2 (C_{Ar}), 123.2 (CH_{Ar}), 121.7 (C_{Ar}), 121.3, 120.4, 119.6 (CH_{Ar}), 118.8 (C_{Ar}), 112.0 (CH_{Ar}).

MS (EI, 70 eV): m/z (%) = 370 (M^+, 100), 339 (4), 292 (13), 263 (6) CH_{Ar}, 185 (8), 169 (7).

HRMS (EI): Calculated for $C_{28}H_{18}O_1$ (M^+): 370.13522, found: 370.13465.

11-Methyl-5-phenyl-11*H*-benzo[*a*]carbazole 4.6a



Yellowish solid, 31% (19 mg). M. p.: 153–154 °C.

IR (ATR, cm^{-1}): 3079.1 (w), 3055.4 (w), 3026.2 (w), 2918.9 (w), 1597.8 (w), 1518.4 (w), 1448.8 (m), 1334.5 (m), 1263.1 (m), 1133.2 (m), 1017.0 (m), 882.1 (m), 769.2 (m), 735.3 (s), 699.5 (s), 578.3 (s).

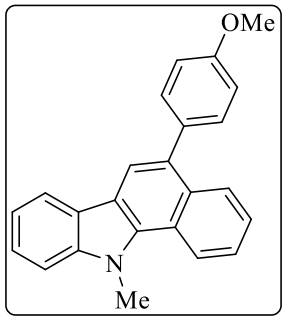
^{1}H NMR (250 MHz, $CDCl_3$) δ 8.81 (d, ^3J = 8.1 Hz, 1H, CH_{Ar}), 8.17 – 8.04 (m, 3H, CH_{Ar}), 7.66 – 7.43 (m, 9H, CH_{Ar}), 7.35 – 7.27 (m, 1H, CH_{Ar}), 4.47 (s, 3H, NCH_3).

^{13}C NMR (63 MHz, $CDCl_3$) δ 142.1, 141.2, 135.3, 132.7, 132.0 (C_{Ar}), 130.7 ($2CH_{Ar}$), 128.4 ($2CH_{Ar}$), 127.9, 127.0, 125.2, 125.0, 124.8 (CH_{Ar}), 123.2, 123.0 (C_{Ar}), 122.4, 120.4, 119.8, 119.8 (CH_{Ar}), 118.6 (C_{Ar}), 109.2 (CH_{Ar}), 34.4 (NCH_3).

MS (EI, 70 eV): m/z (%) = 307 (M^+, 100), 291 (35), 152 (12), 146 (23), 131 (5), 118 (3).

HRMS (EI): Calculated for $C_{23}H_{17}N_1$ (M^+): 307.13555, found: 307.13495.

5-(4-Methoxyphenyl)-11-methyl-11*H*-benzo[*a*]carbazole 4.6b



Yellowish solid, 45% (30 mg). M.p.: 154–155 °C.

IR (ATR, cm^{-1}): 3119.2 (w), 3029.2 (w), 2956.9 (w), 2836.1 (w), 1926.1 (w), 1766.2 (w), 1658.8 (w), 1606.6 (m), 1572.5 (m), 1508.6 (s), 1440.4 (s), 1335.6 (m), 1233.7 (s), 1169.8 (s), 1103.7 (m), 1027.6 (s), 884.2 (m), 835.5 (s), 738.4 (s), 690.2 (m), 547.7 (s).

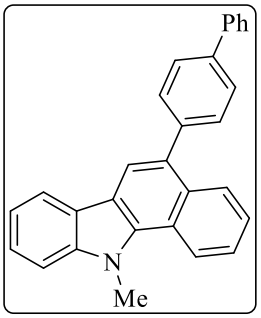
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (d, ^3J = 8.1 Hz, 1H, CH_{Ar}), 8.19 – 8.05 (m, 3H, CH_{Ar}), 7.66 – 7.43 (m, 6H, CH_{Ar}), 7.37 – 7.28 (m, 1H, CH_{Ar}), 7.12 – 7.04 (m, 2H, CH_{Ar}), 4.44 (s, 3H, NCH_3), 3.93 (s, 3H, OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 141.2, 135.2, 134.4, 132.3, 132.3 (C_{Ar}), 131.7 ($2CH_{Ar}$), 127.9, 125.1, 124.9, 124.7 (CH_{Ar}), 123.2, 123.0 (C_{Ar}), 122.4, 120.4, 119.8, 119.7 (CH_{Ar}), 118.6 (C_{Ar}), 113.9 ($2CH_{Ar}$), 109.2 (CH_{Ar}), 55.5 (OCH_3), 34.3 (NCH_3).

MS (EI, 70 eV): m/z (%) = 337 (M^+, 100), 322 (37), 278 (27), 168 (10), 145 (20).

HRMS (EI): Calculated for $C_{24}H_{19}O_1N_1$ (M^+): 337.14612, found: 337.14559.

5-([1,1'-Biphenyl]-4-yl)-11-methyl-11*H*-benzo[*a*]carbazole 4.6c



White solid, 39% (30 mg). M.p.: 218–219 °C.

IR (ATR, cm^{-1}): 3056.4 (w), 3026.0 (w), 1594.1 (w), 1516.7 (w), 1464.9 (w), 1375.0 (w), 1334.9 (w), 1264.7 (w), 1227.0 (w), 1062.7 (w), 897.7 (m), 845.0 (m), 770.6 (m), 726.0 (s), 693.7 (s), 637.5 (m), 583.0 (m).

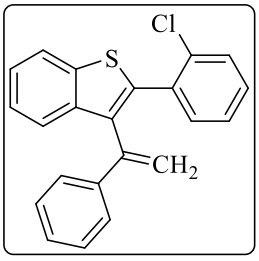
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (d, ^3J = 8.4 Hz, 1H, CH_{Ar}), 8.25 – 8.11 (m, 3H, CH_{Ar}), 7.85 – 7.45 (m, 12H, CH_{Ar}), 7.45 – 7.29 (m, 2H, CH_{Ar}), 4.47 (s, 3H, NCH_3).

^{13}C NMR (63 MHz, $CDCl_3$) δ 141.2, 141.2, 141.1, 139.9, 135.4, 132.3, 132.0 (C_{Ar}), 131.1 ($2CH_{Ar}$), 129.0 ($2CH_{Ar}$), 127.9, 127.4 (CH_{Ar}), 127.3 ($2CH_{Ar}$), 127.2 ($2CH_{Ar}$), 125.3, 125.1, 124.9 (CH_{Ar}), 123.2, 123.1 (C_{Ar}), 122.4, 120.5, 119.8, 119.8 (CH_{Ar}), 118.6 (C_{Ar}), 109.2 (CH_{Ar}), 34.4 (NCH_3).

MS (EI, 70 eV): m/z (%) = 383 (M^+, 100), 367 (14), 341 (1), 291 (10), 184 (9), 152 (4), 77 (4).

HRMS (EI): Calculated for $C_{29}H_{21}N_1$ (M^+): 383.16685, found 383.16645.

2-(2-Chlorophenyl)-3-(1-phenylvinyl)benzo[*b*]thiophene 4.4



Yellowish oil.

IR (ATR, cm^{-1}):3054.8 (w), 3023.3 (w), 1609.9 (m), 1491.6 (m), 1430.9 (m), 1241.0 (w), 1059.9 (m), 1026.7 (w), 904.5 (m), 777.9 (m), 748.6 (s), 732.2 (s), 701.8 (s), 597.7 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 – 7.81 (m, 1H, CH_{Ar}), 7.59 – 7.45 (m, 1H, CH_{Ar}), 7.45 – 7.34 (m, 5H, CH_{Ar}), 7.34 – 7.13 (m, 6H, CH_{Ar}), 5.82 (d, ^2J = 1.3 Hz, 1H, C=CH_2), 5.34 (d, ^2J = 1.3 Hz, 1H, C=CH_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2, 140.1, 139.7, 139.4, 137.8, 135.8, 134.8, 133.4 (C_{Ar}), 132.8, 129.8, 129.7 (CH_{Ar}), 128.3 ($2CH_{Ar}$), 127.8 (CH_{Ar}), 126.9 ($2CH_{Ar}$), 126.4, 124.7, 124.4, 124.2, 122.2 (CH_{Ar}), 118.1 (C=*C*H_2).

MS (EI, 70 eV): m/z (%) = 346 (M^+, 16), 311 (100), 295 (7), 269 (6), 234 (38), 189 (8), 154 (16), 77 (7).

HRMS (EI): Calculated for $C_{22}H_{15}{}^{35}Cl_1S_1$ (M^+): 346.05775, found: 346.05749.

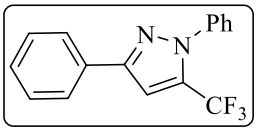
General procedure for the synthesis of pyrazoles

Acetophenone **5.1** (0.5 mmol, 1 eq) and phenylhydrazine (0.525 mmol, 1.05 eq) were dissolved in 2 mL of DCM. The solution was stirred for 1 min at room temperature and then

the solvent was removed under reduced pressure. The residue was stirred at room temperature and 3 drops of acetic acid were added. The reaction mixture was stirred for 5 min to complete the reaction. (In most cases, the product was solid and the reaction mixture became solid as the reaction completed). The reaction carried out nearly qualitative. Then the crude product was dissolved in 10 mL of DCM. After that, solvent, water, and acetic acid were removed under reduced pressure and the product was transferred to the next step without further purification.

To a solution of hyrazone **5.2** (0.5 mmol) in 7 mL of dry THF was added *n*-butyllithium (0.44 mL, 2.2 equiv., 2.5 M solution in hexane) slowly at -78 °C under Ar. After adding *n*--butyllithium, the mixture was allowed to warm to 20 °C and stirred at that temperature for 15 min. Then the reaction was cooled to -78 °C again and ethyl perfluorocarboxylate **5.3** (1.5 eq, solution in 1 mL THF) was added at this temperature. The reaction was allowed to warm to 20 °C and stirred for 30 min, subsequently, 1 mL of TFA was added. The mixture was stirred under reflux for 2 h. After cooling, a saturated aqueous solution of $NaHCO_3$ was added until no CO_2 evolution was observed. Then THF was removed and the remained water was extracted with ethyl acetate (10 mL 3x). Combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by chromatography (silica gel, *n*-heptane/DCM).

1,3-Diphenyl-5-(trifluoromethyl)-1*H*-pyrazole 5.4a



White solid, 89% (128 mg). M.p.: 53–54 °C.

IR (ATR, cm^{-1}): ν = 549 (s), 615 (m), 685 (s), 760 (s), 773 (s), 812 (s), 956 (m), 9872 (s), 1028 (s), 1072 (s), 1118 (s), 1138 (m), 1211 (s), 1232 (s), 1288 (s), 1363 (m), 1444 (s), 1502 (m), 1556 (m), 1593 (m), 3054 (w), 3070 (w), 3139 (w).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 – 7.83 (m, 2H, CH_{Ph}), 7.65 – 7.32 (m, 8H, CH_{Ph}), 7.12 (s, 1H, CH_{Ar}).

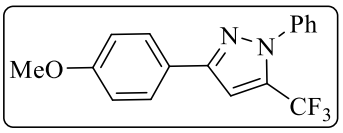
^{19}F NMR (282 MHz, $CDCl_3$) δ -57.59.

