Chapter Five

Section I: Brönsted Acid Hydrotrope Combined Catalyst for Environmentally Benign Synthesis of Quinoxalines and Pyrido[2,3-b]pyrazines in Aqueous Medium

5.1.1. Introduction

Many nitrogen-containing heterocycles [1] are regarded as privileged structures due to their ability to bind multiple cell receptors with high affinity. Among them, quinoxalines and pyrido[2,3-b]pyrazines (Fig. 5.1.1) are the most important and exhibit a wide range of biological activities.

![Quinoxaline and Pyrido[2,3-b]pyrazine](image)

**Fig. 5.1.1 Structures of quinoxaline and pyrido[2,3-b]pyrazine**

While rarely found in nature, quinoxalines are well known in the pharmaceutical industry. It is also noteworthy that by virtue of their thermal stability, intense luminescence and other desirable properties they have been widely used in organic semiconductors, electroluminescent materials. The various applications of quinoxalines and pyrido[2,3-b]pyrazines are listed and discussed as follows:

(a) Biological applications:

The quinoxaline moiety is widely distributed in nature (Fig. 5.1.2), it is part of number of synthetic antibiotics such as Echinomycin and Actinomycin, which are known to inhibit the growth of Gram-positive bacteria and are also active against various transplantable tumors. Besides, quinoxaline structure is recognized in a great number of naturally occurring compounds such as riboflavin (vitamin B$_2$), flavoenzymes, molybdopterines and antibiotics of streptomyces type that are implicated in considerable intra and interelectron transfer biochemical processes. They also show antibacterial, antiviral, anticancer, antifungal, antihelmintic, insecticidal activity [2]. The quinoxaline anticancer drugs CQS (chloroquinoxalinesulphonamide) and XK469 were both found to have activity against solid tumors and it’s (2-
quinoxalinyloxy)phenoxypropanoic acid derivatives, such as Assure® are well documented as herbicides and are used to control annual and perennial grass weeds in broadleaf crops [3].

![Chemical structures](image)

**Fig. 5.I.2** Biologically important quinoxaline compounds

### (b) Optoelectronic applications:

Fluorescent heterocyclic compounds are of interest as functional materials in the emitters of electroluminescence devices. In particular, fluorescent dyes whose fluorescence emission occurs at a longer wavelength in the red light region are expected to play a leading role in full color electroluminescence displays. Quinoxalines are known to emit both the (n, π*) fluorescence and the (π, π*) phosphorescence in the vapor phase and therefore they find many applications as dyes and electroluminescent materials.


A dipolar acenaphthopyrazine derivative [5] containing diphenylamine shows highly tunable fluorescence with emission in green-yellow to red region.

Das *et al.* [6] have synthesized different acceptor–donor–acceptor triads incorporating the donor tetraphiafulvalene (TTF) fused with acceptors quinoxaline and dipyrido[3,2-α:20,3-α]phenazine (dppz) systems. Solutions of all these compounds show large solvent sensitive behavior of emission spectra due to the intramolecular charge transfer.

### (c) Metal complexes of quinoxalines:

The quinoxaline class of ligands [7] meets the expectations of modern metallo-organic chemistry with their low-lying LUMOs, two nitrogen atoms in
para position, suitable for bridging and easy functionalization. The chemistry of transition metal-quinoxaline complexes has rapidly expanded in the past decades due to the variety of ground-state and excited-state redox properties associated with these molecules.

**Synthesis of quinoxalines:**

Quinoxalines were first independently reported by Korner and Hinsberg [8] in 1884. Number of syntheses, each start with diamine as the nucleophilic nitrogen component, and vary in the additional electrophilic carbon compounds added was reported in literature (Scheme 5.I.1).

![Scheme 5.I.1](image)

**Scheme 5.I.1**

Practicable method for the synthesis of quinoxalines and pyrazines comprises:

A) Oxidative trapping of $\alpha$-hydroxy ketones with 1,2-diamines
B) Reactions of 1,2-diamines with dhenacyl bromides
C) 1,4-Addition of 1,2-diamines to diazenylbutene
D) Reactions of 1,2-diamines with 1,4-diarylbut-2-yne-1,4-dione
E) Condensation of 1,2-diamines with 1,2-dicarbonyl compounds
F) Other methods

(A) **Oxidative trapping of $\alpha$-hydroxy ketones with 1,2-diamines:**

Liu *et al.* [9] efficiently synthesized quinoxaline derivatives from 4-chloro-4-deoxy-$\alpha$-D-galactose (Scheme 5.I.2) having cytotoxic activities.

Chung and co-workers [10] have developed an environmental friendly process for MnO$_2$ catalyzed synthesis of quinoxalines, from a variety of $\alpha$-hydroxy ketones with aromatic or aliphatic 1,2-diamines (Scheme 5.I.2) without using a solvent, under microwave irradiation.
The application of TiO₂ in conjunction with 2,2,6,6-tetramethyl piperidine-1-oxyl radical (TEMPO) as an oxidant in the synthesis of quinoxalines, via the tandem oxidation process (Scheme 5.1.2) was described by Robinson and co-workers [11].

An efficient, environmentally benign synthetic route for preparation of quinoxalines using manganese oxide octahedral molecular sieves (OMS-2) (Scheme 5.1.2) was described by Sithambaram and co-workers [12].

![Scheme 5.1.2](image)

(B) Reactions of 1,2-diamines with phenacyl bromides:

Cyclodextrins are cyclic oligosaccharides possessing hydrophobic cavities, which bind substrates selectively and catalyze chemical reactions with high selectivity. In this connection Nageswar et al. [13] presented an elegant and simple methodology for the biomimetic synthesis of quinoxalines (Scheme 5.1.3) in presence of β-cyclodextrin in water.

Zhu et al. [14] synthesized various substituted 3-(quinoxalin-2-yl)-2H-chromen-2-ones from 3-(2-bromoacetyl)coumarins or 3-(2-bromobutanoyl)coumarins and o-phenylenediamines (Scheme 5.1.3) under catalyst-free, microwave irradiation.

An efficient and convenient protocol for the synthesis of quinoxalines and dihydropyrazines via cyclization–oxidation process using HClO₄@SiO₂ as a heterogeneous recyclable catalyst was developed by Majhi and co-workers
Meshram and his group [16] demonstrated an efficient and mild method for the synthesis of functionalized quinoxalines (Scheme 5.I.3) using DABCO catalyst.

![Scheme 5.I.3](image)

(C) 1,4-Addition of 1,2-diamines to diazenylbutenes:

The solution, solid-phase and solvent-free synthesis of tetrahydropyrazines, dihydropyrazines, pyrazines, piperazinones, and quinoxalines by 1,4-addition of 1,2-diamines to 1,2-diaza-1,3-butadienes (Scheme 5.I.4) bearing carboxylate, carboxamide, or phosphorylated groups at the terminal carbon is described by Attanasi and co-workers [17].

