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Cobalt Complex Catalyzed Atom-Economical Synthesis of Quinoxaline, Quinoline and 2-Alkylaminoquinoline Derivatives

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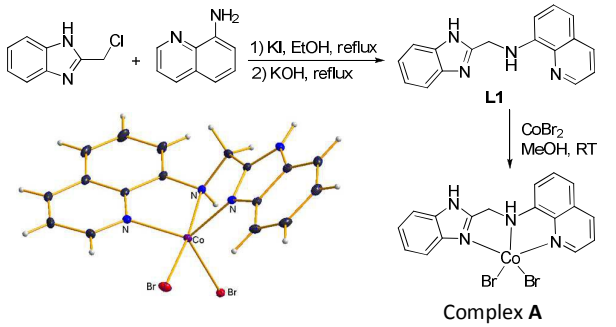
A new phosphine free Co(II) complex catalyzed synthesis of various quinoxalines via dehydrogenative coupling of vicinal diols with both the *o*-phenylenediamines and 2-nitroanilines is reported. This complex was also effective for the synthesis of quinolines. The practical aspect of this catalytic system was revealed by one-pot synthesis of 2-alkylaminoquinolines.

The development of catalysts based on abundant and nonprecious 3d transition metals received significant attention over the past few decades.[1] Cobalt is one of the attractive candidates among the 1st row transition metals and numerous reactions using cobalt catalysts are known.[2] Recently, following the borrowing hydrogen strategy cobalt complex mediated some C-C and C-N bond forming reactions such as N-alkylation of amines,[3] C-alkylation of ketones,[4] amides,[5] and alcohols,[6] and other dehydrogenative coupling reactions[7] were reported. These protocols have significant advantages over the conventional methods as it employs alcohol as a greener alkylating partner. It also does not require precious metal catalysts and avoids the formation of stoichiometric salt waste. However, most of these cobalt complexes are based on expensive, air and moisture sensitive phosphine ligands which limits their applications.[3d, 6, 8]

Sustainable synthesis of quinoxaline, quinoline and 2-alkylaminoquinoline derivatives remains an attractive target to the organic chemists due its wide range of pharmacological and biological activities including antibacterial, antiamoebic, antidepressant, antiviral, anticancer, antitumor, antimalarial, and anti-inflammatory properties.[9] Quinoxaline derivatives also utilized as electroluminescent materials, organic semiconductors, cavitands and fluorescent dyes.[10] Compared to the various conventional methods,[11] the synthesis of quinoxaline and quinoline derivatives via dehydrogenative coupling of biomass-derived vicinal diols with 1,2-diamines or 2-nitroanilines and coupling of amino alcohols with secondary alcohols, respectively are more attractive as it avoids pre-functionalized molecules, halogenated coupling partners or addition of excessive additives. Following these strategies for the synthesis of these molecules mostly precious and less-abundant 4d and 5d transition metals based catalysts are reported.[12]

Herein, we report phosphine free cobalt complex catalyzed environmentally benign synthesis of quinoxaline and quinoline derivatives as well as one-pot synthesis of 2-alkylaminoquinolines. To the best of our knowledge cobalt complex mediated atom-economical synthesis of quinoxalines and 2-alkylaminoquinolines following dehydrogenative coupling and borrowing hydrogen methodology is not reported yet.

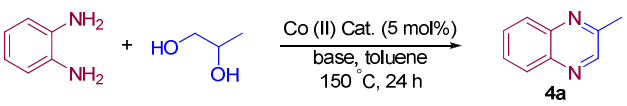
Inspired by the high reactivity of several tridentate ligand containing Co(II) complexes,[13] we synthesized a new nitrogen containing proton responsive ligand **L1** and its corresponding Co(NNN) complex was synthesized in good yield (89%) by reacting **L1** and $CoBr_2$ in methanol at room temperature (Fig. 1). This paramagnetic complex was characterized by elemental analysis, ESI-MS, X-ray crystallography, UV-Vis and IR spectroscopy. The solid state structure of complex **A** showed a distorted square pyramidal structure with a dihedral angle of 36.55 (3) ° between the benzimidazole and quinoline moiety.



Complex **A**

Fig. 1 Synthesis of complex **A** and its molecular structure. Ellipsoids are drawn at 30% thermal probability level.