^{13}C NMR (75 MHz, $CDCl_3$) δ 151.8, 139.3 (C_{Ar}), 134.0 (q, ^2J = 39.2 Hz, *C*-CF_3), 131.9 (C_{Ar}), 129.4 (CH_{Ar}), 129.26 ($2CH_{Ar}$), 128.9 ($2CH_{Ar}$), 128.8 (CH_{Ar}), 126.0 ($2CH_{Ar}$), 125.9, 125.9 (CH_{Ar}), 119.9 (q, ^1J = 269.2 Hz, CF_3), 106.2 (q, ^3J = 2.4 Hz, CH_{HetAr}).

GC-MS (EI, 70 eV): *m/z* (%) = 288 (100), 267 (37), 219 (9), 77 (20).

HRMS (EI): calcd. for $C_{16}H_{11}F_3N_2$ ($[M]^+$): 288.08688, found: 288.08678.

3-(4-Methoxyphenyl)-1-phenyl-5-(trifluoromethyl)-1*H*-pyrazole 5.4b



Yellow solid, 79% (127 mg). M.p.: 77–78 °C.

IR (ATR, cm^{-1}): ν = 548 (m), 617 (m), 685 (s), 767 (s), 810 (s), 833 (m), 956 (m), 987 (s), 1031 (s), 1080 (s), 1088 (s), 1115 (s), 1151 (s), 1209 (s), 1248 (s), 1290 (s), 1359 (w), 1435 (s), 1450 (s), 1502 (s), 1558 (m), 1595 (m), 1614 (m), 2845 (w), 2943 (w), 2970 (w), 3022 (w), 3068 (w), 3130 (w).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 – 7.73 (m, 2H, CH_{Ar}), 7.62 – 7.44 (m, 5H, CH_{Ar}), 7.04 (s, 1H, CH_{Ar}), 7.02 – 6.90 (m, 2H, CH_{Ar}), 3.85 (s, 3H, OCH_3).

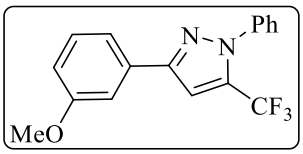
^{19}F NMR (282 MHz, $CDCl_3$) δ -57.59.

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 151.6, 139.4 (C_{Ar}), 133.9 (q, ^{2}J = 39.0 Hz, *C*-CF_3), 129.3 (CH_{Ar}), 129.2 ($2CH_{Ar}$), 127.3 ($2CH_{Ar}$), 125.9, 125.9 (CH_{Ar}), 124.5 (C_{Ar}), 119.9 (q, ^{1}J = 269.1 Hz, CF_3), 114.3 ($2CH_{Ar}$), 105.8 (q, ^{3}J = 2.4 Hz, CH_{HetAr}), 55.47 (OCH_3).

GC-MS (EI, 70 eV): *m/z* (%) = 318 (100), 303 (26), 275 (12), 77 (12).

HRMS (EI): calcd. for $C_{17}H_{13}F_3N_2O$ ($[M]^+$): 318.09745, found: 318.09788.

3-(3-Methoxyphenyl)-1-phenyl-5-(trifluoromethyl)-1*H*-pyrazole 5.4c



Pale yellow oil, 81% (129 mg).

IR (ATR, cm^{-1}): ν = 544 (m), 627 (m), 688 (s), 766 (s), 816 (m), 847 (m), 916 (w), 987 (s), 1041 (s), 1089 (s), 1124 (s), 1143 (s), 1197 (s), 1224 (s), 1257 (m), 1284 (m), 1354 (m), 1433 (s), 1464 (m), 1500 (s), 1556 (m), 1597 (m), 2835 (w), 2939 (w), 3003 (w), 3063 (w), 3138 (w).

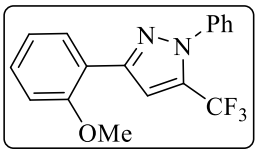
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 – 7.47 (m, 5H, CH_{Ar}), 7.47 – 7.40 (m, 2H, CH_{Ar}), 7.35 (t, ^{3}J = 8.1 Hz, 1H, CH_{Ar}), 7.10 (s, 1H, $CH_{Ar,}$), 6.93 (m, 1H, CH_{Ar}), 3.87 (s, 3H, OCH_3).

^{19}F NMR (282 MHz, $CDCl_3$) δ -57.60.

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 151.6, 139.3 (C_{Ar}), 134.0 (q, ^{2}J = 39.2 Hz, *C*-CF_3), 133.2 (C_{Ar}), 130.0, 129.5 (CH_{Ar}), 129.3 ($2CH_{Ar}$), 125.9, 125.9 (CH_{Ar}), 119.9 (q, ^{1}J = 269.2 Hz, CF_3), 118.5, 114.8, 111.1 (CH_{Ar}), 106.4 (q, ^{3}J = 2.4 Hz, CH_{HetAr}), 55.5 (OCH_3).

GC-MS (EI, 70 eV): *m/z* (%) = 318 (100), 297 (8), 267 (8), 205 (3), 77 (20). HRMS (EI): calcd. for $C_{17}H_{13}F_3N_2O$ ($[M]^+$): 318.09745, found: 318.09718.

3-(2-Methoxyphenyl)-1-phenyl-5-(trifluoromethyl)-1*H*-pyrazole 5.4d



Pale yellow solid, 61% (109 mg). M.p.: 70–71 °C.

IR (ATR, cm^{-1}): ν = 542 (m), 692 (s), 750 (s), 777 (s), 814 (s), 989 (s), 1028 (s), 1068 (s), 1084 (s), 1113 (s), 1157 (s), 1201 (s), 1230 (s), 1246 (s), 1290 (s), 1354 (m), 1421 (m), 1437 (s), 1456 (m), 1473 (s), 1504 (m), 1556 (m), 1585 (m), 1595 (m), 2841 (w), 2943 (w), 3057 (w), 3180 (w).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (dd, ^{3}J = 7.6, ^{4}J = 1.7 Hz, 1H, CH_{Ar}), 7.64 – 7.42 (m, 5H, CH_{Ar}), 7.41 – 7.30 (m, 2H, CH_{Ar}), 7.08 – 6.91 (m, 2H, CH_{Ar}), 3.96 (s, 3H, OCH_3).

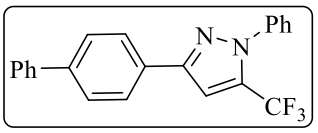
^{19}F NMR (282 MHz, $CDCl_3$) δ -57.38.

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 148.6, 139.4 (C_{Ar}), 132.9 (q, ^{2}J = 39.0 Hz, *C*-CF_3), 129.8, 129.1 (CH_{Ar}), 129.1 ($2CH_{Ar}$), 128.8, 125.8, 125.8, 120.9 (CH_{Ar}), 120.6 (C_{Ar}), 120.0 (q, ^{1}J = 269.0 Hz, CF_3), 111.3, 110.3 (q, ^{3}J = 2.5 Hz, CH_{HetAr}), 55.5 (OCH_3).

GC-MS (EI, 70 eV): *m/z* (%) = 318 (100), 289 (64), 267 (27), 249 (28), 221 (14), 77 (60).

HRMS (EI): calcd. for $C_{17}H_{13}F_3N_2O$ ($[M]^+$): 318.09745, found: 318.09699.

3-([1,1'-Biphenyl]-4-yl)-1-phenyl-5-(trifluoromethyl)-1*H*-pyrazole 5.4e



Pale yellow solid, 74% (134 mg). M.p.: 94–95 °C.

IR (ATR, cm^{-1}): ν = 546 (m), 685 (s), 727 (s), 758 (s), 820 (s), 845 (m), 987 (s), 1086 (s), 1117 (s), 1149 (s), 1159 (s), 1201 (m), 1226 (s), 1290 (s), 1358 (m), 1410 (m), 1443 (s), 1502 (s), 1566 (w), 1595 (m), 2850 (w), 2920 (w), 3032 (w), 3053 (w), 3144 (w).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 – 7.90 (m, 2H, CH_{Ar}), 7.72 – 7.63 (m, 4H, CH_{Ar}), 7.63 – 7.33 (m, 8H, CH_{Ar}), 7.16 (d, ^{5}J = 0.3 Hz, 1H, CH_{Ar}).

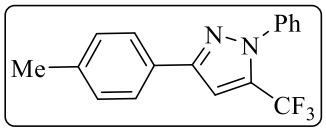
^{19}F NMR (282 MHz, $CDCl_3$) δ -57.57 (s).

^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 141.5, 140.7, 139.4 (C_{Ar}), 134.1 (q, ^{2}J = 39.2 Hz, *C*-CF_3), 130.8 (C_{Ar}), 129.5 (CH), 129.3 ($2CH_{Ar}$), 128.9 ($2CH_{Ar}$), 127.6 (CH_{Ar}), 127.6 ($2CH_{Ar}$), 127.2 ($2CH_{Ar}$), 126.4 ($2CH_{Ar}$), 125.9, 125.9 (CH_{Ar}), 119.9 (q, ^{1}J = 269.1 Hz, CF_3), 106.3 (q, ^{3}J = 2.4 Hz, CH_{HetAr}).

GC-MS (EI, 70 eV): *m/z* (%) = 364 (100), 343 (11), 152 (10), 77(10).

HRMS (EI): calcd. for $C_{22}H_{15}F_3N_2$ ($[M]^+$): 364.11818, found: 364.11765.

1-Phenyl-3-(*p*-tolyl)-5-(trifluoromethyl)-1*H*-pyrazole 5.4f



Pale yellow solid, 87% (140 mg). M.p: 71–72 °C.

IR (ATR, cm^{-1}): ν = 544 (m), 623 (m), 687 (s), 768 (s), 798 (s), 827 (m), 989 (s), 1086 (s), 1122 (s), 1155 (s), 1203 (m), 1232 (s), 1290 (m), 1440 (s), 1504 (m), 1556 (m), 1595 (w), 2357 (w), 2860 (w), 2922 (w), 3022 (w), 3061 (w).

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.82 – 7.65 (m, 2H, CH_{Ar}), 7.63 – 7.44 (m, 5H, CH_{Ar}), 7.33 – 7.18 (m, 2H, CH_{Ar}), 7.08 (s, 1H, CH_{Ar}), 2.40 (s, 3H, CH_3).

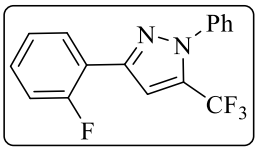
^{19}F NMR (282 MHz, $CDCl_3$) δ -57.58.

^{13}C NMR (63 MHz, $CDCl_3$) δ 151.8, 139.4, 138.7 (C_{Ar}), 133.9 (q, ^{2}J = 39.2 Hz, *C*-CF_3), 129.6 ($2CH_{Ar}$), 129.4 (CH_{Ar}), 129.2 ($2CH_{Ar}$), 129.1 (C_{Ar}), 125.9 ($4CH_{Ar}$), 119.9 (q, ^{1}J = 269.2 Hz, CF_3), 106.1 (q, ^{3}J = 2.4 Hz, CH_{HetAr}), 21.4 (CH_3).

GC-MS (EI, 70 eV): *m/z* (%) = 302 (100), 281 (18), 267 (8), 233 (7), 77 (14).

