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Ni-Catalyzed dehydrogenative coupling of primary and secondary alcohols with methyl-*N*-heteroaromatics†

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Here we report the first base-metal catalyzed dehydrogenative coupling of primary (aromatic, heteroaromatic, and aliphatic) and secondary alcohols with methyl-*N*-heteroaromatics to form various C(sp^3)-alkylated *N*-heteroaromatics. The reaction is enabled by Earth abundant, non-precious $NiBr_2$ as a transition metal catalyst and *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) as a ligand system. Mechanistic studies reveal that a hydrogen auto-transfer process is involved in the direct C(sp^3)-alkylation and the reaction proceeds through an α-olefination process.

N-Heterocyclic compounds play an important role in organic synthesis, in both laboratory and industrial processes. As a consequence, considerable attention has been paid to their construction and functionalization through carbon–carbon or carbon–heteroatom bond forming reactions.[1] Thus, a strategy that proceeds with step- and atom-economy is highly desirable. In this perspective, transition metal catalyzed C(sp^3)–H bond functionalization of methyl-*N*-heteroaromatics, in particular, quinoline and pyrazine derivatives, is important, and thus provides valuable access to C(sp^3)-alkylated products with widespread applications in pharmaceuticals and materials science.[2] Classical synthetic methods involved the employment of pre-functionalized electrophiles, such as alkyl halides, allylic carbonates, or esters.[3] However, the use of harsh reaction conditions and hazardous reagents, as well as the formation of stoichiometric waste are the potential concerns. Recently, Lewis-acid catalyzed C_2-alkylation of *N*-heteroaromatics with alkenes and electron-deficient π-electrophiles has been demostrated.[4,5] However, limited substrate scope and poor functional group tolerance are its major limitations. Hence, the development of a general and robust strategy using readily available lignocellulose derived alcohols as the alkylating agent for the C(sp^3)–H bond alkylation of methyl-*N*-heteroaromatics is desirable and synthetically demanding.

A hydrogen auto-transfer (HA) strategy has been widely applied to construct C–X (X = C, N, S) bonds using primary alcohols as the coupling partner in a sustainable manner.[6] As a consequence, transition-metal (Ru, Ir) catalyzed C(sp^3)–H bond functionalization of *N*-heteroaromatics has been documented by using alcohols as the alkylating agent.[7] Notably, the use of first-row non-precious transition metals is limited and has been rarely reported. Following the pioneering work of Kempe[7a] on a well-defined Ir-complex catalyzed for the preparation of highly functionalized C_2-alkylated *N*-heteroaromatics, Obora and co-workers reported the iridium catalyzed α-alkylation of 2-methyl-*N*-heteroaromatics with alcohols.[7b] A ligand-free $RuCl_3$ catalyzed C-alkylation of methyl-*N*-heteroaromatics has also been documented.[8]

To date, only a handful of examples involving precious metal catalysts (Pd, Rh, Pt, Ru, and Ir) enabling the C(sp^3)–H alkylation of methyl-*N*-heteroaromatics with alcohols *via* the HA strategy have been reported. It is noteworthy that only primary alcohols were employed as the alkylating agent. Recently, Xiao and co-workers reported triflic acid catalyzed C-alkylation of *N*-heteroaromatics. However, this reaction is substrate specific.[9] In recent times, one of the prime goals in transition-metal catalyzed homogeneous catalysis has been the replacement of expensive precious metal catalysts with cheap 3d transition metal based catalysts for similar or better reactivity.[10–12,19,20] Very recently, Kempe and Maji independently reported the Mn-catalyzed α-olefination of *N*-heteroaromatics.[13a,b] Of late, research groups of Wang and Zhou reported iron-catalyzed C-alkylation of nitriles,[13c] and nickel catalyzed *N*-alkylation of acylhydrazines and arylamines[13d] using alcohols as the alkylating agent *via* the hydrogen auto-transfer strategy, respectively. Here the first-base metal-catalyzed direct C(sp^3)-alkylation of primary alcohols with methyl-*N*-heteroaromatics (in particular, quinoline and pyra-

