Chapter 7

Palladium Catalyzed Functionalization of 7-Azaindoles and Indoles
7.1. Introduction

Palladium-catalyzed transformations reactions have been seen a fascinating development in recent years after being for a long time in silence as a “sleeping beauty.”\textsuperscript{161} The importance of palladium as in transition metal catalyst organic synthesis is evident from the huge number of publications as well as name reactions in connection with this field. The great advantage of palladium-catalyzed process is in the formation of C–C, C–N, C–O, C–H activation and even C–S bonds in the mildness of most of these processes, tolerating many functional groups.

On the basis of literature, we estimate that at least one-third of the organic compounds that need to be prepared as part of drug development programs contain a heteroaromatic fragment.\textsuperscript{162} It is therefore little wonder that organic chemists make such expensive efforts to develop new and efficient synthetic transformations to prepare a wide variety of heteroaromatics.\textsuperscript{163} Among the novel synthetic transformations, transition metal catalyzed reactions provide some of the most attractive methodologies for the synthesis and substitution of these heterocyclic structures. In particular, the use of transition metal catalyzed cross coupling reactions has increased tremendously during the past two decades. In industry, these transformations play an important role in discovery chemistry where fast and easy access to small focused libraries is mandatory and where also the preparation of large scales for...
clinical trials as well as for manufacturing is flourishing.\textsuperscript{164} Arguably the most important remaining challenge is the development of universal method for cross-coupling substrates that includes nitrogen Heterocycles.\textsuperscript{165} The presence of such moieties, which are particularly pervasive in medicinal chemistry, too often leads to low reactivity in coupling reactions. This is often caused by binding of heteroatom is the substrate and product to the metal complexes.\textsuperscript{166} Although binding is reversible, the large excess of substrate can lead to a strong inhibitory effect.

Various types of cross-coupling reactions have been known for several decades, and advances in recent years have greatly increased their scope and practicality. This has a significant impact on research and its employment in a variety of synthetic venues. Progress has been greatly facilitated by an increased understanding of the mechanism by which these and related reactions proceed. Furthermore, a tremendous upsurge in the development of new ligands has contributed substantially to recent advances. Cross-coupling reactions have become a standard tool for the synthetic chemist. These processes make use of C–N bond coupling (Buchwald-Hartwig cross coupling), C–C bond formation using boron (Suzuki-Miyaura), alkenyl (or) aryl (sp\textsuperscript{2}) halides or triflates with alkenes (Heck reaction) and C–O bond formation reactions using palladium as a catalyst.

The choice of a suitable palladium for coupling reactions are for more limited than the choice of the ligand. Typically, Pd(0) or Pd(II) precursors which are reduced if necessary insitu to the corresponding zero oxidation state, most often in the presence of phosphine and base are used. The most prominent Pd(0) precursors are Pd\textsubscript{2}(dba)\textsubscript{3} and Pd(dba)\textsubscript{2}. Nevertheless, the release of dba during the catalysis can have an effect on the performance of the reaction and has to be taken into account. The most versatile Pd(0) precursor is Pd(OAc)\textsubscript{2}. Nevertheless, [allPdCl]\textsubscript{2} or Pd(acac)\textsubscript{2} also show remarkable activity in special cases. One of the most abundant Pd(II) salt is PdCl\textsubscript{2}. Nevertheless, it is rarely used and only Buchwald reported for C–N bond formation of arylbromides.\textsuperscript{167} Concerning the
catalyst loading, the range is much broader for coupling reactions. While special substrates can be coupled with palladium loadings down to 0.01 mol%, it is much more typical to start a screening set up with 1-2 mol% of palladium. An important point concerning the reliability of the reaction in general is the purity of the components of the catalyst system and ligand. Organic or inorganic impurities in the ligand or palladium precursor can have a large impact on the performance of the reaction. Especially when moving to a larger scale, commercial palladium precursors should be use-tested and a minimum of different palladium batches (ideally one) should be used during a production campaign.

The bases are also play a important role in the couplings reactions. Owing to this, at least stoichiometric quantities of the bases are needed. Two types of bases can be distinguished, bases that are only sparingly soluble in the typically used apolar solvent (e.g., toluene) and bases that give nearly homogeneous reaction mixtures. The most common bases for coupling reactions are \( t\text{-BuONa} \), \( t\text{-BuOk} \), \( \text{LiHMDS} \), \( \text{Cs}_2\text{CO}_3 \), \( \text{K}_2\text{CO}_3 \), \( \text{K}_3\text{PO}_4 \), \( \text{NaOMe} \), \( \text{NaOH} \) and \( \text{KOH} \). The vast majority of side-reactions found in Buchwald-Hartwig aminations are caused by the added base. The relative base strength determines the functional group tolerance. Due to the larger surface area it is usually advantageous to use finely powdered bases for heterogeneous reaction set-ups. Apart from the base sensitivity of the substrate, the combinations of base and ligand as well as base temperature are also important parameters.

Although a number of coupling reactions are reported because of significance and prevalence we focused on Buchwald-Hartwig, and Heck reactions in this review reported in last two decades.

7.1.1. Buchwald-Hartwig coupling:

Palladium catalyzed amination of aryl halides has become an important method for the synthesis of aryl amines found in pharmaceutical,\textsuperscript{168,169} agrochemicals,\textsuperscript{170} photographic materials,\textsuperscript{171}
xerography,\textsuperscript{172} pigments,\textsuperscript{173} electronic materials,\textsuperscript{174} and natural products.\textsuperscript{175} A number of useful methods for the C–N bond formation have emerged over the years mainly including the Ullmann reaction\textsuperscript{176} and the Goldberg reaction\textsuperscript{177} using Cu reagent. However, these methods suffer from a limited substrate scope due to the requirement of relatively harsh reaction conditions and or the presence of activating electron withdrawing groups. In the mid nineties Buchwald and Hartwig independently discovered the Pd-catalyzed amination of aryl bromides showing a wide surge.\textsuperscript{178} This new procedure has established itself as a very important method for C–N bond formation on aromatic compounds currently available.\textsuperscript{179}

The generally accepted Buchwald-Hartwig reaction mechanism\textsuperscript{180} is depicted in Figure 7.1. It involves a phosphine-palladium (0) complex A (either formed by reduction of Pd(II) or by simple ligand exchange, when a Pd(0) source is used), which undergoes oxidative addition of the aryl halide to form complete B. Amine coordination with B forms palladium(II) complex C. In the presence of base palladium(II) complex C is converted into the corresponding aryl palladium amide D. Reductive elimination finally yields the aryl amine E and regenerated the palladium(0) complex A, closing the catalytic cycle.
Figure 7.1. Reaction mechanism of Buchwald coupling

7.1.1.1. One of the very first examples of palladium-catalyzed amination reactions of vinylic substrates was in fact, the coupling between the anilines (1) and 2-triflatotropana (2, Scheme 1). Tropona derivatives are interesting compounds due to their homoaromaticity and the presence of this structural entity in biologically active natural products.\textsuperscript{181}

\textbf{Scheme 1.} \textit{Reagents and conditions:} Pd\(_2\)(dba)\(_3\), BINAP, Cs\(_2\)CO\(_3\), Toluene, 32-90\%.
7.1.1.2. Tietze et al. reported the synthesis of substituted diphenylamine’s by Buchwald-Hartwig reaction using o-halo aniline and nitro-substituted aryl bromides (Scheme 2). Cyclization of these diphenylamines by the intramolecular Pd(0)-catalyzed N-arylation produces phenazines. Naturally occurring phenazines have various biological activities. Majority of phenazines are produced by strains of *pseudomonas* and *streptomyces species*.

\[ \text{Scheme 2. Reagents and conditions: (a) Pd}_2\text{(dba)}_3, \text{ rac-BINAP, Cs}_2\text{CO}_3, \text{Toluene, } 100 \, ^\circ\text{C, 50 hrs, 59%; (b) Fe, HCl, EtOH, Pd}_2\text{(dba)}_3, \text{ Ligand L, NaOtBu, Toluene, } 100 \, ^\circ\text{C, 32 hrs, 76%}.\]

7.1.1.3. Mori et al. used palladium-catalyzed C–N bond forming reaction for the synthesis of carbapenem antibiotic derivative 3-alkoxycarbonyl-1β-methylcarbapenem. In this, reaction, Mori emphasized that the generation of Pd(0) from Pd(OAc)\(_2\) in the absence of base and use of DPEphos as ligand are necessary to increase the yield of the product.
7.1.2. Heck reaction:

The Heck reaction can be broadly defined as the palladium-catalyzed coupling of alkenyl or aryl (sp\(^2\)) halides or triflates with alkenes (Scheme 4) to yield products which formally result from the substitution of a hydrogen atom in the alkene coupling partner. The first example of this reaction was reported independently by Mizoroki\(^{184}\) and, in an improved form by Heck.\(^{185}\) However, it would be more than a decade before the broader applicability of this transformation began to be investigated by the wider synthetic organic community. The development of catalytic asymmetric Heck reactions in the late 1980s led to a further resurgence of interest in this field.\(^{186}\) The Heck reaction now stands as a remarkably robust and efficient method for carbon-carbon bond formation, particularly in the generation of tertiary and quaternary stereocentres and intramolecular ring formation, and remains a flourishing area of research.

Scheme 3. *Reagents and conditions:* (a) Pd(OAc)_2, DPEphos, K_2CO_3, Toluene, 100 °C, 90%;

Scheme 4. *Reagents and conditions:* (a) Palladium catalyst, Lignad and base.

The presumed catalytic cycle for the Heck reaction is summarized in Figure 7.2. A coordinatively unsaturated 14-electron palladium (0) complex A is the catalytically active species. Once formed,
bis(triphenylphosphine)palladium(0) \(\text{A}\) initiates the first step in catalytic cycle by taking part in an oxidative addition reaction with alkenyl halide or an aryl halide \(\text{R}_1\text{X}\) to give the 16-electron complex \(\text{B}\). Although intermediate \(\text{B}\) possesses an available coordination site which could be occupied by an olefin, it is possible that loss of a neutral donor phosphine ligand from the intermediate \(\text{B}\) precedes the olefin coordination step. In any event, olefin complexation is followed by an insertion of the olefin into the \(\alpha\)-alkenyl or \(\alpha\)-aryl \(\text{C–Pd}\) bond, generating intermediate \(\text{C}\) via a four-center transition state. It is important that the crucial olefin insertion step occurs as a \textit{syn} addition and that the organic ligand from the palladium complex becomes bonded to the less hindered carbon of the olefin, in other words, the regiochemistry of the olefin insertion is determined primarily by steric effects.

\textbf{Figure 7.2. Reaction mechanism of Heck reaction}
From intermediate C, the next step in the catalytic cycle which involves a simple bond rotation to give D. This event is essential because it establishes the necessary syn relationship between a β-hydrogen and the palladium atom. The β-hydride elimination can take place to give the coupling product E and the hydridopalladium complex F with a β-hydrogen and the transition metal in a common plane. Finally, a base-assisted reductive elimination of HX from the intermediate F regenerates the palladium(0) catalyst, thus permitting a subsequent turn through the cycle. It is important to note that R₁ in complex B must not contain any sp³-bonded hydrogen atoms at the β-position, otherwise a premature β-hydride elimination can compete with the desired coupling reaction.

Several research groups have utilized the Heck reaction in the synthesis of a variety of organic molecules. These molecules range from intermediates to final compounds in the synthesis of natural products, biologically active compounds or, synthetic targets. In many cases, the heck reaction was used in the final step for the synthesis of target molecules.

7.1.2.1. Rawal et al. have cleverly used palladium-mediated intramolecular Heck reaction for the stereocontrolled synthesis of Strychnos alkaloid (±)-dehydrotubifoline (13) from compound 12, using 5 mol% of Pd(OAc)₂, potassium carbonate, and tetrabutyl ammonium chloride in DMF at 60 °C (Scheme 5).¹⁸⁷

**Scheme 5.** *Reagents and conditions:* (a) Pd(OAc)₂, K₂CO₃, nBu₄NCl, DMF, 60 °C, 79%
7.1.2.2. The Danishefsky et al. accomplished the assembly of tetracyclic compound 14 using again an intramolecular Heck arylation as a key step towards the synthesis of the multifunctional (±)-FR-900482 molecule (16), which exhibit potent antitumor property (Scheme 6). This intramolecular reaction proceeded very efficiently and the success of this cyclization reaction is important in view of the potentially sensitive functionality contained within compound 14.

Scheme 6. Reagents and conditions: (a) Pd(PPh₃)₄, Et₃N, ACN, 80 °C, 93%

7.1.2.3. Tozer et al. reported that, where the endo mode is favored for electronic reasons the reaction can lead to the formation of larger macrocycles. The reaction eases as the size of the newly forming macrocycle increases, generally a behavior not common in the cyclization chemistry Scheme 7).

Scheme 7. Reagents and conditions: (a) Pd(OAc)₂, NaHCO₃, MS 3A, Bu₄NCl, DMF, 105-110 °C, n = 1, 41%, n = 2, 63%, n = 3, 89%

The above Buchwald-Hartwig and Heck reactions, we want to apply for the functionalization of indoles and 7-azaindoles because of their potential pharmaceutical importance.
7.1.3. Indoles:

The indole is an aromatic N-containing heterocyclic compound. It has a bicyclic structure, consisting of six-membered benzene ring fused to a five member pyrrole ring. Indole alkaloids, their activity, synthesis, and potential use in medicine have been already reviewed in several articles. The indole moiety is present in a number of drugs currently on the market. Most of these belong to triptans which are used mainly in the treatment of migraine headaches. All member of this group are agonists of migraine associated 5HT$_{1B}$ and 5HT$_{1D}$ serotonin receptors. Sumatriptan (19) (Imitrex) was developed by Glaxo for the treatment of migraines. Frovatriptan (20, Frova) was developed by Vernalis for the treatment of menstruation associated headaches. Frovatriptan’s affinity for migraine specific serotonin receptors 5HT$_{1B}$ is believed to be the highest among all triptans. In addition, Frovatriptan binds to 5HT1D and 5HT7 receptor subtypes. Zolmitriptan (21) discovered by AstraZeneca is used to treat acute migraine attacks and cluster headaches. GlaxoSmithKline’s Naratriptan (22, Amerge) is also used in the treatment of migraines and some of its effects include dizziness, tiredness, tingling of the hands and feet’s and dry mouth. All available triptans are well tolerated and effective.
7.1.4. Azaindoles:

Azaindoles are biosisters of indoles. Replacing one of the carbon atoms at positions 4-7 in the indole template with a nitrogen atom gives the so called 4-, 5-, 6- and 7-azaindoles respectively. Most of the azaindole derivatives are synthetic products, although some azaindole containing compounds do exist in nature. For example, 7-azaindole was isolated from coal tar in 1943. Other well-known 7-azaindole containing natural products are variolins which are isolated from marine sponge *kirkpatrickia variolosa*. Variolins, particularly Variolin B, have exhibited notable anti-cancer properties. We want explore the functionalization of 7-azaindoles only because they have unique biological importance. Marie-Claude Viaud-Massuard described 7-azaindole derivatives of cytokinin analogues. Cytokinins are one of the known classes of plant growth regulators, also called phytohormones. They play a major role in many different processes in plant development including cell growth and division control and the plant’s cell differentiation with auxins. Moreover, they regulate the storage of various metabolites as alkaloids. All naturally occurring cytokinins are N-6 substituted adenine derivatives which contain an aromatic ring or an isoprenic chain in N6 position (Figure 7.4).