HRMS (ESI): calcd. for $C_{17}H_{13}F_3N_2$ ($[M+H]^+$): 303.11036, found: 303.11038.

3-(2-Fluorophenyl)-1-phenyl-5-(trifluoromethyl)-1*H*-pyrazole 5.4g



Pale yellow solid, 90% (138 mg). M.p. 73–74 °C.

IR (ATR, cm^{-1}): ν = 553 (m), 625 (m), 661 (m), 686 (s), 750 (s), 771 (s), 820 (s), 833 (s), 947 (m), 960 (m), 989 (s), 1028 (m), 1070 (s), 1115 (s), 1165 (s), 1201 (s), 1238 (s), 1261 (m), 1290 (s), 1358 (m), 1423 (m), 1444 (s), 1471 (m), 1500 (m), 1554 (m), 1581 (m), 1587 (m), 1913 (w), 3056 (w), 3076 (w), 3165 (w).

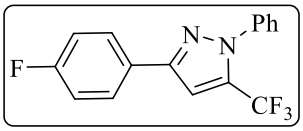
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 – 8.07 (m, 1H, CH_{Ar}), 7.68 – 7.50 (m, 5H, CH_{Ar}), 7.50 – 7.35 (m, 1H, CH_{Ar}), 7.35 – 7.15 (m, 3H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$) δ -57.59, -116.00.

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.5 (d, ^{1}J = 250.0 Hz, CF), 146.5, 139.3 (C_{Ar}), 134.3 – 133.3 (m, 1C, C_{Ar}), 130.2 (d, ^{3}J = 8.5 Hz, CH_{Ar}), 129.5 (CH_{Ar}), 129.3 ($2CH_{Ar}$), 128.6 (d, ^{3}J = 11.5 Hz, CH_{Ar}), 125.9, 125.9 (CH_{Ar}), 124.6 (d, ^{4}J = 3.5 Hz, CH_{Ar}), 119.9 (q, ^{1}J = 269.2 Hz, CF_3), 119.9 (d, ^{2}J = 20.8 Hz, C_{Ar}), 116.3 (d, ^{2}J = 22.0 Hz, CH_{Ar}), 109.9-109.5 (m, 1C, CH_{HetAr}).

GC-MS (EI, 70 eV): *m/z* (%) = 306 (100), 285 (38), 267 (9), 237 (7), 77 (15).

3-(4-Fluorophenyl)-1-phenyl-5-(trifluoromethyl)-1*H*-pyrazole 5.4h



Yellow solid, 82% (125 mg). M.p.: 64–65 °C.

IR (ATR, cm^{-1}): ν = 544 (m), 619 (m), 692 (s), 750 (m), 769 (s), 808 (s), 837 (s), 956 (m), 987 (s), 1028 (m), 1066 (s), 1076 (s), 1086 (s), 1111 (s), 1155 (s), 1207 (s), 1228 (s), 1290 (s), 1440 (s), 1502 (s), 1525 (m), 1558 (m), 1595 (m), 1606 (m), 1888 (w), 3058 (w), 3141 (w).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 – 7.75 (m, 2H, CH_{Ar}), 7.63 – 7.44 (m, 5H, CH_{Ar}), 7.20 – 7.07 (m, 2H, CH_{Ar}), 7.06 (s, 1H, CH_{Ar}).

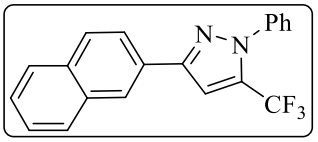
^{19}F NMR (282 MHz, $CDCl_3$) δ -57.65, -112.97.

^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2 (d, ^{1}J = 247.9 Hz, CF), 150.9, 139.3 (C_{Ar}), 134.2 (q, ^{2}J = 39.2 Hz, *C*-CF_3), 129.5 (CH_{Ar}), 129.3 ($2CH_{Ar}$), 128.1 (d, ^{4}J = 3.2 Hz, C_{Ar}), 127.8 (d, ^{3}J = 8.2 Hz, $2CH_{Ar}$), 125.8, 125.8 (CH_{Ar}), 119.8 (q, ^{1}J = 269.2 Hz, CF_3), 115.9 (d, ^{2}J = 21.8 Hz, $2CH_{Ar}$), 106.0 (q, ^{3}J = 2.4 Hz, CH_{HetAr}).

GC-MS (EI, 70 eV): *m/z* (%) = 306 (100), 285 (40), 237 (9), 77 (17).

HRMS (EI): calcd. for $C_{16}H_{10}F_4N_2$ ($[M]^+$): 306.07746, found: 306.07713.

3-(Naphthalen-2-yl)-1-phenyl-5-(trifluoromethyl)-1*H*-pyrazole 5.4i



Pale yellow solid, 78% (102 mg). M.p.: 71–71 °C.

IR (ATR, cm^{-1}): ν = 542 (m), 687 (s), 742 (s), 767 (s), 798 (s), 804 (s), 819 (m), 856 (s), 885 (m), 945 (m), 989 (s), 1028 (m), 1057 (s), 1074 (s), 1086 (s), 1113 (s), 1153 (s), 1230 (s), 1246 (s), 1290 (s), 1431 (m), 1485 (m), 1504 (s), 1556 (w), 1595 (m), 3028 (w), 3055 (w).

^{1}H NMR (300 MHz, Acetone) δ 8.50 (s, 1H, CH_{Ar}), 8.13 (d, ^{3}J = 8.3 Hz, 1H, CH_{Ar}), 8.04 – 7.88 (m, 3H, CH_{Ar}), 7.72 – 7.47 (m, 8H, CH_{Ar}).

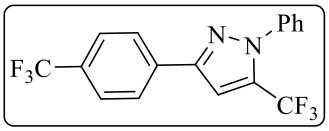
^{19}F NMR (282 MHz, Acetone) δ 119.44.

^{13}C NMR (75 MHz, Acetone) δ 152.5, 140.4, 134.6, 134.6 (C_{Ar}), 134.5 (q, ^{2}J = 39.0 Hz, *C*-CF_3), 130.6 (C_{Ar}), 130.3 (CH_{Ar}), 130.3 ($2CH_{Ar}$), 129.5, 129.3, 128.8, 127.6, 127.4, 126.9, 126.9, 125.7, 124.6 (CH_{Ar}), 121.1 (q, ^{1}J = 268.4 Hz, CF_3), 107.6 (q, ^{4}J = 2.5 Hz, CH_{HetAr}).

GC-MS (EI, 70 eV): *m/z* (%) = 338 (100), 317 (14), 127 (17), 77 (20).

HRMS (EI): calcd. for $C_{20}H_{13}F_3N_2$ ($[M]^+$): 338.10253, found: 338.10259.

1-Phenyl-5-(trifluoromethyl)-3-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole 5.4j



Yellow solid, 64% (113 mg). M.p.: 50–51 °C.

IR (ATR, cm^{-1}): ν = 552 (m), 592 (s), 625 (m), 687 (s), 766 (s), 804 (s), 845 (s), 991 (s), 1062 (s), 1068 (s), 1089 (s), 1093 (s), 1109 (s), 1132 (s), 1232 (s), 1288 (s), 1323 (s), 1419 (w), 1446 (m), 1504 (m), 1531 (w), 1558 (w), 1595 (m), 1622 (m), 3063 (w), 3145 (w).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, ^{3}J = 8.1 Hz, 2H, CH_{Ar}), 7.69 (d, ^{3}J = 8.1 Hz, 2H, CH_{Ar}), 7.62 – 7.46 (m, 5H, CH_{Ar}), 7.16 (s, 1H, CH_{Ar}).

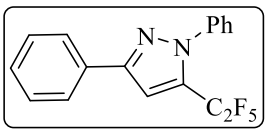
^{19}F NMR (282 MHz, $CDCl_3$) δ -57.71, -62.63.

^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3, 139.1 (C_{Ar}), 135.3 (d, ^{4}J = 1.3 Hz, C_{Ar}), 134.5 (q, ^{2}J = 39.6 Hz, *C*-CF_3), 130.7 (q, ^{2}J = 32.5 Hz, C_{Ar}), 129.7 (CH_{Ar}), 129.4 ($2CH_{Ar}$), 126.17 ($2CH_{Ar}$), 125.9 (q, ^{3}J = 3.8 Hz, $2CH_{Ar}$), 125.8 (q, ^{4}J = 1.0 Hz, $2CH_{Ar}$), 124.3 (q, ^{1}J = 272.3 Hz, CF_3), 119.7 (q, ^{1}J = 269.3 Hz, CF_3), 106.5 (q, ^{3}J = 2.4 Hz, CH_{HetAr}).

GC-MS (EI, 70 eV): *m/z* (%) = 356 (100), 335 (51), 287 (10), 267 (10), 77 (27).

HRMS (EI): calcd. for $C_{17}H_{10}F_6N_2$ ($[M]^+$): 356.07427, found: 356.07482.

5-(Perfluoroethyl)-1,3-diphenyl-1*H*-pyrazole 5.4k.



Pale yellow solid, 95% (161 mg). M.p.: 140–142 °C.

IR (ATR, cm^{-1}): ν = 544 (w), 580 (w), 602 (m), 619 (m), 630 (m), 688 (s), 711 (m), 750 (s), 765 (s), 777 (s), 814 (m), 914 (m), 937 (s), 958 (s), 1020 (m), 1041 (s), 1076 (m), 1092 (s), 1134 (s), 1190 (s), 1203 (s), 1223 (s), 1331 (m), 1444 (m), 1498 (m), 1595 (w), 3076 (w), 3151 (w).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 – 7.82 (m, 2H, CH_{Ar}), 7.55 – 7.48 (m, 5H, CH_{Ar}), 7.48 – 7.32 (m, 3H, CH_{Ar}), 7.10 (d, ^{5}J = 0.9 Hz, 1H, CH_{Ar}).

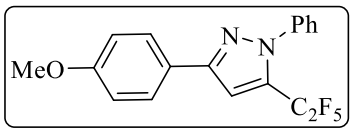
^{19}F NMR (282 MHz, $CDCl_3$) δ -83.38 (t, $^{3}J_{F\text{-}F}$ = 2.9 Hz), -106.28 (q, $^{3}J_{F\text{-}F}$ = 2.9 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ 152.1, 139.9 (C_{Ar}), 132.0 (t, ^{2}J = 27.6 Hz, *C*-CF_3), 131.7 (C_{Ar}), 129.7 (CH_{Ar}), 129.1 ($2CH_{Ar}$), 128.9 ($2CH_{Ar}$), 128.9 (CH_{Ar}), 126.9 ($2CH_{Ar}$), 126.0 ($2CH_{Ar}$), 107.4 – 107.0 (m, CH_{Ar}), signal of CF_2CF_3 could not be detected.

GC-MS (EI, 70 eV): *m/z* (%) = 338 (100), 319 (6), 269 (14), 219 (8), 77 (24).

HRMS (EI): calcd. for $C_{17}H_{11}F_5N_2$ ($[M]^+$): 388.08369, found: 388.08322.

3-(4-Methoxyphenyl)-5-(perfluoroethyl)-1-phenyl-1*H*-pyrazole 5.4l



Pale yellow solid, 91% (168 mg). M.p.: 82–83 °C.

