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Direct Access to *N*-Alkylated Amines and Imines *via* Acceptorless Dehydrogenative Coupling Catalyzed by Cobalt(II)-NNN Pincer Complex

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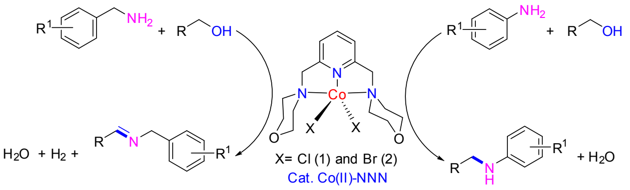
A simple, phosphine-free Co(II)-NNN pincer complex catalyzed direct *N*-alkylation of anilines with alcohols *via* hydrogen auto-transfer strategy (HA), and selective acceptorless dehydrogenative coupling (ADC) of benzylamines with alcohols affording imines with the liberation of molecular hydrogen and water is reported.

Amines and imines are the versatile functional groups in synthetic chemistry. They are ubiquitous in pharmaceuticals, agrochemicals, fungicides, lubricants, surfactants, fine chemical and dye industries, and materials science.[1] Thus, development of a new synthetic strategy for their production is very important. Generally, *N*-alkylation of amines (C-N bond formation) has been performed by the reaction of primary amines with organic halides,[2] reductive *N*-alkylation,[3] hydroamination,[4] and hydroamino-methylation[5] reactions. In contrast, imines are being synthesized by acid-base promoted condensation of primary amines with highly reactive carbonyl compounds,[6] oxidative coupling of amines,[7] hydroamination of alkynes,[8] and the oxidative coupling of alcohols with amines.[9] In recent times, there has been growing interest in catalytic processes based on earth-abundant base-metals and utilizing biomass-derived alcohols for sustainable transformations.[10] In this context, the direct synthesis of *N*-alkylated amines by the reaction of primary amines with alcohols catalyzed by the base-metal catalysts *via* borrowing hydrogen (BH)/hydrogen auto-transfer (HA) strategy has been paid much attention in contemporary science. Various base-metal (Mn, Fe, and Co) catalysts stabilized by electron-rich phosphine ligands have been reported for ADC and HA reactions.[11] Of late, cobalt(II) catalyst based on a pincer PNP or PNN ligand has been employed for the efficient *N*-alkylation of both aromatic and aliphatic amines with alcohols.[12] Molecularly-defined cobalt complex catalyzed dehydrogenative coupling of primary alcohols with aromatic diamines to afford benzimidazoles is also reported.[13] Kempe and co-workers described the cobalt-PNP pincer (triazine-based) complex catalyzedamination of alcohols.[12a] Equally, base-metal catalyzed the direct synthesis of imines by ADC of alcohols and amines is very important and rarely reported. Despite significant progress of transition-metal complexes bearing electron-rich phosphine ligands in homogeneous catalysis, they have encountered common drawbacks. Typically, their preparation often with far from trivial methods, multi-step syntheses, and handling under an inert atmosphere. As a consequence, the electron-rich phosphine ligands are expensive and potentially challenging to make on a large scale production. In addition, the high-cost and limited availability of the noble metal catalysts significantly impede their large-scale industrial applications. Herein, efficient phosphine-free Co(II)-NNN pincer complex catalyzed direct *N*-alkylation of anilines with alcohols, and selective acceptorless dehydrogenative coupling of benzylamines with alcohols affording imines with the liberation of molecular hydrogen and water is reported.



Scheme 1.Co-NNN catalyzed selective synthesis of amine and imine derivatives *via* Hydrogen auto-transfer (HA), and acceptorless dehydrogenation coupling (ADC) strategy.

The paramagnetic cobalt(II)-complexes Co(II)-NNN (**1-4**) have been synthesized by reaction of air-stable tridentate NNN-pincer ligands with cobalt(II) salts (CoX_2, X = Cl, Br) in MeOH at room temperature (see ESI). All the Co-complexes were characterized by HRMS, IR, and UV-Vis spectroscopic analysis.