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**Figure 7.4. Naturally occurring cytokinins**

Cytokinins and their derivatives exert their biological effects on several levels. Certain 6-alkynyl and alkenyl pyrines have a profound inhibiting effect on 15-lipoxygenase which is implicated in the
development of atherosclerosis. Their anti proliferative and proapoptotic effects are related to their capacity to inhibit the cyclindependent kinase proteins (CDK) especially CDK1 and CDK2.

Figure 7.5. Design of different cytokinin analogue

Compounds 26 a-d and 27 a-d (Figure 7.5) were evaluated in vitro for their antiproliferative activity using the human myeloblastic leukemia HL-60 cell line. Studies revealed interesting cytotoxic properties of compound 26, in contrast to derivatives 27 a-d which displayed no activity in this assay. On the other hand, the activities of 26a, 26c, 26d and kinetin were similar. Overall the results show that the replacements of the purine ring by 7-azaindole led to an increased inhibitory activity compared to benzylaminopurine. Guillard and co-workers have prepared eight new cytokinin analogues where the purine ring of benzylaminopurine (BAP) was replaced with 7-azaindole. The biological tests showed that the NH group is essential for potent activity and the benzylamino substitution was the optimal structure. Amino substituted 7-azaindoles appear in a variety of biologically active molecules (Figure 7.6). In which 28 and 29 are kinase inhibitors developed by Merck 30 and 31 are checkpoint kinase (CHK1) inhibitors developed by Array BioPharma.
Indoles and azaindoles (also called pyrrolopyridines) constitute essential subunits in many pharmaceutically important compounds such as anti-inflammatory agents, anti-psychotic agents etc. Many classical methods available for indole synthesis (such as Fischer and Madelung cyclizations) often cannot be effectively applied to the synthesis of the corresponding azaindoles. In particular, a report on the functionalization at 4-position of 7-azaindoles is very scarce. In recent years, advances in organometallic chemistry have enabled a number of novel and efficient methodologies for azaindole formation as well as synthesis of highly functionalized azaindoles.

Palladium catalyzed C–N and C–O bond forming reactions between 4-substituted 7-azaindole and amides, amines, amino acid esters or phenols have recently gained popularity among the scientific community for different discovery drug development programmes.
Particularly, various 7-azaindoles (1H-pyrrole[2,3-b]pyridine),\textsuperscript{198} including 4-substituted compounds\textsuperscript{199} have found applications in various therapeutic areas. Despite their utility in various drug development programs, methods for the synthesis and functionalization of 7-azaindole scaffolds remain limited. Although literature enumerates various methods for the synthesis of substituted azaindole motif, they are limited to N-1, C-2 or C-3 functionalization structures.\textsuperscript{200} Furthermore, the regioselective C–O bond forming reactions are interesting in organic synthesis due to the presence of these bonds in numerous natural products, biological compounds, pharmaceuticals, fragrances, cosmetics and polymers.\textsuperscript{201} Buchwald and co-workers followed by many other groups during the past decade reported the metal-catalyzed formation of carbon-hetero atom bonds.\textsuperscript{202} Most of the literature reports are limited to aryl halides and indoles only. Clearly, each of these protocols has its own virtues; however, limitations still exist with respect to substrate scope, reagents as well as solvents etc. Thus, palladium catalyzed intra- and intermolecular cross-coupling reactions of azaindoles with amides, amines, amino acid esters or phenols offer an interesting complementary method for the synthesis of C–N and C–O bond under comparably mild conditions. It is important to note that, in contrast to well established palladium-catalyzed coupling reactions of indole with amines, alcohols and phenols,\textsuperscript{203} only a few studies on the formation of C–N and C–O bond formation over 7-azaindole have been performed.\textsuperscript{204} On the other hand, the chemistry of 4-bromo-7-azaindole is not explored in depth till today.

Amino and phenol-substituted 7-azaindoles appear in a variety of biologically active molecules (Figure 7.6) which are very challenging and lengthy to prepare \textit{via} the traditional methods. In general, amino-7-azaindoles are accessed from the corresponding halide \textit{via} \textit{S\textsubscript{N}}\textsubscript{Ar} reaction, which require high temperatures (>180°C or microwave heating), longer reaction times
and large excess of the amine counterpart. Furthermore, similar conditions using primary alkyl amines or anilines gave only the 4-amino-5-azaindole (1H-Pyrrolo[3,2-c]-pyridine) products of displacement rearrangement. Very recently Buchwald et al reported palladium-catalyzed lamination of unprotected halo-7-azaindoles using biarylphosphine ligands (DavePhos), palladium precatalyst (RuPhos)-based reagents, and LiHDMS as a base. However, the inconsistency of the results was observed when carried out in large scale.
We herein report new Pd-catalyzed coupling reaction of $N$-protected-4-bromo-7-azaindoles with amides, amines, amino acids and phenols (Figure 7.7), to yield new important intermediates for one of our medicinal chemistry program. We selected 4-bromo-7-azaindole as the key starting material for the entire program due to its easy access, stability and ease of operations. Most of the literature methods limited to 4-chloro or 4-iodo-7-azaindoles only. Although, literature enumerates various synthetic methods of functionalization of 7-Azaindoles derivatives, they suffer from longer reaction time and poor yields.

Figure 7.7. Coupling of 4-bromo-7-azaindole with amides, amines, amino acid esters and phenols

7.2. Results and discussion

4-Bromo-7-azaindole derivative (32) was prepared from 7-azaindole by the literature procedure. Most of the cases we have used the $N$-protection of 4-bromo-7-azaindole. It is worth mentioning that 7-
azaindole, i.e. (1H-pyrrole[2,3-b]pyridine) has a [4.3]-bicyclical indene skeleton with a fused electron rich pyrrole ring and an electron deficient pyridine ring. The pKa value of 7-azaindole is ~4.9 and can self-associate via hydrogen-bonding into a dimer in solution and phototautomerize via an excited-state double proton transfer (ESDPT) process.206 Azaindoles have previously been reported to undergo arylation of the heterocyclic N–H nitrogen in the presence of copper or palladium catalyst.207

**Scheme 8. Reagents and conditions:** (a) Palladium catalyst, Ligand Lₙ, Base, dioxane, 100 °C.

**Table 7.1. Reaction optimization for coupling of 32e with benzamide 33a under various conditions**

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<th>Entry</th>
<th>Pd-catalyst (5 mol%)</th>
<th>Lₙ</th>
<th>Base</th>
<th>Time (hrs)</th>
<th>Yield (%)</th>
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*aReactions of 33e (1.0 mmol) 32a (1.2 mmol) were performed in a sealed Schlenk tube at 100 °C in 1,4-dioxane (2 mL) by using Pd-catalyst (5 mol%), ligand (10 mol%) and base (1.5 mmol).

b Yields reported are isolated yield.

c No reaction occurred without palladium catalyst.

d No reaction occurred at room temperature.
To determine efficient method for amide coupling processes for 7-azaindole motif, we undertook an intensive screening of a variety of ligands, palladium catalyst and reaction variables using electron-deficient N-protected 4-bromo-7-azaindole (32) as substrates (Table 7.1). We found that a catalyst combination employing XantPhos (L₁), as a chelating ligand developed by van Leeuwen, with Cs₂CO₃ as the base and dioxane as the solvent provided the most successful results (Table 7.1, entry 1). The reaction temperature is ~100 °C for all the cases. Switching the Pd source to Pd₂(dba)₃ results slight decline in yield (Table 7.1, entry 2). Other ligands e.g. SPhos L₂ and Xphos L₃ did not work well even after longer reaction time (Table 7.1, entries 3 to 6). The ligand PCy₃ L₄ did not work at all in our hand for this purpose. Xantphos (L₁), in particular, has been widely employed as a supporting ligand in Pd-catalyzed amidation reactions and on this basis, was chosen for further evaluation in this process.

Scheme 9. Reagents and conditions: (a) Pd(OAc)₂, XantPhos L₁, Cs₂CO₃, dioxane, 100 °C.

Table 7.2. C–N bond formation-cross coupling of N-protected 4-bromo-7-azaindole (32) with amides (33).
<table>
<thead>
<tr>
<th>Entry</th>
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<th>Amide 33</th>
<th>Product 34&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Time (hrs)</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<tr>
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Reactions of 32 (1.0 mmol) with 33 (1.2 mmol) were performed in a sealed Schlenk tube at 100 °C in dioxane (2 mL) by using Pd(OAc)$_2$ (5 mol%), XantPhos (10 mol%) and base (1.5 mmol). Yields reported are isolated yield. NR no reaction. Desulfonation reaction takes place.

With optimized conditions in hand, we embarked on an investigation of the reaction scope by subjecting various N-protected 7-azaindole (32) with wide range of amides (33). The experimental results are summarized in Table 7.2. The reaction did not proceed at all without N-protection (Table 7.2, entry 1). When the reaction was carried out with N-sulfonyl protected 4-bromo-7-azaindole only the
desulfonated product (Table 7.2, entry 2) was obtained. It is worth mentioning that N-sulfonyl protection of 7-azaindoles were efficiently deprotected under basic conditions in dioxane.\textsuperscript{211} The optimized reaction conditions work well with benzamide (Table 7.2, entry 3) and phenyl sulfonamide (Table 7.2, entry 4) to obtain good yield. A cyclic secondary amide (lactam) also reacted efficiently (Table 7.2, entry 5). The methodology works equally well with 2-methoxybenzamide (Table 7.2, entry 6) and 4-fluorobenzamide (Table 7.2, entry 7). We have checked the selectivity between amide and amine coupling by reacting N-ethyl-7-bromoazaindole (32d) with 2-aminobenzamide (33f) and obtained 2-amino-N-(1-ethyl-1H-pyrrolo[2,3-b]pyridin-4-yl)benzamide (34f) in 85% yield (Table 7.2 entry 8). We found that amide is more reactive than amine under the reaction condition we studied. The use of Cs\textsubscript{2}CO\textsubscript{3} as the base is advantageous because the common functional groups such as fluoro, methoxy etc are well tolerated. We have found that the N-protection of 4-bromo-7-azaindole (32) have marginal effect on reaction yield and time. The amide formation reaction was demonstrated in multi-gram synthesis in our hand. Next we diverted our attention towards coupling of N-protected 4-bromo-7-azaindole (32) with amines (35).

**Scheme 10. Reagents and conditions:** (a) Palladium catalyst, Ligand L\textsubscript{n}, Base, dioxane, 100 °C.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd-catalyst (5 mol%)</th>
<th>L\textsubscript{n}</th>
<th>Base</th>
<th>Time (hrs)</th>
<th>Yield (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd\textsubscript{2}(dba)\textsubscript{3}</td>
<td>L\textsubscript{1}</td>
<td>Cs\textsubscript{2}CO\textsubscript{3}</td>
<td>1</td>
<td>93</td>
</tr>
</tbody>
</table>

Table 7.3. Optimization coupling reaction of 32d with benzyl amine 35a\textsuperscript{a}
Amino-7-azaindoles are often accessed from the corresponding halide via $S_NAr$ displacement reactions, which typically require high temperatures, extended reaction times, and a large excess of the amine partner. Alternative approaches employ the amino-substituted azaindole as the key intermediate, which can be challenging to prepare. To select the best reaction conditions for the preparation of 4-substituted amino-7-azaindoles (36), the coupling of 4-bromo-1-ethyl-1H-pyrrolo[2,3-b]pyridine (32d) with phenylmethanamine (35a) was initially selected as a model reaction for investigating the effect of various ligands (Scheme 10), palladium catalyst and base. The results are summarized in Table 7.3. As can be seen from Table 7.3, the reaction of 32d with 35a occurred rapidly using Pd$_2$(dba)$_3$ as a catalyst, XantPhos $L_1$ as a ligand and Cs$_2$CO$_3$ as a base in dioxane at 100 °C in very short reaction time (Table 7.3, entry 1). Interestingly Pd(OAc)$_2$, results in poor yields of the product (Table 7.3, entries 6-12). Given this surprising result, we hypothesized that the amination product 36 may be interfering with catalyst turnover by promoting the formation of an inactive Pd–chelate complex. While a viable coupling procedure in hand, attention was turned to the generality of the process, and couplings of structurally
diverse nucleophilic amines. Results summarized in Table 7.4 show that the optimized conditions described proved to be general for the coupling with a wide variety of amines.