IR (ATR, cm^{-1}): ν = 532 (s), 576 (m), 602 (m), 617 (m), 634 (m), 694 (s), 748 (s), 771 (s), 804 (s), 835 (s), 935 (s), 958 (s), 1026 (s), 1036 (s), 1092 (s), 1134 (s), 1176 (s), 1190 (s), 1215 (s), 1250 (s), 1292 (m), 1331 (m), 1443 (m), 1502 (m), 1552 (w), 1596 (m), 1614 (m), 2839 (w), 2943 (w), 3010 (w), 3139 (w).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 – 7.68 (m, 2H, CH_{Ar}), 7.57 – 7.44 (m, 5H, CH_{Ar}), 7.02 (s, 1H, CH_{Ar}), 7.00 – 6.92 (m, 2H, CH_{Ar}), 3.85 (s, 3H, CH_3).

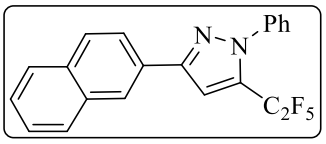
^{19}F NMR (282 MHz, $CDCl_3$) δ -83.39 (t, $^{3}J_{F\text{-}F}$ = 2.7 Hz), -106.26 (q, $^{3}J_{F\text{-}F}$ = 2.6 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ 160.2, 151.9, 139.9 (C_{Ar}), 131.9 (t, ^{2}J = 27.6 Hz, *C*-CF_3), 129.6 (CH_{Ar}), 129.0 ($2CH_{Ar}$), 127.3 ($2CH_{Ar}$), 126.9 ($2CH_{Ar}$), 124.5 (C_{Ar}), 114.3 (2 CH_{Ar}), 106.9 – 106.5 (m, CH_{Ar}), 55.5 (OCH_3), signal of CF_2CF_3 could not be detected.

GC-MS (EI, 70 eV): *m/z* (%) = 368 (100), 353 (20), 77 (14).

HRMS (EI): calcd. for $C_{18}H_{13}F_5N_2O$ ($[M]^+$): 368.09426, found: 368.09390.

3-(Naphthalen-2-yl)-5-(perfluoroethyl)-1-phenyl-1*H*-pyrazole 5.4m



Pale brown solid, 93% (181 mg). M.p.: 104–106 °C.

IR (ATR, cm^{-1}): ν = 544 (w), 575 (m), 617 (m), 628 (m), 642 (m), 685 (s), 748 (s), 771 (s), 804 (s), 860 (s), 887 (m), 941 (s), 980 (m), 1020 (s), 1043 (s), 1095 (s), 1134 (s), 1190 (s), 1329 (m), 1431 (m), 1487 (m), 1504 (m), 1594.92 (m), 3043 (w), 3058 (w).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (s, 1H, CH_{Ar}), 8.01 (dd, ^{3}J = 8.6, ^{4}J = 1.7 Hz, 1H, CH_{Ar}), 7.95 – 7.79 (m, 3H, CH_{Ar}), 7.64 – 7.41 (m, 7H, CH_{Ar}), 7.23 (d, ^{5}J = 0.7 Hz, 1H, CH_{Ar}).

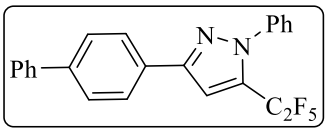
^{19}F NMR (282 MHz, $CDCl_3$) δ -83.31 (t, $^{3}J_{F\text{-}F}$ = 2.9 Hz), -106.28 (q, $^{3}J_{F\text{-}F}$ = 2.9 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1, 139.9 (C_{Ar}), 133.6 ($2C_{Ar}$), 132.2 (t, ^{2}J = 27.9 Hz, *C*-CF_3), 129.8 (CH_{Ar}), 129.1 ($2CH_{Ar}$), 128.7, 128.4, 127.9 (CH_{Ar}), 126.9 ($2CH_{Ar}$), 126.6, 126.5, 125.0, 123.9 (CH_{Ar}), 107.6 – 107.3 (m, $1CH_{Ar}$), signal of one C_{Ar} and CF_2CF_3 could not be detected.

GC-MS (EI, 70 eV): *m/z* (%) = 388 (100), 269 (7), 194 (6), 127 (16), 77 (18).

HRMS (EI): calcd. for $C_{21}H_{13}F_5N_2$ ($[M]^+$): 388.09934, found: 388.09878.

3-([1,1'-Biphenyl]-4-yl)-5-(perfluoroethyl)-1-phenyl-1*H*-pyrazole 5.4n



Pale yellow solid, 85% (178 mg). M.p.: 140–142 °C.

IR (ATR, cm^{-1}): ν = 694 (s), 727 (s), 746 (s), 765 (s), 819 (s), 846 (m), 937 (s), 958 (s), 1020 (m), 1041 (s), 1072 (m), 1093 (s), 1134 (s), 1186 (s), 1219 (s), 1278 (w), 1331 (m), 1409 (w), 1441 (m), 1502 (m), 1597 (m), 3061 (w), 3132 (w).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, ^{3}J = 8.0 Hz, 2H, CH_{Ar}), 7.73 – 7.51 (m, 4H, CH_{Ar}), 7.51 – 7.21 (m, 8H, CH_{Ar}), 7.04 (s, 1H, CH_{Ar}).

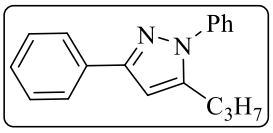
^{19}F NMR (282 MHz, $CDCl_3$) δ -83.33 (t, $^{3}J_{F\text{-}F}$ = 2.5 Hz), -106.24 (q, $^{3}J_{F\text{-}F}$ = 2.5 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ 151.7, 141.6, 140.7, 139.9 (C_{Ar}), 132.1 (t, ^{2}J = 27.4 Hz, *C*-CF_3), 130.7 (C_{Ar}), 129.7 (CH_{Ar}), 129.1 ($2CH_{Ar}$), 129.0 ($2CH_{Ar}$), 127.7 (CH_{Ar}), 127.6 ($2CH_{Ar}$), 127.2 ($2CH_{Ar}$), 126.9 ($2CH_{Ar}$), 126.4 ($2CH_{Ar}$), 125.4 – 110.9 (m, CF_2CF_3), 107.4 – 107.1 (m, $1CH_{Ar}$).

GC-MS (EI, 70 eV): *m/z* (%) = 414 (100), 395 (3), 345 (5), 295 (4), 207 (3), 152 (8), 116 (1), 77 (8).

HRMS (EI): calcd. for $C_{23}H_{15}F_5N_2$ ($[M]^+$): 414.11499, found: 414.11460.

5-(Perfluoropropyl)-1,3-diphenyl-1*H*-pyrazole 5.4o



White solid, 83% (161 mg). M.p.: 90–91 °C.

IR (ATR, cm^{-1}): ν = 532 (m), 590 (m), 648 (s), 692 (s), 746 (s), 765 (s), 777 (s), 814 (s), 874 (s), 957 (m), 1003 (m), 1026 (m), 1078 (m), 1109 (s), 1138 (s), 1182 (s), 1223 (s), 1344 (s), 1443 (m), 1500 (s), 1595 (w), 3053 (w), 3157 (w).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 – 7.82 (m, 2H, CH_{Ar}), 7.50 (s, 5H, CH_{Ar}), 7.48 – 7.32 (m, 3H, CH_{Ar}), 7.12 (s, 1H, CH_{Ar}).

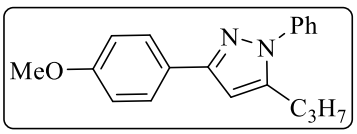
^{19}F NMR (282 MHz, $CDCl_3$) δ -80.04 (t, $^{3}J_{F\text{-}F}$ = 10.1 Hz), -103.84 – -104.15 (m), -124.86 – -125.05 (m).

^{13}C NMR (63 MHz, $CDCl_3$) δ 152.1, 139.9 (C_{Ar}), 132.3 (t, ^{2}J = 28.7 Hz, *C*-CF_3), 131.7 (C_{Ar}), 130.0 (CH_{Ar}), 129.3 ($2CH_{Ar}$), 129.2 ($2CH_{Ar}$), 129.1 (CH_{Ar}), 127.4 ($2CH_{Ar}$), 126.3 ($2CH_{Ar}$), 125.8 – 92.5 ($CF_2CF_2CF_3$), 108.0 – 107.6 (m, $1CH_{Ar}$).

GC-MS (EI, 70 eV): *m/z* (%) = 388 (100), 269 (39), 77 (18).

HRMS (EI): calcd. for $C_{18}H_{11}F_7N_2$ ($[M]^+$): 388.08050, found: 388.07991.

3-(4-Methoxyphenyl)-5-(perfluoropropyl)-1-phenyl-1*H*-pyrazole (4p):



Pale solid, 76% (160 mg). M.p.: 97–98 °C.

IR (ATR, cm^{-1}): ν = 644 (m), 692 (s), 744 (s), 773 (s), 800 (s), 872 (s), 904 (m), 958 (m), 1006 (s), 1030 (s), 1070 (m), 1078 (m), 1109 (s), 1138 (s), 1178 (s), 1184 (s), 1223 (s), 1251 (s), 1344 (m), 1435 (s), 1446 (s), 1502 (s), 1523 (m), 1552 (w), 1596 (w), 1614 (m), 2835 (w), 2939 (w), 2964 (w), 3001 (w), 3066 (w).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 – 7.79 (m, 1H, CH_{Ar}), 7.79 – 7.76 (m, 1H, CH_{Ar}), 7.49 (s, 5H, CH_{Ar}), 7.03 (s, 1H, CH_{Ar}), 7.01 – 6.96 (m, 1H, CH_{Ar}), 6.96 – 6.92 (m, 1H, CH_{Ar}), 3.85 (s, 3H, OCH_3).

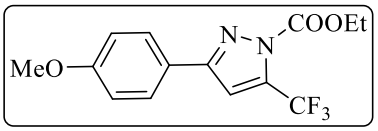
^{19}F NMR (282 MHz, $CDCl_3$) δ -80.05 (t, $^{3}J_{F\text{-}F}$ = 10.1 Hz), -103.83 – -104.18 (m), -124.90 – -125.02 (m).

^{13}C NMR (63 MHz, $CDCl_3$) δ 160.2, 151.9, 139.9 (C_{Ar}), 132.9 – 131.6 (m, 1C_{Ar}), 129.6 (CH_{Ar}), 128.9 (2CH_{Ar}), 127.3 (2CH_{Ar}), 127.1 (2CH_{Ar}), 124.5 (C_{Ar}), 114.3 (2CH_{Ar}), 107.2 – 106.9 (m, 1CH_{HetAr}), 55.5 (OCH_3). (signals of $CF_2CF_2CF_3$ could not be detected).

GC-MS (EI, 70 eV): *m/z* (%) = 418 (100), 375 (4), 299 (12), 77 (9).

HRMS (EI): calcd. for $C_{19}H_{13}F_7N_2O$ ($[M]^+$): 418.09106, found: 418.09036.

Ethyl 3-(4-methoxyphenyl)-5-(trifluoromethyl)-1*H*-pyrazole-1-carboxylate 5.4q



White solid, 57% (89 mg). M.p.: 73–74 °C.