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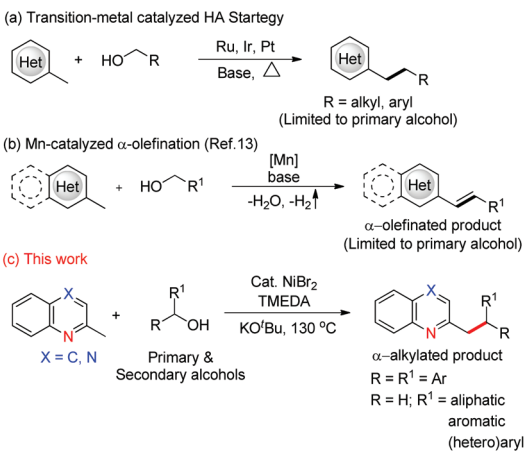
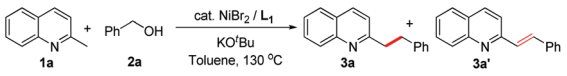
zine derivatives) with primary (aromatic, heteroaromatic, and aliphatic) and secondary alcohols is reported (Scheme 1). This C–C bond forming reaction is catalyzed by cheap, commercially available $NiBr_2$ as the transition metal catalyst and TMEDA as the ligand and proceeds through the dehydrogenative pathway releasing water as the only by-product. Indeed, utilization of the nickel-catalyst for dehydrogenation and related HA reactions to construct C–C and C–N bonds remains elusive and in high demand.[14–18]

The reaction of 2-methyl quinoline (**1a**) with benzyl alcohol (**2a**) was chosen as a model reaction for the α-alkylation of *N*-heteroaromatics (Table 1). The initial reaction of **1a** (0.5 mmol) with **2a** (1.5 mmol) in the presence of a catalytic amount of $NiBr_2$, *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) (**L1**), and KO^{t}Bu (1.0 mmol) at 130 °C in toluene afforded the α-alkylated (**3a**) and α-olefinated products (**3a′**) in 88% and 6% yields, respectively (Table 1, entry 1). The same reaction proceeded smoothly with $NiCl_2$ and offered the α-alkylated product in 81% yield (Table 1, entry 2). Under standard reaction conditions, other nickel salts, such as $Ni(acac)_2$, $Ni(OTf)_2$ and $NiCl_2(PMe_3)_2$, gave unselective products in moderate yields (Table 1, entries 3–5). Next, the effect of the base on the dehydrogenative coupling of **2a** with **1a** (Table 1, entries 1, 6–7) was studied. It was found that KO^{t}Bu selectively yielded **3a** in an excellent yield while LiO^{t}Bu gave **3a**/**3a′** in 2 : 1 ratio in 75% yield. A series of solvents was examined; among them, toluene was found to be the optimal solvent for this transformation (Table 1, entries 1, 8 and 9). The necessity of each component (nickel salt, ligand, and base) was systematically studied under optimized conditions. The control experiment reveals that in the absence of a nickel salt, and/or base no formation of product **3a** was observed (Table 1, entries 10 and 11). Under standard conditions, the effects of nitrogen and phosphine ligands **L2–L10** were investigated to obtain the optimal yield of **3a** (Table 2). Surprisingly, the ligands triphos (**L7**), BINAP (**L9**), and dppf (**L10**) were inactive. Interestingly,



Scheme 1 Dehydrogenative coupling of alcohols with methyl-*N*-heteroaromatics.