**Scheme 11. Reagents and conditions**: (a) Pd$_2$(dba)$_3$, XantPhos L$_1$, Cs$_2$CO$_3$, dioxane, 100 °C.

**Table 7.4. C–N bond formation-cross coupling of N-protected 4-bromo-7-azaindole (32) with amines (35).**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Types of 7-Azaindole 32</th>
<th>Amine 35</th>
<th>Product 36$^a$</th>
<th>Time (hrs)</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>24</td>
<td>NR$^c$</td>
</tr>
<tr>
<td>2</td>
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<td>-</td>
<td>3</td>
<td>0$^d$</td>
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<tr>
<td>3</td>
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<td>-</td>
<td>-</td>
<td>2.5</td>
<td>92</td>
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</tr>
<tr>
<td>4</td>
<td>3.0</td>
<td>91</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3.0</td>
<td>88</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2.5</td>
<td>93</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2.5</td>
<td>90</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>3.0</td>
<td>94</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) All reactions were carried out at 100 °C.
\(^b\) Yields reported are isolated yield.
\(^c\) NR no reaction
\(^d\) No reaction takes place. Only desulfonated product isolated.
The coupling was found to be compatible with primary aromatic and aliphatic amines (Table 7.4, entries 3-4 & 6-7) providing excellent yields of the corresponding coupling products 36a-36b and 36d-36e respectively. The reaction was also effective for cyclic amines (Table 7.4, entry 5 & 8). The reaction works equally well for aliphatic primary amine too (Table 7.4, entry 7) resulting 90% of the isolated yield. There was a feeble change in yield by changing substitution on 7-azaindole nitrogen (N1) from methyl to ethyl group (Table 7.4, entries 1-7). There was no reaction without the N-protection (Table 7.4, entry 1). Heating of reaction mass of 4-bromo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine (32b) with phenylmethanamine (35a) in presence of base and palladium reagent resulted only the desulfonated 4-bromo-7-azaindole as the sole product (Table 7.4 entry 2).

Our continuous efforts to develop a synthetic methods for the formation of C-N bond formation by coupling of N-protected 7-azaindole (32) with amino acids or esters results development of interesting intermediates in our own medicinal chemistry program based on 7-aza-indole. To our knowledge, there have been no reports on coupling of amino acids or esters with azaindole and indole derivatives. Large molecular architectures designed by cross coupling strategies with the introduction of amino acid functionality on 7-azaindole results new scaffolding. It is worth mentioning that N-aryl amino acids are important synthetic intermediates and structural components of medicinally molecules. As a result, amino acids or esters are very attractive coupling partners for the transition metal catalyzed processes.

**Scheme 12. Reagents and conditions:** (a) Palladium catalyst, Ligand L, Base, dioxane, 100 °C.
Table 7.5. Optimization coupling reaction of 32c with D-alanine 37a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd-catalyst (5 mol%)</th>
<th>L_n</th>
<th>Base</th>
<th>Time (hrs)</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd₂(dba)₃</td>
<td>L₁</td>
<td>Cs₂CO₃</td>
<td>1</td>
<td>93</td>
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<tr>
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<td>Pd₂(dba)₃</td>
<td>L₁</td>
<td>K₂CO₃</td>
<td>3</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>Pd₂(dba)₃</td>
<td>L₁</td>
<td>NaOt-Bu</td>
<td>3</td>
<td>44</td>
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<td>Pd₂(dba)₃</td>
<td>L₁</td>
<td>KOH</td>
<td>3</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>Pd₂(dba)₃</td>
<td>L₁</td>
<td>K₃PO₄</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>Pd₂(dba)₃</td>
<td>L₂</td>
<td>Cs₂CO₃</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>7</td>
<td>Pd₂(dba)₃</td>
<td>L₃</td>
<td>Cs₂CO₃</td>
<td>6</td>
<td>traces</td>
</tr>
<tr>
<td>8</td>
<td>Pd₂(dba)₃</td>
<td>L₄</td>
<td>Cs₂CO₃</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)₂</td>
<td>L₁</td>
<td>Cs₂CO₃</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>Pd(OAc)₂</td>
<td>L₁</td>
<td>K₂CO₃</td>
<td>24</td>
<td>15</td>
</tr>
<tr>
<td>11</td>
<td>Pd(OAc)₂</td>
<td>L₁</td>
<td>NaOt-Bu</td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td>12</td>
<td>Pd(OAc)₂</td>
<td>L₁</td>
<td>K₃PO₄</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>13</td>
<td>Pd(OAc)₂</td>
<td>L₂</td>
<td>Cs₂CO₃</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td>14</td>
<td>Pd(OAc)₂</td>
<td>L₃</td>
<td>Cs₂CO₃</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>Pd(OAc)₂</td>
<td>L₄</td>
<td>Cs₂CO₃</td>
<td>24</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction conditions: N-substituted 4-bromo7-azaindole (1.0 mmol), amino acid esters (1.2 mmol), base (3.0 mmol), palladium catalyst (5 mole %), ligand (10 mole %), and 2 mL of dioxane, 100 °C, 1-24 h.

<sup>b</sup>Yields reported are isolated yield.

Amino acids are commercially available and are one of the best building blocks for a peptides and the synthesis of lactam, heterocycles and physiologically active substances. Furthermore, amino acids containing indole and azaindole are believed to be an important synthetic intermediates and structural component of medicinally (pharmaceutical) molecules. The coupling of N-methyl-4-bromo-7-azaindole (32c) with D-alanine metylester (37b) was chosen as the model reaction to test the feasibility of palladium assisted coupling reaction of 7-azaindole and amino acids. The experimental results are summarized in Table 7.5. In our initial endeavor the coupling of N-methyl-4-bromo-7-azaindole (32c)
with D-alanine (37a) results only in trace amount of product (38a) using XantPhos L₁, bidentate aryl phosphine ligands L₂, and L₃. The tertiary phosphine ligand L₄ were ineffective in the arylation of 7-azaindole with D-alanine. This might be ascribed to the coordination of the central metal with the carboxyl group of amino acids, which retained after the formation of Pd–N bond, making the 7-azaindole-Pd-N complexes too stable to reductive elimination. As can be seen from Table 7.5, the reaction of 32c with 37b alanine methyl ester occurred rapidly using Pd₂(dba)₃ as a catalyst, Xanthphos (L₃) as a ligand and Cs₂CO₃ as a base in dioxane at 100 °C in short reaction time (Table 7.5, entry1). Other palladium catalyst Pd(OAc)₂ results in poor yields of the product (Table 7.5, entry 4). Ligand containing the dicyclohexyl phosphino group (SPhos L₂) was used as ligand; and the coupling yield was decreased to 14% (Table 7.5, entry 3). When the dialkyl-biarylphosphino ligand (XPhos L₃) was used as ligand, hardly any or traces product was obtained (Table 7.5 entry 4 and 10). These results in accordance with the reports that increasing the steric hindrance of the ligands would promote the reductive elimination during the C–N bond forming step. We found that dioxane is the optional solvent for the transformation presumably because amino acid methyl esters are much more soluble in a protic solvent (Table 7.5, entries 1 and 2). Finally, Cs₂CO₃ as a base (Table 7.5 entry 1) was found to be more effective than stronger base such as NaOt-Bu, KOH, phosphates potassium carbonates (Table 7.5, entries 3, 4, 5 and 2 respectively).

While a viable coupling procedure in hand, attention was turned to the generality of the process, and couplings of structurally diverse amino acid building blocks. Results summarized in Table 7.6 show that the optimized conditions described proved to be general for the coupling with a wide variety of amino acid building blocks. As can be seen from Table 7.6, the catalytic system works well with diversified amino acid building blocks. Coupling of N-methyl-4-bromo-7-azaindole (32c) with D-alanine methyl ester (37b) results good yield of the product (38b) in short reaction time (Table 7.6, entry 1). The chiral purity of the product was determined by chiral HPLC using Chiral Pak AD-H Column. Amino acids
without extra coordinating groups gave good coupling yields (Table 7.6, entries 2, 5 & 6). Coupling of L-serine(O-t-Bu)-OMe (37d) with 32c results moderate yield of the product in 3 hrs of time (Table 7.6, entry 3). Moreover, our catalytic system was ineffective for proline, serine, glutamic acid (Table 7.6, entries 7-9). This may be due to the fact that such substrates have more heteroatoms or functional groups binding to the palladium catalyst, which enhance the stability of the 7-azaindolyl-Pd–N complex and consequently inhibit it from reductive elimination.

Scheme 13. Reagents and conditions: (a) Pd$_2$(dba)$_3$, XantPhos L$_1$, Cs$_2$CO$_3$, dioxane, 100 °C.

Table 7.6. C–N bond formation-cross coupling of N-protected 4-bromo-7-azaindole (32) with amino acid esters (37).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Types of 7-Azaindole 32</th>
<th>Amino acids 37</th>
<th>Product 38$^a$</th>
<th>Time (hrs)</th>
<th>Yield (%)$^b$</th>
<th>ee (%)$^d$</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
<td>2.0</td>
<td>70</td>
<td>98.79</td>
</tr>
<tr>
<td>2</td>
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<td></td>
<td></td>
<td>2.0</td>
<td>72</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.0</td>
<td>65</td>
<td>95.48</td>
<td></td>
<td></td>
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<td>------</td>
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<td></td>
<td></td>
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<tr>
<td>3</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>2.0</td>
<td>71</td>
<td>98.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>2.1</td>
<td>72</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>2.0</td>
<td>70</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>5.0</td>
<td>0</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>
All reactions were carried out at 100 °C. 1.1 eq of amino acid ester, 3.0 eq. of Cs$_2$CO$_3$, 0.05 eq of Pd$_2$(dba)$_3$ and 0.10 eq of XanthPhos are used for all the reactions.

Yields reported are isolated yield.

No reaction takes place. Only desulfonated product isolated.

ee was determined by chiral HPLC.

After successful demonstration of the C–N bond formation reaction of 4-bromo-7-azaindole derivatives with amides, amines and amino acids, we wanted to expand the scope of the reaction towards C–O bond. Till today no general method exists for the C–O bond formation reaction of 4-halo-azaindole with phenols or alcohols. Most of the literature reports on C–O bond formation reaction are limited to aryl halides and phenols or alcohols only. Santiago, E-P et al. reported that 4-chloro, 4-nitro, and 4-bromo-1H-pyrrolo[2,3-b]pyridine proved to be inert when heated with 4-amino-2-fluorophenol in the presence of KOt-Bu. The corresponding N-oxides also did not afford any substitution product when reacted with 4-amino-2-fluorophenol under the same conditions. The palladium or copper catalyzed coupling between either 4-chloro or 4-bromo-1H-pyrrolo[2,3-b]pyridine and N-protected-amino-2-fluorophenol also failed to afford an acceptable yield of the diary ether. To select the best reaction condition for C–O bond formation, we envisaged the synthesis of an activated 7-azaindole building block that could be coupled with phenols. The coupling of 4-bromo-1-methy-1H-pyrrolo[2,3-b]pyridine (32c) with m-cresol (39a) was initially selected as model reaction for investigating the effects of various ligands (Figure 2), palladium catalyst and base. The results are summarized in Table 7.7. As can be seen from Table 7.7, the reaction of (32c) with (39a) proceed rapidly using Pd(OAc)$_2$ as a catalyst, XantPhos L$_1$ as a ligand and K$_2$CO$_3$ as a base in dioxane at 100 °C in 10 hrs. The C–O bond formation reaction gave very less yield (30%) in our initial experiment when heated at 100 °C for 3 hrs (Table 7.7, entry 2). But
upon continuous heating for 7 hrs we observed 70% (Table 7.7, entry 3) of the expected product. Interestingly Pd$_2$(dba)$_3$, resulted poor yields of the product (Table 7.7, entries 4 & 5). Most of the cases we have observed decomposition of Pd$_2$(dba)$_3$ reagent. In comparison to the conditions described for the amines and amides, a much longer reaction time was required.

Scheme 14. Reagents and conditions: (a) Palladium catalyst, Ligand L$_n$, Base, dioxane, 100 °C.

Table 7.7. Optimization of coupling reaction of 32c with m-cresol 39a$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd-catalyst (5 mol%)</th>
<th>L$_n$</th>
<th>Base</th>
<th>Solvent</th>
<th>Time (hrs)</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$</td>
<td>L$_1$</td>
<td>Cs$_2$CO$_3$</td>
<td>dioxane</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$</td>
<td>L$_1$</td>
<td>K$_2$CO$_3$</td>
<td>dioxane</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$</td>
<td>L$_1$</td>
<td>K$_2$CO$_3$</td>
<td>dioxane</td>
<td>10</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)$_2$</td>
<td>L$_1$</td>
<td>K$_2$CO$_3$</td>
<td>THF</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>Pd$_2$(dba)$_3$</td>
<td>L$_1$</td>
<td>Cs$_2$CO$_3$</td>
<td>dioxane</td>
<td>3</td>
<td>10$^c$</td>
</tr>
<tr>
<td>6</td>
<td>Pd$_2$(dba)$_3$</td>
<td>L$_1$</td>
<td>K$_2$CO$_3$</td>
<td>dioxane</td>
<td>10</td>
<td>32$^c$</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)$_2$</td>
<td>L$_2$</td>
<td>Cs$_2$CO$_3$</td>
<td>dioxane</td>
<td>24</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)$_2$</td>
<td>L$_3$</td>
<td>Cs$_2$CO$_3$</td>
<td>dioxane</td>
<td>24</td>
<td>61</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)$_2$</td>
<td>L$_1$</td>
<td>K$_2$CO$_3$</td>
<td>dioxane</td>
<td>12</td>
<td>68</td>
</tr>
<tr>
<td>10</td>
<td>Pd(OAc)$_2$</td>
<td>L$_1$</td>
<td>K$_2$CO$_3$</td>
<td>dioxane</td>
<td>24</td>
<td>65</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: 32c (1.0 mmol), 39a (1.2 mmol), base (3.0 mmol), palladium catalyst (5 mole %), ligand (10 mole %), and 2 mL of dioxane, 100 °C, 1-24 h.

$^b$Yields reported are isolated yield.
While a viable coupling procedure in hand, attention was turned to the generality of the process, and couplings of structurally diverse phenols. Results are summarized in Table 7.8. The C–O bond formation was established with good yields with phenol derivatives and 1-naphthol (Table 7.8, entries 1-3). Moreover, the outcome of the reaction strongly depended on the electronic character of the appropriate phenol (Table 7.8). The more electron-rich nucleophiles (39a, 39b) furnished the desired ethers (40a-40b) in good yields. Further studies are in progress in our laboratory to investigate different substrate scope and mechanistic aspect of the C-O bond forming reaction.

