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Cobalt-catalyzed alkylation of methyl-substituted N-heteroarenes with primary alcohols: direct access to functionalized N-heteroaromatics†

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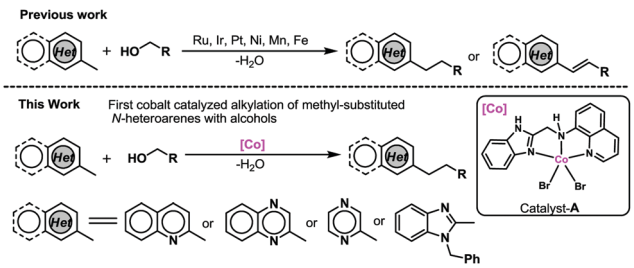
Phosphine free, air and moisture stable Co(NNN) complex catalyzed alkylation of various methyl-substituted N-heteroarenes with alcohols is reported. Following the borrowing hydrogen methodology, a variety of methyl-substituted N-heteroarenes can be functionalized efficiently. To understand the mechanism of this reaction various kinetic and control experiments were carried out.

Development of new synthetic methods to replace the rare noble metal based-catalysts by more economical and earth-abundant base metal catalysts has been in high demand in the past few decades.[1] In this respect, cobalt-based catalysts have been receiving increasing attention from the scientific community because of their availability, low cost, and low toxicity. By using cobalt complexes a variety of organic transformations, such as (de)hydrogenation,[2] C–C coupling,[3] C–H bond activation,[4] borylation,[5] hydrosilylation,[6] polymerization,[7] *etc.*, were explored.[8]

N-heteroarenes and their alkyl derivatives are one of the important building blocks in the synthesis of various pharmaceutical, agricultural, and materials science related compounds.[9] Metal catalyzed C(sp^3)–H bond functionalization provides a useful tool to access diverse N-heteroaromatic products.[10] Traditionally, alkylation of N-heteroarenes was accomplished by using pre-functionalized electrophiles, such as alkyl halides, allylic carbonates, or esters. However, these methods suffer from the generation of undesired excess amount of salt waste and harsh reaction conditions.[11] Therefore, the use of lignocellulose derived alcohols as the alkylating agent becomes a promising alternative for the C(sp^3)–H bond alkylation of methyl-N-heteroaromatics.[12] The borrowing hydrogen methodology has been widely used for the construction of C–X (X = C, N) bonds, by using alcohols as an alkylating agent.[13] In this eco-friendly process, only water is produced as the by-product which makes this process cleaner and greener.



Scheme 1 Transition-metal catalyzed alkylation of methyl-substituted N-heteroarenes with alcohols.

Following this strategy, several precious metal (*e.g.* Ir, Ru, and Pt) complex catalyzed C(sp^3)–H bond functionalizations of N-heteroaromatics using alcohols were well explored in the literature.[14] Recently, a few reports were published for the base metal-catalyzed α-olefination as well as alkylation of methyl-substituted N-heteroarenes.[15] However, to the best of our knowledge cobalt catalyzed alkylation of C(sp^3)–H bonds of N-heteroarenes using alcohols following the borrowing hydrogen methodology has not been reported yet (Scheme 1).

We recently developed an air and moisture-stable Co(NNN)Br_2 complex which was found to be effective for the sustainable synthesis of a variety of N-heterocyclic compounds like quinoxalines, quinolines, and 2-alkylaminoquinolines.[16] In our continuous effort toward developing efficient protocols to construct new C–C bonds *via* a hydrogen auto-transfer strategy,[17] herein, we report Co(NNN) complex catalyzed C(sp^3)–H bond functionalization of methyl-substituted N-heteroarenes by using alcohols as an alkylating agent.

To find the optimum reaction conditions for the alkylation of methyl-substituted N-heteroarenes, 2-methylquinoline (**1a**) and benzyl alcohol (**2a**) were selected as model substrates and the reaction between them was thoroughly investigated. Initially, the reaction of **1a** (0.6 mmol) with **2a** (0.3 mmol) in the presence of catalyst-**A** and KO^{t}Bu was carried out in toluene for 24 h which gave 87% yield of **3a**. The yield of the desired alkylated product was much higher in the presence of catalyst-**A** as compared to the

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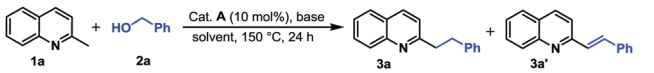
Table 1 Optimization of the cobalt-catalyzed alkylation of 2-methylquinoline with benzyl alcohol[a]