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† Electronic Supplementary Information (ESI) available: All experimental procedure, spectral data and copies of ^1H and ^{13}C NMR spectra and of all new compounds, X-ray structural data for compounds. CCDC: 1557308(**1**); CCDC: 1836378(**3**).See DOI: 10.1039/x0xx00000x

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The structure of complex **1** was confirmed by a single-crystal X-ray diffraction study. The complex **3** crystallized as protonated form, where BF_4^- was counter anion. Both the complexes crystallized in the triclinic space group $P\bar{1}$. In complex **1** and **3**, the NNN ligand is coordinated to the cobalt center in the typical tridentate mode, with N2–Co1–N3 and N4–Co1–N2 angle of 150.23(6)° and 153.96(8)°, respectively. A thermal ellipsoidal plot of complex **1** and **3** are shown in Fig. 1.

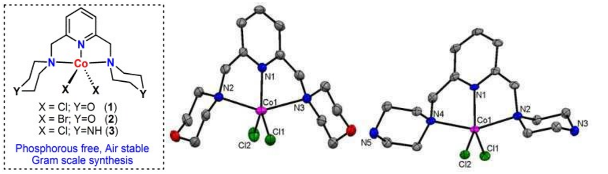
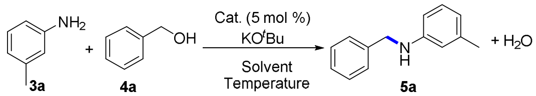


Figure 1. Single crystal X-ray structure of **1** (middle) and **3** (right). Hydrogen atoms and anions were omitted for clarity.

Intially, complexes **1-4** were studied for the *N*-alkylation of anilines using alcohols as alkylating agent. Thus, the reaction of *m*-toluidine (**3a**) with benzyl alcohol (**4a**) was chosen as a model system for the dehydrogenative coupling to form *N*-alkylated amine **5a** (Table 1). Thus, refluxing an equimolar amount of *m*-toluidine (**3a**), benzyl alcohol (**4a**) and KO^{t}Bu in toluene in the presence of 5 mol% complex **1** gave 32% yield of *N*-benzyl-3-methyl aniline (**5a**; Table 1, entry 1). Under the same reaction conditions, complexes **2** and **3** yielded 56% and 51% of **5a**, respectively (Table 2, entries 2-3). Notably, $CoBr_2$ gave only 12% of the desired product **5a** (Table 1, entry 4). Delightfully, the effective *N*-alkylation of **3a** proceeded in 93% yield using catalyst **2** (5 mol %) in n-octane at 150 °C after 32 hours (Table 1, entry 6). With this optimal reaction conditions in hand, we have investigated *N*-alkylation of *m*-toluidine with various alcohols catalyzed by cobalt-NNN pincer complex (**2**) to extend the substrate scope and the generality of the reaction. The results are presented in Table 2.

Table 1: Optimization of alkylation of *m*-toluidine with benzyl alcohol.[a,b]

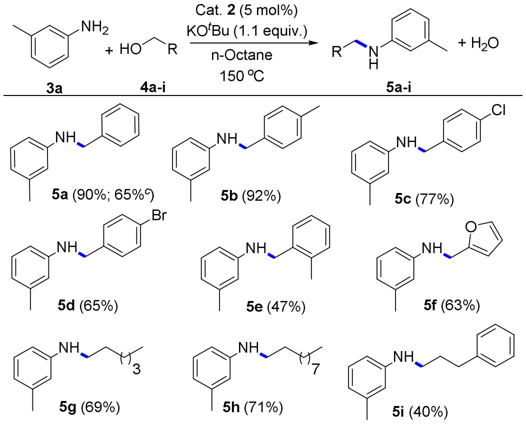


Entry	Catalyst	Solvent	Temperature (°C)	Yield (%)[b]
1	**1**	Toluene	130	32
2	**2**	Toluene	130	56
3	**3**	Toluene	130	51
4	$CoBr_2$	Toluene	130	12
5	**2**	n-octane	130	72
6	**2**	n-octane	150	93
7	**4**	n-octane	150	88
8	**2**	n-octane	150	82[c]