**Scheme 15.** Reagents and conditions: (a) Pd(OAc)$_2$, XantPhos L$_1$, K$_2$CO$_3$, dioxane, 100 °C.

**Table 7.8.** C–O bond formation-cross coupling of 4-bromo-7-azaindole with phenols.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Type of 7-Azaindole 32</th>
<th>Type of Phenol 39</th>
<th>Product $^a$ 40</th>
<th>Time (hrs)</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>70</td>
</tr>
</tbody>
</table>
All reactions were carried out at 100 °C.

Yields reported are isolated yield.

We further expanded the scope of the catalyst from C–N and C–O bond formation to aryl ketones for α-arylation. In recent years, advances in organometallic chemistry have enabled a number of novel and efficient methodologies for azaindole formation as well as synthesis of highly functionalized azaindoles. Recently developed palladium-mediated C–N and C–O bond formation reactions prompted us to apply this methodology for the synthesis of various highly functionalized 7-azaindoles. Herein, we report the efficient synthesis of various indole and 7-azaindole derivatives via Palladium (0) mediated α-arylation with Xantphos as ligand.
Scheme 16. Reagents and conditions: (a) Palladium catalyst, Ligand Lₙ, Base, dioxane, 100 °C.

We initiated our studies, by treating 4-bromo-7-azaindole with 4-methoxy acetophenone in the presence of Pd(OAc)₂, Xantphos L₁, NaO'Bu and dioxane as a solvent. We did not observe any of the expected products. Protecting the free nitrogen of 4-bromo-7-azaindole with methyl substitution followed by coupling under the above conditions provided the expected compound (42a) in 42% yield. Upon optimizing the reaction conditions (screening various ligands and bases) Table no 7.9, the following conditions proved to be better for this transformation: Pd(OAc)₂ (0.05 mol%), Xantphos (0.10 mol%), NaO'Bu and dioxane as a solvent.

Scheme 17. Reagents and conditions: (a) Pd(OAc)₂, XantPhos L₁, NaO'Bu, dioxane, 100 °C.

Table 7.9. Optimization of reaction conditions for C–arylation azaindole

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal catalyst (5 mol%)</th>
<th>Lₙ</th>
<th>Base</th>
<th>Time (hrs)</th>
<th>Yield (%)ᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)₂</td>
<td>L₂</td>
<td>NaOt-Bu</td>
<td>1.3</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)₂</td>
<td>L₁</td>
<td>NaOt-Bu</td>
<td>0.50</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)₂</td>
<td>L₁</td>
<td>K₂CO₃</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)₂</td>
<td>L₁</td>
<td>Cs₂CO₃</td>
<td>24</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)₂</td>
<td>L₁</td>
<td>t-BuOK</td>
<td>1.3</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)₂</td>
<td>L₁</td>
<td>K₃PO₄</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)₂</td>
<td>L₃</td>
<td>NaOt-Bu</td>
<td>24</td>
<td>26</td>
</tr>
</tbody>
</table>
After finding the suitable reaction conditions, we have investigated the scope of the developed methodology for the synthesis of various densely functionalized 7-azaindole derivatives. The reaction with ketones having electron withdrawing and donating substitutions proceeded equally well with 1-methyl 4-bromo-7-azaindole with yields ranging from 60-75% (Table 7.10, entries 1-9). In exploring the viability of our developed methodology, we have subjected various indole compounds in the place of azaindoles, to our delight the expected products observed in very good yields (Table 7.11, entries 2-9). Moreover subjecting 5-bromo indole did not provide the expected product at all (Table 7.11, entry 1), hence we believe the free NH group in indoles and azaindoles might be poisoning the palladium catalyst consequently stalling the reaction. The free NH group was then protected with methyl and benzyl groups and subjected for the coupling reaction. Further, the benzyl group can be de-protected and used to synthesize the biologically active compounds.

Table 7.10. Heck reaction of N-protected 4-bromo-7-azaindole (32) with different acetophenones (41).

<table>
<thead>
<tr>
<th>S.No</th>
<th>Aryl halide</th>
<th>Ketone</th>
<th>Product</th>
<th>Temp (°C)</th>
<th>Time (Hrs)</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>95</td>
<td>1.2</td>
<td>60</td>
</tr>
</tbody>
</table>

*a* All reactions were carried out at 95 °C.

*b* Yields reported are isolated yield.

*c* Dioxane used as a solvent.
<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>95</td>
<td>1.5</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>95</td>
<td>2.0</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td>95</td>
<td>1.4</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>95</td>
<td>2.0</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>95</td>
<td>2.0</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>95</td>
<td>1.4</td>
<td>69</td>
</tr>
</tbody>
</table>
All reactions were carried out at 95 °C. 1.2 eq of ketone, 1.5 eq. of NaO\textsubscript{t}Bu, 0.05 eq of Pd\textsubscript{2}(OAc)\textsubscript{2} and 0.10 eq of XantPhos are used for all the reactions.

Yields reported are isolated yield.

dioxane used as a solvent.

---

**Scheme 18. Reagents and conditions:** (a) Pd(OAc)\textsubscript{2}, XantPhos L\textsubscript{1}, NaO\textsubscript{t}Bu, dioxane, 100 °C.

**Table 7.11.** Heck reaction of $N$-protected 5-bromo-indole (43) with different acetophenones (41).
<table>
<thead>
<tr>
<th></th>
<th>Reaction</th>
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<tbody>
<tr>
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<td>12</td>
</tr>
<tr>
<td>2</td>
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<td>1.3</td>
</tr>
<tr>
<td>6</td>
<td>95</td>
<td>1.2</td>
<td>84</td>
</tr>
<tr>
<td>7</td>
<td>95</td>
<td>1.2</td>
<td>75</td>
</tr>
<tr>
<td>8</td>
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<td>74</td>
</tr>
<tr>
<td>10</td>
<td>95</td>
<td>0.50</td>
<td>89</td>
</tr>
</tbody>
</table>

\(^a\)All reactions were carried out at 95 °C. 1.2 eq of ketone, 1.5 eq. of NaO\(^-\)Bu, 0.05 eq of Pd\(_2\)(OAc)\(_2\) and 0.10 eq of XantPhos are used for all the reactions.

\(^b\)Yields reported are isolated yield.
1,4-dioxane used as a solvent.

After developing the coupling methodology for the synthesis various densely functionalized indoles and azaindoles, we wanted further explore the synthetic applicability of the synthesized functionalized indoles, azaindoles and quinolines for various derivatives. In that direction we have embarked on synthesis of Quinoxaline derivatives. Quinoxaline is described as a bioisoster of quinoline, naphthalene, benzothiophene and other aromatic rings such as pyridine and pyrazine. Because of the similarity between some anti tubercular drugs and quinoxaline, as well as prevalence of quinoxaline moiety in various antifungal compounds, we hoped that these quinoxaline compounds will exhibit an important biological activity.

The most common method for the synthesis of quinoxaline is the condensation of diamine compounds with diketo compounds.\textsuperscript{215} Recently Charong Qi demonstrated the synthesis of quinoxaline by subjecting carbonyl compounds with di-amine compounds in the presence of DABCO as catalyst.\textsuperscript{216} We have adopted the Qi conditions and successfully synthesized various densely functionalized quinoxalines (Table 7.12, entires 1-6) in very good yields.

**Synthesis of substituted indole and azaindole quinoxalines**

**Scheme 19. Reagents and conditions:** (a) DABCO, Air, DMF, 90 °C.

**Table 7.12. Synthesis of quinoxalines from ketones and diamines.**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Benzyl Ketone</th>
<th>o-phenylene</th>
<th>Product</th>
<th>Time</th>
<th>Yield\textsuperscript{b}</th>
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</thead>
<tbody>
<tr>
<td>Diamine</td>
<td>(Hrs)</td>
<td>(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>-------</td>
<td>-----</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>6.0</td>
<td>92</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6.0</td>
<td>90</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>74</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>70</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>80</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
All reactions were carried out at 90 °C. 1.0 eq of ketone, 1.0 eq of o-phenylenediamine, and 0.20 eq DABCO are used for all the reactions.

Yields reported are isolated yield.

DMF used as a solvent.

7.3. Nature of the products and product characterization

Numbers of compounds which were synthesized in the research program are stable at room temperature and could be handled safely and stored at ambient conditions. However, compounds 34c and 40a are obtained as low melting solids but all other compounds were obtained as solids. All the compounds were purified by column chromatography using appropriate solvents. All the synthesized products were well characterized by spectroscopic data (IR, $^1$H NMR, $^{13}$C NMR, and mass) and HRMS data. A representative example of $^1$H NMR and $^{13}$C NMR of N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-4-
yl)benzamide (34a) is shown in Figure 7.8 and 7.9. When with 4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridine (32c) reacted benzamide (33a) in the presence of Pd(OAc)$_2$ and XantPhos as a catalyst system in 1,4-dioxane, peak observed in $^1$H NMR at $\delta$ 10.42 (br, s, 1H) corresponds to amide bond formation of azaindoles with benzamide. Singlet peak appeared near $\delta$ 6.81 in $^1$H NMR spectra, is corresponding to C$_3$ of N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)benzamide (34a). In $^{13}$C NMR, peak for compound 34a at $\delta$ 166.41 as shown in Figure 7.9 C=O group of amide. IR peak at 1656 cm$^{-1}$ is C=O stretching of amide and peaks observed at 3400 cm$^{-1}$ and 1608 cm$^{-1}$ are stretching and bending vibrations of amide group. In mass data, molecular ion peak at 262.4 (M+H), for compound (34a) which is in agreement with the structure, is further confirmed by HRMS data C$_{15}$H$_{14}$N$_3$O$_2$: 262.1126; found 262.1137.

7.4. Conclusion

In conclusion we have developed the best coupling conditions for C–N bond formation and α-arylation of ketones with N-substituted-4-bromo-7-azaindole with amides, amines, amino acid esters and demonstrated well for the synthesis of various N-substituted-7-azaindole compounds, which are very difficult to synthesize otherwise. We have enhanced the methodology towards the C–O bond formation with various phenols which is very difficult to synthesize. This is the first report on coupling of amides, amino acids and phenols with N-substituted-4-bromo-7-azaindole. Further we have also reported coupling of N-protected indole and N-substituted-4-bromo-7-azaindole first time with ketone. We feel that we have developed an efficient palladium mediated methodology for the synthesis of substituted azaindoles and demonstrated the applicability of the methodology by synthesizing various compounds and some these compounds proven to be really important for with good biological activity for cancer cell lines and other compounds activity investigation is in progress.

7.5. Experimental Section
7.5.1. General procedure for C–N bond formation by coupling of 4-bromo-7-azaindole derivatives with amides

To a 100 mL dried sealed Schlenk tube charged N-substituted 4-bromo 7-azaindole (1.0 mmol), amide (1.2 mmol), cesium carbonate (1.5 mmol), Pd(OAc)$_2$ (5 mole%), Xantphos (10 mole %), and 2 mL of dioxane were added. Nitrogen was bubbled through the reaction mass for 2 minutes. The reaction mixture was heated to 100 °C and stirred for appropriate time as mentioned in Table no. 7.2. After confirming the complete consumption of starting material by TLC, the reaction mass cooled to room temperature and diluted with ethyl acetate (20 mL), filtered through the celite bed and wash with ethyl acetate (10 mL). The filtrate was concentrated in vacuum. The crude product was purified by column chromatography on silica gel (100-200) using ethyl acetate and hexane mixture as an eluent to afford the pure titled products.

7.5.2. General procedure for C–N bond formation by coupling of 4-bromo-7-azaindole derivatives with amines

To a 100 mL dried sealed Schlenk tube charged N-substituted 4-bromo azaindole (1.0 mmol), amine (1.2 mmol), cesium carbonate (1.5 mmol), Pd$_2$(dba)$_3$ (5 mole %), Xantphos (10 mole %), and 2 mL of dioxane were added. Nitrogen gas was bubbled through the reaction mass for 10 minutes. The reaction mixture was heated to 100 °C and stirred for appropriate time as mentioned in Table no. 7.4. After confirming the complete consumption of starting material by TLC, the reaction mass was cooled to room temperature and diluted with ethyl acetate (20 mL), filtered through a celite bed and wash with ethyl acetate (10 mL). The filtrate was concentrated in vacuum. The crude product was purified by column chromatography over silica gel (100-200) using ethyl acetate and hexane mixture as an eluent to afford the pure titled products.
7.5.3. General procedure for C–N bond formation by coupling of 4-bromo-7-azaindole derivatives with amino acid esters.

To a 100 mL dried sealed Schlenk tube charged N-substituted 4-bromo azaindole (1.0 mmol), amino acid esters (1.2 mmol), cesium carbonate (3.0 mmol), Pd$_2$(dba)$_3$ (5 mole %), Xantphos (10 mole %), and 2 mL of dioxane were added. Nitrogen gas was bubbled through the reaction mass for 10 minutes. The reaction mixture was heated to 100 °C and stirred for appropriate time as mentioned in Table no. 7.6. After confirming the complete consumption of starting material by TLC, the reaction mass was cooled to room temperature and diluted with ethyl acetate (20 mL), filtered through a celite bed and wash with ethyl acetate (10 mL). The filtrate was concentrated in vacuum. The crude product was purified by column chromatography on silica gel (100-200) using ethyl acetate and hexane mixture as an eluent to afford the pure titled products.

7.5.4. General procedure for C–O bond formation by coupling of 4-bromo-7-azaindole derivatives with phenols

To a 100 mL dried sealed Schlenk tube charged N-substituted 4-bromo azaindole (1.0 mmol), Phenol (1.2 mmol), potassium carbonate (1.5 mmol), Pd(OAc)$_2$ (5 mole %), Xantphos (10 mole %), and 2 mL of dioxane were added. Nitrogen gas was bubbled through the reaction mass for 2 minutes. The reaction mixture was heated to 100 °C and stirred for appropriate time as mentioned in Table no. 7.8. After confirming the complete consumption of starting material by TLC, the reaction mass cooled to room temperature and diluted with ethyl acetate (20 mL), filtered through a celite bed and wash with ethyl acetate (10 mL). The filtrate was concentrated in vacuum. The crude product was purified by column chromatography on silica gel (100-200) using ethyl acetate and hexane mixture as an eluent to afford the pure titled products.