![Scheme 5.I.4](image)

(D) Reactions of 1,2-diamines with 1,4-diarylbut-2-yn-1,4-dione:

Quinoxalines have also been used for the synthesis of poly(phenylquinoxalines), which possess excellent thermal stabilities, low dielectric constants, high glass-transition temperatures, and good mechanical properties. Yavari et al. [18] developed new synthetic route for synthesis of dialkyl(2Z)-2-[(E)-1-aryl-2-(3-arylquinoxalin-2-yl)ethenyl]but-2-enedioates (Scheme 5.I.5) by reacting benzene-1,2-diamine with the corresponding 1,4-
diarylbut-2-yne-1,4-dione through 1-aryl-2-[(3-arylquinoxalin-2(1H)-ylidene)ethanone intermediate.

\[
\text{Scheme 5.I.5}
\]

(E) Condensation of 1,2-diamines with 1,2-dicarbonyl compounds:

Recently, ionic liquids have received much attention due to their unique properties such as non-volatility, non-flammability, reusability and great potential as environmentally benign media. Zare and co-workers [19] synthesized quinoxaline derivatives from 1,2-diamines and 1,2-diketones in the [(bmim)Br] IL under microwave irradiation. Alternatively, Darabi et al. [20] introduced NH₄Cl-CH₃OH as a cost effective and environmentally benign catalytic system for quinoxaline synthesis (Scheme 5.I.6).

Water emerged as an useful alternative solvent for several organic reactions owing to many of its potential advantages. Yao et al. [21] developed more efficient and environmentally benign method to synthesize various biologically important quinoxalines (Scheme 5.I.6) using Cerium (IV) ammonium nitrate in tap water.

\[
\text{Scheme 5.I.6}
\]

Recently, the literature has seen a plethora of Microwave Assisted Organic Synthesis (MAOS), protocols for various chemical transformations
due to reduction in reaction time, improved yields and suppression of side products relative to traditional thermal heating. Among the methodologies described in the literature, the one disclosed by Lindsley and co-workers [22] which combines 1,2-diketone, and variety of aryl/heteroaryl 1,2-diamines under microwave irradiation. Somewhat modified approach was developed by Darabi et al. [20] using both mineral supports (acidic alumina) and a polar paste system (Scheme 5.I.6).

In recent years, molecular iodine has received considerable attention as an inexpensive, nontoxic and readily available mild Lewis acid catalyst. In 2005, Yao and co-workers as well as Pawar et al. [23] described the use of molecular iodine in the synthesis of quinoxalines (Scheme 5.I.6) at room temperature.

Wang and co-workers [24] showed that PEG (Polyethylene glycol) can be used for synthesis of quinoxalines (Scheme 5.I.6), as it is non-toxic, inexpensive, thermally stable, recoverable and biologically acceptable reagent.

Cellulose is the most abundant natural material, inexpensive, biodegradable and renewable resource. Shaabani et al. [25] synthesized quinoxaline derivatives (Scheme 5.I.6) using cellulose sulfuric acid as recyclable and biodegradable solid acid catalyst.

Heteropolyacids (HPAs) are environmentally benign and economically feasible solid catalysts that offer several advantages such as excellent solubility in water, high catalytic activities and reactivity, ease of handling, non-toxicity and experimental simplicity. Using Keggin type heteropolyacids (H₄SiW₁₂O₄₀) which are roughly spherical and involves three fold M₅O₁₃ groups, Lu et al. [26] recognized that the reaction gave high yields of quinoxalines as compared to Wells–Dawson type heteropolyacids (H₆P₂W₁₈O₆₂) which is ellipsoidal structure (Scheme 5.I.6).

Williams et al. [27] reported a simple and convenient method for the synthesis of photochromic benzo[g]quinoxalines (Scheme 5.I.7) having good photo-physical properties.
Lopez and co-workers [28] introduced 10,11-[1,4
naphtalendione]dipyrido[3,2-a:2',3'-c]phenazine, and dipyrido[3,2-a:2',3'-c]-benzo[3,4]-phenazine-11,16-quinone, (Scheme 5.I.8) as ligands with acceptor properties.

(F) Other methods:

Espinosa et al. [29] synthesized 9-alkyl-6-amino[1,2,4]triazolo[3,4-c]-5-azaquinoxalines (Scheme 5.I.9) through a mild and effective S_N Ar amination.

Neves et al. [30] synthesized new α,α’-diimine ligands based on condensation of 1,10-phenanthroline-5,6-dione with 1,2-phenylenediamine derivatives (Fig. 5.I.3) having biological potential and are of synthetic and technological importance.
Patal and co-workers [31] synthesized a new chiral 1,2,3,4,4a,10a-Hexahydrodinaphtho[2,1-h;1',2'-j]-phenazine (Fig.5.I.4) and predicted their more stable configuration of diastereoisomer by chemical correlation.

Fig. 5.I.4 Chiral 1,2,3,4,4a,10a-Hexahydrodinaphtho[2,1-h;1',2'-j]-phenazine

5.I.2. Present work

Organic reactions in aqueous media have attracted increasing interest offering many practical and economical advantages. From a viewpoint of ecological advantage and greenness of water, it is desirable to use water as a reaction solvent; since it is safe, harmless, and environmentally benign [32]. Our goal is to develop a novel catalytic system which will enable the use of water as a solvent for a wide range of reactions of organic materials. The limited solubility of organic reactants in water may be overcome by using hydrotropy phenomenon.

Hydrotropes are the class of compounds though amphiphilic in character, they have hydrophobic regions and thus differ from classical surfactants yet, they display substantial ability to solubilize, non-polar compounds in water [33]. The self aggregation of hydrotropes has been considered to be a prerequisite for a huge number of applications in various fields such as drug solubilization, separation sciences and nanocarriers for poorly soluble drugs [34]. There is also growing interests for the use of hydrotropes as a reaction media in organic synthesis [35]. The key focus of the use of hydrotropes as a reaction media depends on the nature of hydrotropes used and its minimum hydrotropic concentration (MHC) above which there is maximum solubility of reactants.

As hydrotropes increase the solubility of compounds in many fold excess, this effect is attributed to a direct interaction between the reactants which are practically insoluble in water. Secondly, the product precipitates on
dilution with water from hydrotropic solution, which leads to the product formation in crystalline form with an improved purity, and the mother liquor could be used to concentrate the hydrotrope for recycling. This technique will avoid the use of highly inflammable and expensive organic solvents as normally used in organic synthesis. These interactive properties of hydrotropes and our ongoing efforts in the development of newer methods for organic synthesis rendered us to explore the use of the Brönsted Acid Hydrotrope Combined (BAHC) catalyst for the synthesis of medicinally important pyrido[2,3-\(b\)]pyrazine and quinoxalines in aqueous medium with an enhanced reaction rate and improved product purity.

5.1.3. Results and discussion

Our first aim was to optimize various reaction conditions in order to get maximum yield of desired product in minimum time. For this, initially, the condensation of \(o\)-phenylenediamine 1 and benzil 2 were chosen as reaction partners at room temperature (Scheme 5.1.10).

![Scheme 5.1.10](image)

Table 5.1.1: Effect of reaction conditions on the synthesis of quinoxaline\(^a\)

<table>
<thead>
<tr>
<th>Reaction condition</th>
<th>Reaction medium</th>
<th>PTSA (mol %)</th>
<th>Time</th>
<th>Yield(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{H}_2\text{O})</td>
<td>-</td>
<td>10 h</td>
<td>Trace</td>
</tr>
<tr>
<td>2</td>
<td>(\text{H}_2\text{O})</td>
<td>5</td>
<td>3.0 h</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>20 % aq.\text{NaPTS}</td>
<td>-</td>
<td>1.5 h</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>20 % aq. \text{NaPTS}</td>
<td>5</td>
<td>20 min</td>
<td>90</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: Benzil (1.0 mmol), \(o\)-phenylenediamine (1.0 mmol), reaction medium (5 mL), RT.