[a]Reaction conditions: 0.25 mmol of **3**, 0.5 mmol of **4**, 2.5 mol% of catalyst **1**, KO^{t}Bu (0.26 mmol), and 1 mL of solvent heated at reflux under argon atm for 32 h. [b]Yield determined by GC using 1,4-dibromo butane as an internal standard. [c] in presence of Hg (10 equiv)

Notably, the *N*-alkylation of *m*-toluidine with a wide range of benzylic alcohols afforded the corresponding *N*-alkylated products in excellent yields up to 92%. Benzyl alcohols that contain both electron-donating and electron-withdrawing groups at the *para* position were well tolerated and gave the corresponding alkylated products (**5b**-**d**) in good yields. The 2-methyl benzyl alcohol led to **5e** in 47% isolated yield under standard reaction conditions and the low-yield is due to the steric effect of the *ortho*-methyl group. The present Co-NNN catalyzed *N*-alkylation strategy was successfully applied to aliphatic alcohols (**5g**-**h**), and heterocyclic alcohols (**5f**) and yielded the desired products in good to moderate yields (products **5g** in 69%, **5h** in 71%, and **5f** in 63% isolated yields). Interestingly, cinnamyl alcohol (**4i**) underwent *N*-alkylation with **3a** under optimal conditions and gave the product **5i** in 40% withthe olefinic bond hydrogenation. Notably, a gram-scale synthesis of *N*-alkylated amine **5a** (65% yield) was achieved with the present catalytic system under standard reaction conditions.

Table 2: Alkylation of *m*-toluidine with various alcohols.[a,b]



[a]Reaction conditions: *m*-toluidine **3a** (0.5 mmol), alcohol (0.55 mmol), cat.**2** (5 mol%), KO^{t}Bu (0.55 mmol) and n-octane (1 mL) were heated at 150 °C for 32 h. [b]Isolated yields. [c]Reaction conditions: Aniline **3a** (10 mmol), benzyl alcohol **4a** (11 mmol), catalyst **2** (2 mol%), KO^{t}Bu (1.1 equiv.) using 10 mL of n-Octane at 150 °C.

Next, we have studied the scope of anilines under optimized conditions (Table 3). It was observed that electron-donating groups (-OMe, -SMe and -Me) at the *para* position of the aniline affording the corresponding *N*-alkylated products (**6a**-**c**) in good yields up to 80%. Similarly, the electron-withdrawing substituents (-F and $-CF_3$) on the aniline also yielded the desired *N*-alkylated products in very good yields (products **6d** in 86%, **6e** in 83% and **6f** in 88% yields). Importantly, aromatic heterocyclic amines, such as 8-aminoquinoline and 2-aminopyridine also underwent the *N*-alkylation reactions with benzylic alcohol (**4a**) to afford **6j** in 52%, and **6k** in 63% isolated yields, respectively.

Furthermore, we have investigated the *N*-alkylation of *o*-phenylenediamine (OPDA) with benzylic alcohols (2 equivalents). Under optimized conditions, bis-alkylated amine as a major and mono-alkylated amine as a minor product were observed. However, when increases the alcohol equivalents from 2 to 4, the yield of bis-alkylated product increased as illustrated in Table 4. Notably, the yield of the both mono- and bis-alkylated OPDA increases by