7.5.5. General procedure for α-arylation of ketones:
To a 100 mL dried sealed Schlenk tube containing magnetic stir bar charged aryl halide (1.0 mmol), Ketone (1.2 mmol), sodium tertiary butoxide (1.5 mmol), Pd(OAc)$_2$ (5 mole %), Xantphos (10 mole %), and 2 mL of dioxane were added. Nitrogen gas was bubbled through the reaction mass for 2 minutes. The reaction mixture was heated to 100 °C and stirred for appropriate time as mentioned in Table no. 7.10 and 7.11. After confirming the complete consumption of starting material by TLC, the reaction mass was cooled to room temperature and diluted with ethyl acetate (20 mL), filtered through the celite bed and wash with ethyl acetate (10 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (100-200) using ethyl acetate and hexane mixture as an eluent to afford the pure titled products.

### 7.5.6. General procedure for preparation of Quinoxalines:

To a mixture of ketone (1.0 mmol), o-phenylenediamine (1.0 mmol) and DABCO (20 mol%) in DMF was stirred at 90 °C under an atmosphere of air for appropriate time as mentioned in Table no. 7.12. After confirming the complete consumption of starting material by TLC, the reaction mixture was cooled to room temperature, then poured the reaction mass into water (25 mL) and extracted with Ethyl acetate (3×25 mL). The combined organic layer washed with brine solution (3×25 mL), dried the ethyl acetate layer with anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was then purified by column chromatography on silica gel (100-200 mesh) using n-Hexane and ethyl acetate as eluent to give pure quinoxalines.
**N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)benzamide (34a).**

Off white solid; **MP**: 145-147 °C; **IR (KBr)**: 3400, 3178, 3061, 1656, 1608, 1575, 1498, 1394, 1317, 713, 555; **¹H NMR** (400MHz, DMSO-d₆): δ 10.42 (br s, 1H. NH), 8.20 (d, J = 5.2 Hz, 1H), 7.99-7.97 (m, 2H), 7.72 (d, J = 5.2 Hz, 1H), 7.64-7.53 (m, 3H), 7.41 (d, J = 3.6 Hz, 1H), 6.81 (d, J = 3.6 Hz, 1H), 3.81 (s, 3H, N-CH₃); **¹³C NMR** (50MHz, DMSO-d₆): δ 166.41, 148.75, 142.96, 138.29, 134.61, 131.73, 128.28, 128.05, 127.90, 111.76, 106.87, 98.08, 30.95; **MS (ES)**: m/z = 262.4 (M+H); **ESI-HRMS**: m/z [M+H]+ calculated for C₁₅H₁₄N₃O₂: 262.1126; found 262.1137.

**N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)benzene sulfonamide (34b).**

Off white solid; **MP**: 175-177 °C; **IR (KBr)**: 3259, 3111, 1604, 1571, 1517, 1444, 1398, 1330, 1309, 1161, 1091, 894, 713, 580; **¹H NMR** (400MHz, DMSO-d₆): δ 10.88 (brs, 1H. NH), 8.03 (d, J = 5.6 Hz, 1H), 7.90 (d, J = 2.0 Hz, 1H), 7.87 (d, J = 1.6 Hz, 1H), 7.52-7.60 (m, 3H), 7.33 (d, J = 3.6 Hz, 1H), 6.99 (d, J = 5.6 Hz, 1H), 6.78 (d, J = 3.6 Hz, 1H), 3.72 (s, 3H, N-CH₃); **¹³C NMR** (50MHz, DMSO-d₆): δ 143.02, 139.61, 133.08, 128.28, 128.83, 128.18, 126.56, 125.50, 110.77, 103.50, 97.17, 30.96; **MS (ES)**: m/z = 288.3 (M+H); **ESI-HRMS**: m/z [M+H]+ calculated for C₁₄H₁₄N₃O₂S: 288.0807; found 288.0820.
1-(1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)pyrrolidin-2-one (34c).

Brown thick liquid; IR (KBr): 2924, 1705, 1568, 1384, 1309, 823, 754, 721; \(^1\)H NMR (400MHz, DMSO-\(d_6\)): \(\delta 8.19\ (d, J = 5.2 \text{ Hz}, 1\text{H}), 7.45\ (d, J = 3.6 \text{ Hz}, 1\text{H}), 7.34\ (d, J = 5.2 \text{ Hz}, 1\text{H}), 6.52\ (d, J = 3.6 \text{ Hz}, 1\text{H}), 4.05\ (t, J = 6.8 \text{ Hz}, 2\text{H}), 3.80\ (s, 3\text{H, }\text{N-CH}_3), 2.50\ (t, J = 2.0 \text{ Hz}, 2\text{H}), 2.16\text{-}2.09\ (m, 2\text{H}); \(^{13}\)C NMR (50MHz, DMSO-\(d_6\)): \(\delta 173.98, 149.10, 142.55, 139.13, 128.42, 112.45, 107.72, 99.32, 49.40, 31.78, 31.00, 18.58;\) MS (ES): \(m/z = 216.3\) (M+H).

\(N\)-(1-ethyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-2-methoxybenzamide (34d).

Off white solid; \(^1\)H NMR (400MHz, DMSO-\(d_6\)): \(\delta 10.44\) (br s, 1H. NH), 8.20 (d, J = 5.2 Hz, 1H), 8.08 (d, J = 4.8 Hz, 1H), 7.82 (d, J = 3.6 Hz, 1H), 7.65 (d, J = 4.2 Hz, 1H), 7.53 (m, 1H), 7.22 (d, J = 3.4 Hz, 1H), 7.18 (t, J = 7.2 Hz, 1H), 6.68 (d, J = 3.6 Hz, 1H), 4.30 (m, 2H), 4.03 (s, 3H), 139 (t, 3H, J = 7.2 Hz); \(^{13}\)C NMR (50MHz, DMSO-\(d_6\)): \(\delta 164.22, 157.11, 147.82, 143.34, 137.77, 132.98, 130.60, 126.73, 122.78, 120.78, 112.30, 110.52, 105.14, 96.02, 56.26, 55.69, 15.43;\) MS (ES): \(m/z = 296.30\) (M+H); ESI-HRMS: \(m/z \ [\text{M+H}]^+\) calculated for \(C_{17}H_{18}N_3O_2\): 296.1399; found 296.1397.
N-(1-ethyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-fluorobenzamide (34e).

Off white solid; $^1$H NMR (400MHz, DMSO-$d_6$): $\delta$ 10.47 (br s, 1H, NH), 8.20 (d, $J$ = 4.4 Hz, 1H), 8.08 (d, $J$ = 4.8 Hz, 1H), 8.06 (d, $J$ = 4.4Hz, 1H), 7.69 (d, $J$ = 4.4 Hz, 1H), 7.49 (d, $J$ = 2.8 Hz, 1H), 7.41 (d, $J$ = 7.2 Hz, 2H), 6.81 (d, $J$ = 2.8 Hz, 1H), 4.31 (m, 2H), 1.39 (t, 3H, $J$ = 6.0 Hz); $^{13}$C NMR (100MHz, DMSO-$d_6$): $\delta$ 165.38, 148.24, 142.92, 138.22, 131.14, 131.11, 130.97, 130.88, 126.54, 115.41, 115.19, 112.04, 107.08, 98.28, 38.80, 15.45; MS (ES): $m/z$ = 284.30 (M+H); ESI-HRMS: $m/z$ [M+H]$^+$ calculated for C$_{16}$H$_{15}$N$_3$OF: 284.1199; found 284.1198.

2-amino-N-(1-ethyl-1H-pyrrolo[2,3-b]pyridin-4-yl)benzamide (34f).

Light yellow solid; $^1$H NMR (400MHz, DMSO-$d_6$): $\delta$ 10.51 (s, 1H), 8.16-8.15 (d, $J$ = 5.2 Hz, 1H), 7.69-7.67 (d, $J$ = 7.6 Hz, 1H), 7.62-7.60 (d, $J$ = 5.2 Hz, 1H), 7.46-7.45 (d, $J$ = 3.6 Hz, 1H), 7.26-7.22 (t, $J$ = 6.8 Hz, 1H), 6.79-6.75 (m, 2H), 6.64-6.60 (t, $J$ = 7.6 Hz, 1H), 6.33 (s, 2H), 4.30-4.25 (m, 2H), 1.39-1.35 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR (100MHz, DMSO-$d_6$): $\delta$ 168.36, 149.90, 148.21, 142.88, 138.68, 132.57, 129.53, 126.44,
116.48, 115.07, 114.92, 112.13, 107.08, 98.39, 38.87, 15.62; **MS (ES):** m/z = 281.20 (M+H); **ESI-HRMS: m/z** [M+H]^+ calculated for C\textsubscript{16}H\textsubscript{17}N\textsubscript{4}O: 281.1402; found 281.1395.

\textit{N-(1-benzyl-1H-pyrrolo[2,3-b]pyridin-4-yl)benzamide (34g).}

Light greenish solid; mp: 165-167 °C; **IR (KBr):** 3244, 2924, 1876, 1654, 1575, 1346, 1307, 1055, 902, 821, 721, 704, 557; **\textsuperscript{1}H NMR** (400MHz, DMSO-\textsubscript{d}6): δ 10.44 (brs, s, 1H, NH), 8.20 (d, J = 5.2 Hz, 1H), 7.98–7.96 (m, 2H), 7.74 (d, J = 5.2 Hz, 1H), 7.65-7.54 (m, 3H), 7.53 (d, J = 3.6 Hz, 1H), 7.36-7.21 (m, 4H), 6.87 (d, J = 3.2 Hz, 1H), 5.48 (s, 2H, -N-CH\textsubscript{2}-); **\textsuperscript{13}C NMR** (50MHz, DMSO-\textsubscript{d}6): δ 166.46, 148.50, 143.24, 138.51, 138.45, 134.60, 131.79, 128.40, 128.32, 128.06, 127.21, 127.13, 111.86, 107.23, 98.90, 47.23; **MS (ES):** m/z = 328.4 (M+H); **ESI-HRMS: m/z** [M+H]^+ calculated for C\textsubscript{21}H\textsubscript{18}N\textsubscript{3}O: 328.1450; found 328.1459.

\textit{N-benzyl-1-methyl-1H-pyrrolo[2,3-b]pyridin-4-amine (36a).}

Light brown solid; **MP:** 136-138 °C; **IR (KBr):** 3238, 3028, 1604, 1504, 1336, 1305, 1103, 1076, 869, 707, 623; **\textsuperscript{1}H NMR** (400MHz, DMSO-\textsubscript{d}6): δ 7.77 (d, J = 5.6 Hz, 1H), 7.36-7.28 (m, 4H), 7.23-7.18 (m, 2H), 7.11 (d, J = 3.2 Hz, 1H), 6.60 (d, J = 3.6 Hz, 1H), 6.07 (d, J = 5.6 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 3.69 (s, 3H, N-
\(^{13}\)C NMR (50MHz, DMSO-\(d_6\)): \(\delta\) 147.92, 147.46, 143.86, 139.74, 128.23, 126.81, 126.60, 124.70, 107.44, 96.89, 96.18, 45.48, 30.80; MS (ES): \(m/z = 238.4\) (M+H); ESI-HRMS: \(m/z\) \([M+H]^+\) calculated for \(C_{15}H_{16}N_3\): 238.1344; found 238.1348.

\(N\)-phenyl-1-methyl-1H-pyrrolo[2,3-b]pyridin-4-amine (36b).

Light brown solid; MP: 220.-224 °C; IR (KBr): 3238, 3095, 1610, 1570, 1490, 1330, 1240, 1207, 729, 646; \(^1\)H NMR (400MHz, DMSO-\(d_6\)): \(\delta\) 8.62 (br s, 1H, NH), 7.94 (d, \(J = 5.6\) Hz, 1H), 7.37-7.27 (m, 5H), 7.24 (d, \(J = 3.2\) Hz, 1H), 7.01-7.05 (m, 1H), 6.70 (d, \(J = 5.6\) Hz, 1H), 6.60 (d, \(J = 3.6\) Hz, 1H), 3.75 (s, 3H, N-CH3); \(^{13}\)C NMR (50MHz, DMSO-\(d_6\)): \(\delta\) 148.72, 143.67, 141.07, 129.06, 125.97, 122.30, 120.62, 108.95, 98.62, 97.27, 30.93; MS (ES): \(m/z = 224.2\) (M+H); ESI-HRMS: \(m/z\) \([M+H]^+\) calculated for \(C_{14}H_{14}N_3\): 224.1188; found 224.1186.

4-(1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)morpholine (36c).

Brown solid; MP: 82-84 °C; IR (KBr): 2954, 2816, 1874, 1575, 1355, 1309, 1251, 1112, 991, 812, 709, 628; \(^1\)H NMR (400MHz, DMSO-\(d_6\)): \(\delta\) 8.01 (d, \(J = 5.2\) Hz, 1H), 7.30 (d, \(J = 3.6\) Hz, 1H), 6.50 (d, \(J = 3.6\) Hz, 1H),
6.45 (d, J = 5.2 Hz, 1H), 3.79-3.77 (t, J = 4.8 Hz, 4H), 3.75 (s, 3H, N-CH₃), 3.37-3.35 (t, J = 4.8 Hz, 4H); $^{13}$C NMR (50 MHz, DMSO-$d_6$): δ 150.78, 148.82, 143.49, 126.25, 109.78, 101.16, 98.57, 66.02, 49.07, 30.98; MS (ES): m/z = 218.3 (M+H); ESI-HRMS: m/z [M+H]$^+$ calculated for C$_{12}$H$_{16}$N$_3$O: 218.1293; found 218.1291.

1-ethyl-N-(4-methoxybenzyl)-1H-pyrrolo[2,3-b]pyridin-4-amine (36d).