\(^b\)Isolated yields after purification.
In the absence of any catalyst the product 3a was produced in water with very trace amount after 10 h (Table 5.I.1, condition 1), but on addition of PTSA (p-Toluene Sulphonic Acid) as Brönsted acid catalyst (5 mol %) in water, yield of the product was 70 % in 3 h (Table 5.I.1, condition 2). On the other hand, the hydrotrope aided acid catalysis was studied in the model reaction using aqueous NaPTS (Sodium p-Toluene Sulphonate) solution and PTSA as catalyst. The reaction which proceeded sluggishly in the aqueous NaPTS (5 mL, 20 % w/v) solution (Table 5.I.1, condition 3), enhanced remarkably in the presence of 5 mol % PTSA combined with aqueous NaPTS (5 mL, 20 % w/v) solution, and the corresponding product was obtained in 90 % within 20 min (Table 5.I.1, condition 4). On the completion of reaction as monitored by TLC, the reaction mixture was diluted with cold water and product separated out (Scheme 5.I.11). The filtration of reaction mixture afforded the corresponding product of high purity. From these observations, it was revealed that most of the substrates and catalyst molecules were concentrated in the hydrophobic reaction environment and enabled the rapid organic reactions in water.

Scheme 5.I.11

With these results in hand, we have determined the hydrotropic concentration for maximum solubilization of the reactants in water to give maximum yield of the product. Thus, the model reaction was carried out with various concentrations (% w/v) of NaPTS in water at ambient temperature in presence of 5 mol % PTSA. By changing concentration, dramatic effect on the conversion rate of quinoxaline has been observed. As shown in Table 5.I.2, linear relationship was observed with concentration. The yield of the product is
highest at 40% of hydrotropic concentration since this concentration was suitable for the maximum solubilization of organic compounds (Table 5.I.2, entry 4). On the other hand, further increase in concentration resulted in decrease in the product yield due to lesser solubility of substrates in solution (Table 5.I.2, entry 5).

Table 5.I.2: Effect of concentration on the synthesis of quinoxaline

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydrotrope</th>
<th>Hydroscopic concentration (% w/v)</th>
<th>Catalyst (mol %)</th>
<th>Time (min)</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaPTS</td>
<td>10</td>
<td>5</td>
<td>30</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>NaPTS</td>
<td>20</td>
<td>5</td>
<td>20</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>NaPTS</td>
<td>30</td>
<td>5</td>
<td>20</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>NaPTS</td>
<td>40</td>
<td>5</td>
<td>7</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>NaPTS</td>
<td>50</td>
<td>5</td>
<td>15</td>
<td>90</td>
</tr>
</tbody>
</table>

a Reaction conditions: Benzil (1.0 mmol), o-phenylenediamine (1.0 mmol), catalyst (5 mol %), aqueous NaPTS solution (5 mL), RT.
bIsolated yields after purification.

After the optimization of hydrotropic concentration, various hydrotropes such as, NaXS (Sodium Xylene Sulphonate), NaBS (Sodium Benzene Sulphonate) were used along with NaPTS for model reaction with 5 mol % PTSA. Results revealed that PTSA is more active when combined with NaPTS as compared to NaXS and NaBS (Table 5.I.3). The higher activity of NaPTS hydrotrope was rationalized on the basis of an overall planar structure of hydrophobic and hydrophilic regions giving rise to self association configuration, offering a good micro-environment of lower polarity and stabilizes the reactants through a cooperative mechanism [33].

Table 5.I.3: Screening of the various hydrotropes in synthesis of quinoxaline

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydrotrope</th>
<th>Hydroscopic concentration (% w/v)</th>
<th>Catalyst (mol %)</th>
<th>Time (min)</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaPTS</td>
<td>40</td>
<td>5</td>
<td>7</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>NaXS</td>
<td>40</td>
<td>5</td>
<td>10</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>NaBS</td>
<td>40</td>
<td>5</td>
<td>12</td>
<td>89</td>
</tr>
</tbody>
</table>

a Reaction conditions: Benzil (1.0 mmol), o-phenylenediamine (1.0 mmol), PTSA (5 mol %), aqueous hydrotropic solution (5 mL), RT.
bIsolated yields after purification.
After the selection of appropriate hydrotrope and optimized conditions, a series of diketones was treated with various 1,2-diamines in 40 % aqueous NaPTS solution at ambient temperature with 5 mol % PTSA (Table 5.1.4). The reactions proceeded at room temperature within a short time to afford the desired products in excellent yields.

Table 5.1.4: Synthesis of quinoxaline and pyrido[2,3-b]pyrazine derivatives in BAHC

<table>
<thead>
<tr>
<th>Entry</th>
<th>1,2-diamine</th>
<th>1,2-diketone</th>
<th>Product&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Time (min)</th>
<th>Yield&lt;sup&gt;c&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{NH}_2\text{NH}_2 )</td>
<td>( \text{O} \text{O} \text{N} \text{N} )</td>
<td>( \text{3a} )</td>
<td>7</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>( \text{NH}_2\text{NH}_2 )</td>
<td>( \text{O} \text{O} \text{N} \text{N} )</td>
<td>( \text{3b} )</td>
<td>20</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>( \text{NH}_2\text{NH}_2 )</td>
<td>( \text{O} \text{O} \text{N} \text{N} )</td>
<td>( \text{3c} )</td>
<td>10</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>( \text{NH}_2\text{NH}_2 )</td>
<td>( \text{O} \text{O} \text{N} \text{N} )</td>
<td>( \text{3d} )</td>
<td>7</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>( \text{NH}_2\text{NH}_2 )</td>
<td>( \text{O} \text{O} \text{N} \text{N} )</td>
<td>( \text{3e} )</td>
<td>15</td>
<td>92</td>
</tr>
</tbody>
</table>
Brönsted Acid Hydrotrope Combined Catalyst for Environmentally Benign Synthesis of Quinoxalines and Pyrido[2,3-b]pyrazines in Aqueous Medium

Next we have extended this protocol for the tetra amines such as 3,3’,4,4’-tetraamino-1,1’-biphenyl 4. It underwent condensation with diketone 2 in the presence of 5 mol % PTSA combined with 40 % aq. NaPTS (5 mL) affording the sterically hindered product 2,3,2’,3’-tетra aryl[6,6’]biquinoxalinyl 6a-b in 83 and 81 % yield respectively in 20 min (Scheme 5.I.12).

\[
\begin{align*}
6 & \\
7 & \\
8 & \\
9 & \\
10 & \\
\end{align*}
\]

\[
\begin{align*}
3f & \\
3g & \\
3h & \\
3i & \\
3j & \\
\end{align*}
\]

\[\text{Reaction conditions: diketone (1.0 mmol), diamine (1.0 mmol), PTSA (5 mol %), 40 % aq. NaPTS (5 mL), RT.}\]
\[\text{All products were analyzed by IR, }^1\text{H NMR, }^{13}\text{C NMR and Mass Spectroscopy.}\]
\[\text{Isolated yields after purification.}\]

Scheme 5.I.12
Another striking feature of BAHC catalyst is easy recovery from the reaction mixture. As PTSA and hydrotrpores are highly soluble in water than in organic solvents, almost 100% of BAHC was quite easily recovered from the aqueous solution after the completion of reaction. The reactions are quenched with water and the products precipitated are simply separated by filtration. The BAHC is in the aqueous layer, and removal of water gives the catalyst which can be used in the next reaction. To assess the reusability of BAHC, recycling experiments were carried out with o-phenylenediamine and benzil as substrates over the four reaction cycles. After each experiment, the aqueous solution of BAHC was recovered by filtration, washed thoroughly with diethyl ether, concentrated and then subjected to a new run with fresh reactants under identical reaction conditions. The results are shown in Fig. 5.I.5 and the BAHC could be reused for at least five runs with modest change in yield of the product.