Entry	Catalyst	Base (equiv.)	Solvent	Yield of 3a[b] (%)
1	Cat. **A**	KO^{t}Bu (1.5)	Toluene	87
2	$CoBr_2$	KO^{t}Bu (1.5)	Toluene	20
3	Cat. **A**	NaOH (1.5)	Toluene	5
4	Cat. **A**	KOH (1.5)	Toluene	31
5	Cat. **A**	CsOH (1.5)	Toluene	32
6	Cat. **A**	Cs_2CO_3 (1.5)	Toluene	0
7	Cat. **A**	NaOMe (1.5)	Toluene	34
8	Cat. **A**	KO^{t}Bu (1.0)	Toluene	47
9	—	KO^{t}Bu (1.5)	Toluene	1
10	Cat. **A**	—	Toluene	1
11[c]	Cat. **A**	KO^{t}Bu (1.5)	Toluene	74
12	Cat. **A**	KO^{t}Bu (1.5)	1,4-Dioxane	2
13	Cat. **A**	KO^{t}Bu (1.5)	*m*-Xylene	37
14	Cat. **A**	KO^{t}Bu (1.5)	*p*-Xylene	18
15[d]	Cat. **A**	KO^{t}Bu (1.5)	Toluene	57
16[e]	Cat. **A**	KO^{t}Bu (1.5)	Toluene	68

[a] Reaction conditions: 2-methylquinoline (**1a**) (0.6 mmol), benzyl alcohol (**2a**) (0.3 mmol), catalyst-**A** (10 mol%), KO^{t}Bu (0.45 mmol), toluene (2 mL), 150 °C (oil bath temperature), 24 h. [b] GC yields (*n*-dodecane was used as the internal standard). [c] Catalyst-**A** (5 mol%). [d] 140 °C (oil bath temperature). [e] 2-Methylquinoline (0.3 mmol), benzyl alcohol (0.6 mmol).

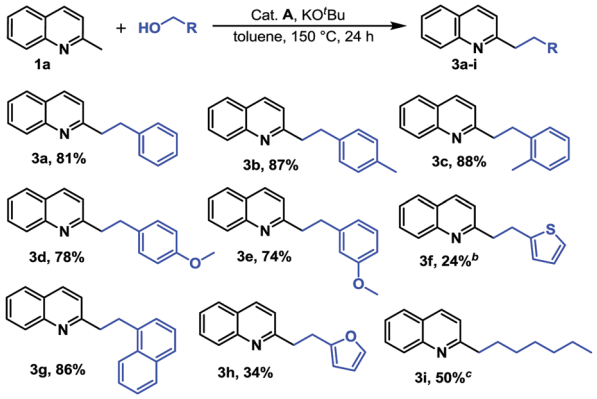
metal precursor $CoBr_2$ (Table 1, entries 1–2). Subsequently, we screened the different bases; out of them KO^{t}Bu gave the maximum yield as compared to the others (Table 1, entries 3–7).

Afterward, other solvents such as 1,4-dioxane, *m*-xylene, *p*-xylene, and toluene were screened and toluene delivered the highest yield of **3a** (Table 1, entries 12–14). The yield of **3a** was reduced by decreasing the oil bath temperature and by lowering the amount of 2-methylquinoline (Table 1, entries 15 and 16). Finally, the optimized reaction conditions were found to be 10 mol% of catalyst-**A** and 1.5 equivalent of KO^{t}Bu at 150 °C in 24 h using toluene as a solvent which furnished 87% of **3a**.

With the optimized reaction conditions in hand, the applicability of the present catalytic system was explored by taking a variety of primary alcohols and the results are summarized in Table 2. Alkylation of 2-methylquinolines tolerated various primary alcohols. The reaction of 4-methyl benzyl alcohol and 2-methyl benzyl alcohol with 2-methylquinoline gave 87% and 88% yields of the desired alkylated products (Table 2, **3b–3c**). Alkylation with 4-methoxy and 3-methoxybenzyl alcohols afforded the corresponding products in 78% and 74% yields, respectively (Table 2, **3d–3e**). However, heteroatom-containing alcohols such as thiophen-2-ylmethanol and furan-2-ylmethanol provided lower yields of the desired products (**3f, 3h**). Additionally, 1-naphthylmethanol afforded smooth conversion to the expected α-alkylated product under the optimized reaction conditions (**3g**). The possibilities of expanding this reaction for the synthesis of long-chain alkylated N-heteroarenes were also explored by reacting them with aliphatic alcohols such as *n*-hexanol (**3i**).