Light brown solid; MP: 98-100 °C; IR (KBr): 3240, 2927, 1861, 1606, 1572, 1502, 1344, 1317, 1209, 1082, 935, 867, 794, 773, 723, 623; $^1$H NMR (400MHz, DMSO-$d_6$): δ 7.76 (d, J = 5.6 Hz, 1H), 7.29-7.26 (m, 2H), 7.16-7.12 (m, 2H), 6.89-6.85 (m, 2H), 6.58 (d, J = 3.2 Hz, 1H), 6.07 (d, J = 5.6 Hz, 1H), 4.39 (d, J = 6.0 Hz, 1H), 4.17-4.12 (q, J = 7.2 Hz, 2H, N-CH$_3$), 3.70 (s, 3H, O-CH$_3$), 1.33-1.29 (t, J = 7.2 Hz, 3H); $^{13}$C NMR (50MHz, DMSO-$d_6$): δ 158.05, 147.48, 147.29, 143.72, 131.53, 128.09, 123.09, 113.67, 107.55, 97.00, 96.20, 54.97, 44.95, 38.51, 15.66; MS (ES): m/z = 282.4 (M+H); ESI-HRMS: m/z [M+H]$^+$ calculated for C$_{17}$H$_{20}$N$_3$O: 282.1606; found 282.1609.

N-butyl-1-ethyl-1H-pyrrolo[2,3-b]pyridin-4-amine (36e).
Brown solid; **MP**: 93-95 °C; **IR** (KBr): 3234, 2927, 1872, 1604, 1568, 1512, 1340, 1244, 1035, 819, 799, 617; **$^1$H NMR** (400MHz, DMSO-$d_6$): $\delta$ 7.82 (d, $J$ = 5.2 Hz, 1H), 7.13 (d, $J$ = 3.6 Hz, 1H), 6.55 (d, $J$ = 3.2 Hz, 1H), 6.48 (t, $J$ = 5.6 Hz, 1H, NH), 6.11 (d, $J$ = 5.6 Hz, 1H), 4.17 (q, $J$ = 7.2 Hz, 2H), 3.22 (q, $J$ = 6.8 Hz, 2H), 1.61-1.55 (m, 2H), 1.41 (q, $J$ = 7.2 Hz, 2H), 1.33 (t, $J$ = 7.2 Hz, 3H), 0.94 (t, $J$ = 7.2 Hz, 3H); **$^{13}$C NMR** (50MHz, DMSO-$d_6$): $\delta$ 147.71, 147.32, 143.86, 122.80, 107.35, 97.06, 95.50, 41.79, 38.48, 30.82, 19.77, 15.65, 13.76; **MS** (ES): m/z = 218.5 (M+H); **ESI-HRMS**: m/z [M+H]$^+$ calculated for C$_{13}$H$_{20}$N$_3$: 218.1657; found 218.1658.

**Tert-butyl 4-(1-ethyl-1H-pyrrolo[2,3-b]pyridin-4-yl)piperazine-1-carboxylate (36f).**

Brick red solid; **MP**: 82-84 °C; **IR** (KBr): 2976, 1693, 1573, 1498, 1417, 1365, 1240, 1168, 1001, 756, 663; **$^1$H NMR** (400MHz, DMSO-$d_6$): $\delta$ 7.99 (d, $J$ = 5.6 Hz, 1H), 7.36 (d, $J$ = 3.2 Hz, 1H), 6.51 (d, $J$ = 3.6 Hz, 1H), 6.45 (d, $J$ = 5.6 Hz, 1H), 4.24 (q, $J$ = 7.6 Hz, 2H), 3.53 (t, $J$ = 4.8 Hz, 4H), 3.38 (t, $J$ = 4.8 Hz, 4H), 1.43 (s, 9H, C-(CH$_3$)$_3$), 1.35 (t, $J$ = 7.6 Hz, 3H); **$^{13}$C NMR** (50MHz, DMSO-$d_6$): $\delta$ 153.79, 150.54, 148.14, 143.36, 124.75, 110.04, 101.47, 98.63, 78.95, 48.45, 43.08, 28.03, 15.50; **MS** (ES): m/z = 331.5 (M+H); **ESI-HRMS**: m/z [M+H]$^+$ calculated for C$_{18}$H$_{27}$N$_4$O$_2$: 331.2134; found 331.2139.
(R)-methyl 2-((1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)amino)propanoate (38b).

Pale yellow solid; $^1$H NMR (400MHz, CDCl$_3$): δ 8.08 (d, $J$ = 5.2 Hz, 1H), 6.98 (d, $J$ = 3.6 Hz, 1H), 6.38 (d, $J$ = 3.6 Hz, 1H), 6.15 (d, $J$ = 5.2 Hz, 1H), 4.94 (d, $J$ = 8.0 Hz, 1H), 4.42-4.35 (m, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 1.58 (d, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100MHz, CDCl$_3$): δ 174.19, 148.30, 146.01, 144.53, 125.53, 108.13, 96.80, 95.60, 52.43, 50.97, 31.42, 18.75; MS (ES): m/z = 234.20 (M+H); ESI-HRMS: m/z [M+H]$^+$ calculated for C$_{12}$H$_{15}$N$_3$O$_2$: 234.1234; found 234.1236; ee% 98.79 (the methyl ester) (HPLC: Chiral Pak AD-H Column, n-heptane:ethanol:IP amine (60:40:0.10), 1.0 mL/min, 240nm, t = 30 °C).

Ethyl 2-((1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)amino)acetate (38c).

Pale yellow solid; $^1$H NMR (400MHz, CDCl$_3$): δ 8.10 (d, $J$ = 5.6 Hz, 1H), 6.98 (d, $J$ = 3.6 Hz, 1H), 6.40 (d, $J$ = 3.6 Hz, 1H), 6.13 (d, $J$ = 5.6 Hz, 1H), 5.02 (s, 1H), 4.31-4.26 (m, 2H), 4.09 (d, $J$ = 4.8 Hz, 2H), 3.83 (s, 3H), 1.34-1.30 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100MHz, CDCl$_3$): δ 170.35, 148.22, 146.48, 144.54, 125.48, 107.99, 96.73, 95.64, 61.54, 44.74, 31.38, 14.09; MS (ES): m/z = 234.20 (M+H); ESI-HRMS: m/z [M+H]$^+$ calculated for C$_{12}$H$_{16}$N$_3$O$_2$: 234.1243; found 234.1237.
(R)-methyl 3-(tert-butoxy)-2-((1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl) amino)propanoate (38d).

Pale yellow solid; $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 8.07 (d, $J$ = 5.2 Hz, 1H), 6.98 (d, $J$ = 3.2 Hz, 1H), 6.40 (d, $J$ = 3.6 Hz, 1H), 6.14 (d, $J$ = 5.2 Hz, 1H), 5.23 (d, $J$ = 8.8 Hz, 1H), 4.4-4.40 (m, 1H), 3.88 (dd, $J$ = 4.0 & 8.8 Hz, 1H), 3.83 (s, 3H), 3.77 (m, 1H), 3.76 (s, 3H), 1.17 (s, 9H); $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 171.95, 148.38, 146.46, 144.47, 125.50, 108.34, 97.02, 95.74, 73.67, 62.19, 56.08, 52.34, 31.46, 27.30; MS (ES): m/z = 306.20 (M+H); ESI-HRMS: m/z [M+H]$^+$ calculated for C$_{16}$H$_{24}$N$_3$O$_3$: 361.1818; found 361.1815; ee% 95.48 (the methyl ester) (HPLC: Chiral Pak AD-H Column, n-heptane:ethanol:IP amine (60:40:0.10), 1.0 mL/min, 240nm, t = 30 °C).

(R)-methyl 2-((1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)amino)propanoate (38e).

Pale yellow solid; $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 8.07 (d, $J$ = 6.0 Hz, 1H), 7.04 (d, $J$ = 3.6 Hz, 1H), 6.39 (d, $J$ = 3.6 Hz, 1H), 6.15 (d, $J$ = 5.2 Hz, 1H), 4.91 (d, $J$ = 8.0 Hz, 1H), 4.40-4.35 (m, 1H), 4.31-4.25 (m, 2H), 3.77 (s, 3H), 1.58 (d, $J$ = 6.8 Hz, 3H), 1.47 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 174.20, 147.68, 145.97, 144.39, 123.79, 108.21, 96.76, 95.65, 52.39, 50.94, 39.36, 18.74, 15.68; MS (ES): m/z = 248.20 (M+H);
**ESI-HRMS:** $m/z \ [M+H]^+ \text{ calculated for } C_{13}H_{18}N_3O_2: \ 248.1399; \text{ found 248.1398; } \text{ee\% \ 98.91 (the methyl ester); (HPLC: Chiral Pak AD-H Column, n-heptane:ethanol:IP amine (60:40:0.10), 1.0 mL/min, 240nm, } t = \ 30 \ ^{\circ}\text{C}).}$

**Ethyl 2-((1-ethyl-1H-pyrrolo[2,3-b]pyridin-4-yl)amino)acetate (38f).**

Pale yellow solid; $^1\text{H NMR (400MHz, CDCl}_3): \delta \ 8.09 (d, J = 5.6 \text{ Hz, 1H}), 7.04 (d, J = 3.6 \text{ Hz, 1H}), 6.40 (d, J = 3.2 \text{ Hz, 1H}), 6.12 (d, J = 5.2 \text{ Hz, 1H}), 5.08 (s, 1H), 4.31-4.26 (m, 4H), 4.09 (d, J = 4.8 \text{ Hz, 2H}), 1.47-1.43 (t, J = 7.2 \text{ Hz, 3H}), 1.34-1.31 (t, J = 6.8 \text{ Hz, 3H}); ^{13}\text{C NMR (100MHz, CDCl}_3): \delta \ 170.37, 147.62, 146.47, 144.42, 123.75, 108.11, 96.72, 95.69, 61.53, 44.75, 39.33, 15.68, 14.09; \textbf{MS (ES): } m/z = 248.20 (M+H); \textbf{ESI-HRMS: } m/z \ [M+H]^+ \text{ calculated for } C_{13}H_{18}N_3O_2: \ 248.1399; \text{ found 248.1397.}$

**Methyl 2-((1-ethyl-1H-pyrrolo[2,3-b]pyridin-4-yl)amino)acetate (38g).**

Pale yellow solid; $^1\text{H NMR (400MHz, CDCl}_3): \delta \ 8.09 (d, J = 5.2 \text{ Hz, 1H}), 7.04 (d, J = 3.2 \text{ Hz, 1H}), 6.41 (d, J = 4.0 \text{ Hz, 1H}), 6.12 (d, J = 5.2 \text{ Hz, 1H}), 4.99 (s, 1H), 4.31-4.26 (m, 2H), 4.11 (d, J = 5.6 \text{ Hz, 2H}), 3.83 (s, 3H), 1.47-1.44 (t, J = 7.2 \text{ Hz, 3H}); ^{13}\text{C NMR (100MHz, CDCl}_3): \delta \ 170.84, 147.58, 146.42, 144.38, 123.78, 108.09,$
96.65, 95.67, 52.33, 44.55, 39.32, 15.65; **MS (ES):** m/z = 234.20 (M+H); **ESI-HRMS:** m/z [M+H]^+ calculated for C_{12}H_{16}N_{3}O_{2}: 234.1243; found 234.1236.

1-methyl-4-(m-tolyloxy)-1H-pyrrolo[2,3-b]pyridine (40a).

**^1H NMR** (400MHz, CDCl$_3$): δ 8.18 (d, J = 5.6 Hz, 1H), 7.29-7.25 (m, 2H), 7.05-6.91 (m, 3H), 6.48 (d, J = 5.6 Hz, 1H), 6.32 (d, J = 3.6 Hz, 1H), 3.88 (s, 3H, N-CH$_3$), 2.36 (s, 3H, -CH$_3$); **^13C NMR** (100MHz, CDCl$_3$): δ 158.11, 155.17, 144.33, 140.04, 129.48, 127.40, 125.46, 121.04, 117.39, 111.36, 102.81, 97.02, 31.53, 21.35; **MS (ES):** m/z = 239.10 (M+H); **ESI-HRMS:** m/z [M+H]^+ calculated for C$_{15}$H$_{15}$N$_2$O: 239.1184; found 239.1174.

4-(4-methoxyphenoxy)-1-methyl-1H-pyrrolo[2,3-b]pyridine (40b).

**^1H NMR** (400MHz, CDCl$_3$): δ 8.15 (d, J = 5.2 Hz, 1H), 7.12-7.07 (m, 2H), 7.05 (d, J = 3.6 Hz, 1H), 6.95-6.92 (m, 2H), 6.40 (d, J = 5.2 Hz, 1H), 6.33 (d, J = 3.2 Hz, 1H), 3.88 (s, 3H, N-CH$_3$), 3.84 (s, 3H, O-CH$_3$); **^13C NMR** (100MHz, CDCl$_3$): δ 159.03, 156.75, 148.36, 144.23, 127.34, 121.84, 116.13, 114.85, 110.99, 101.91,
97.05, 55.63, 31.62; **MS (ES)**: m/z = 255.10 (M+H); **ESI-HRMS**: m/z [M+H]$^+$ calculated for C$_{15}$H$_{15}$N$_2$O$_2$: 255.1134; found 255.1144.

1-methyl-4-(naphthalen-1-yloxy)-1H-pyrrolo[2,3-b]pyridine (40c).

$^1$H NMR (400MHz, CDCl$_3$): $\delta$ 8.14 (d, $J = 5.6$ Hz, 1H), 8.07 (d, $J = 8.4$, 1H)), 7.92 (d, $J = 8.4$ Hz, 1H), 7.76 (d, $J = 8.4$ Hz, 1H), 7.55-7.44 (m, 4H), 7.23 (t, $J = 7.6$ Hz, 1H), 7.08 (d, $J = 3.6$ Hz, 1H), 6.39 (d, $J = 3.6$ Hz, 1H), 3.90 (s, 3H, N-CH$_3$; 13C NMR (100MHz, CDCl$_3$): $\delta$ 158.69, 150.85, 144.43, 134.96, 127.89, 127.55, 128.08, 126.67, 126.29, 125.68, 125.01, 121.99, 116.26, 111.07, 102.55, 102.44, 96.99, 31.60; **MS (ES)**: m/z = 275.10 (M+H); **ESI-HRMS**: m/z [M+H]$^+$ calculated for C$_{18}$H$_{15}$N$_2$O: 275.1184; found 275.1175.