![Fig. 5.I.5 Recyclability of BAHC](image)

### Characterization of compounds:

**2,3-di(pyridin-2-yl)quinoxaline (Table 5.I.4, entry 5):** The $^1$H NMR spectrum (Fig. 5.I.10) of the compound showed doublet of doublet (dd) for two Ha protons present on benzene ring at $\delta$ 8.22 ppm ($J = 6.6$ and 3.6 Hz) (Fig. 5.I.6). Out of eight protons present on two pyridine rings, two Hf protons
appeared as doublet at $\delta$ 8.34 ppm ($J = 4.2$ Hz), while two Hd protons resonated at $\delta$ 8.00 ppm as doublet ($J = 7.00$ Hz). Spectrum showed two sets of multiplets one at $\delta$ 7.21-7.25 ppm for two He protons and other at $\delta$ 7.80-7.85 ppm for two Hb protons. $^{13}$C NMR spectrum (Fig. 5.1.11) of same compound exhibited nine signals in the aromatic region from $\delta$ 122.8 to 157.5 ppm.

![Chemical Structure](image_url)

Fig. 5.1.6

7-bromo-2,3-bis(4-bromophenyl)pyrido[2,3-b]pyrazine (Table 5.1.4, entry 9): The $^1$H NMR spectrum (Fig. 5.1.12) of the compound exhibited two doublets, one doublet at $\delta$ 9.18 ppm for single Hb proton ($J = 2.4$ Hz) coupled to Ha proton, while Ha proton resonated at $\delta$ 8.65 ppm ($J = 2.4$ Hz) coupled to Hb proton present at meta position of the pyridine ring (Fig. 5.1.7). In case of two bromophenyl rings, there are two sets of protons which are resonated at $\delta$ 7.41-7.45 ppm (four Hc protons) and $\delta$ 7.53-7.56 ppm (four Hd protons) in the form of two multiplets. In the $^{13}$C NMR spectrum (Fig. 5.1.13) the presence of aromatic carbons is noted in the region $\delta$ 121.3-155.5ppm.
Plausible mechanism

The plausible mechanism of product formation was conceptualized in the following Fig. 5.I.8 [36]. The water molecules hydrate the hydrotrope head groups decreasing the electrostatic interaction between these groups. The two head groups move apart and displace the water molecules interacting hydrophobic chains. This may be the driving force for two hydrophobic chains to interact and force the diamine to interact with diketone which is activated by acid. The eliminated water molecules then get easily absorbed by hydrophilic head groups. As a result of the overall effect, there is rate enhancement of the reaction.
5.1.4. Conclusion

In conclusion, we have presented a simple, efficient and green protocol for the synthesis of quinoxaline and pyrido[2,3-b]pyrazine derivatives in a novel Brønsted Acid Hydrotrope Combined (BAHC) catalysts in water at ambient temperature. The merits of the present method are easy workup, faster reactions with milder reaction conditions and satisfactory yields which avoid hazardous organic solvents and toxic catalysts. Interestingly, it was found that the BAHC could be reused for at least five runs with modest change in the product yield. Thus the BAHC in water makes the organic compounds to dissolve and solubility is generally considered a prerequisite for the reactivity.

5.1.5. Experimental section

\(^1\)H NMR and \(^{13}\)C NMR spectra were recorded on a Brucker AC (300 MHz for \(^1\)H NMR and 75 MHz for \(^{13}\)C NMR) spectrometer using CDCl\(_3\) as solvent and tetramethylsilane (TMS) as an internal standard. Infrared spectra were recorded on a Perkin-Elimer FTIR spectrometer. The samples were examined as KBr discs \(\sim 5\%\) w/w. Elemental analysis was carried on EURO EA 3000 elemental analyzer. Melting points were determined on a DBK melting point apparatus and are uncorrected. The Sodium Xylene Sulphonate (ZEONOL) used in the present study was gifted from the Pharma products, Panvel, Maharashtra. The hydrotropes NaPTS and NaBS were prepared following the literature procedure [37]. All other chemicals were obtained from Aldrich and Spectrochem and were used without further purification.

General method for preparation of Sodium \(p\)-Toluene Sulphonate

A mixture of 0.65 mol (60 g) toluene and 33 mL of concentrated sulphuric acid was taken in a 500 mL three-necked flask, provided with a sealed mechanical stirrer and a reflux condenser. The mixture was heated with stirring in an oil bath maintained at 110-120 °C. When the toluene layer was disappeared, the reaction mixture was cooled to room temperature and poured with stirring into 250 mL cold water. The acid in solution was partly neutralized by adding cautiously in small portions 30 g of sodium hydrogen
carbonate. The resulting solution was heated to boiling and saturated with 100 g sodium chloride. The hot solution was filtered through a Buchner funnel. The filtrate was cooled in ice with stirring to form precipitate of sodium p-toluene sulphonate. The resulting crude product was recrystallized by dissolving in 200-250 mL of water and heated to boil and then saturated with sodium chloride. The solution was allowed to cool somewhat, and then stirred with 2-3 g of decolorizing charcoal and filtered while hot with suction through a Buchner funnel. The warm filtrate was transferred to a beaker and cooled in ice to get the precipitate of sodium p-toluene sulphonate. The precipitate was pressed well and finally washed with a little alcohol and was dried in air and finally in an oven at 100-110 °C.

**General method for preparation of Sodium Benzene Sulphonate**

The Sodium Benzene Sulphonate was prepared according to reported method [37].

**General procedure for the synthesis of Quinoxaline and Pyrido[2,3-b]pyrazine**

In a small Schlenk tube, 1,2-diamine (1 mmol), 1,2-diketone (1 mmol), PTSA (5 mol %) and 40 % aq. NaPTS (5 mL) were taken and the reaction mixture was stirred at room temperature. The reaction process was monitored by thin layer chromatography (TLC). After completion of the reaction, the mixture was diluted with water (20 mL). The filtrate was washed with water and dried affording the corresponding product and was purified in ethanol.

**Spectral data of representative compounds:**

3d (Table 5.1.4, entry 4): Yellow solid, observed mp 228–229 °C. Lit. mp 228–230 °C [19]. $^1$H NMR (CDCl$_3$, 300 MHz): $\delta_H$ (ppm) 7.73–7.89 (m, 6H), 8.31–8.37 (m, 2H), 8.59 (d, 2H, $J = 8.7$ Hz), 9.42 (dd, 2H, $J = 7.8$ Hz, 1.8 Hz). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta_C$ (ppm) 122.9, 126.2, 127.9, 129.4, 129.7, 130.3, 132.0, 142.1, 142.4. MS (ESI): m/z 280.
Brönsted Acid Hydrotrope Combined Catalyst for Environmentally Benign Synthesis of Quinoxalines and Pyrido[2,3-b]pyrazines in Aqueous Medium

Elemental analysis:

<table>
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<tr>
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<th>C_{20}H_{12}N_{2}</th>
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<th>H %</th>
<th>N %</th>
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<td></td>
<td>86.0</td>
<td>4.2</td>
<td>9.8</td>
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3g (Table 5.I.4, entry 7): Yellow Solid, observed mp 217–219 °C. Lit. mp 218-219°C [38]. \(^1\)H NMR (CDCl₃, 300 MHz): \(\delta_H\) (ppm) 7.71–7.85 (m, 5H), 8.55 (d, 2H, \(J = 7.8\) Hz), 8.67 (dd, 1H, \(J = 8.4\) Hz, 1.8 Hz), 9.29-9.36 (m, 2H), 9.54 (dd, 1H, \(J = 7.8\) Hz, 1.5 Hz). \(^{13}\)C NMR (CDCl₃, 75 MHz): \(\delta_C\) (ppm) 123.9, 126.2, 127.3, 129.5, 129.8, 130.8, 132.1, 132.5, 138.1, 145.0, 152.4, 154.3. MS (ESI): m/z 281.