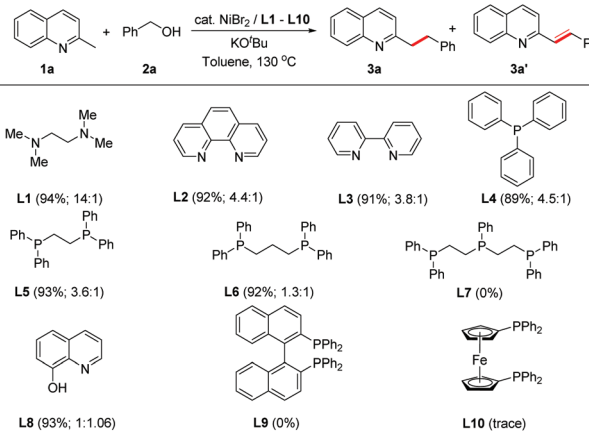
Table 1 Optimization of the reaction conditions[a]



Entry	Ni-Catalyst	Base	Solvent	Conversion (%) 3a	3a′
1	$NiBr_2$	KO^{t}Bu	Toluene	88(82)[b]	6
2	$NiCl_2$	KO^{t}Bu	Toluene	81(75)[b]	10
3	$Ni(acac)_2$	KO^{t}Bu	Toluene	52	5
4	$Ni(OTf)_2$	KO^{t}Bu	Toluene	14	46
5	$NiCl_2(PMe_3)_2$	KO^{t}Bu	Toluene	31	52
6	$NiBr_2$	LiO^{t}Bu	Toluene	50	25
7	$NiBr_2$	K_2CO_3	Toluene	0	0
8	$NiBr_2$	KO^{t}Bu	1,4-Dioxane	76	10
9	$NiBr_2$	KO^{t}Bu	DMF	8	0
10	—	KO^{t}Bu	Toluene	0	0
11	$NiBr_2$	—	Toluene	0	0
12	$NiBr_2$	KO^{t}Bu	Toluene	Trace[c]	0

[a] The reaction was carried out with **1a** (0.5 mmol), **2a** (1.5 mmol), Ni-catalyst (10 mol%), *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) (**L1**, 0.25 mmol) and a base (1.0 mmol) in toluene (2 mL) at 130 °C (oil-bath temperature) for 24 h. [b] Isolated yield. [c] Without **L1**.

Table 2 Ligand screening for nickel-catalyzed C_2-alkylation of **1a** with **2a**[a,b]

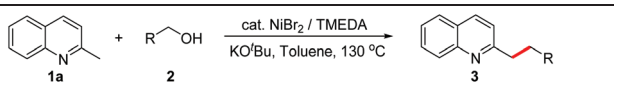


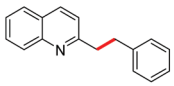
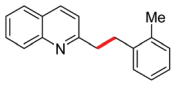
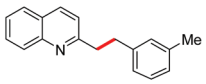
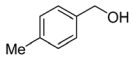
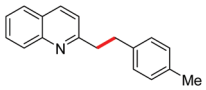
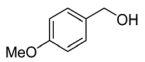
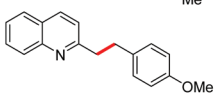
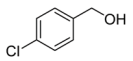
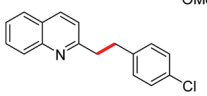
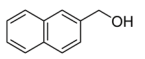
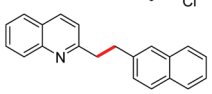
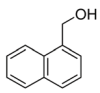
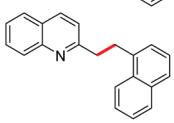
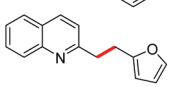
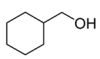
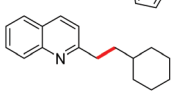
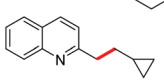
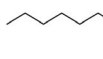
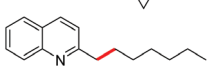
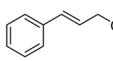
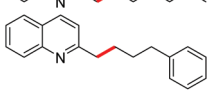
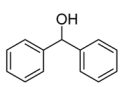
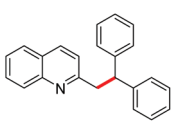
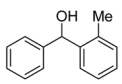
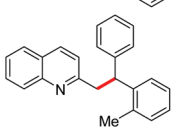
[a] The reaction was carried out with **1a** (0.5 mmol), **2a** (1.5 mmol), Ni-catalyst (10 mol%), a ligand (0.25 mmol) and a base (1.0 mmol) in toluene (2 mL) at 130 °C (oil-bath temperature) for 24 h. [b] Combined yield (**3a** + **3a′**) and the ratio of **3a** + **3a′** are given in the parentheses based on GC analysis.

no product formation was observed in the absence of ligand **L1** (Table 1, entry 12).