Encouraged by the finding that Co(NNN) complex is an effective catalyst for the α-alkylation of 2-methylquinolines, the potential of this catalytic procedure for the alkylation of a

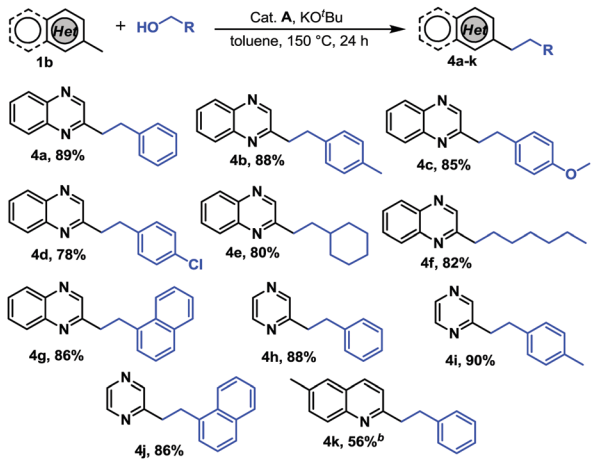
Table 2 Alkylation of 2-methylquinoline with various primary alcohols[a]



[a] Reaction conditions: 2-methylquinoline (**1a**) (0.6 mmol), alcohol derivatives (0.3 mmol), catalyst-**A** (10 mol%), KO^{t}Bu (0.45 mmol), toluene (2 mL), 150 °C (oil bath temperature), 24 h, isolated yields. [b] Catalyst-**A** (15 mol%). [c] 36 h.

variety of methyl-substituted N-heteroarenes using various primary alcohols was explored and the results are summarised in Table 3. First, the alkylation of 2-methylquinoxalines with primary alcohols was selected. Utilizing this catalytic system, alkylation of 2-methylquinoxalines worked well using a variety of alcohols bearing both electron-donating and electron-withdrawing groups (Table 3, entries **4a–4g**). For instance, primary alcohols substituted with methyl, methoxy, and chloro groups under the standard reaction conditions afforded the desired products in excellent yields (Table 3, entries **4b–4d**). Interestingly, cyclic aliphatic alcohols and more challenging long-chain alkyl alcohols also reacted smoothly under the optimized reaction conditions and furnished the expected alkylated N-heteroarenes in good yields (Table 3, entries **4e–4f**). In addition, 1-naphthylmethanol also reacted efficiently (Table 3, entry **4g**). This catalytic protocol was

Table 3 Alkylation of methyl-substituted N-heteroarenes with various primary alcohols[a]



[a] Reaction conditions: alcohol derivatives (0.3 mmol), methyl-substituted N-heteroarenes (0.6 mmol), catalyst-**A** (10 mol%), KO^{t}Bu (0.45 mmol), toluene (2 mL), 150 °C (oil bath temperature), 24 h, isolated yields. [b] 36 h.

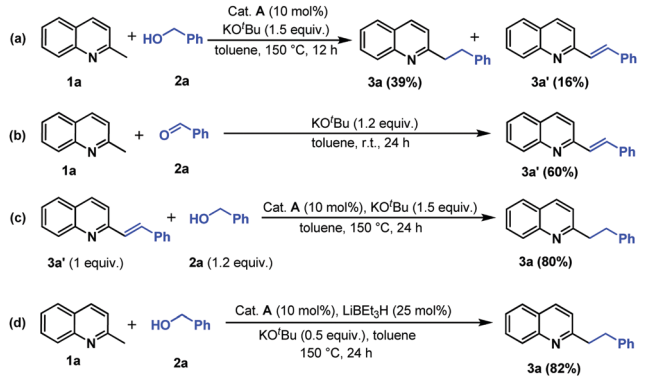
also successfully extended for the alkylation of 2-methylpyrazine. The reaction was well tolerated with different substituted benzyl alcohols under the standard reaction conditions (Table 3, entries **4h–4j**). Afterward, the alkylation of 2,6-dimethylquinoline was carried out which gave the corresponding product in moderate yield (Table 3, entry **4k**).

Alkyl derivatives of 1-benzyl-2-methylbenzimidazole are regarded as an important heterocyclic motif due to their wide range of pharmacological and biological activities including anticancer, antiviral, antihypertensive, anti-HIV and anti-diabetic activity.[18] In view of their wide-ranging activities, the synthesis of benzimidazoles and their alkyl derivatives becomes highly significant. Hence, we tested alkylation of 1-benzyl-2-methyl-1*H*-benzoimidazole following the optimized reaction conditions. To our delight, several alcohols efficiently participated in this C(sp^3)–H bond functionalization of 1-benzyl-2-methyl-1*H*-benzoimidazole and afforded the corresponding alkylated products in excellent yields (Table 4).