IR (ATR, cm^{-1}): ν = 3519.0 (w), 3117.7 (w), 2966.8 (w), 2842.0 (w), 1766.3 (s), 1613.6 (m), 1587.0 (m), 1464.0 (m), 1441.8 (m), 1293.7 (s), 1143.8 (s), 1006.6 (m), 946.1 (m), 834.4 (s), 746.3 (m), 680.4 (m), 554.2 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 – 7.71 (m, 2H, CH_{Ar}), 7.10 (s, 1H, CH_{Ar}), 7.01 – 6.89 (m, 2H, CH_{Ar}), 4.57 (q, ^{3}J = 7.1 Hz, 2H, OCH_2CH_3), 3.85 (s, 3H, OCH_3), 1.49 (t, ^{3}J = 7.1 Hz, 3H, OCH_2CH_3).

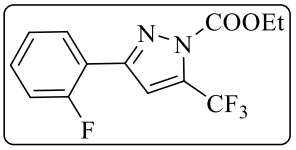
^{19}F NMR (282 MHz, $CDCl_3$) δ -60.03.

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1 (*C*-OCH_3), 153.5 (C_{Ar}), 148.3 (C=O), 135.8 (q, ^{2}J = 41.3 Hz, *C*-CF_3), 128.0 (2CH_{Ar}), 123.1 (C_{Ar}), 119.3 (q, ^{1}J = 269.1 Hz, CF_3), 114.4 (2CH_{Ar}), 110.8 (q, ^{3}J = 3.2 Hz, CH_{HetAr}), 65.5 (OCH_2CH_3), 55.5 (OCH_3), 14.1 (OCH_2CH_3).

GC-MS (EI, 70 eV): *m/z* (%) = 314 (47), 270 (12), 255 (17), 242 (100), 227 (58), 213 (17), 199 (36), 170 (12), 151 (22), 120 (5), 101 (5), 75 (6), 63 (5).

HRMS (+EI): calcd. for $C_{14}H_{13}O_3F_3N_2$ ($[M]^+$): 314.08728, found: 314.08732.

Ethyl 3-(2-fluorophenyl)-5-(trifluoromethyl)-1*H*-pyrazole-1-carboxylate (4r):



White solid, 57% (86 mg). M.p.: 84–85 °C.

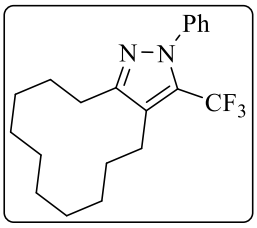
IR (ATR, cm^{-1}): ν = 3505.3 (w), 3171.4 (w), 3076.4 (w), 2996.6 (w), 2918.6 (w), 1761.2 (s), 1620.7 (w), 1591.2 (w), 1446.9 (s), 1304.1 (m), 1229.2 (m), 1141.8 (s), 1026.1 (m), 1032.2 (m), 949.0 (m), 840.6 (m), 747.9 (m), 676.2 (m), 552.1 (w).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (td, ^3J = 7.7, ^4J = 1.8 Hz, 1H, CH_{Ar}), 7.47 – 7.34 (m, 1H, CH_{Ar}), 7.30 (d, ^4J = 3.5 Hz, 1H, CH_{Ar}), 7.27 – 7.10 (m, 2H, CH_{Ar}), 4.59 (q, ^3J = 7.1 Hz, 2H, OCH_2CH_3), 1.50 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3).

^{19}F NMR (282 MHz, $CDCl_3$) δ -60.00, -115.67.

^{13}C NMR (63 MHz, $CDCl_3$) δ 160.8 (d, ^1J = 251.0 Hz, CF), 148.8 (C_{Ar}), 148.1 (C=O), 135.5 (q, ^2J = 42.0 Hz *C*-CF_3), 131.5 (d, ^3J = 8.6 Hz, CH_{Ar}), 129.2 (d, ^4J = 2.8 Hz, CH_{Ar}), 124.7 (d, ^3J = 3.5 Hz, CH_{Ar}), 119.3 (q, ^1J = 269.2 Hz, CF_3), 118.5 (d, ^2J = 11.5 Hz, C_{Ar}), 116.4 (d, ^2J = 21.9 Hz, CH_{Ar}), 114.5 – 113.4 (m, CH_{Ar}), 65.7 (OCH_2CH_3), 14.1 (OCH_2CH_3).

2-Phenyl-3-(trifluoromethyl)-4,5,6,7,8,9,10,11,12,13-decahydro-2*H*-cyclododeca[*c*]pyrazole 5.4s



White solid, 80% (140 mg). M.p.: 56–57 °C.

IR (ATR, cm^{-1}): ν = 546 (m), 692 (s), 771 (s), 993 (s), 1086 (s), 1111 (s), 1168 (s), 1242 (m), 1309 (m), 1329 (m), 1350 (m), 1452 (m), 1504 (s), 1556 (w), 1595 (m), 2856 (m), 2904 (m), 2933 (m).

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.44 (s, 5H, CH_{Ar}), 2.73 – 2.47 (m, 4H, CH_2), 1.90 – 1.62 (m, 4H, CH_2), 1.59 – 1.30 (m, 12H, CH_2).

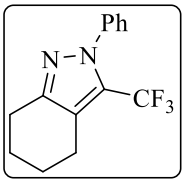
^{19}F NMR (282 MHz, $CDCl_3$) δ -55.61.

^{13}C NMR (63 MHz, $CDCl_3$) δ 153.2, 140.1 (C_{Ar}), 129.0 ($2CH_{Ar}$), 129.0 (q, ^2J = 37.2 Hz, *C*-CF_3), 128.9 (CH_{Ar}), 126.2 ($2CH_{Ar}$), 122.9 (q, ^3J = 3.2 Hz, C_{Ar}), 120.9 (q, ^1J = 269.4 Hz, CF_3), 28.9, 28.3, 26.0, 25.8, 25.4, 25.2 (CH_2), 23.0 ($2CH_2$), 22.9, 20.8(CH_2).

GC-MS (EI, 70 eV): *m/z* (%) = 350 (100), 331 (9), 307 (50), 293 (41), 281 (71), 267 (36), 253 (43), 240 (79), 77 (40).

HRMS (EI): calcd. for $C_{20}H_{25}F_3N_2$ ($[M]^+$): 350.19643, found: 350.19626.

2-Phenyl-3-(trifluoromethyl)-4,5,6,7-tetrahydro-2*H*-indazole 5.4t



Yellow oil, 82% (109 mg).

IR (ATR, cm^{-1}): ν = 546 (m), 681 (m), 692 (s), 744 (m), 766 (s), 914 (m), 964 (m), 993 (s), 1028 (m), 1074 (s), 1097 (s), 1116 (s), 1149 (s), 1170 (s), 1213 (m), 1296 (m), 1352 (m), 1377 (m), 1464 (m), 1504 (s), 1574 (w), 1598 (m), 2854 (w), 2939 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.37 (m, 5H, CH_{Ar}), 3.07 – 2.53 (m, 4H, CH_2), 2.13 – 1.61 (m, 4H, CH_2).

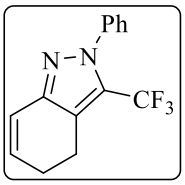
^{19}F NMR (282 MHz, $CDCl_3$) δ -55.92.

^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 139.8 (C_{Ar}), 129.0 ($2CH_{Ar}$), 128.9 (CH_{Ar}), 128.1 (q, ^{2}J = 38.2 Hz, *C*-CF_3), 125.9 ($2CH_{Ar}$), 120.9 (q, ^{1}J = 269.4 Hz, CF_3), 119.8 (q, ^{3}J = 1.7 Hz, C_{Ar}), 23.4, 22.8, 22.8 (CH_2), 20.9 (q, ^{4}J= 1.3 Hz, CH_2).

GC-MS (EI, 70 eV): *m/z* (%) = 266 (100), 247 (6), 238 (48), 217 (4), 197 (52), 77(39).

HRMS (EI): calcd. For $C_{14}H_{13}F_3N_2$ ($[M]^+$): 266.10253, found: 266.10212.

2-Phenyl-3-(trifluoromethyl)-4,5-dihydro-2*H*-indazole 5.4u



Brown oil, 66% (87 mg).

IR (ATR, cm^{-1}): ν = 536 (m), 596 (m), 661 (m), 690 (s), 765 (s), 993 (s), 1095 (s), 1117 (s), 1163 (s), 1207 (m), 1304 (m), 1325 (m), 1377 (m), 1462 (m), 1502 (s), 1577 (w), 1597 (m), 1705 (w), 2837 (w), 2898 (w), 2937 (w), 3060 (w).

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.53 – 7.32 (m, 5H, CH_{Ar}), 6.60 (dt, ^{3}J = 9.9, ^{4}J = 2.0 Hz, 1H, CH=CH), 6.14 (dt, ^{3}J = 9.9, ^{3}J = 4.3 Hz, 1H, CH=CH), 3.08 – 2.78 (m, 2H, CH_2), 2.55 – 2.36 (m, 2H, CH_2).

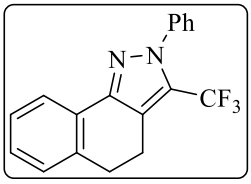
^{19}F NMR (282 MHz, $CDCl_3$) δ -56.16.

^{13}C NMR (63 MHz, $CDCl_3$) δ 148.6, 139.7 (C_{Ar}), 131.5 (CH=CH), 129.1 ($2CH_{Ar}$), 128.9 (CH_{Ar}), 127.7 (q, ^{2}J = 38.4 Hz, *C*-CF_3), 125.9 (2C, CH_{Ar}), 120.8 (q, ^{1}J = 269.6 Hz, CF_3), 119.7 (CH_{Ar}). 118.7 (q, ^{3}J = 1.8 Hz, C_{Ar}), 23.4 (CH_2), 18.5 (q, ^{4}J = 1.3 Hz, CH_2).

GC-MS (EI, 70 eV): *m/z* (%) = 314 (100), 245 (33), 218 (10), 77 (27), 51 (12).

HRMS (EI): calcd. for $C_{14}H_{11}F_3N_2$ ($[M]^+$): 264.08688, found: 264.08643.

2-Phenyl-3-(trifluoromethyl)-4,5-dihydro-2*H*-benzo[g]indazole 5.4v



Brown solid, 82% (130 mg). M.p.: 78–79 °C.

IR (ATR, cm^{-1}): ν = 549 (m), 648 (m), 696 (s), 731 (s), 781 (s), 897 (m), 945 (m), 987 (s), 1026 (m), 1047 (s), 1103 (s), 1157 (s), 1174 (s), 1226 (s), 1267 (m), 1307 (m), 1331 (m), 1352 (m), 1377 (m), 1446 (s), 1500 (s), 1595 (m), 2848 (w), 2901 (w), 2964 (w).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 – 7.75 (m, 1H, CH_{Ar}), 7.67 – 7.35 (m, 5H, CH_{Ar}), 7.36 – 7.26 (m, 3H, CH_{Ar}), 3.16 – 2.77 (m, 4H, CH_2).

^{19}F NMR (282 MHz, $CDCl_3$) δ -56.04.