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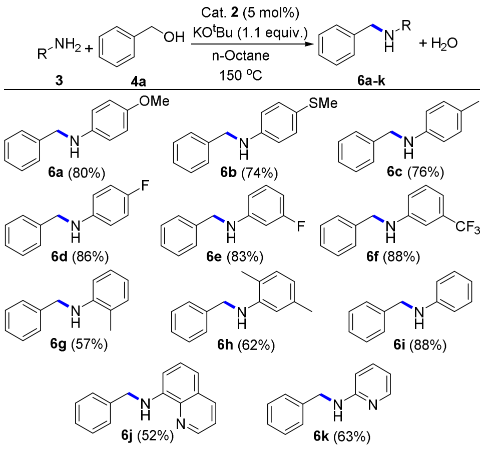
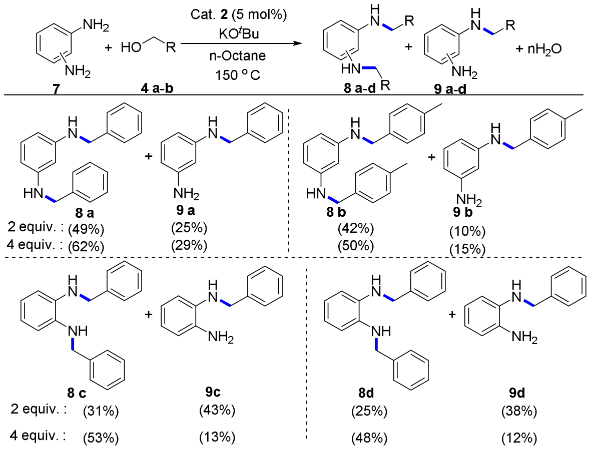
increasing the alcohol equivalents (Table 4, products **8c-d**, and **9c-d**).

Table 3: Alkylation of various anilines with benzyl alcohols[a,b]



[a]Reaction conditions: aniline (0.5 mmol), benzyl alcohol **4a** (0.55 mmol), cat. **2** (5 mol %), KO^{t}Bu (0.55 mmol) and n-octane (1 mL) heated at 150 °C for 32 h. [b]Isolated yields.

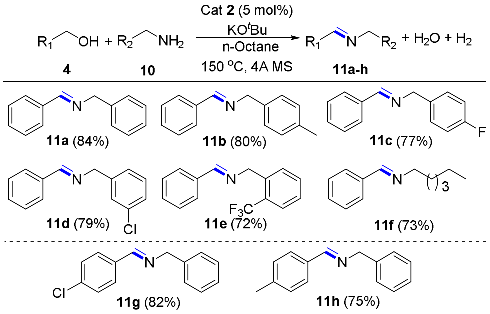
Table 4: Alkylation of diamines with various substituted benzyl alcohols[a,b]



[a]Reaction conditions: Diamines **7** (0.5 mmol), alcohol (1 mmol or 2 mmol), cat. **2** (5 mol %), KO^{t}Bu (1 mmol or 2 mmol) and n-octane (1 mL) were heated at 150 °C for 32 h. [b]Isolated yields.

Having established optimized conditions for direct mono-, and di *N*-alkylation of anilines with alcohols as alkylating agents catalyzed by the Co-NNN complex (**2**), we sought to alkylate benzyl amines or alkyl amines. Remarkably, under the optimized reaction conditions benzylamine (**10**) gave imine rather than the expected amine with the liberation of molecular hydrogen (GC analysis). Indeed, a significant progress has been made for the direct synthesis of imine derivatives from feedstock alcohols and amines using the noble-metal (Ru and Ir) catalysts *via* the acceptorless dehydrogenation coupling (ADC).[14] In 2013, Hanson and co-workers reported aliphatic PNP-ligand based cobalt catalyst for imine synthesis.[15] Subsequently, Milstein and co-workers reported the aromatic PNP-ligand stabilized manganese catalyst for the direct synthesis of imine from the reaction of alcohols and amines.[16] However, the discovery of new catalysts based on non-precious metals and non-phosphine ligands are still highly desirable. Thus, herein we report cobalt-NNN catalyzed ADC of benzylic or aliphatic amines with alcohols to the corresponding imine with the liberation of hydrogen gas and water. It was observed that the formation of imine occurred in high yields in the presence of 4Å molecular sieves (4 ÅMS). As shown in Table 5, the present Co-catalysis is general and compatible with various benzylic amines and benzylic alcohols containing electron-rich and electron-deficient substituents, affording the desired imines in good yields (up to 84%). Interestingly, the reaction proceeded successfully with aliphatic amine with benzyl alcohol, and aliphatic alcohol with benzyl amine and gave the corresponding imines **11f** (73%) yield.