The practical applicability of this catalytic protocol was further extended by the preparative scale synthesis of various alkylated N-heteroarenes. Following the optimized reaction conditions, alkylation of various substrates using alcohols as an alkylating agent was carried out which smoothly provided the corresponding products in good yields (Scheme 2).

To get insight into the reaction mechanism, a series of control experiments were performed. The coupling of **1a** with **2a** was monitored at different time intervals (ESI,† Fig. S1). Initially, the formation of **3a** and **3a′** was observed with a sharp decrease in the concentration of **2a** which eventually led to the formation of product **3a**. Under the optimized reaction conditions, after 12 h, yields of **3a** and **3a′** were 39% and 16% respectively (Scheme 3a). The formation of 2-styrylquinoline (**3a′**) in the initial stage of the reaction (as shown in ESI,† Fig. S1) certainly indicated that **3a′** was an intermediate in this reaction.

The reaction of benzaldehyde with **1a** in the presence of KO^{t}Bu as a base produced 2-styrylquinoline (**3a′**) in 60% yield (Scheme 3b). The transfer hydrogenation of **3a′** by benzyl alcohol under optimized reaction conditions afforded the hydrogenated product **3a** in 80% yield (Scheme 3c). These experiments clearly indicate that the reaction proceeds through the α-olefinated intermediate **3a′** which further undergoes catalytic hydrogenation (Scheme 3c) to afford the desired α-alkylated product **3a** and in this reaction benzyl alcohol acts as the hydrogen donor. In another experiment, initially, catalyst-**A** (10 mol%) was treated with 2.5 equiv. of $LiBEt_3H$ and subsequently it was utilized for the coupling between 2-methylquinoline and benzyl alcohol in the presence of a slightly lower amount of base (0.5 equiv.) which afforded the desired alkylated product in 82% yield (Scheme 3d). This result indicated that probably the *in situ* generated (NNN)Co(I)–H complex is the active catalyst for the reaction.[16,19] However, we were unable to characterize this active Co(I)–H species by ^{1}H-NMR spectroscopy probably due to its paramagnetic nature.[20]

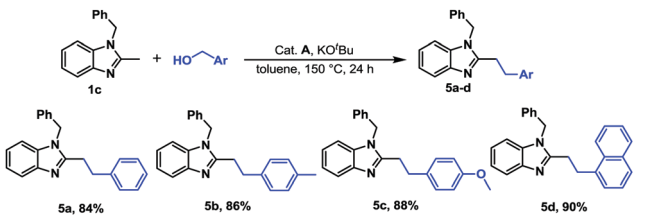


Scheme 3 Control experiments for the alkylation of 2-methylquinolines.

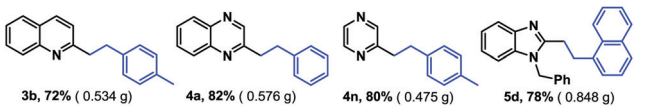
Based on the result of these mechanistic investigations and the previous literature reports[14b–d,15c,d] a plausible mechanism for the C(sp^3)–H bond alkylation of methyl-substituted N-heteroarenes was proposed (ESI,† Fig. S2). In the initial step, dehydrogenation of the alcohol leads to the formation of an aldehyde which undergoes base mediated aldol condensation with methyl-substituted N-heteroarenes to afford an α-olefinated intermediate. Further catalytic hydrogenation of the α-olefinated intermediate gave the desired α-alkylated N-heteroarenes.

In summary, an effective, economical and greener strategy for the Co(II) catalyzed alkylation of methyl-substituted N-heteroarenes with alcohols was developed. To the best of our knowledge, this is the first example of the cobalt-catalyzed functionalization of C(sp^3)–H bonds in methyl N-heteroarenes using alcohols. A variety of alkylated N-heteroarenes were synthesized by coupling of various alcohol derivatives with different methyl-substituted N-heteroarenes. The synthetic utility of this process was also established by the preparative scale synthesis of different alkylated N-heteroarenes. To understand the mechanism various kinetic and control experiments were carried out. Notably, the absence of any expensive and sensitive phosphine ligands and an easy-to-synthesize air and moisture stable Co(NNN) complex make this an appealing methodology for accessing a variety of alkylated N-heteroarenes.

Table 4 Alkylation of 1-benzyl-2-methyl-1*H*-benzoimidazole with various benzyl alcohols[a]



[a] Reaction conditions: alcohol derivatives (0.3 mmol), 1-benzyl-2-methyl-benzimidazole (0.6 mmol), catalyst-**A** (10 mol%), KO^{t}Bu (0.45 mmol), toluene (2 mL), 150 °C, 24 h, isolated yields.



Scheme 2 Preparative scale synthesis.

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Conflicts of interest

There are no conflicts to declare.

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