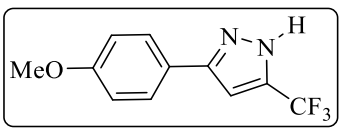
^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9, 139.8, 136.5 (C_{Ar}), 129.2 (CH_{Ar}), 129.2 ($2CH_{Ar}$), 128.6 (C_{Ar}), 128.5, 128.5 (CH_{Ar}), 128.3 (q, ^{2}J = 38.3 Hz, *C*-CF_3), 127.2 (CH_{Ar}), 126.2 ($2CH_{Ar}$), 122.8 (CH_{Ar}), 120.7 (q, ^{1}J = 269.6 Hz, CF_3), 120.1 (q, ^{3}J = 1.8 Hz, C_{Ar}), 28.9 (CH_2), 19.4 (q, ^{4}J = 1.3 Hz, CH_2).

GC-MS (EI, 70 eV): *m/z* (%) = 314 (100), 245 (33), 218 (10), 142 (13), 115 (10), 77 (27).

HRMS (EI): calcd. For $C_{18}H_{13}F_3N_2$ ($[M]^+$): 314.10253, found: 314.10234.

5-(4-Methoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazole 5.5a

Compound **5.5a** was synthesized following the general procedure using 4-methoxyacetophenone, ethyl carbamate for the first step and ethyl trifluoroacetate for the next step. After adding ethyl trifluoroacetate, the reaction temperature was allowed to rise to 20 °C and stirred for 30 min. Then the solvent was removed under reduced pressure. After that, the residue was dissolved in toluene and 2 mmol (4 eq) of PTSA was added. The reaction mixture was stirred under reflux for 8 h. After cooling, a saturated aqueous solution of $NaHCO_3$ was added until no evolution of CO_2 was observed. Then THF was removed and the remained water was extracted with ethyl acetate (10 mLx3). Combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by chromatography (silica gel, heptane/DCM). The product was isolated as a white solid (51%, 62 mge).



M.p.: 147–148 °C.

IR (ATR, cm^{-1}): ν = 3225.7 (w), 2974.4 (w), 2845.7 (w), 1614.5 (m), 1574.2 (m), 1516.7 (m), 1490.1 (m), 1458.8 (s), 1440.5 (m), 1274.9 (s), 1243.7 (s), 1109.9 (s), 1056.2 (s), 980.9 (m), 836.3 (s), 795.3 (s), 742.4 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.24 (s, br, 1H), 7.95 – 7.31 (m, 2H, CH_{Ar}), 7.11 – 6.77 (m, 2H, CH_{Ar}), 6.66 – 6.62 (m, 1H, CH_{Ar}), 3.85 (s, 3H, OCH_3).

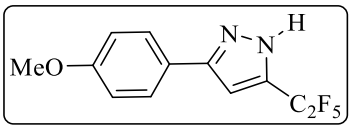
^{19}F NMR (282 MHz, $CDCl_3$) δ -62.17 (s).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 145.2(C_{Ar}), 143.7 (q, ^{2}J = 38.1 Hz, *C*-CF_3), 127.3 (2CH_{Ar}), 121.3 (q, ^{1}J = 268.6 Hz, CF_3), 120.7 (C_{Ar}), 114.8 (2CH_{Ar}), 100.5 (q, ^{3}J = 1.8 Hz, CH_{HetAr}), 55.5 (OCH_3).

GC-MS (EI, 70 eV): *m/z* (%) = 242 (100), 227 (41), 223 (10), 199 (41), 169 (3), 151 (24).

HRMS (+EI): calcd. for $C_{11}H_9O_1F_3N_2$ ($[M]^+$): 242.06615, found: 242.0660.

5-(4-Methoxyphenyl)-3-(perfluoroethyl)-1*H*-pyrazole 5.5b



Compound **5.5b** was synthesized following the procedure for compound **5.5a** using 4-methoxyacetophenone for the first step and ethyl pentafluoropropionate for the next step. The product was isolated as pale yellow solid (56%, 82 mg). M.p.: 137–138 °C.

IR (ATR, cm^{-1}): ν = 3185.5 (w), 3142.1 (w), 3033.4 (w), 1619.0 (m), 1513.2 (s), 1330.6 (m), 1258.5 (s), 1185.6 (s), 1029.1 (s), 933.0 (s), 830.5 (m), 747.8 (m), 614.4 (m).

^{1}H NMR (300 MHz, MeOD) δ 7.90 – 7.49 (m, 2H, CH_{Ar}), 7.16 – 6.94 (m, 2H, CH_{Ar}), 6.86 (s, 1H, CH_{Ar}), 3.86 (s, 3H, OCH_3).

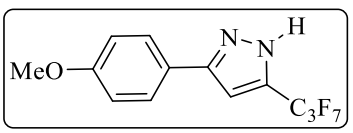
^{19}F NMR (282 MHz, MeOD) δ -86.12, -114.10.

^{13}C NMR (63 MHz, MeOD) δ 161.9 (*C*-OCH_3), 128.3 (2CH_{Ar}), 115.6 (2CH_{Ar}), 102.2 (CH_{HetAr}), 55.8 (OCH_3), (signals of 3C_{Ar} and CF_2CF_3 could not be detected).

GC-MS (EI, 70 eV): *m/z* (%) = 292 (199), 277 (30), 249 (39), 223 (12), 151 (20), 111 (6).

HRMS (EI): calcd. for $C_{12}H_9O_1N_2F_5$ ($[M]^+$): 292.06296, found: 292.06263.

5-(4-Methoxyphenyl)-3-(perfluoropropyl)-1*H*-pyrazole 5.5c



Compound **5.5c** was synthesized following the procedure for compound **5.5a** using 4-methoxyacetophenone for the first step and ethyl heptafluorobutyrate for the next step. The product was isolated as pale yellow solid (57%, 98 mg). M.p.: 127–128 °C.

IR (ATR, cm^{-1}): ν = 3144.1 (w), 3031.2 (w), 2947.1 (w), 1890.6 (w), 1617.6 (m), 1512.5 (s), 1427.8 (m), 1348.6 (m), 1311.7 (m), 1255.9 (m), 1229.3 (s), 1178.2 (s), 1106.6 (s), 1029.6 (m), 1000.1 (m), 874.2 (s), 829.8 (m), 746.3 (s), 652.1 (m), 620.4 (m).

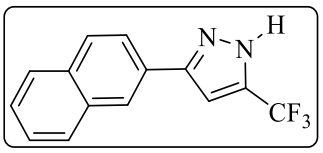
^{1}H NMR (300 MHz, MeOD) δ 7.78 – 7.47 (m, 2H, CH_{Ar}), 7.22 – 6.91 (m, 2H, CH_{Ar}), 6.85 (s, 1H, CH_{Ar}), 3.85 (s, 3H).

^{19}F NMR (282 MHz, MeOD) δ -81.15 – -82.64 (m), -111.79 (d, ^{3}J = 9.5 Hz), -127.00 – -130.06 (m).

^{13}C NMR (63 MHz, MeOD) δ 161.9 (*C*-OCH_3), 146.4, 143.0 (C_{Ar}), 128.3 ($2CH_{Ar}$), 122.2 (C_{Ar}), 115.6 ($2CH_{Ar}$), 102.4 (CH_{HetAr}), 55.8 (OCH_3) (signals of $CF_2CF_2CF_3$ could not be detected).

GC-MS (EI, 70 eV): *m/z* (%) = 342 (100), 327 (18), 299 (25), 223 (29), 208 (4), 180 (5), 151 (15), 111 (6). HRMS (EI): calcd. for $C_{13}H_9O_1N_2F_7$ ($[M]^+$): 342.05976, found: 342.05959.

5-(Naphthalen-2-yl)-3-(trifluoromethyl)-1*H*-pyrazole 5.5d



Compound **5.5d** was synthesized following the procedure for compound **5.5a** using 2-acetonaphthone for the first step and ethyl trifluoroacetate for the next step. The product was isolated as white solid (78%,102 mg). M.p.: 180–181 °C.

IR (ATR, cm^{-1}): ν = 3227.5 (w), 3043.6 (w), 2923.5 (w), 1631.9 (w), 1608.5 (w), 1582.5 (w), 1567.3 (w), 1500.0 (m), 1474.0 (w), 1255.6 (m), 1150.1 (s), 1120.6 (s), 1103.6 (s), 992.0 (m), 860.5 (m), 803.6 (s), 741.1 (s), 713.1 (m), 679.4 (m), 601.7 (m).

^{1}H NMR (300 MHz, MeOD) δ 8.26 (s, 1H, CH_{Ar}), 8.11 – 7.72 (m, 4H, CH_{Ar}), 7.56 (dd, ^{3}J = 6.3 Hz, ^{4}J = 3.0 Hz, 2H, CH_{Ar}), 7.10 (s, 1H, CH_{Ar}).

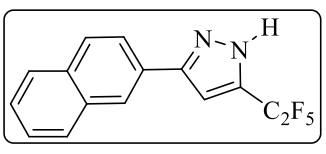
^{19}F NMR (282 MHz, MeOD) δ -63.58.

^{13}C NMR (75 MHz, Acetone) δ 145.5 (C_{Ar}), 144.3 (q, ^{2}J = 37.5 Hz, *C*-CF_3), 134.4, 134.4 (C_{Ar}), 129.9, 129.1, 128.7, 127.8, 127.7 (CH_{Ar}), 126.7 (C_{Ar}), 125.6, 124.3 (CH_{Ar}), 122.9 (q, ^{1}J = 267.5 Hz, CF_3), 102.1 (CH_{Ar}).

GC-MS (EI, 70 eV): *m/z* (%) = 262 (100), 243 (7), 214 (10), 183 (6), 165 (22), 152 (1), 139 (4), 127 (7), 69 (3).

HRMS (+ESI): calcd. for $C_{14}H_{10}F_3N_2$ ($[M+H]^+$): 263.07906, found: 263.07925.

5-(Naphthalen-2-yl)-3-(perfluoroethyl)-1*H*-pyrazole 5.5e



Compound **5.5e** was synthesized following the procedure for compound **5.5a** using 2-acetonaphthone for the first step and ethyl pentafluoropropionate for the next step. The product was isolated as pale yellow solid (86%, 134 mg). M.p.: 124–126 °C.

IR (ATR, cm^{-1}): ν = 3147.0 (w), 3114.4 (w), 2933.1 (w), 1955.6 (w), 1906.3 (w), 1785.8 (w), 1679.0 (w), 1583.7 (w), 1566.5 (w), 1513.6 (w), 1431.1 (w), 1332.5 (s), 1214.1 (s), 1183.3 (s), 1131.7 (s), 1069.4 (m), 1028.9 (s), 940.5 (s), 801.5 (m), 745.4 (s), 619.4 (m).

^{1}H NMR (300 MHz, MeOD) δ 8.21 (d, ^{4}J = 4.6 Hz, 1H, CH_{Ar}), 8.08 – 7.70 (m, 4H, CH_{Ar}), 7.62 – 7.42 (m, 2H, CH_{Ar}), 7.07 (s, 1H, CH_{Ar}).

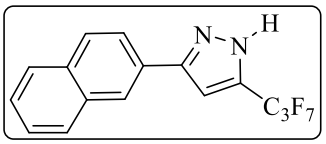
^{19}F NMR (282 MHz, MeOD) δ -86.02, -114.00.

^{13}C NMR (63 MHz, MeOD) δ 146.4, 134.8 (C_{Ar}), 130.1, 129.3, 128.8 (CH_{Ar}), 127.9 ($2CH_{Ar}$), 126.9 (C_{Ar}), 125.8, 124.4, 103.3 (CH_{Ar}), (signals of $2C_{Ar}$ and CF_2CF_3 could not be detected).

