N-Arylation of heterocycles by mixed ligand transition metal complexes under mild conditions

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Mixed ligand transition metal complexes [M(L)(PPh₃)₂][X] (1-4 where L- 2-phenyl, 3-benzoylamino-1,2-dihydroquinazolin-4(3H)-one (PBADQ), where M is Co, Ni, Cu, Zn and X is Cl have been synthesized and characterized by elemental analysis, IR, NMR spectral studies and their role as catalyst in N-arylation of indole and isatin with aryl halides. It has been observed that all the complexes worked as efficient catalysts, especially [Ni(L)(PPh₃)₂]Cl₂ complex 2 is found to be most suitable for N-arylation of indole and isatin.

Keywords: Quinazolinone Schiff base, mixed ligand transition metal complex, N-arylation, heterocycles

The formation of aryl-nitrogen bonds via cross-coupling reactions represents a powerful technique for the preparation of various compounds (e.g., arylpyroles, arylpyrazoles, arylimidazoles, aryltriazoles, arylindoles, arylcarbazoles, etc.) that are of biological, biochemical, pharmaceutical and materials interest. Traditionally, these compounds have been synthesized via nucleophilic aromatic substitution of N–H containing p-electron-rich nitrogen heterocycles with electrondeficient aryl halides, which limits its scope or by coupling with organometallic reagents. Today, catalysts play a significant role in the production of chemicals and nanomaterials have the potential for improving efficiency, selectivity, and yield of the catalytic process. The higher surface to volume ratio means that much more catalyst actively participates in the reaction. The potential for cost saving is tremendous from a material, equipment, labour, and time standpoint. Higher selectivity means less waste and fewer impurities, which could lead to safer and reduced environmental impact. The study of application of metal nanoparticles in catalysis, particularly, on organic transformations, has become a frontier area of research in nanocatalysis. Among the different metal nanocatalysts, immobilized Pd(II) complexes have gained a notable reputation, because palladium is a versatile catalyst in modern organic synthesis and is widely used for a significant number of synthetic transformations such as, Heck, Suzuki, Stille, Sonogashira cross coupling reactions and N-arylation of heterocycles. The arylation of indole and similar compounds is usually carried out by Ullmann-type coupling reactions. However, these reactions have limitations such as high-temperature reaction conditions, moderate yields, use of highly polar solvents as well as the use of large amounts of copper-based catalysts; and these aspects greatly limit their applications. To overcome these drawbacks, a breakthrough was achieved by Buchwald et al. who reported the combination of copper iodide with N,N-bidentate ligands as effective catalyst systems for the N-arylation of nitrogen-containing heterocycles with aryl halides. Under mild conditions, they obtained good product yields using these catalyst systems. However, an efficient separation and subsequent recycling of these homogeneous transition metal catalysts remain a challenge and an economic concern. One of the best ways to overcome these difficulties is to employ heterogeneous catalysis, as it enables a convenient recovery and reuse of the catalyst from the reaction mixture through simple filtration or decantation.

Isatin (1H-indole-2, 3-Dione) consist of indole nucleus and two types of carbonyl groups i.e. keto and lactam group. It has been discovered 150 years ago and now known as oxindole and Endogenous
polyfunctional heterocyclic compounds. It was first investigated by Erdman and Laurent in 1841 as a product from the oxidation of indigo by nitric and chromic acids. Isatin has a wide variety of pharmacological activities such as antimicrobial, anticancer, antiviral, anticonvulsant, anti-inflammatory and analgesic. Different research groups attempted study on isatin synthetic aspect and biological activity.

The Schiff base transition metal complexes are a family of attractive oxidation catalysts for a variety of organic substrates because of their cheap and easy synthesis and their chemical and thermal stability. The catalytic activities of the Mn(II), Fe(III), Co(II) and Cu(II) complexes are observed for their activity towards phenol hydroxylation reaction. All the complexes show good activity (Figure 1). The activities of these cobalt complexes are slightly lower than that of copper(II), iron(II) and manganese(II) analogues of the investigated Schiff bases.