Table 1 Screening of the optimal conditions[a]



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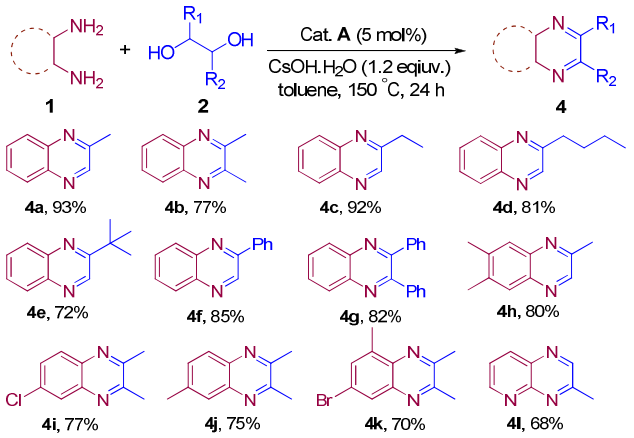
Entry	Co (II) Cat.	Base (equiv.)	Yield of **4a** (%)
1	$CoBr_2$	KO^{t}Bu (1.2)	25
2	A	KO^{t}Bu (1.2)	88
3	-	KO^{t}Bu (1.2)	2
4	A	NaO^{i}Pr (1.2)	73
5	A	KOH (1.2)	75
6	A	$CsOH.H_2O$ (1.2)	96
7[b]	A	$CsOH.H_2O$ (1.2)	70

[a]Reaction conditions: *o*-phenylenediamine (0.5 mmol), 1,2-propanediol (2.5 mmol), toluene (2 mL), heated at 150 °C for 24 h under closed condition; GC yield (*n*-dodecane as internal standard). [b]refluxed at 140 °C.

Initially, dehydrogenative coupling of 1,2-propanediol with *o*-phenylenediamine was selected as model reaction to determine the optimum reaction conditions and the reaction was carried in toluene for 24 h using Co(II) complexes (5 mol%) and 1.2 equiv. of KO^{t}Bu (Table 1). The yield of the desired 2-methylquinoxaline (**4a**) product was significantly higher in presence of complex **A** compare to the metal precursor $CoBr_2$. Next, in the presence of complex **A**, different bases were tested and $CsOH.H_2O$ delivered the best results. The yield of **4a** was reduced by lowering the ratio of 1,2-diol to diamine and also by decreasing the oil bath temperature (SI, Table S1). Similar phenomenon was also reported for the Co(II) catalyzed coupling of amino alcohols with secondary alcohols and the reaction was carried out at high temperature (180 °C).[14]

Next, different quinoxaline were synthesized from various vicinal diols and diamines (Scheme 1). Reaction of *o*-phenylenediamine with different mono substituted vicinal diols provided good to excellent yields of the expected products (Scheme 1, **4a, 4c**-**4f**). However, yields of the quinoxalines was slightly lower with both disubstituted vicinal diol and substituted aryl diamines under the same reaction conditions (**4b**, **4g**-**4k**). Notably, challenging pyridine containing diamine also afforded 3-methylpyrido[2,3-b]pyrazine (**4l**) in moderate yields under this reaction conditions.

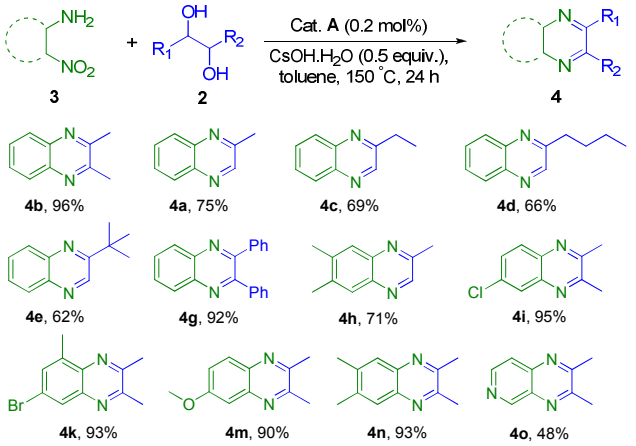
After establishing the potential of this system to catalyze the coupling of diamines with diols, we sought out the synthesis of quinoxaline from 2-nitroaniline and diol. In this process the nitro group of 2-nitroanilines and the vicinal diols serve as the hydrogen acceptor and donors respectively. This eco-friendly strategy is attractive as it avoids the use of any external reducing agents and produces only water as by product.[12a, 15] For this purpose 2-nitroaniline and 2,3-butanediol were chosen as primary substrates for the optimization of the reaction parameters. Interestingly, complex **A** in presence of 0.5 equiv. of $CsOH.H_2O$ delivered 96% yield for the desired product after 24 h. Notably, the catalyst loading in this reaction was significantly lower (0.2 mol %) compare to the