Elemental analysis:

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<td>Observed</td>
<td></td>
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<td>4.0</td>
<td>14.9</td>
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</table>

3j (Table 5.I.4, entry 10): White solid, mp 235–238 °C. \(^1\)H NMR (CDCl₃, 300 MHz): \(\delta_H\) (ppm) 7.72–7.87 (m, 4H), 8.56 (d, 2H, \(J = 8.1\) Hz), 8.81-8.83 (m, 1H), 9.25-9.29 (m, 2H), 9.47 (d, 1H, \(J = 7.9\) Hz). \(^{13}\)C NMR (CDCl₃, 75 MHz): \(\delta_C\) (ppm) 120.6, 122.9, 123.1, 126.7, 127.3, 128.2, 128.3, 129.2, 129.5, 131.3, 131.4, 132.5, 137.4, 139.4, 144.2, 155.5. MS (ESI): m/z 359.

Elemental analysis:

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<th>H %</th>
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<tbody>
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<td>63.3</td>
<td>2.8</td>
<td>11.6</td>
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<tr>
<td>Observed</td>
<td></td>
<td>63.5</td>
<td>2.8</td>
<td>11.5</td>
<td>22.2</td>
</tr>
</tbody>
</table>

6b (Scheme 5.I.12, X=N): Yellow Solid, mp > 300 °C. \(^1\)H NMR (CDCl₃, 300 MHz): \(\delta_H\) (ppm) 7.84-7.90 (m, 4H) 8.07-8.10 (m, 4H), 8.27-8.38 (m, 8H), 8.65 (d, 2H, \(J = 1.8\) Hz). MS (ESI): m/z 566.

Elemental analysis:

<table>
<thead>
<tr>
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<th>C_{36}H_{22}N_{8}</th>
<th>C %</th>
<th>H %</th>
<th>N %</th>
</tr>
</thead>
<tbody>
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<td>Calculated</td>
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<tr>
<td>Observed</td>
<td></td>
<td>76.4</td>
<td>3.8</td>
<td>19.7</td>
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</tbody>
</table>
5.1.7. References


Brönsted Acid Hydrotrope Combined Catalyst for Environmentally Benign Synthesis of Quinoxalines and Pyrido[2,3-b]pyrazines in Aqueous Medium


Brönsted Acid Hydrotrope Combined Catalyst for Environmentally Benign Synthesis of Quinoxalines and Pyrido[2,3-b]pyrazines in Aqueous Medium


5.1.6. Spectra

Fig. 5.1.9 IR spectrum of 2,3-di(pyridin-2-yl)quinoxaline
Fig. 5.I.10 $^1$H NMR spectrum of 2,3-di(pyridin-2-yl)quinoxaline
Fig. 5.I.11 $^{13}$C NMR spectrum of 2,3-di(pyridin-2-yl)quinoxaline
Fig. 5.1.12 $^1$H NMR spectrum of 7-bromo-2,3-bis(4-bromophenyl)pyrido[2,3-b]pyrazine
Fig. 5.1.13 $^{13}$C NMR spectrum of 7-bromo-2,3-bis(4-bromophenyl)pyrido[2,3-$b$]pyrazine
Chapter Five

Section II: Synthesis of Quinoxalines and Pyrido[2,3-b]pyrazines Through the Application of the Suzuki–Miyaura Cross-coupling Reaction

5.II.1 Introduction

Quinoxaline, a fused aromatic system, is known as benzopyrazine and has a great synthetic advantage which is generally prepared by a high-yield synthetic route from diketone and diamine condensation. In addition, the introduction of internal diimine units to the aromatic ring system allows electronic alterations to impart highly electrophilic characteristics to the ring. As a consequence, benzopyrazines are widely used in light-emitting and electron transporting materials [1] for the manufacture of highly efficient Organic Light-Emitting Diodes (OLEDs).

The synthesis of π-extended quinoxaline and pyrazine derivatives are usually carried out in two step reaction. In first step as described in Chapter 5 (Section I), appropriate quinoxaline and pyrazine derivatives containing one/more bromo substituents are synthesized from corresponding diketone and diamine compounds. Secondly, the classical Suzuki-Miyaura cross-coupling protocol between bromo compounds and aryl boronic acids employing Pd(dppf)Cl₂ results in almost quantitative yield of desired product (see Results and discussion).

These π-extended quinoxaline derivatives have interesting properties for their use as OLED device and it is well documented in literature. Kang and co-workers [2] described a coherent green fluorescence compounds 2-butyl-2,3-diaryl-5,8-diaryl-1H-quinoxalines (Fig 5.II.1), which is obtained from panchromatic 2,3-diaryl-5,8-diarylquinoxalines. Full color quinoxaline derivatives were prepared from electronic modification at either the 2,3- or 5,8-positions of the quinoxalines. 2-butylation converted one imine unit of the pyrazine ring to an amine group, which effectively altered the electron donor and acceptor functions to produce a coherent green fluorescence.
OLEDs based on conjugated polymers such as poly(p-phenylenevinylene) (PPV) and polyfluorene have attracted much attention in the past decade as promising candidates for the next generation full-color, flat-panel displays.

Quinoxalines are interesting functional materials due to their fluorescence properties with high quantum yields. Çarbas et al. [3] prepared new fluorescent materials from 4-(thiophen-3-yl)-pyrrolo[1,2-a]quinoxaline, 4-((5-thiophen-2-yl)thiophen-3-yl)pyrrolo[1,2-a]quinoxaline and 4-((2,5-dithiophen-2-yl)thiophen-3-yl)pyrrolo[1,2-a]quinoxaline (Scheme 5.II.1), which exhibits a reversible redox behavior accompanied with a reversible electrochromic behavior; yellowish orange in the neutral state and green in the oxidized state.

Lunxiang and Liebscher [4] reported first examples of palladium-catalyzed cross-coupling reactions, in the pyrido[2,3-b]pyrazine series (Scheme 5.II.2). This methodology circumvents problems found in
uncatalyzed nucleophilic substitution used so far to introduce substituents into the pyrido[2,3-\(b\)]pyrazine ring.

**Scheme 5.II.2**

Abhishek Kulkarni and his group [5] synthesized and characterized six new copolymers of 9,9'-dioctylfluorene and 2,3-bis(\(p\)-phenylene)quinoxaline (Scheme 5.II.3) which involves SM reaction as a key step. These polymers are used as blue light-emitting materials in light-emitting diodes.

**Scheme 5.II.3**

Moon and co-worker [6] described synthesis of quinoxaline-based alternating copolymers (Scheme 5.II.4) and studied their photovoltaic properties for high efficiency bulk hetero-junction polymer solar cells.
Reddy and Reddy [7] synthesized various quinoxaline derivatives via cyclization-oxidation of α-bromo carbonyl compounds with o-phenyl diamines and further coupling at 6-position via SM reaction using PdCl₂(dppf)CH₂Cl₂ (Scheme 5.II.5), and their antibacterial screening tests were done by paper disc method.