GC-MS (EI, 70 eV): *m/z* (%) = 312 (100), 293 (5), 243 (18), 214 (13), 194 (4), 165 (17), 121 (11), 82 (3), 69 (2).

HRMS (+ESI): calcd. for $C_{15}H_{10}F_5N_2$ ($[M+H]^+$): 313.07587, found: 313.07617.

3-(Perfluoropropyl)-5-(naphthalen-2-yl)-1*H*-pyrazole 5.5f



Compound **5.5f** was synthesized following the procedure for compound **5.5a** using 2-acetonaphthone for the first step and ethyl heptafluorobutyrate for the next step. The product was isolated as pale yellow solid (64%, 116 mg). M.p.: 181–182 °C.

IR (ATR, cm^{-1}): ν = 3183.6 (w), 3067.3 (w), 2877.8 (w), 1565.2 (w), 1512.8 (w), 1415.8 (w), 1349.1 (m), 1224.1 (m), 1176.5 (s), 1103.7 (m), 1000.7 (m), 874.8 (m), 791.3 (m), 744.3 (m), 651.2 (m).

^{1}H NMR (300 MHz, MeOD) δ 8.26 (s, 1H, CH_{Ar}), 8.12 – 7.72 (m, 4H, CH_{Ar}), 7.68 – 7.44 (m, 2H, CH_{Ar}), 7.11 (s, 1H, CH_{Ar}).

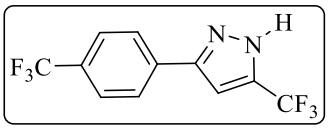
^{19}F NMR (282 MHz, MeOD) δ -81.78 (t, $^{3}J_{F\text{-}F}$ = 9.5 Hz), -111.71 (d, $^{3}J_{F\text{-}F}$ = 8.6 Hz), -128.28 (s).

^{13}C NMR (75 MHz, Acetone) δ 145.7, 134.4, 134.4 (C_{Ar}), 129.9, 129.2, 128.7, 127.8, 127.8, 125.7, 124.3, 103.6 (CH_{Ar}), (signals of $2C_{Ar}$ and $CF_2CF_2CF_3$ could not be detected).

GC-MS (EI, 70 eV): *m/z* (%) = 362 (100), 343 (9), 243 (34), 214 (17), 194 (4), 165 (14), 122 (13), 83 (4), 69 (4).

HRMS (+ESI): calcd. for $C_{16}H_{10}F_7N_2$ ($[M+H]^+$): 363.007267, found: 363.07305.

3-(Trifluoromethyl)-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole 5.5g



Compound **5.5g** was synthesized following the procedure for compound **5.5a** using 4-trifluoromethylacetophenone for the first step and ethyl trifluoroacetate for the next step. The product was isolated as white solid (75%, 105 mg). M.p.: 135–136 °C.

IR (ATR, cm^{-1}): ν = 3239.9 (w), 3161.7 (w), 3066.3 (w), 2987.4 (w), 1914.8 (w), 1790.5 (w), 1738.4 (w), 1671.9 (w), 1622.3 (w), 1587.6 (w), 1494.7 (w), 1325.4 (m), 1253.0 (m), 1172.6 (m), 1109.0 (s), 1068.0 (m), 982.9 (m), 916.7 (m), 813.6 (m), 747.3 (m), 661.5 (m), 592.3 (m).

^{1}H NMR (300 MHz, MeOD) δ 7.95 (d, ^{3}J = 8.2 Hz, 2H, CH_{Ar}), 7.80 (d, ^{3}J = 8.3 Hz, 2H, CH_{Ar}), 7.12 (s, 1H, CH_{Ar}).

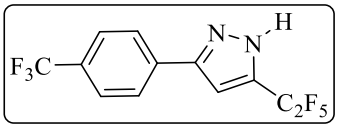
^{19}F NMR (282 MHz, MeOD) δ -63.66, -64.34.

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2 (C_{Ar}), 143.5 (q, ^{2}J = 38.0 Hz, C_{Ar}), 131.5 (q, ^{2}J = 33.0 Hz, *C*-CF_3), 131.2 (C_{Ar}), 126.4 (q, ^{4}J = 3.8 Hz, $2CH_{Ar}$), 125.8 ($2CH_{Ar}$), 123.7 (q, ^{1}J = 272.3 Hz, CF_3), 120.7 (q, ^{1}J = 269.0 Hz, CF_3), 102.1 (CH_{HetAr}).

GC-MS (EI, 70 eV): *m/z* (%) = 280 (100), 261 (23), 231 (7), 211 (20), 201 (5), 182 (15), 164 (4), 145 (8), 133 (49, 87 (2), 69 (6).

HRMS (+ESI): calcd. for $C_{11}H_7F_6N_2$ ($[M+H]^+$): 281.05579, found: 281.05099.

5-(Perfluoroethyl)-3-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole 5.5h



Compound **5.5h** was synthesized following the procedure for compound **5.5a** using 4-trifluoromethylacetophenone for the first step and ethyl pentafluoropropionatefor the next step. The product was isolated as white solid (74%, 122 mg). M.p.: 142–143 °C.

IR (ATR, cm^{-1}): ν = 3191.2 (w), 3032.7 (w), 2887.0 (w), 1623.7 (w), 1590.6 (w), 1465.6 (w), 1429.3 (w), 1325.2 (s), 1225.8 (s), 1194.1 (s), 1125.4 (s), 1063.8 (m), 1030.5 (m), 973,8 (m), 939.2 (m), 841.6 (m), 807.8 (m), 750.1 (m), 693.5 (m), 622.0 (w), 591.5 (w).

^{1}H NMR (300 MHz, MeOD) δ 7.96 (d, ^{3}J = 8.2 Hz, 2H, CH_{Ar}), 7.80 (d, ^{3}J = 8.3 Hz, 2H, CH_{Ar}), 7.14 (s, 1H, CH_{Ar}).

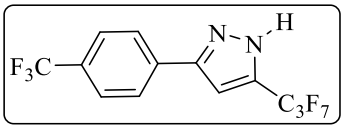
^{19}F NMR (282 MHz, MeOD) δ -64.34, -86.12, -114.07.

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6 (C_{Ar}), 131.7 (q, ^{2}J = 32.9 Hz, *C*-CF_3), 129.2 (C_{Ar}), 126.4 (q, ^{4}J = 3.8 Hz, $2CH_{Ar}$), 125.9 ($2CH_{Ar}$), 123.8 (q, ^{1}J = 272.2 Hz, CF_3), 103.9 (CH_{HetAr}), (signals of $1C_{Ar}$ and CF_2CF_3 could not be detected).

GC-MS (EI, 70 eV): *m/z* (%) = 330 (81), 311 (21), 261 (100), 232 (4), 213 (9), 182 (6), 164 (18), 145 (5), 121 (5), 105 (5), 69 (6).

HRMS (+ESI): calcd. for $C_{12}H_7F_8N_2$ ($[M+H]^+$): 331.04760, found: 331.04806.

5-(Perfluoropropyl)-3-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole 5.5i



Compound **5.5i** was synthesized following the procedure for compound **5.5a** using 4-trifluoromethylacetophenone for the first step and ethyl heptafluorobutyrate for the next step. The product was isolated as white solid (67%, 127 mg). M.p. 109–110 °C.

IR (ATR, cm^{-1}): ν = 3171.2 (w), 3034.4 (w), 2950.7 (w), 2887.4 (w), 1623.5 (w), 1591.8 (w), 1467.1 (w), 1424.8 (w), 1326.4 (s), 1276.0 (w), 1232.3 (s), 1171.5 (m), 1109.2 (s), 1063.0 (s), 1001.4 (m), 876.1 (m), 842.4 (m), 810.1 (m), 747.9 (m), 652.6 (m), 592.2 (m).

^{1}H NMR (300 MHz, MeOD) δ 7.96 (d, ^3J = 8.2 Hz, 2H, CH_{Ar}), 7.80 (d, ^3J = 8.3 Hz, 2H, CH_{Ar}), 7.14 (s, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, MeOD) δ -64.35 (s), -81.84 (t, ^3J = 9.6 Hz), -111.76 (s), -128.29 – -128.38 (m).

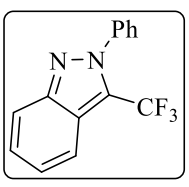
(Due to there are many Fs in the molecule, the signals of carbons are splited and very difficult to identify.)

GC-MS (EI, 70 eV): *m/z* (%) = 380 (64), 361 (23), 261 (100), 213 (8), 182 (5), 164 (17), 69 (6).

HRMS (+ESI): calcd. for $C_{13}H_7F_{10}N_2$ ($[M+H]^+$): 381.04441, found: 381.04428.

Synthesis of 2-phenyl-3-(trifluoromethyl)-2*H*-indazole 5.6a

To a solution of **5.4s** (100 mg) in toluene (7 mL), DDQ (2 equiv.) was added. The reaction mixture was stirred under reflux for 3h. Then the reaction mixture was cooled to room temperature and ethyl acetate (10 mL) and water (10 mL) were added. The organic layer was separated and washed with water three times. After drying and removal of solvent, the residue was purified by chromatography (silica gel, *n*-heptane/DCM). The product was isolated as a yellow oil (71%, 71 mg).



IR (ATR, cm^{-1}): ν = 534 (m), 567 (m), 627 (m), 640 (m), 692 (s), 743 (s), 768 (s), 829 (m), 914 (m), 933 (m), 989 (s), 1001 (s), 1030 (m), 1074 (s), 1103 (s), 1147 (s), 1174 (s), 1223 (s), 1298 (s), 1381 (w), 1429 (s), 1469 (m), 1500 (s), 1522 (m), 1551 (w), 1597 (m), 2361 (w), 2858 (w), 2929 (w), 3066 (w).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 – 7.76 (m, 2H, CH_{Ar}), 7.64 – 7.49 (m, 5H, CH_{Ar}), 7.49 – 7.37 (m, 1H, CH_{Ar}), 7.37 – 7.27 (m, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$) δ -54.47.

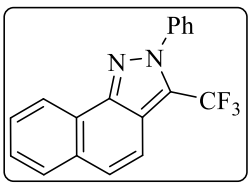
^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 139.7 (C_{Ar}), 130.1 (CH_{Ar}), 129.2 ($2CH_{Ar}$), 127.4 (CH_{Ar}), 126.3 ($2CH_{Ar}$), 125.2 (CH_{Ar}), 123.8 (q, ^{2}J = 39.5 Hz, *C*-CF_3), 121.7 (C_{Ar}), 121.1 (q, ^{1}J = 269.0 Hz, CF_3), 119.5 (q, ^{4}J = 1.7 Hz, CH_{Ar}), 118.6 (CH_{Ar}).

GC-MS (EI, 70 eV): *m/z* (%) = 262 (100), 236 (7), 193 (34), 166 (11), 77 (15), 51 (12).

HRMS (EI): calcd. for $C_{14}H_9F_3N_2$ ($[M]^+$): 262.07123, found: 262.07106.