**Results and Discussion**

We have synthesized mixed ligand transition metal complexes \([M(L)(PPh_3)]_2X_2\) where \(M=\text{Co (II), Ni(II), Cu(II) and Zn(II)}\), \(X=\text{Cl and L= 2-Phenyl 3-benzoylamino 1,2-dihydroquinazolin-4(3H)-one (PBADQ)}\) by the reaction of Schiff base and transition metal salts in acetonitrile. All the mixed ligand transition metal complexes were in stable and soluble in DMSO. The elemental analysis (C, H and N, Table I) of the Schiff Base ligand and Schiff Base mixed ligand transition metal complexes synthesized are relatively close to those calculated based on molecular formulae proposed, which indicates the correctness of composition proposed. In IR spectrum (Table II) of free ligand \(L\) the medium intensity band at 3336 cm\(^{-1}\) is due to the \(\nu(NH)\) of the quinazoline ring is observed in the spectra of all of the complexes ruling out the possibility of deprotonation of N-H group and suggests noninvolvement of the N-H in coordination with metal. The characteristic \(\nu(C=O)\) frequency of ligand \(L\) occurs at 1706 cm\(^{-1}\) is shifted to lower frequency around 1661 cm\(^{-1}\) in all complexes provide the strong evidence for involvement of carbonyl oxygen in coordination with metal ion. The IR spectra of ligand shows a strong band at 1633 cm\(^{-1}\) which is attributed band of azomethine (HC=N) group which is shifting towards the lower frequency region by 18-29 cm\(^{-1}\) complexes indicates involvement of azomethine nitrogen in coordination with metal ion. This view is further supported by the appearance of a

**Table I — Analytical and physico-chemical data of mixed ligand transition metal complexes**

<table>
<thead>
<tr>
<th>Complexes</th>
<th>M. F.</th>
<th>Yield %</th>
<th>M. P.(^\circ)C</th>
<th>Analytical data% found (calcd.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Co(L)(PPh_3)]_2Cl_2 (1)</td>
<td>C_7H_4N_3O_2P_2Cl_2Co</td>
<td>64</td>
<td>163</td>
<td>70.61 (70.88) 4.80 (4.91) 4.24 (4.35)</td>
</tr>
<tr>
<td>[Ni(L)(PPh_3)]_2Cl_2 (2)</td>
<td>C_7H_4N_3O_2P_2Cl_2Ni</td>
<td>67</td>
<td>151</td>
<td>70.81 (70.90) 4.74 (4.91) 4.22 (4.35)</td>
</tr>
<tr>
<td>[Cu(L)(PPh_3)]_2Cl_2 (3)</td>
<td>C_7H_4N_3O_2P_2Cl_2Cu</td>
<td>73</td>
<td>155</td>
<td>70.33 (70.54) 4.80 (4.89) 4.20 (4.33)</td>
</tr>
<tr>
<td>[Zn(L)(PPh_3)]_2Cl_2 (4)</td>
<td>C_7H_4N_3O_2P_2Cl_2Zn</td>
<td>68</td>
<td>158</td>
<td>70.29 (70.41) 4.72 (4.88) 4.19 (4.32)</td>
</tr>
</tbody>
</table>

**Table II — Infrared spectral data of mixed ligand transition metal complexes**

<table>
<thead>
<tr>
<th>Complexes</th>
<th>(\nu(NH))</th>
<th>(\nu(C=O))</th>
<th>(\nu(C=\text{N}))</th>
<th>(\nu(PPh_3))</th>
<th>(\nu(M-N))</th>
<th>(\nu(M-O))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3277</td>
<td>1661</td>
<td>1615</td>
<td>1489, 1433, 690, 530</td>
<td>517</td>
<td>448</td>
</tr>
<tr>
<td>2</td>
<td>3277</td>
<td>1661</td>
<td>1614</td>
<td>1488, 1434, 690, 511</td>
<td>488</td>
<td>426</td>
</tr>
<tr>
<td>3</td>
<td>3225</td>
<td>1669</td>
<td>1604</td>
<td>1483, 1452, 689, 535</td>
<td>514</td>
<td>458</td>
</tr>
<tr>
<td>4</td>
<td>3277</td>
<td>1661</td>
<td>1614</td>
<td>1481, 1433, 690, 539</td>
<td>523</td>
<td>490</td>
</tr>
</tbody>
</table>
band complexes corresponding to the metal-nitrogen υ(M-N) stretching vibration around 517 cm⁻¹ in all complexes. The ¹H NMR spectral data of the Schiff base ligand (L) as well as their transition metal complexes (1-4) shows shift of the resonance is on complexation in each case. The proton assigned due to azomethine (HC=N) were found at δ 9.25 ppm in L undergo downfield shift in the transition metal complexes around δ 9.02 ppm confirms the coordination of azomethine nitrogen with metal ion. The aromatic proton peaks observed between δ 7.52-8.56 ppm in L also shows slight down field shifts in their respective complexes.