Holder and co-workers [8] described alternating fluorene-di(thiophene)quinoxaline copolymers (Scheme 5.II.6) via microwave-assisted SM cross-coupling reactions.
Synthesis of Quinoxalines and Pyrido[2,3-b]pyrazines Through the Application of the Suzuki–Miyaura Cross-coupling Reaction

Jo et al. [9] synthesized a series of low-band gap alternating copolymers consisting of electron-accepting quinoxaline derivatives and electron-donating carbazole or fluorene were synthesized via a SM coupling reaction (Scheme 5.II.7).

Scheme 5.II.6

Scheme 5.II.7
Hirano et al. [10] synthesized a new red fluorescent nitrogen-rich heterocycle of bis(pyrazino[20,30:4,5]imidazole)-fused 1,2,5,6-tetrahydro-1,4,5,8,9,10-hexaazaanthracenes (Scheme 5.II.8).

Scheme 5.II.8

Yong Cao and co-workers [11] synthesized a series of narrow-band-gap donor-acceptor (D-A) conjugated polymers, with thiophene substituted quinoxaline monomer 5,8-bis(5-bromothiophen-2-yl)-2,3-bis(5-octylthiophen-2-yl)quinoxaline (TTQx) or its cyclized phenazine derivative monomer 8,11-bis(5-bromothiophen-2-yl)-2,5-dioctyldithieno-[2,3-a:30,20-c]phenazine (TTPz) as acceptors, via SM coupling reaction (Scheme 5.II.9).
Hirao et al. [12] synthesized 2,3-disubstituted quinoxalines (Scheme 5.II.10) by Suzuki-Miyaura coupling using Pd(PPh₃)₄ catalyst.

![Scheme 5.II.10](image)

5.II.2 Present work

During the last few years, extensive efforts from different groups have led to the discovery of a wide variety of transition metal catalyzed methods for the formation of heterocycles [13]. Among them, palladium-catalyzed reactions, in particular, Suzuki-Miyaura coupling reaction is a powerful, versatile and popular tool for construction of variety of pharmaceutically active heterocyclic compounds [14]. To the best of our knowledge, the first approach to introduce substituents into the pyrido[2,3-b]pyrazine ring by palladium catalyzed cross-coupling was disclosed by Liebscher and co-workers in 2005 [4].

We now wish to report an exceptionally concise synthesis of these compounds which further demonstrate the synthetic power of direct coupling of two or three nucleophiles to bromo compounds as an extension. This methodology furnishes an elegant entry to diverse pteridine analogue by Suzuki-Miyaura cross-coupling via the formation of key precursor 1, 2, 3, and 4 (Fig. 5.II.2) which is readily accessed from aromatic 1,2-diamino and 1,2-diketone compounds.

5.II.3 Results and discussion

Our work began with the intention of developing general reaction conditions for the palladium-catalyzed arylation of pyrido[2,3-b]pyrazines and quinoxalines. Fig. 5.II.2 shows four precursors used for the palladium-
catalyzed Suzuki-Miyaura cross coupling reactions (Scheme 5.II.11), which are synthesized following the literature procedure [15].

Fig. 5.II.2

The key precursors 1, 2, and 3 were obtained in good to excellent yields from the reaction of commercially available 5-bromo-2,3-diaminopyridine with benzil or 9,10-phenanthroquinone or 4,4'-dibromobenzil respectively in aqueous hydrotrope NaPTS in presence of catalytic amounts of PTSA. While 4 was prepared from o-phenylenediamine and 4,4'-dibromobenzil adopting the same reaction procedure. All the four compounds were solids and easily soluble in chlorinated solvents and THF, while insoluble in ethanol. Their chemical structures were confirmed by spectroscopic analysis.

Scheme 5.II.11
It is known that uncatalyzed substitution at the 7 position in compound 7-bromo-2,3-diphenylpyrido[2,3-b]pyrazine (1) is problematic because these reactions however, provide low yields, give mixtures of regioisomeric products due to elimination/addition mechanism and often addition competes with substitution [16]. Considering these problems, palladium-catalyzed cross-coupling can expected to be one of the best advantageous alternatives to introduce functionalized side chains and other substituents in compound 1 without facing the problems found in uncatalyzed transformation.

In order to optimize the reaction conditions, we began our studies by examining the coupling reaction of compound 1 with phenyl boronic acid as shown in Table 1. Initial studies were carried out on a 1.0 mmol scale at reflux temperature using a variety of palladium sources (2 mol %) like Pd(OAc)$_2$, PdCl$_2$ and Pd(dppf)Cl$_2$ using K$_2$CO$_3$ as a base and THF as solvent. We found that in the coupling of compound 1 with phenyl boronic acid Pd(OAc)$_2$ and PdCl$_2$ are less effective as compared to Pd(dppf)Cl$_2$ and as expected, 89 % yield of the desired product was obtained after 4 h at reflux temperature (Table 5.II.1, entry 1). The next important initial goal of our investigations was to find a base that would effect the desired reaction. Soluble organic bases such as triethylamine, and DBU (diazabicyclo[5.4.0]undec-7-ene) could not work satisfactorily. Upon screening commonly used inorganic bases, it was found that the use of K$_2$CO$_3$ is crucial to the success of the reaction. K$_3$PO$_4$ was considerably less effective, while Na$_2$CO$_3$ and Cs$_2$CO$_3$ did job well. With the best base determined, the effects of various solvents to the reaction were surveyed. Among the effective solvents discovered, we found that the use of THF as the solvent provided the optimal yield of product.
Table 5.II.1: Optimization of various reaction conditions of Pd-catalyzed arylation of compound 1 with phenyl boronic acid

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd source</th>
<th>Ligand</th>
<th>Base</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Pd(DPPF)Cl₂</td>
<td>-</td>
<td>K₂CO₃</td>
<td>THF</td>
<td>4</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)₂</td>
<td>PPh₃</td>
<td>K₂CO₃</td>
<td>THF</td>
<td>14</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>PdCl₂</td>
<td>PPh₃</td>
<td>K₂CO₃</td>
<td>THF</td>
<td>14</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>Pd(DPPF)Cl₂</td>
<td>-</td>
<td>Cs₂CO₃</td>
<td>THF</td>
<td>8</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>Pd(DPPF)Cl₂</td>
<td>-</td>
<td>Na₂CO₃</td>
<td>THF</td>
<td>5</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
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<td>-</td>
<td>K₂PO₄</td>
<td>THF</td>
<td>10</td>
<td>59</td>
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<td>7</td>
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<td>-</td>
<td>TEA</td>
<td>THF</td>
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<td>51</td>
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<tr>
<td>8</td>
<td>Pd(DPPF)Cl₂</td>
<td>-</td>
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<td>THF</td>
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<td>-</td>
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<td>70</td>
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<td>Pd(DPPF)Cl₂</td>
<td>-</td>
<td>K₂CO₃</td>
<td>Dioxane</td>
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<td>69</td>
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<tr>
<td>12</td>
<td>Pd(DPPF)Cl₂</td>
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<td>K₂CO₃</td>
<td>Toluene</td>
<td>10</td>
<td>66</td>
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</table>

*aReaction conditions: 1 (1.0 mmol), phenylboronic acid (1.2 mmol), Pd catalyst (1 mol %), base (2.0 mmol), solvent (5 mL), reflux under aerobic conditions.