Scheme 1 Substrate scope for quinoxaline Synthesis. Reaction conditions: diamine (0.5 mmol), vicinal diol (2.5 mmol), Cat. **A** (5 mol%), $CsOH.H_2O$ (0.6 mmol), toluene (2 mL), heated at 150 °C for 24 h under closed condition; isolated yields.

coupling of diamine and diol. To our delight, in comparison to the recently reported Zhang group's system (3 mol% Ru(II)/dppp), complex **A** exhibited much higher activity.[12a]

With this optimized conditions the coupling of various diols with substituted nitroanilines was carried out to examine the generality of this protocol (Scheme 2). At first verities of quinoxaline were synthesized using different vicinal diols keeping 2-nitroaniline as a fixed coupling partner. Similar reaction with 3,4-dimethyl-2-nitroaniline also provided good to excellent yields (71-93%) of the desired quinoxaline (**4h, 4n**). However, yields were relatively lower with less substituted unsymmetrical diols compare to the more substituted diols under this reaction conditions (Scheme 2, **4a**-**4g**). Zhang's group also observed similar phenomenon.[12a] Different substituted nitroanilines were also smoothly converted to the desired product with excellent yield (**4i, 4k, 4m**) whereas pyridine containing nitroamine showed moderate reactivity (**4o**).



Scheme 2 Quinoxaline synthesis from 2-nitroanilines and vicinal diols. Reaction conditions: 2-nitroaniline (0.5 mmol), vicinal diol (1.5 mmol), Cat. **A** (0.2 mol%),

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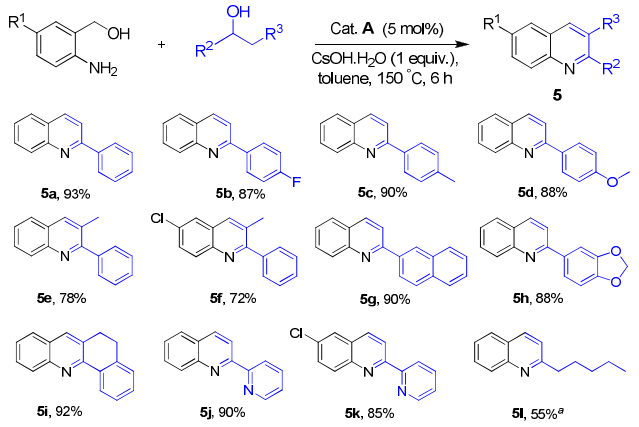
$CsOH.H_2O$ (0.25 mmol), toluene (2 mL), heated at 150 °C for 24 h under closed condition; isolated yields.

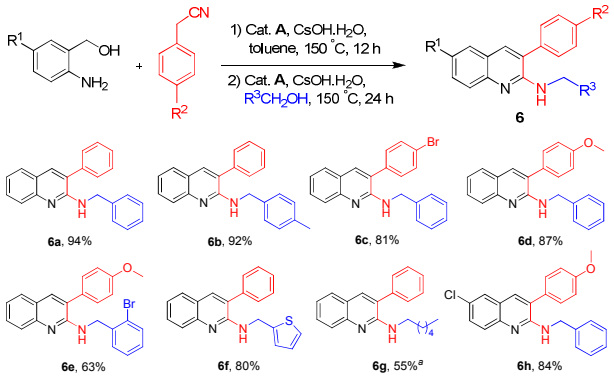


Scheme 3 Synthesis of quinoline derivatives. Reaction conditions: 2-aminoaryl alcohol (0.5 mmol), secondary alcohol (0.6 mmol), Cat. **A** (5 mol%), $CsOH.H_2O$ (0.5 mmol), toluene (2 mL) at 150 °C for 6 h; isolated yields. [a]12 h.