Initially, the catalytic activity of the mixed ligand complexes 1-4 evaluated by using the C-N coupling of bromobenzene with indole and isatin as a model reaction in the presence of NaOH at 120°C for 10 h in DMSO. As expected, the four Schiff base mixed ligand transition metals Co, Ni, Cu, Zn complexes, all exhibited catalytic activity for this process and which gave the desired product A is 76-90% and product B is 66-82% (Table III entries 2-5). The coupling reaction did not occur in the absence of complex as catalyst (Table III entry 1). Subsequently we select the complex 2 as catalyst to further investigate the effect of the other reaction conditions on the N-arylation reaction because it gives high yield, including reaction temperature, base, solvent and catalyst loading. The result showed that 100°C was enough for the coupling reaction to give 90% yield for product A and 82% yield for product B (Table III entry 6), and the lower temperature decelerated the reaction rate for example when the reaction was carried out at 80°C then 70% yield for product A and 61% yield for product B (Table III entry 7). It was found that DMSO performed as the prime solvent. Both DME and DMF were not as good as DMSO (Table III entries 10, 11). Meanwhile 1,4 dioxane, DCM, H₂O was not suitable as a solvent (Table III entries 8, 9, 12). Furthermore, increasing the loading base from 0.1 mol% to 0.5 mol% led to an increase the yield (Table III entry 13). Furthermore, decreasing the loading of complex 2 from 10 mol% to 5 mol% led to a decrease of the yield (Table III entry 14). Finally, the complex 2 as [Ni (L) (PPh₃)₂]Cl₂ 10 mol%, NaOH

<table>
<thead>
<tr>
<th>Entry</th>
<th>Complex</th>
<th>Base (NaOH) mol %</th>
<th>Complex</th>
<th>Solvent</th>
<th>Temp °C</th>
<th>Yield % Product A</th>
<th>Yield % Product B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>0.1</td>
<td>10 mole %</td>
<td>DMSO</td>
<td>120</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0.1</td>
<td>10 mole %</td>
<td>DMSO</td>
<td>120</td>
<td>81</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>0.1</td>
<td>10 mole %</td>
<td>DMSO</td>
<td>120</td>
<td>91</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>0.1</td>
<td>10 mole %</td>
<td>DMSO</td>
<td>120</td>
<td>77</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>0.1</td>
<td>10 mole %</td>
<td>DMSO</td>
<td>120</td>
<td>76</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>0.1</td>
<td>10 mole %</td>
<td>DMSO</td>
<td>100</td>
<td>91</td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>0.1</td>
<td>10 mole %</td>
<td>DMSO</td>
<td>80</td>
<td>70a</td>
<td>61a</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>0.1</td>
<td>10 mole %</td>
<td>1,4 dioxane</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>0.1</td>
<td>10 mole %</td>
<td>DCM</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>0.1</td>
<td>10 mole %</td>
<td>DME</td>
<td>100</td>
<td>48</td>
<td>51</td>
</tr>
<tr>
<td>11</td>
<td>2</td>
<td>0.1</td>
<td>10 mole %</td>
<td>DMF</td>
<td>100</td>
<td>42</td>
<td>58</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>0.1</td>
<td>10 mole %</td>
<td>H₂O</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>2</td>
<td>0.5</td>
<td>10 mole %</td>
<td>DMSO</td>
<td>100</td>
<td>96b</td>
<td>88b</td>
</tr>
<tr>
<td>14</td>
<td>2</td>
<td>0.1</td>
<td>5 mole %</td>
<td>DMSO</td>
<td>100</td>
<td>77c</td>
<td>65c</td>
</tr>
</tbody>
</table>

Table III — N-Arylation of indole and isatin with bromobenzene

Nu-H + [ M(L)(PPh₃)₂]Cl₂ \( \text{NaOH, DMSO, 100°C, 10 Hrs} \)

Nu : Indole, Isatin

a- The reaction was carried out at 80°C
b- The use of 0.5 mol % of base
c- The use of 5 mol % of complex
0.1 mol% at 100°C for 10 hrs in DMSO was chosen as the optimal conditions for N-arylation of indol and isatin with different aryl halides and their derivatives (Scheme I).