With the optimized reaction conditions in hand, a variety of benzyl alcohols bearing electron-rich and -withdrawing substituents were examined (Table 3). The electronic nature of the substituents on the aryl ring of the alcohols had some effect on the catalytic activity. Thus, unsubstituted benzyl alcohol gave a better yield (**3a** in 82% isolated yield) than that with the electron-rich substituents (69–73% yield of products **3b–3e**). Under optimized reaction conditions, (4-chlorophenyl)metha-

Table 3 Ni-Catalyzed dehydrogenative coupling of alcohols with 2-methyl quinoline (**1a**): scope of alcohols[a,b]



Entry	Alcohol (2)	Product (3)		Yield[b] (%)
1			(**3a**)	82(67)[c]
2			(**3b**)	69
3			(**3c**)	71
4			(**3d**)	73
5			(**3e**)	70
6			(**3f**)	58
7			(**3g**)	91(72)[c]
8			(**3h**)	83
9			(**3i**)	72
10			(**3j**)	71
11			(**3k**)	70(58)[c]
12			(**3l**)	68
13			(**3m**)	68
14			(**3n**)	45
15			(**3o**)	42

[a] Reaction conditions: **1a** (0.5 mmol), **2** (1.5 mmol), $NiBr_2$ (10 mol%), TMEDA (0.25 mmol), and KO^{t}Bu (1.0 mmol) in toluene (2 mL) heated at 130 °C (oil-bath temperature) for 24 h. [b] Isolated yield. [c] 2 mol% of $NiBr_2$.

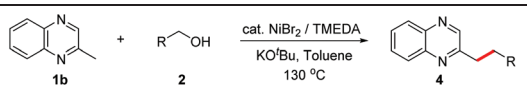
nol with an electron-withdrawing group on the phenyl ring provided **3f** in 58% isolated yield. Interestingly, 2-naphtholmethanol and 1-naphtholmethanol reacted smoothly under optimized reaction conditions and gave the expected C_2-alkylated *N*-heteroaromatics in good yields (products **3g** in 91% and **3h** in 83% yields, respectively). Heteroatom-containing alcohols such as furan-2-yl-methanol (**2i**) also reacted efficiently to afford 2-(2-furan-3-yl-ethyl)-quinoline (**3i**) in 72% isolated yield. It is noteworthy that a non-activated primary cyclic aliphatic alcohol (cyclohexyl methanol) provided the C_2-alkylated product **3j** in 71% isolated yield.

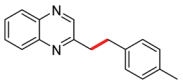
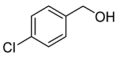
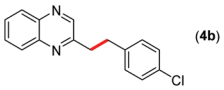
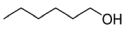
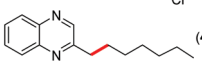
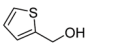
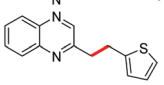
Notably, under optimized conditions, the cyclopropyl ring was not affected. Thus, the reaction of cyclopropanemethanol (**2k**) with **1a** under nickel catalysis gave the expected dehydrogenative coupled product **3k** in 70% yield. Indeed, under standard reaction conditions, aliphatic alcohol (1-hexanol; **2l**) gave the desired C_2-alkylated product in 68% yield. The reaction of cinnamyl alcohol (**2m**) with 2-methyl quinoline (**1a**) gave **3m** in very good yield, and it is noteworthy that the hydrogenation of the double bond (by *in situ* generated hydrogen gas) was observed. These results indicate that the reaction proceeds *via* the dehydrogenative pathway. It is noteworthy that the present Ni-catalyzed dehydrogenative coupling reaction proceeds smoothly under a low-catalyst loading (2 mol% of [Ni]; see Table 3 entries 1, 7, and 11). In all cases, we observed a trace amount of (~8%) the intermediate α-olefinated product (not isolated). Outstandingly, the secondary alcohol (diphenylmethanol; **2n**) underwent the dehydrogenative cross-coupling reaction with **1a** and gave the expected product **3n** in 45% yield, which was not discussed in the previously reported Ir and Ru-catalyzed C_2 alkylation (α-alkylation) reactions.[7] Thus, the present nickel-catalyzed α-alkylation *via* dehydrogenative coupling is very robust and efficient, and hence various primary alcohols and sterically demanding secondary alcohols were effectively used as alkylating agents under mild conditions.