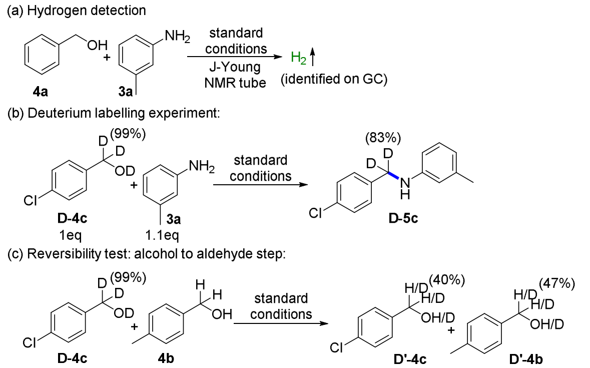
Table 5: Dehydrogenative coupling of various amines with alcohols[a,b]



[a]Reaction conditions: amine **10** (0.5 mmol), alcohol **4** (0.55 mmol), cat. **2** (5 mol %), KO^{t}Bu (0.55 mmol) and n-octane (1 mL) heated at 150 °C for 32 h. [b]Isolated yields.

However, To get insights into the detailed mechanism for cobalt-catalyzed *N*-alkylation of anilines with alcohols, we have carried out the benchmark reaction with the substrate **3a** and **4a** under the optimal conditions. Notably, the formation of molecular hydrogen was detected by gas chromatography (Scheme 2a). This result showed that the present *N*-alkylation reaction proceeds *via* the hydrogen auto-transfer strategy. This was further supported by the deuterium labelling experiment (Scheme 2b). Besides, the reversibility of the initial alcohol dehydrogenation was observed as the percentage of deuterium for D-4-chlorobenzyl alcohol reduced from 99% to 40% in the presence of 4-methylbenzyl alcohol under standard conditions (without amine partner). The mercury poisoning experiment reveals that the present Co-catalysis is homogeneous in nature (Table , entry 8).

Scheme 2: Mechanistic studies



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In summary, an air-stable, phosphine-free, non-precious cobalt(II)-NNN pincer complex catalyzed direct *N*-alkylation of anilines with alcohols *via* hydrogen auto-transfer strategy (HA), and selective acceptorlessdehydrogenative coupling (ADC) of benzyl amines or alkyl amines with alcohols affording imines with the liberation of molecular hydrogen and water is reported.Control and deuterium labelling experiments showed that the initial dehydrogenation of alcohol is reversible and operated via ADC strategy.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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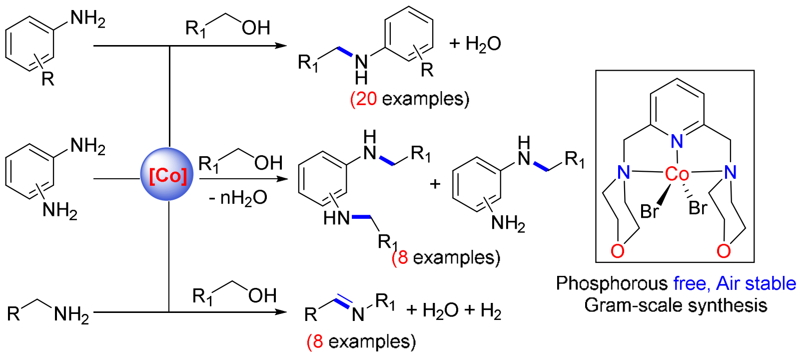

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