1-(4-methoxyphenyl)-2-(1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)ethanone (42a)

White solid; $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 8.27 (d, $J = 4.8$ Hz, 1H), 8.00 (d, $J = 8.8$ Hz, 2H), 7.18 (d, $J = 3.2$ Hz, 1H), 6.95 (d, $J = 4.8$ Hz, 1H), 6.91 (d, $J = 8.8$ Hz, 2H), 6.50 (d, $J = 4.0$ Hz, 1H), 4.47 (s, 2H), 3.87 (s, 3H), 3.84 (s, 3H); $^{13}$C NMR (50MHz, CDCl$_3$): $\delta$ 194.97, 163.64, 143.04, 136.37, 130.93, 129.55, 128.92, 116.38,
113.84, 97.81, 55.48, 42.83, 31.43; **MS (ES):** m/z = 281.30 (M+H); **ESI-HRMS:** m/z [M+H]^+ calculated for C_{17}H_{17}N_{2}O_{2}: 281.1290, found: 281.1284.

1-(3-hydroxyphenyl)-2-(1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)ethanone (42b)

White solid; **IR (KBr):** 3350, 2934, 1684, 1580, 1514, 1409, 1351, 1275, 1160, 890, 877, 717, 706, 554; **^1H NMR (400MHz, DMSO-d_6):** δ 9.78 (s, 1H), 8.18 (d, J = 4.8 Hz, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.47 (d, J = 4.0 Hz, 1H), 7.38-7.37 (t, J = 2.4 Hz, 1H), 7.34-7.30 (t, J = 7.6 Hz, 1H), 7.03 (dd, J = 2.0 & 8.0 Hz, 1H), 6.97 (d, J = 4.8 Hz, 1H), 6.49 (d, J = 3.2 Hz, 1H), 4.59 (s, 2H), 3.80 (s, 3H); **^{13}C NMR (50MHz, CDCl_3+DMSO-d_6):** δ 195.62, 157.09, 147.04, 142.01, 137.06, 135.48, 128.94, 128.35, 120.16, 119.91, 118.88, 115.88, 114.39, 97.15, 42.14, 30.64; **MS (ES):** m/z = 267.10 (M+H); **ESI-HRMS:** m/z [M+H]^+ calculated for C_{16}H_{15}N_{2}O_{2}: 267.1134, found: 267.1135.

1-(4-chlorophenyl)-2-(1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)ethanone (41c)

White solid; **^1H NMR (400MHz, CDCl_3):** δ 8.29 (d, J = 4.4 Hz, 1H), 7.96 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 3.2 Hz, 1H), 6.94 (d, J = 5.2 Hz, 1H), 6.48 (d, J = 3.2 Hz, 1H), 4.49 (s, 2H), 3.89 (s, 3H); **^{13}C NMR (100MHz, CDCl_3):** δ 195.17, 142.72, 139.84, 135.92, 134.64, 129.96, 129.79, 129.49, 129.31,
129.21, 116.40, 97.75, 43.02, 31.59; **MS (ES):** m/z = 285.10 (M+H); **ESI-HRMS:** m/z [M+H]^+ calculated for C_{16}H_{14}N_{2}OCl: 285.0795, found: 285.0783.

2-(1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-1-(m-tolyl)ethanone (42d)
White solid; **^1H NMR** (400MHz, CDCl$_3$): δ 8.28 (d, $J = 4.8$ Hz, 1H), 7.84 (s, 1H), 7.83 (d, $J = 8.4$ Hz, 1H), 7.38-7.30 (m, 2H), 7.18 (d, $J = 2.8$ Hz, 1H), 6.96 (d, $J = 4.8$ Hz, 1H), 6.49 (d, $J = 3.6$ Hz, 1H) 4.52 (s, 2H), 3.88 (s, 3H), 2.39 (s, 3H); **^13C NMR** (100MHz, CDCl$_3$): δ 196.52, 147.64, 142.76, 138.46, 136.43, 136.24, 134.09, 129.02, 129.01, 128.43, 125.78, 120.70, 116.46, 97.79, 42.95, 31.45, 21.28; **MS (ES):** m/z = 265.20 (M+H); **ESI-HRMS:** m/z [M+H]^+ calculated for C$_{17}$H$_{17}$N$_2$O: 265.1341, found: 265.1331.

2-(1-ethyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-1-(3-(trifluoromethyl)phenyl)ethanone (42e)
White solid; **^1H NMR** (400MHz, CDCl$_3$): δ 8.30 (d, $J = 3.6$ Hz, 1H), 8.28 (s, 1H), 8.19 (d, $J = 7.6$ Hz, 1H), 7.82 (d, $J = 8.0$ Hz, 1H), 7.60-7.56 (t, $J = 7.6$ Hz, 1H), 7.27 (d, $J = 5.2$ Hz, 1H), 6.96 (d, $J = 4.8$ Hz, 1H), 6.49 (d, $J = 3.2$ Hz, 1H) 4.55 (s, 2H), 4.37-4.32 (m, 2H), 1.49 (t, $J = 7.2$ Hz, 3H); **^13C NMR** (100MHz, CDCl$_3$): δ 194.98, 146.98, 142.61, 136.80, 135.28, 131.68, 129.75, 129.72, 129.38, 127.68, 125.39, 125.35, 120.80, 116.45, 97.74, 43.11, 39.65, 15.58; **MS (ES):** m/z = 333.20 (M+H); **ESI-HRMS:** m/z [M+H]^+ calculated for C$_{18}$H$_{16}$N$_2$OF$_3$: 333.1215, found: 333.1206.
2-(1-ethyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-1-phenylethanone (42f)

Pale yellow solid; $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 8.27 (d, $J = 4.8$ Hz, 1H), 8.04 (d, $J = 6.8$ Hz, 2H), 7.57-7.52 (m, 1H), 7.46-7.42 (t, $J = 8.4$ Hz, 2H), 7.24 (d, $J = 4.0$ Hz, 1H), 6.95 (d, $J = 4.8$ Hz, 1H), 6.49 (d, $J = 3.2$ Hz, 1H), 4.53 (s, 2H), 4.36-4.31 (m, 2H), 1.49 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 196.37, 147.10, 142.68, 136.39, 135.96, 133.29, 128.63, 128.53, 127.33, 120.74, 116.47, 97.79, 42.91, 39.48, 15.59; MS (ES): m/z = 265.20 (M+H);

2-(1-ethyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-1-(4-methoxyphenyl)ethanone (42g)

Pale yellow solid; $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 8.26 (d, $J = 4.8$ Hz, 1H), 8.02 (d, $J = 6.8$ Hz, 2H), 7.24 (d, $J = 3.6$ Hz, 1H), 6.95 (d, $J = 4.8$ Hz, 1H), 6.92 (d, $J = 8.8$ Hz, 2H), 6.51 (d, $J = 3.6$ Hz, 1H), 4.47 (s, 2H), 4.36-4.31 (m, 2H), 3.85 (s, 3H), 1.49-1.46 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 194.98, 163.59, 147.20, 142.75, 136.30, 130.87, 129.45, 127.21, 120.61, 116.35, 113.76, 97.79, 55.39, 42.68, 39.41, 15.60; MS (ES): m/z = 295.20 (M+H); ESI-HRMS: m/z [M+H]$^+$ calculated for C$_{18}$H$_{19}$N$_2$O$_2$: 295.1447, found: 295.1444.
1-(benzo[d][1,3]dioxol-5-yl)-2-(1-benzyl-1H-pyrrolo[2,3-b]pyridin-4-yl)ethanone (42h)

Pale yellow solid; \(^1^H\) NMR (400MHz, CDCl\(_3\)): \(\delta\) 8.29 (d, \(J = 4.8\) Hz, 1H), 7.66 (d, \(J = 7.6\) Hz, 1H), 7.48 (s, 1H), 7.32-7.17 (m, 6H), 6.97 (d, \(J = 5.2\) Hz, 1H), 6.84 (d, \(J = 8.4\) Hz, 1H), 6.52 (d, \(J = 3.6\) Hz, 1H), 6.03 (s, 2H), 5.48 (s, 2H), 4.46 (s, 2H); \(^{13}^C\) NMR (100MHz, CDCl\(_3\)): \(\delta\) 194.46, 151.98, 148.24, 147.73, 143.16, 137.57, 136.29, 131.25, 128.64, 127.85, 127.57, 127.52, 125.04, 120.43, 116.69, 108.27, 107.89, 101.87, 98.51, 47.95, 42.73; \(\text{MS (ES)}\): \(m/z = 371.20\) (M+H); \(\text{ESI-HRMS}\): \(m/z [M+H]^+\) calculated for \(C_{23}H_{18}N_2O_3\): 371.1396, found: 371.1393.

2-(1-benzyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-1-(furan-2-yl)ethanone (41i)

White solid; \(^1^H\) NMR (400MHz, CDCl\(_3\)): \(\delta\) 8.30 (d, \(J = 4.4\) Hz, 1H), 7.60 (s, 1H), 7.31-7.17 (m, 7H), 7.05 (d, \(J = 4.4\) Hz, 1H), 6.58-6.57 (t, \(J = 2.0\) Hz, 1H), 6.54-6.53 (t, \(J = 2.0\) Hz, 1H), 5.48 (s, 2H), 4.39 (s, 2H); \(^{13}^C\) NMR (100MHz, CDCl\(_3\)): \(\delta\) 185.12, 152.25, 147.59, 146.66, 143.01, 137.53, 135.55, 128.64, 127.92, 127.57, 127.49, 120.66, 118.00, 116.90, 112.51, 98.70, 47.99, 42.69; \(\text{MS (ES)}\): \(m/z = 317.20\) (M+H); \(\text{ESI-HRMS}\): \(m/z [M+H]^+\) calculated for \(C_{20}H_{17}N_2O_2\): 317.1290, found: 317.1287.
2-(1-methyl-1H-indol-5-yl)-1-(m-tolyl)ethanone (44a)

Pale yellow solid; \(^1\)H NMR (400MHz, CDCl\(_3\)): \(\delta\) 7.85 (s, 1H), 7.83 (d, \(J = 1.2\) Hz, 1H), 7.50 (s, 1H), 7.34-7.25 (m, 3H), 7.13 (dd, \(J = 1.6\) & 8.0 Hz, 1H), 7.01 (d, \(J = 2.8\) Hz, 1H), 6.42 (d, \(J = 2.8\) Hz, 1H), 4.35 (s, 2H), 3.75 (s, 3H), 2.38 (s, 3H); \(^{13}\)C NMR (100MHz, CDCl\(_3\)): \(\delta\) 198.75, 138.27, 136.81, 135.77, 133.63, 129.17, 129.12, 128.81, 128.35, 126.00, 125.34, 122.96, 121.39, 109.39, 100.72, 45.76, 32.80, 21.35; MS (ES): \(m/z = 264.20\) (M+H); ESI-HRMS: \(m/z\) [M+H]\(^+\) calculated for C\(_{18}\)H\(_{18}\)NO: 264.1388, found: 264.1379.

1-(4-chlorophenyl)-2-(1-methyl-1H-indol-5-yl)ethanone (44b)

Pale yellow solid; \(^1\)H NMR (400MHz, CDCl\(_3\)): \(\delta\) 7.97 (d, \(J = 8.8\) Hz, 2H), 7.49 (s, 1H), 7.39 (d, \(J = 2.0\) Hz, 2H), 7.28 (d, \(J = 8.8\) Hz, 1H), 7.11 (dd, \(J = 1.6\) & 8.4 Hz, 1H), 7.03 (d, \(J = 3.2\) Hz, 1H), 6.42 (d, \(J = 2.8\) Hz, 1H), 4.32 (s, 2H), 3.76 (s, 3H); \(^{13}\)C NMR (100MHz, CDCl\(_3\)): \(\delta\) 197.28, 139.24, 135.82, 134.99, 130.19, 129.28, 128.80, 124.89, 122.76, 121.32, 109.53, 100.74, 45.88, 32.83; MS (ES): \(m/z = 284.10\) (M+H); ESI-HRMS: \(m/z\) [M+H]\(^+\) calculated for C\(_{17}\)H\(_{15}\)NOCl: 284.0842, found: 284.0840.
1-(4-fluorophenyl)-2-(1-methyl-1H-indol-5-yl)ethanone (44c)

White solid; $^1$H NMR (400MHz, CDCl$_3$): δ 8.07 (d, $J = 8.8$ Hz, 2H), 7.49 (s, 1H), 7.28 (d, $J = 2.0$ Hz, 1H), 7.12 (d, $J = 1.2$ Hz, 1H), 7.10 (d, $J = 8.8$ Hz, 2H), 7.02 (d, $J = 3.2$ Hz, 1H), 6.42 (d, $J = 3.2$ Hz, 1H), 4.33 (s, 2H), 3.76 (s, 3H); $^{13}$C NMR (100MHz, CDCl$_3$): δ 196.91, 166.79, 135.80, 133.10, 131.42, 131.33, 129.26, 128.85, 125.06, 122.77, 121.31, 115.68, 115.46, 109.50, 100.72, 45.83, 32.82; MS (ES): m/z = 268.20 (M+H); ESI-HRMS: m/z [M+H]$^+$ calculated for C$_{17}$H$_{15}$NOF: 268.1138, found: 268.1135.

2-(1-ethyl-1H-indol-5-y1)-1-(4-isopropylphenyl)ethanone (44d)

White solid; $^1$H NMR (400MHz, CDCl$_3$): δ 7.99 (d, $J = 8.4$ Hz, 2H), 7.52 (s, 1H), 7.29 (d, $J = 8.4$ Hz, 2H), 7.26 (d, $J = 3.2$ Hz, 1H), 7.13 (dd, $J = 1.6$&$8.4$ Hz, 1H), 7.08 (d, $J = 3.2$ Hz, 1H), 6.42 (d, $J = 4.0$ Hz, 1H), 4.34 (s, 2H), 4.16-4.10 (m, 2H), 2.94-2.91 (m, 1H), 1.45-1.42 (t, $J = 7.2$ Hz, 3H), 1.25 (d, $J = 7.2$ Hz, 6H); $^{13}$C NMR (100MHz, CDCl$_3$): δ 198.11, 154.25, 134.74, 134.56, 128.99, 128.95, 127.28, 126.56, 125.40, 122.75, 121.42, 109.42, 100.80, 45.66, 40.92, 34.12, 23.58, 15.39; MS (ES): m/z = 306.30 (M+H); ESI-HRMS: m/z [M+H]$^+$ calculated for C$_{21}$H$_{24}$NO: 306.1858, found: 306.1848.
2-(1-benzyl-1H-indol-5-yl)-1-(m-tolyl)ethanone (44e)

Pink solid; $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 7.84 (d, $J = 6.4$ Hz, 2H), 7.53 (s, 1H), 7.34-7.26 (m, 4H), 7.24-7.21 (m, 2H), 7.10-7.06 (m, 4H), 6.48 (d, $J = 2.8$ Hz, 1H), 5.28 (s, 2H), 4.34 (s, 2H), 2.39 (s, 3H); $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 198.66, 138.27, 137.42, 136.81, 135.37, 133.65, 129.15, 129.05, 128.69, 128.56, 128.36, 127.55, 126.76, 125.98, 125.58, 123.19, 121.53, 109.84, 101.50, 50.08, 45.60, 21.33; MS (ES): m/z = 340.20 (M+H); ESI-HRMS: m/z [M+H]$^+$ calculated for C$_{24}$H$_{22}$NO: 340.1701, found: 340.1689.