The present catalytic system was successfully extended to 2-methyl quinoxaline (Table 4). The reaction was well tolerated with different substituted benzyl alcohols provided the corresponding C_2-alkylated products **4a** and **4b** in 78% and 71% yields, respectively. Remarkably, the aliphatic alcohol (*e.g.*, 1-hexanol) also afforded the desired product **4c** in 70% isolated yield. Heteroatom-containing alcohols such as thiophen-2-ylmethanol also dehydrogenatively coupled with **1b** to afford 2-(2-(thiophen-2-yl)ethyl)quinoxaline (**4d**) in 62% isolated yield. Gratifyingly, we have successfully shown the scalability of this catalytic protocol under mild conditions. In this regard, the present nickel-catalyzed dehydrogenative coupling was tested for gram-scale synthesis of **4b** (5.0 mmol scale) and it worked excellently with an expected α-alkylated product (**4b**) in 68% yield.

Next, we explored our strategy to other methyl-*N*-heteroaromatics to access a variety of C_2-alkylated *N*-heteroaromatics under our nickel catalyzed conditions (Table 5). Thus, the dehydrogenative coupling reaction is compatible for 2-methyl quinoline and 2-methyl quinoxaline. Importantly, the methoxy group present at the C_6-position of the quinoline derivative underwent the dehydrogenative coupling reaction to give **5a** in 81% yield. The reaction of benzyl alcohol (**2a**) with 2-methyl quinoxaline offered **5b** in excellent yield (86%). The

Table 4 Ni-Catalyzed C_2-alkylation of 2-methylquinoxaline: scope of alcohols[a,b]



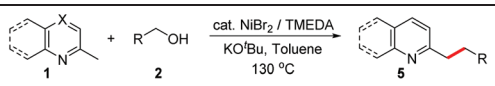
Entry	Alcohol (2)	Product (5)	Yield (%)
1		 (4a)	78
2		 (4b)	71(68)[c]
3		 (4c)	70
4		 (4d)	62

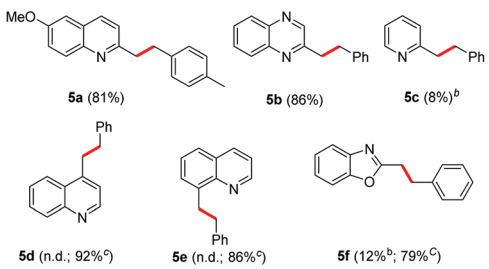
[a] Reaction conditions: **1b** (0.5 mmol), **2** (1.5 mmol), $NiBr_2$ (10 mol%), TMEDA (0.25 mmol), and KO^{t}Bu (1.0 mmol) in toluene (2 mL) heated at 130 °C (oil-bath temperature) for 24 h. [b] Isolated yield. [c] Gram-scale synthesis (5 mmol).

α-alkylation of 2-methyl pyridine and 2-methyl benzoxazole afforded trace amounts of the corresponding products under standard reaction conditions. However, 4-methyl quinoline and 8-methyl quinoline were inactive under the optimized conditions.