In an attempt to prove the generality of the method, the reaction of compound 1 with a variety of substituted phenyl boronic acids were conducted (Table 5.II.2). As expected, the reaction of compound 1 with 4-methyl phenyl boronic acid, and (3,5-dimethyl, 4-methoxy) phenyl boronic acid afforded the desired single products in good yields (Table 5.II.2, entries 2 and 3). The reaction of stericly hindered naphthyl boronic acid with compound 1 could also be effected in 84 % yield in 14 h (Table 5.II.2, entry 4). Similarly,
compound 2 is also reactive against phenyl boronic acid with good product yield (Table 5.II.2, entry 5).

Encouraged by this finding, we sought to ascertain coupling of tribromo substituted pyrazine 3 with various aryl boronic acids under same optimized conditions. For example, we have been able to couple first time tribromide with substituted phenyl boronic acids, which were proceeded with good to excellent yields (Table 5.II.2, entries 7 and 8) using 6 mol % catalyst based on compound 3.

Table 5.II.2: Suzuki- Miyaura coupling of pyrido[2,3-b]pyrazines (1, 2 and 3) with various aryl boronic acids

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pyrazine</th>
<th>Arylboronic acid</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
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<tr>
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<td>1</td>
<td>( \text{B(OH)}_2 \text{OH} )</td>
<td><img src="example.png" alt="Image" /></td>
<td>10</td>
<td>90</td>
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<tr>
<td>2</td>
<td>1</td>
<td>( \text{B(OH)}_2 \text{OH} )</td>
<td><img src="example.png" alt="Image" /></td>
<td>11</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>( \text{B(OH)}_2 \text{OH} )</td>
<td><img src="example.png" alt="Image" /></td>
<td>12</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
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<td><img src="example.png" alt="Image" /></td>
<td>14</td>
<td>84</td>
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<tr>
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<td><img src="example.png" alt="Image" /></td>
<td>18</td>
<td>72</td>
</tr>
</tbody>
</table>
Synthesis of Quinoxalines and Pyrido[2,3-b]pyrazines Through the Application of the Suzuki–Miyaura Cross-coupling Reaction

As an expansion of this study, we next explored the preparation of structurally related quinoxaline derivatives. For this study, precursor 4 was prepared from commercially available o-phenylenediamine and benzil with 91% yield and applied for Suzuki-Miyaura coupling under conditions similar to those in pyrazine coupling. The reactions are detailed in Table 5.II.3. Different boronic acids were successfully coupled with compound 4 using 4 mol % catalyst loading. As can be seen, in all cases examined compound 4 is efficiently transformed into the product in good yield.

Table 5.II.3: Suzuki-Miyaura coupling of quinoxaline (4) with various aryl boronic acids

<table>
<thead>
<tr>
<th>Entry</th>
<th>Arylboronic acid</th>
<th>Product</th>
<th>Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HO-B(OH)₂</td>
<td>8a-d</td>
<td>16</td>
<td>90</td>
</tr>
</tbody>
</table>
Synthesis of Quinoxalines and Pyrido[2,3-b]pyrazines Through the Application of the Suzuki–Miyaura Cross-coupling Reaction

8a

2

8b

Reaction conditions: 1 (1.0 mmol), phenylboronic acid (2.2 mmol), Pd catalyst (2 mol %), base (4.0 mmol), solvent (5 mL), reflux under aerobic conditions.

Products are characterized by $^1$H NMR, $^{13}$C NMR and Mass spectroscopy.

Isolated yields after purification.

Characterization of compounds:

Compound 8a (Table 5.II.3, entry 1): The $^1$H NMR spectrum of the compound (Fig. 5.II.5) showed one doublet of doublet (dd) for two Ha protons present on benzene ring A at $\delta$ 8.22 ppm ($J = 3.6$ Hz and 6.3 Hz) and another dd at $\delta$ 7.79 ppm ($J = 3.3$ Hz and 6.3 Hz) for two Hb protons present on same ring A (Fig. 5.II.3). Two Hf protons of two phenyl rings D are resonated at $\delta$ 7.31-7.36 ppm, while four He protons of same ring shows multiplet at $\delta$ 7.41-7.45 ppm. The multipet at $\delta$ 7.59-7.80 ppm is for twelve protons (8Hc + 4Hd) present on ring C and D. $^{13}$C NMR spectrum (Fig. 5.II.6) of same compound exhibited twelve signals in the aromatic region from $\delta$ 126.9 to 152.7 ppm.

Fig. 5.II.3
Compound 7a (Table 5.II.2, entry 1): The $^1$H NMR spectrum of the compound (Fig. 5.II.7) showed one doublet for two Hb protons present on pyridine ring A at $\delta$ 9.45 ppm ($J = 3.0$ Hz) and another doublet at $\delta$ 8.66 ppm ($J = 2.4$ Hz) for two Ha protons present on same ring A (Fig. 5.II.4). Spectrum also showed one multiplet at $\delta$ 7.37-7.82 ppm is for twenty three aromatic protons ($5Hc + 8Hd + 10He$) present on ring C, D and E. $^{13}$C NMR spectrum (Fig. 5.II.8) of same compound exhibited nineteen signals in the aromatic region from $\delta$ 127.1 to 155.3 ppm.

![Compound 7a](image)

**Fig. 5.II.4**

5.II.4 Conclusion

In conclusion, we have developed highly active catalytic system comprising Pd(dppf)Cl$_2$ for the Suzuki–Miyaura cross-coupling of Pyrido[2,3-b]pyrazines and Quinoxalines with a variety of arylboronic acids.

5.II.5 Experimental section

$^1$H NMR and $^{13}$C NMR spectra were recorded on a Brucker AC (300 MHz for $^1$H NMR and 75 MHz for $^{13}$C NMR) spectrometer using CDCl$_3$ as solvent and tetramethylsilane (TMS) as an internal standard. Infrared spectra were recorded on a Perkin-Elimer FTIR spectrometer. The samples were examined as KBr discs $\sim$ 5 % w/w. Melting points were determined with a
Synthesis of Quinoxalines and Pyrido[2,3-b]pyrazines Through the Application of the Suzuki–Miyaura Cross-coupling Reaction

DBK melting point apparatus and are uncorrected. All the chemicals were obtained from Aldrich and Spectrochem and used without further purification.

**General procedure for the synthesis of Pyrido[2,3-b]pyrazine derivatives (Table 5.II.2, compounds 5a-5d)**

7-bromo-2,3-diphenylpyrido[2,3-b]pyrazine 1 (1.0 mmol), arylboronic acid (1.2 mmol), K$_2$CO$_3$ (2 mmol), Pd(dppf)$_2$Cl$_2$ (0.017 g, 2 mol %) were stirred in Schlenk flask, equipped with a magnetic stir bar and a condenser in THF (5 mL). The reaction mixture was refluxed for desired time. Upon complete consumption of starting materials as determined by TLC analysis, the water (20 mL) was added and aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were collected, dried over anhydrous Na$_2$SO$_4$, concentrated in vacuum to afford product which was purified by silica gel column chromatography (n-hexane/ethyl acetate = 9:1).