Next, complex **A** mediated acceptorless dehydrogenative coupling reaction between 2-aminoaryl alcohols and secondary alcohols was explored. First row transition metal complex catalyzed similar reaction for the synthesis of quinolines is less explored in literature.[14, 16] For this purpose all the reaction parameters was optimized and 93% isolated yield of **5a** was observed for the cross coupling of 2-aminobenzyl alcohol and 1-phenylethanol in presence of 5 mol% complex **A** after 6 h of reflux in toluene. Afterwards, coupling of 2-aminobenzyl alcohol with various substituted 1-phenylethanol bearing electron donating and withdrawing groups were carried out which produced the desired products in good to excellent yields (Scheme 3, **5b**-**5f**). 1,2,3,4-Tetrahydro-1-naphthol showed 92% yield whereas straight chain 2-heptanol provided moderate yield. Interestingly, following this protocol heteroaromatic 1-(pyridin-2-yl)ethanol also delivered excellent results (**5j**, **5k**).

We were further interested to explore the one-pot synthesis of 2-alkylaminoquinolines encouraged by the recent Ru(II) catalyzed only two reports.[17] These nitrogen containing heteroaromatics are important building block for the synthesis of variety of organic molecules and also present in several biologically active compounds.[9b, 18] Gratifyingly, this cobalt system was also able to catalyze the same reaction in one-pot manner and yielded 94% of **6a** using 2-aminobenzyl alcohol, benzyl cyanide and benzyl alcohol (Scheme 4 and SI Table S3). To the best of our knowledge, this is the first example of Co(II) catalyzed synthesis of 2-alkylaminoquinolines via acceptorless dehydrogenative annulation followed by N-alkylation reaction.

Afterward, a range of 2-alkylaminoquinolines was synthesized in good to excellent yields following the one-pot three component coupling of 2-aminobenzyl alcohols with a number of substituted 2-arylacetonitriles and primary alcohols (Scheme 4, **6a**-**6f**). This system tolerated both the electron donating and withdrawing as well as heteroatom-bearing 2-arylacetonitriles and primary alcohols. Likewise, chloro substituted 2-aminobenzyl alcohol provided good yield of **6h** under the same reaction conditions. The yield of the desired



Scheme 4 One-pot synthesis of 2-alkylaminoquinolines. Reaction conditions: 2-aminoaryl alcohol (0.5 mmol), nitrile (0.5 mmol), Cat. **A** (5 mol%), and $CsOH.H_2O$ (0.5 mmol) in toluene (2 mL) at 150 °C for 12 h followed by addition of Cat. **A** (5 mol%), $CsOH.H_2O$ (0.5 mmol) and primary alcohol (2.5 mmol) heated for 24 h; isolated yields. [a]second step: Cat. **A** (10 mol%).

product with 1-hexanol was poor due to the lower reactivity for the coupling of 2-aminoquinoline with 1-hexanol (**6g**).

To examine the practical applicability of this catalytic system, preparative scale reactions were carried out which smoothly provided the corresponding products in 68-84% isolated yields (SI, Scheme S1). Complex **A** was found to be effective for the dehydrogenation of alcohol in presence of a sacrificial hydrogen acceptor (SI, Scheme S2). Formation of H_2 during the quinoxaline synthesis from vicinal diols and diamines was confirmed by GC analysis. This catalytic system showed the similar reactivity in presence of mercury that suggested the homogeneity of the reaction (SI, S7). For the synthesis of quinoxaline from *o*-phenylenediamine when complex **A** (5 mol%) was treated with 1.1 equiv. $LiBEt_3H$ (5.5 mol%) it showed similar reactivity in presence of significantly lower amount of base (8 mol%) (SI, S6.2). This data suggested that probably *in situ* generated paramagnetic (NNN)Co(I)Br complex is the active catalyst for the reaction.[8, 13c, 19] Unfortunately, we were unable to get the single crystal of this Co(I) complex after numerous attempts. Undoubtedly, several kinetic experiments and theoretical calculations are needed to understand this mechanism clearly which is currently going on in our laboratory.

In summary, a new air and moisture-stable Co(NNN) complex catalyzed sustainable synthesis of variety of N-heterocyclic compounds (quinoxalines, quinolines and 2-alkylaminoquinolines) was developed. Following this protocol several quinoxalines were synthesized from coupling of both the diamines and 2-nitroanilines with the vicinal diols. Additionally, this catalyst was also effective in one-pot synthesis of 2-alkylaminoquinolines. To the best of our knowledge this is the first example of cobalt complex mediated atom-economical synthesis of quinoxalines and 2-alkylaminoquinolines. Utilization of non-precious metal based

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catalyst and phosphine free ligand system makes this an appealing methodology.

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Conflicts of interest

There are no conflicts to declare.

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