The importance of substrate was then investigated by using [Ni (L) (PPh₃)₂]Cl₂ as catalytic system under the optimized reaction conditions. As shown in Table IV, In general indole reacts with aryl iodides the desired products gives to excellent yield. For example iodo benzene led to the N-arylated product is 96% yield. (Table IV entry 3). Furthermore the catalytic system could variety of functional groups including methyl, nitro and phenyl groups. It was noted that 4-methyl iodo benzene did not hamper the arylation reaction (Table IV, entry 4). 4 iodo 1,1 biphenylled to the N-arylated product is 90% yield (Table IV, entry 6). 1 iodo 4 nitro benzene as coupling partner the yield dropped as 61% (Table IV, entry 5). Further this catalytic system is applied to a isatin. Most of the aryl iodides reacted with the isatin it gives good yield under the optimized reaction conditions (78%-89%). Electron withdrawing group to be a little beneficial for the catalysis as compared to electron donating group. For example 1-iodo 4-nitro benzene afforded the 45% (Table IV, entry 11). Furthermore aryl iodides treated with electron donating groups to give good yield (Table IV, entry 10 and 12).

Materials and Methods
All the chemicals used were analytical grade quality reagents sigma Aldrich and used without further purification. IR spectral data were recorded on Perkin Elmer, FT-IR/FIR Spectrometer with KBr. ¹H NMR spectral data were recorded on a Bruker, AVANCE II-300 MHZ using CDCl₃ as solvent. Mass spectra were recorded on SHIMADZU GC-MS Q 2010 UTRA instrument.

Experimental Section
Synthesis of Schiff base 2-phenyl, 3-benzoylamino, 1, 2-dihydroquinazolin-4(3H)-one (PBADQ).
The Schiff base 2-phenyl, 3-benzoylamino, 1,2-dihydroquinazolin-4(3H)-one is obtained by the reported method from 2-aminobenzoyl hydrazide (1.510g;0.01mol) and benzaldehyde (02.12g; 0.02mol) in MeOH. The reaction mixture was refluxed for 3-4 hrs and cooled. The yellow colored solid formed was filtered and dried in air. Recrystallization from hot EtOH lead to yellow solid. The purity of the compound was checked by TLC on precoated silica gel which gave a single spot yield 92%,
Analytical data % found (calcd) For \( [\text{C}_2\text{H}_17\text{N}_3\text{O}] \) C, 77.04 (77.01); H, 5.23 (5.28) and N, 12.84 (12.88). IR (KBr) cm\(^{-1}\) \( \nu_{1633} \)(C=N), \( \nu_{1706} \)(C=O), \( \nu_{3336} \)(N-H) and \( ^1\text{H} \) NMR (CDCl\(_3\), 300 MHz): \( \delta_{9.25} \)(HC=N): \( \delta_{4.93} \)(Ar-H): \( \delta_{3.64} \)(N-H).

Synthesis of complexes
To a solution of metal chlorides MX\(_2\) (1mmol) in a 10 mL acetonitrile, a solution of two equivalent of triphenylphosphine (2mmol, 0.524 g) was added. The reaction mixture was stirred for 30 min at room temperature and allowed to evaporate slowly. The crystalline product \([\text{M} (\text{MeCN})_2\text{(PPh}_3^2\text{)}_2\text{]}\text{Cl}_2\) (1mmol, 0.735) obtained was subsequently added to a stirred solution of Schiff base ligand L (1 mmol, 0.327) in a 10 mL dichloromethane. The mixture was stirred at room temperature for 2h and the solution was evaporated to small volume under vacuum. The yellow colored complexes were developed by diffusion of diethyl ether into the solution.