2-(1-benzyl-1H-indol-5-yl)-1-(4-fluorophenyl)ethanone (44f)

White solid; $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 8.06 (d, $J = 8.8$ Hz, 2H), 7.52 (s, 1H), 7.30-7.22 (m, 4H), 7.10-7.04 (m, 6H), 6.49 (d, $J = 2.8$ Hz, 1H), 5.28 (s, 2H), 4.32 (s, 2H); $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 196.82, 166.79, 164.27, 137.34, 135.39, 133.09, 131.39, 131.30, 129.08, 128.69, 127.57, 126.75, 125.29, 123.01, 121.43, 115.67, 115.46, 109.94, 101.49, 50.08, 45.65; MS (ES): m/z = 344.20 (M+H); ESI-HRMS: m/z [M+H]$^+$ calculated for C$_{23}$H$_{19}$NOF: 344.1451, found: 344.1444.
2-(1-benzyl-1H-indol-5-yl)-1-(4-isopropylphenyl)ethanone (44g)

White solid; $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 7.99 (d, $J = 8.4$ Hz, 2H), 7.53 (s, 1H), 7.30-7.21 (m, 6H), 7.11-7.07 (m, 4H), 6.48 (d, $J = 2.4$ Hz, 1H), 5.28 (s, 2H), 4.33 (s, 2H), 2.95-2.92 (m, 1H), 1.25 (d, $J = 7.2$ Hz, 6H); $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 198.05, 154.31, 137.41, 135.36, 134.58, 129.04, 128.98, 128.69, 128.55, 127.54, 126.75, 126.59, 125.74, 123.16, 121.48, 109.83, 101.49, 50.06, 45.56, 34.16, 23.60; MS (ES): m/z = 368.20 (M+H); ESI-HRMS: m/z [M+H]$^+$ calculated for C$_{26}$H$_{26}$NO: 368.2014, found: 368.2007.

2-(1-benzyl-1H-indol-5-yl)-1-(furan-2-yl)ethanone (44h)

Pink solid; $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 7.57 (s, 2H), 7.29-7.23 (m, 4H), 7.20 (d, $J = 3.2$ Hz, 1H), 7.12-7.08 (m, 4H), 6.49 (t, $J = 2.0$ Hz, 2H), 5.28 (s, 2H), 4.18 (s, 2H); $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 187.45, 152.47, 146.38, 137.39, 135.46, 129.02, 128.72, 128.66, 127.58, 126.75, 125.09, 123.22, 121.66, 117.86, 112.24, 109.84, 101.53, 50.12, 45.58; MS (ES): m/z = 316.20 (M+H); ESI-HRMS: m/z [M+H]$^+$ calculated for C$_{21}$H$_{18}$NO$_2$: 316.1338, found: 316.1326.
1-{benzo[d][1,3]dioxol-5-yl}-2-(quinolin-3-yl)ethanone (46)

Pale yellow solid; IR (KBr): 2904, 1680, 1600, 1500, 1492, 1436, 1261, 1246, 1096, 1032, 812, 804, 752; ¹H NMR (400MHz, CDCl₃): δ 8.83 (d, J = 2.0 Hz, 1H), 8.10 (d, J = 8.8 Hz, 1H), 8.04 (d, J = 1.6 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.71-7.66 (m, 2H), 7.55-7.50 (m, 2H), 6.89 (d, J = 8.0 Hz, 1H), 6.05 (s, 2H), 4.40 (s, 2H); ¹³C NMR (100MHz, CDCl₃): δ 194.74, 152.06, 151.77, 148.28, 146.98, 136.01, 130.95, 129.10, 129.03, 127.86, 127.56, 127.45, 126.65, 124.82, 108.06, 107.92, 101.89, 42.20; MS (ES): m/z = 292.10 (M+H); ESI-HRMS: m/z [M+H]⁺ calculated for C₁₉H₁₄NO₃: 292.0974, found: 292.0972.

2-{benzo[d][1,3]dioxol-5-yl}-3-(quinolin-3-yl)quinoxalines (50)

Pale yellow solid; ¹H NMR (400MHz, CDCl₃): δ 8.87 (d, J = 2.0 Hz, 1H), 8.63 (d, J = 2.0 Hz, 1H), 8.22-8.17 (m, 2H), 8.05 (dd, J = 2.0 & 8.0 Hz, 2H), 7.95-7.85 (m, 2H), 7.83-7.80 (m, 1H), 7.68 (t, J = 8.0 Hz, 1H), 7.16 (d, J = 1.6 Hz, 1H), 6.99 (dd, J = 1.2 & 7.6 Hz, 1H), 6.89 (d, J = 7.6 Hz, 1H), 6.06 (s, 2H); ¹³C NMR (100MHz, CDCl₃): δ 152.80, 150.78, 150.16, 148.64, 148.06, 147.54, 141.29, 136.97, 132.36, 130.46, 130.30, 130.11, 129.22, 129.12, 128.37, 127.53, 127.02, 124.52, 109.98, 108.52, 101.38; MS (ES): m/z = 378.30 (M+H); ESI-HRMS: m/z [M+H]⁺ calculated for C₂₄H₁₆N₂O₂: 378.1243, found: 378.1259.
2-(benzo[d][1,3]dioxol-5-yl)-6-chloro-3-(quinolin-3-yl)quinoxalines (51)

Yellow solid; $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 8.94 (d, $J = 2.0$ Hz, 1H), 8.54 (d, $J = 2.0$ Hz, 1H), 8.19 (dd, $J = 2.0$ & 6.8 Hz, 1H), 8.13 (d, $J = 5.2$ Hz, 1H), 8.11 (d, $J = 5.2$ Hz, 1H), 7.88 (d, $J = 7.6$ Hz, 1H), 7.80-7.72 (m, 2H), 7.62-7.58 (m, 1H), 7.12 (d, $J = 1.6$ Hz, 1H), 6.96 (d, $J = 8.0$ Hz, 1H), 6.74 (d, $J = 8.4$ Hz, 1H), 5.99 (s, 2H); $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 153.54, 152.85, 150.57, 148.87, 148.09, 147.59, 141.46, 139.70, 137.09, 136.17, 135.77, 131.98, 131.40, 131.04, 130.42, 130.29, 129.20, 128.37, 127.94, 127.08, 124.60, 109.89, 108.50, 101.43; MS (ES): m/z = 412.10 (M+H); ESI-HRMS: m/z [M+H]$^+$ calculated for C$_{24}$H$_{15}$N$_3$O$_2$Cl: 412.0853, found: 412.0863.

2-(1-ethyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-3-phenylquinoxaline (52)

Pale yellow solid; $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 8.25 (d, $J = 4.4$ Hz, 2H), 8.23-8.20 (m, 1H), 7.84-7.80 (m, 2H), 7.53 (d, $J = 6.8$ Hz, 2H), 7.32 (d, $J = 6.8$ Hz, 1H), 7.28 (d, $J = 3.6$ Hz, 2H), 7.24-7.22 (m, 1H), 6.96 (d, $J = 4.8$ Hz, 1H), 6.49 (d, $J = 3.2$ Hz, 1H), 4.38-4.35 (m, 2H), 1.50 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 153.64, 151.53, 147.84, 142.18, 141.46, 140.96, 138.93, 138.43, 130.46, 130.08, 129.46, 129.28,
128.95, 128.53, 128.24, 119.44, 116.66, 99.11, 39.49, 15.63; **MS (ES):** m/z = 351.20 (M+H); **ESI-HRMS:** m/z [M+H]^+ calculated for C_{23}H_{19}N_4: 351.1610, found: 351.1599.

2-(benzo[d][1,3]dioxol-5-yl)-3-(1-benzyl-1H-pyrrolo[2,3-b]pyridin-4-yl)quinoxalines (53)
Pale yellow solid; ^1H NMR (400MHz, CDCl_3): δ 8.35 (d, J = 4.8 Hz, 1H), 8.20-8.17 (m, 2H), 7.88 (s, 1H), 7.81-7.79 (m, 2H), 7.19 (d, J = 2.8 Hz, 2H), 7.12-7.10 (t, J = 2.4 Hz, 2H), 6.94 (dd, J = 2.4&8.0 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 6.44 (d, J = 3.6 Hz, 1H), 5.94 (s, 2H), 5.53 (s, 2H); ^13C NMR (100MHz, CDCl_3): δ 152.99, 151.29, 148.43, 148.36, 147.66, 142.82, 141.43, 140.82, 139.25, 137.58, 132.39, 130.51, 129.96, 129.25, 129.14, 129.11, 128.65, 127.60, 127.40, 124.20, 119.12, 116.77, 109.74, 108.11, 101.23, 99.79, 47.96; **MS (ES):** m/z = 457.20 (M+H); **ESI-HRMS:** m/z [M+H]^+ calculated for C_{29}H_{21}N_4O_2: 457.1665, found: 457.1664.

2-(1-methyl-1H-indol-5-yl)-3-(m-tolyl)quinoxalines (54)
Pale yellow solid; ^1H NMR (400MHz, CDCl_3): δ 8.18 (d, J = 6.8 Hz, 2H), 7.93 (s, 1H), 7.74-7.72 (t, J = 4.0 Hz, 2H), 7.54 (s, 1H), 7.28 (d, J = 1.6 Hz, 1H), 7.21-7.09 (m, 4H), 7.05 (d, J = 2.8 Hz, 1H), 6.48 (d, J = 2.8 Hz, 1H), 3.78 (s, 3H), 2.34 (s, 3H); ^13C NMR (100MHz, CDCl_3): δ 154.71, 153.94, 141.34, 140.84, 139.66,
138.04, 136.91, 130.29, 130.18, 129.59, 129.47, 129.30, 129.25, 129.07, 129.05, 128.42, 127.79, 127.03, 123.75, 123.04, 108.70, 101.92, 39.90, 21.48; **MS (ES):** m/z = 350.20 (M+H); **ESI-HRMS:** m/z [M+H]^+ calculated for C_{24}H_{20}N_{3}: 350.1657, found: 350.1646.

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2-(4-fluorophenyl)-3-(1-methyl-1H-indol-5-yl)quinoxalines (55)

Light pink solid; **^1^H NMR (400MHz, CDCl\textsubscript{3}):** δ 8.16 (d, J = 10.4 Hz, 2H), 7.89 (s, 1H), 7.76 (d, J = 3.6 Hz, 1H), 7.74 (d, J = 2.4 Hz, 1H), 7.56-7.52 (dd, J = 5.2&8.8 Hz, 2H), 7.27-7.24 (m, 2H), 7.08 (d, J = 2.8 Hz, 1H), 7.00-6.96 (t, J = 8.8 Hz, 2H), 6.49 (d, J = 2.8 Hz, 1H), 3.80 (s, 3H); **^13^C NMR (100MHz, CDCl\textsubscript{3}):** δ 164.22, 161.75, 154.55, 152.59, 141.36, 140.83, 136.89, 135.77, 135.74, 131.76, 130.08, 129.78, 129.44, 129.05, 129.01, 128.48, 123.58, 122.97, 115.31, 115.10, 108.95, 101.91, 32.90; **ESI-HRMS:** m/z = 354.20 (M+H); **ESI-HRMS:** m/z [M+H]^+ calculated for C_{23}H_{17}N_{3}F: 354.1407, found: 354.1397.
7.6. Spectral data of selected compounds (\( ^{1} \text{H} \) NMR and \( ^{13} \text{C} \) NMR)

Figure 7.8. \( ^{1} \text{H} \) NMR spectra of compound 34a
Figure 7.9. $^{13}$C NMR spectra of compound 34a

Figure 7.10. $^1$H NMR spectra of compound 34d
Figure 7.11. $^{13}$C NMR spectra of compound 34d

Figure 7.12. $^1$H NMR spectra of compound 36d
Figure 7.13. $^{13}$C NMR spectra of compound 36d
Figure 7.14. $^1$H NMR spectra of compound 36f

Figure 7.15. $^{13}$C NMR spectra of compound 36f
Figure 7.16. $^1$H NMR spectra of compound 38d
Figure 7.17. $^{13}$C NMR spectra of compound 38d

Figure 7.18. $^1$H NMR spectra of compound 38e
Figure 7.19. $^{13}$C NMR spectra of compound 38e
Figure 7.20. $^1$H NMR spectra of compound 40a

Figure 7.21. $^{13}$C NMR spectra of compound 40a
Figure 7.22. $^1$H NMR spectra of compound 42f

Figure 7.23. $^{13}$C NMR spectra of compound 42f
Figure 7.24. $^1$H NMR spectra of compound 42h
Figure 7.25. $^{13}$C NMR spectra of compound 42h

Figure 7.26. $^1$H NMR spectra of compound 44d
Figure 7.27. $^{13}$C NMR spectra of compound 44d
Figure 7.28. $^1$H NMR spectra of compound 44h

Figure 7.29. $^{13}$C NMR spectra of compound 44h
Figure 7.30. $^1$H NMR spectra of compound 53
Figure 7.31. $^{13}$C NMR spectra of compound 53

Figure 7.32. $^1$H NMR spectra of compound 55
Figure 7.33. $^{13}$C NMR spectra of compound 55