Synthesis of 2-phenyl-3-(trifluoromethyl)-2H-benzo[g]indazole 5.6b

To a solution of **5.4t** (100 mg) in toluene (7 mL), DDQ (2 equiv.) was added. The reaction mixture was stirred under reflux for 3h. Then the reaction mixture was cooled to room temperature and ethyl acetate (10 mL) and water (10 mL) were added. The organic layer was separated and washed with water three times. After drying and removal of solvent, the residue was purified by chromatography (silica gel, *n*-heptane/DCM). The product was isolated as a pale yellow solid (90%, 90 mg). M.p.: 100–102 °C.



IR (ATR, cm^{-1}): ν = 549 (s), 681 (s), 746 (s), 767 (s), 804 (s), 885 (m), 982 (s), 1045 (s), 1099 (s), 1176 (s), 1217 (s), 1238 (m), 1269 (m), 1309 (m), 1385 (w), 1441 (s), 1473 (m), 1504 (s), 1558 (w), 1597 (m), 3024 (w), 3049 (w).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (dd, ^{3}J = 5.7, ^{4}J = 3.5 Hz, 1H), 7.93 – 7.80 (m, 1H), 7.76 – 7.52 (m, 9H).

^{19}F NMR (282 MHz, $CDCl_3$) δ -54.74 (s).

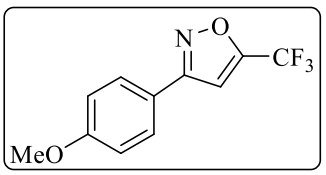
^{13}C NMR (63 MHz, $CDCl_3$) δ 146.1, 139.7, 132.3 (C_{Ar}), 129.8 (CH_{Ar}), 129.1 ($2CH_{Ar}$), 128.5, 127.7, 127.5, 127.3, 126.4, 126.3 (CH_{Ar}), 125.0 (C_{Ar}), 124.7 (q, ^{2}J = 39.8 Hz, *C*-CF_3), 122.5 (CH_{Ar}), 120.9 (q, ^{1}J = 269.2 Hz, CF_3), 119.3 (C_{Ar}), 116.9 (q, ^{4}J = 1.9 Hz, CH_{Ar}).

GC-MS (EI, 70 eV): *m/z* (%) = 312 (100), 242 (30), 77 (10).

HRMS (EI): calcd. for $C_{18}H_{11}F_3N_2$($[M]^+$): 312.08688, found: 312.08667.

3-(4-methoxyphenyl)-5-(trifluoromethyl)isoxazole 5.8a

Compound **5.8a** was synthesized following the general procedure using 4-methoxyacetophenone, hydroxylamine for the first step and ethyl trifluoroacetate for the next step. The product was isolated as a white solid (57%, 69 mg). M.p. 76-78 °C.



IR (ATR, cm^{-1}): ν = 3114.5 (w), 2963.7 (w), 2844.2 (w), 1611.5 (m), 1532.2 (w), 1459.8 (m), 1432.7 (m), 1319.7 (m), 1242.4 (m), 1174.7 (m), 1114.0 (s), 1023.3 (m), 966.8 (m), 915.7 (m), 837.2 (m), 821.7 (m), 747.2 (m), 680.0 (w).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 – 7.68 (m, 2H, CH_{Ar}), 7.04 – 6.96 (m, 2H, CH_{Ar}), 6.94 (d, ^{5}J = 0.9 Hz, 1H, CH_{Ar}), 3.87 (s, 3H, OCH_3).

^{19}F NMR (282 MHz, $CDCl_3$) δ -64.24.

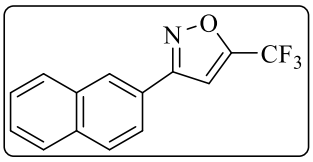
^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 161.8 (C_{Ar}), 159.1 (q, ^{2}J = 42.4 Hz, *C*-CF_3), 128.6 ($2CH_{Ar}$), 119.9 (C_{Ar}), 118.1 (q, ^{1}J = 270.3 Hz, CF_3), 114.7 ($2CH_{Ar}$), 103.3 (d, ^{3}J = 2.1 Hz, CH_{HetAr}), 55.5 (OCH_3).

GC-MS (EI, 70 eV): *m/z* (%) = 243 (82), 174 (82), 146 (100), 131 (14), 119 (7), 103 (9), 92 (11), 76 (18), 63 (15), 50 (9).

HRMS (+EI): calcd. for $C_{11}H_8O_2F_3N_1$ ($[M]^+$): 243.05016, found: 243.05028.

3-(naphthalen-2-yl)-5-(trifluoromethyl)isoxazole 5.8b

Compound **5.8b** was synthesized following the general procedure using 2-acetonaphthone, hydroxylamine for the first step and ethyl trifluoroacetate for the next step. The product was isolated as a white (62%, 82 mg). M.p. 103–104 °C.



IR (ATR, cm^{-1}): ν = 3232.3 (w), 3126.3 (w), 2921.0 (w), 1631.3 (w), 1486.7 (m), 1438.6 (m), 1303.8 (m), 1143.6 (s), 1104.9 (s), 1057.6 (m), 964.1 (m), 901.5 (m), 827.7 (s), 745.5 (m), 633.1 (w).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, ^{4}J = 0.7 Hz, 1H, CH_{Ar}), 8.00 – 7.84 (m, 4H, CH_{Ar}), 7.64 – 7.48 (m, 2H, CH_{Ar}), 7.14 (d, ^{4}J = 0.9 Hz, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$) δ -64.15.

^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8 (C_{Ar}), 159.4 (q, ^{2}J = 42.7 Hz, *C*-CF_3), 134.5, 133.2 (C_{Ar}), 129.3, 128.7, 128.1, 127.7, 127.3, 127.2 (CH_{Ar}), 124.8 (C_{Ar}), 123.7 (CH_{Ar}), 118.1 (d, ^{1}J = 270.5 Hz, CF_3), 103.7 (d, ^{3}J = 2.1 Hz, CH_{HetAr}).

GC-MS (EI, 70 eV): *m/z* (%) = 263 (100), 194 (72), 166 (41), 139 (21), 127 (68), 115 (12), 97 (8), 69 (10).

HRMS (+ESI): calcd. for $C_{14}H_9O_1F_3N_1$ ($[M+H]^+$): 264.06307, found: 264.06321.

Crystal data and structure refinement

Crystal data and structure refinement for compound 2.6h

	is_cm11
Crystal data	
Chemical formula	$C_{24}H_{16}FNO_2$
M_r	369.38
Crystal system, space group	Monoclinic, $P2_1/c$
Temperature (K)	173
a, b, c (Å)	7.7148 (5), 20.3158 (13), 11.7110 (8)
β (°)	91.418 (4)
V (Å^3)	1834.9 (2)
Z	4
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.09
Crystal size (mm)	0.46 × 0.12 × 0.10
Data collection	
Diffractometer	Bruker Apex Kappa II-CCD-diffractometer
Absorption correction	Multi-scan (*SADABS*; Sheldrick, 2004)
T_{min}, T_{max}	0.959, 0.991
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	25493, 4882, 2572
R_{int}	0.071
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.682
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.049, 0.126, 1.00
No. of reflections	4882
No. of parameters	253
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.20, −0.21

Crystal data and structure refinement for compound 3.3i

	is_indolo_d2
Crystal data	
Chemical formula	$C_{21}H_{14}FN$
M_r	299.33
Crystal system, space group	Monoclinic, $P2_1/c$
Temperature (K)	173
a, b, c (Å)	10.5670 (7), 20.0282 (12), 6.8420 (5)
β (°)	95.652 (2)
V (Å^3)	1440.99 (17)
Z	4
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.09
Crystal size (mm)	0.33 × 0.27 × 0.22
Data collection	
Diffractometer	Bruker Apex Kappa II-CCD-diffractometer
Absorption correction	Multi-scan (*SADABS*; Sheldrick, 2004)
T_{min}, T_{max}	0.671, 0.746
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	19527, 3832, 2993
R_{int}	0.038
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.682
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.052, 0.129, 1.10
No. of reflections	3832
No. of parameters	279
No. of restraints	68
H-atom treatment	H-atom parameters constrained

$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.21, −0.20

Crystal data and structure refinement for compound 3.7j

	is_es4
Crystal data	
Chemical formula	$C_{20}H_{14}N_2O$
M_r	298.33
Crystal system, space group	Triclinic, *P*
Temperature (K)	173
a, *b*, *c* (Å)	12.2153 (2), 13.5599 (2), 18.6521 (3)
α, β, γ (°)	95.666 (1), 104.369 (1), 107.679 (1)
V (Å^3)	2800.32 (8)
Z	8
Radiation type	Mo *K*α
μ (mm^{-1})	0.09
Crystal size (mm)	0.55 × 0.28 × 0.19
Data collection	
Diffractometer	Bruker-Nonius Apex X8-CCD-diffractometer
Absorption correction	Multi-scan (*SADABS*; Sheldrick, 2004)
T_{min}, T_{max}	0.707, 0.746
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	93666, 18586, 13060
R_{int}	0.033
(sin θ/λ)$_{max}$ (Å^{-1})	0.735
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.050, 0.147, 1.01
No. of reflections	18586
No. of parameters	833
H-atom treatment	H-atom parameters constrained

$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.47, −0.28

Crystal data and structure refinement for compound 4.3a

	is_tn_hb
Crystal data	
Chemical formula	$C_{22}H_{14}S$
M_r	310.39
Crystal system, space group	Triclinic, *P*
Temperature (K)	123
a, *b*, *c* (Å)	6.0433 (2), 10.7998 (3), 12.1236 (3)
α, β, γ (°)	108.612 (1), 92.292 (1), 95.272 (1)
V (Å^3)	744.69 (4)
Z	2
Radiation type	Mo *K*α
μ (mm^{-1})	0.21
Crystal size (mm)	0.29 × 0.20 × 0.14
Data collection	
Diffractometer	Bruker-Nonius Apex X8-CCD-diffractometer
Absorption correction	Multi-scan (*SADABS*; Sheldrick, 2004)
T_{min}, T_{max}	0.722, 0.746
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	16019, 4325, 3897
R_{int}	0.021
(sin θ/λ)$_{max}$ (Å^{-1})	0.703
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.035, 0.096, 1.06
No. of reflections	4325
No. of parameters	208
H-atom treatment	H-atom parameters constrained

$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.45, −0.26

Crystal data and structure refinement for compound 4.3b

	is_thang1203
Crystal data	
Chemical formula	$C_{23}H_{16}S$
M_r	324.42
Crystal system, space group	Triclinic, *P*
Temperature (K)	123
a, *b*, *c* (Å)	5.9864 (2), 11.0375 (4), 13.4379 (5)
α, β, γ (°)	112.071 (2), 96.127 (2), 92.844 (2)
V (Å^3)	814.25 (5)
Z	2
Radiation type	Mo *K*α
μ (mm^{-1})	0.20
Crystal size (mm)	0.19 × 0.15 × 0.10
Data collection	
Diffractometer	Bruker-Nonius Apex X8-CCD-diffractometer
Absorption correction	Multi-scan (*SADABS*; Sheldrick, 2004)
T_{min}, T_{max}	0.710, 0.746
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	27542, 5885, 4610
R_{int}	0.029
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.756
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.041, 0.112, 1.02
No. of reflections	5885
No. of parameters	218
H-atom treatment	H-atom parameters constrained

$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.46, −0.26

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