1. \([\text{Co(L)(PPh}_3^2\text{)}_2\text{]}\text{Cl}_2\) Yield 64%. IR (KBr) cm\(^{-1}\) \( \nu_{1615} \)(C=N), \( \nu_{1661} \)(C=O), \( \nu_{3277} \)(N-H) and \( ^1\text{H} \) NMR (CDCl\(_3\), 300 MHz): \( \delta_{9.06} \)(HC=N): \( \delta_{3.64} \)(N-H).

2. \([\text{Ni(L)(PPh}_3^2\text{)}_2\text{]}\text{Cl}_2\) Yield 67%. IR (KBr) cm\(^{-1}\) \( \nu_{1614} \)(C=N), \( \nu_{1661} \)(C=O), \( \nu_{3277} \)(N-H) and \( ^1\text{H} \) NMR (CDCl\(_3\), 300 MHz): \( \delta_{9.02} \)(HC=N): \( \delta_{3.64} \)(N-H).

3. \([\text{Cu(L)(PPh}_3^2\text{)}_2\text{]}\text{Cl}_2\) Yield 73%. IR (KBr) cm\(^{-1}\) \( \nu_{1604} \)(C=N), \( \nu_{1669} \)(C=O), \( \nu_{3225} \)(N-H) and \( ^1\text{H} \) NMR (CDCl\(_3\), 300 MHz): \( \delta_{9.08} \)(HC=N): \( \delta_{3.64} \)(N-H).

General procedure for N-arylation of indole and isatin with bromobenzene
In round bottom flask, complexes \([\text{M(L)(PPh}_3^2\text{)}_2\text{]}\text{Cl}_2\) (0.05 mmol), aryl halides (0.5mmol), heterocycles (1.0 mmol), NaOH (1.0 mmol) and 1 mL DMSO was refluxed at 100°C in a preheated oil bath for 10 hrs. The reaction is monitored with TLC. After the completion of reaction 10 mL H\(_2\)O added and extracted with ethyl acetate (3×20 mL). The combined organic phase was washed with water and dried over anhydrous Na\(_2\)SO\(_4\) and concentrated in vacuo. The residue was purified by flash column chromatograph on silica gel (ethyl acetate/petroleum ether 2:1 to pure ethyl acetate) to afford the target product A, (91% yield). N-Phenyl-Indole, Mol. formula C\(_{14}\)H\(_{11}\)N, Mol formula Wt 193.26. Anal. Calcd. For C\(_{14}\)H\(_{11}\)N, %: C, 87.00; H, 5.74; N, 7.26; Found: C, 86.95; H, 5.71; N, 7.30. \( ^1\text{H} \) NMR (CDCl\(_3\), 300 MHz): \( \delta_{9.08} \)(HC=N): \( \delta_{3.64} \)(N-H).

4. \([\text{Zn(L)(PPh}_3^2\text{)}_2\text{]}\text{Cl}_2\) Yield 68%. IR (KBr) cm\(^{-1}\) \( \nu_{1614} \)(C=N), \( \nu_{1661} \)(C=O), \( \nu_{3277} \)(N-H) and \( ^1\text{H} \) NMR (CDCl\(_3\), 300 MHz): \( \delta_{9.10} \)(HC=N): \( \delta_{3.64} \)(N-H).

Table IV — N-Arylation of indole and isatin with different aryl halides catalysed by complex-2.
Conclusion
The catalytic role of complexes 1-4 is tested for N-arylation of indole and isatin with different aryl halides. It was observed that all the complexes worked as the efficient catalysts. We have developed general catalytic method for N-arylation of indole and isatin using mixed ligand transition metal complexes, especially \([\text{Ni}(\text{L})(\text{PPh}_3)_2]\text{Cl}_2\) complex 2 is more suitable for these reactions. The system is sufficient for the coupling of indole and isatin with Ar-X (X=Cl, Br, I) to give excellent yield. Specially aryl iodides and its derivatives give excellent yield. The mild reaction conditions, easy synthesis of complex, simplicity in experiment and broad substrate scope are the features of the catalytic method. Further catalytic applications of these mixed ligand transition metal complexes for these organic reactions are currently going on in our chemical laboratory.

Supplementary Information
Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

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