**General procedure for the synthesis of Pyrido[2,3-b]pyrazine derivatives (Table 5.II.2, compounds 6a-6b)**

The reaction mixture containing compound 2 (1.0 mmol), arylboronic acid (1.2 mmol), K$_2$CO$_3$ (2 mmol), Pd(dppf)$_2$Cl$_2$ (0.017 g, 2 mol %) were stirred in Schlenk flask, equipped with a magnetic stir bar and a condenser in THF (5 mL). The reaction mixture was refluxed for desired time. Upon complete consumption of starting materials as determined by TLC analysis, the water (20 mL) was added and aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were collected, dried over anhydrous Na$_2$SO$_4$, concentrated in vacuum to afford product which was purified by silica gel column chromatography (n-hexane/ethyl acetate = 9:1).

**General procedure for the synthesis of Pyrido[2,3-b]pyrazine derivatives (Table 5.II.2, compound 7a)**

The reaction mixture containing compound 3 (1.0 mmol), arylboronic acid (3.2 mmol), K$_2$CO$_3$ (6 mmol), Pd(dppf)$_2$Cl$_2$ (0.051 g, 6 mol %) were stirred in Schlenk flask, equipped with a magnetic stir bar and a condenser in THF (5 mL). The reaction mixture was refluxed for desired time. Upon complete consumption of starting materials as determined by TLC analysis, the
water (20 mL) was added and aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were collected, dried over anhydrous Na$_2$SO$_4$, concentrated in vacuum to afford product which was purified by silica gel column chromatography (n-hexane/ethyl acetate = 9:1).

**General procedure for the synthesis of Quinoxaline derivatives (Table 5.II.3, compounds 8a-8b)**

An oven-dried Schlenk flask, equipped with a magnetic stir bar, septum and a condenser was charged with 4 (1.0 mmol), arylboronic acid (2.2 mmol), K$_2$CO$_3$ (4 mmol), Pd(dppf)$_2$Cl$_2$ (0.034 g, 4 mol %) and THF (5 mL). The reaction mixture was refluxed for desired time. Upon complete consumption of starting materials as determined by TLC analysis, the water (20 mL) was added and aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were collected, dried over Na$_2$SO$_4$, concentrated in vacuum to afford product which was purified by silica gel column chromatography (n-hexane/ethyl acetate = 9:1).

**Spectral data of representative compounds:**

**5a (Table 5.II.2, entry 1):** Yellow solid, observed mp 174–176 °C. Lit. 172–173 °C [19]. $^1$H NMR (CDCl$_3$, 300 MHz): δ$_H$ (ppm) 7.32–7.39 (m, 6H), 7.46-7.48 (m, 1H), 7.54-7.58 (m, 4H), 7.63-7.66 (m, 2H), 7.79-7.82 (m, 2H), 8.65 (d, 1H, $J = 3.3$ Hz), 9.44 (d, 2H, $J = 3.6$ Hz). $^{13}$C NMR (CDCl$_3$, 75 MHz): δ$_C$ (ppm) 127.6, 128.1, 128.2, 129.8, 129.2, 129.3, 129.9, 130.4, 134.5, 136.0, 136.5, 138.1, 138.5, 148.8, 153.3, 154.9, 155.8.

**5c (Table 5.II.2, entry 3):** Yellow solid, observed mp 182–184 °C. $^1$H NMR (CDCl$_3$, 300 MHz): δ$_H$ (ppm) 2.41 (s, 6H), 3.80 (s, 3H), 7.31–7.40 (m, 6H), 7.45 (s, 2H), 7.55 (d, 2H, $J = 7.8$ Hz), 7.64 (d, 2H, $J = 6.6$ Hz), 8.59 (d, 1H, $J = 1.8$ Hz), 9.41 (d, 2H, $J = 1.8$ Hz). $^{13}$C NMR (CDCl$_3$, 75 MHz): δ$_C$ (ppm) 16.1, 59.4, 128.0, 128.2, 129.2, 129.4, 129.8, 130.4, 131.6, 132.1, 134.1, 134.3, 136.0, 137.9, 138.1, 138.5, 148.2, 152.8, 155.0, 156.7, 158.1.

HRMS: [Mass (Calculated- 418.1929, Observed-418.1940)].

**5d (Table 5.II.2, entry 4):** Yellow solid, observed mp 162–165 °C. $^1$H NMR (CDCl$_3$, 300 MHz): δ$_H$ (ppm) 7.34–7.41 (m, 6H), 7.49-7.63 (m, 6H), 7.65-7.69 (m, 2H), 7.92-7.98 (m, 3H), 8.63 (d, 1H, $J = 2.7$ Hz), 9.33 (d, 1H, $J = 2.1$ Hz). $^{13}$C NMR
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(CDCl$_3$, 75 MHz): $\delta_C$ (ppm) 125.0, 125.4, 126.2, 127.0, 127.9, 128.1, 128.3, 128.6, 129.2, 129.3, 129.9, 130.3, 131.3, 133.9, 135.0, 135.7, 137.7, 138.1, 138.2, 138.6, 143.7, 149.0, 154.9, 156.7, 158.1.

**HRMS:** [Mass (Calculated- 410.1657, Observed-410.1650)].

6a (Table 5.II.2, entry 5): Yellow solid, observed mp > 300 °C. $^1$H NMR (CDCl$_3$, 300 MHz, ppm): $\delta_H$ 7.49–7.63 (m, 3H), 7.74-7.90 (m, 6H), 8.59 (dd, 2H, $J = 2.8$ Hz), 8.82 (d, 1H, $J = 2.4$ Hz), 9.37 (d, 1H, $J = 7.8$ Hz), 9.56 (d, 2H, $J = 9.3$ Hz). **HR-MS:** (357.1260).

8b (Table 5.II.3, entry 2): White solid, observed mp 217-219 °C. $^1$H NMR (CDCl$_3$, 300 MHz, ppm): $\delta$ 7.10–7.15 (m, 4H), 7.53-7.60 (m, 8H), 7.65 (d, 4H, $J = 8.1$ Hz), 7.78 (dd, 2H, $J = 3.3$ Hz), 8.18 (dd, 2H, $J = 3.3$ Hz). **HR-MS:** (471.1680).

**HRMS:** [Mass (Calculated- 471.1680, Observed-471.1673)].
5.II.7 References


Fig. 5.II.5 $^1$H NMR spectrum of compound 8a
Fig. 5.II.6 $^{13}$C NMR spectrum of compound 8a
Fig. 5.II.7 $^1$H NMR spectrum of compound 7a
Fig. 5.II.8 $^{13}$C NMR spectrum of compound 8a
Fig. 5.II.9 $^1$H NMR spectrum of compound 8b
Elemental Composition Report

Single Mass Analysis (displaying only valid results)
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 200.0
Isotope cluster parameters: Separation = 1.0  Abundance = 1.0%

Monoisotopic Mass, Odd and Even Electron Ions
15 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Micromass: Q-Tof micro (YA-105)
C32H20F2N2
SSK-4-VAS-SA3 40 (0.399) AM (Med,5, Ht,5000.0,311.08,1.00); Sm (Md, 6.00); Sb (5,40.00 ); Cm (1:42)

TOF MS ES+
3.64e3

Fig. 5.II.10 HRMS spectrum of compound 8b
Elemental Composition Report

Single Mass Analysis (displaying only valid results)
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 200.0
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

Monoisotopic Mass, Odd and Even Electron Ions
1 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Micromass: Q-Tof micro (YA-105)
C29H19N3
SSK-4-VAS-SA1-1 6 (0.059) AM (Cen,5, 80.00, Hl,5000.0,311.08,1.00); Sb (5,40.00 ); Cm (1:33)

Fig. 5.II.10 HRMS spectrum of compound 5d