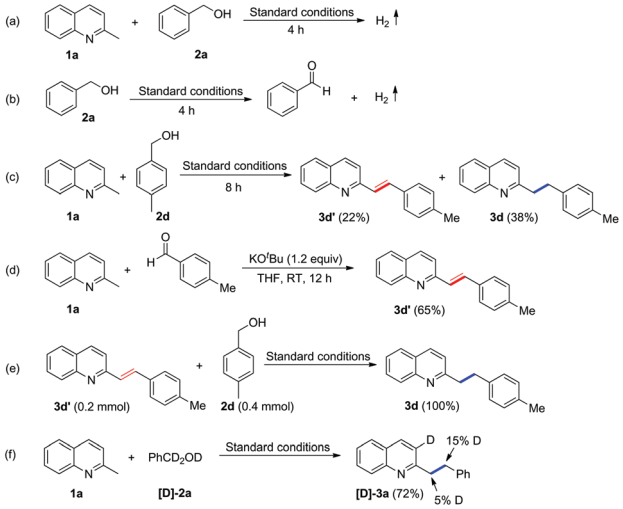
A series of control experiments were performed under the optimized reaction conditions to get insights into the reaction mechanism (Scheme 2). Analysis of the gaseous mixture of the present Ni-catalyzed reaction proved that the reaction proceeds *via* the dehydrogenation pathway. The formation of hydrogen gas was qualitatively analyzed by gas chromatography. Indeed, on treatment of **2a** (in the absence of **1a**) under nickel catalysis, the formation of a dehydrogenated product, benzaldehyde, was observed. Notably, on performing the reaction under our

Table 5 Ni-Catalyzed C_2-alkylation of *N*-heteroaromatics: scope of *N*-heteroaromatics[a]





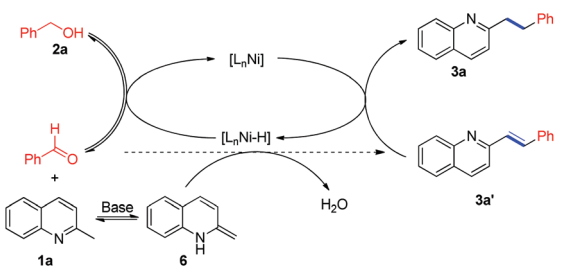
[a] Reaction conditions: **1** (0.5 mmol), **2** (1.5 mmol), $NiBr_2$ (10 mol%), TMEDA (0.25 mmol), and KO^{t}Bu (1.0 mmol) in toluene (2 mL) heated at 130 °C (oil-bath temperature) for 24 h and the yields are isolated yields. [b] GC yield. [c] Recovered starting material (**1**). n.d – Not detected.



Scheme 2 Control experiments.

reaction conditions for 8 h, a mixture of an α-olefinated product (**3d′**) and the hydrogenated product (**3d**) was observed in 22% and 38% yields, respectively. In a separate experiment, the reaction of *p*-tolualdehyde and 2-methyl quinoline (**1a**) in the presence of KO^{t}Bu resulted in the α-olefinated product **3d′** in 65% isolated yield. The transfer hydrogenation of **3d′** by 4-methylbenzyl alcohol (**2d**) under standard conditions gave the hydrogenated product **3d** with the complete conversion of **3d′** (confirmed by GC-MS). These experiments clearly indicate that the reaction proceeds through the α-olefination process and a dehydrogenative hydrogen auto-transfer is operative. The reaction of deuterated alcohol **[D]-2a** with **1a** showed the formation of deuterated product **[D]-3a**, where the deuteration of C_3–H of the *N*-heteroaromatic was observed (Scheme 2f). The formation of α-alkylated **[D]-3a** is in agreement with the initial dehydrogenation and the base-mediated isomerization (**1a** to **6**) process.

Thus, the catalytic cycle involves the initial dehydrogenation of alcohol, followed by condensation with **6** to yield the α-olefinated intermediate **3a′** which further undergoes catalytic hydrogenation to lead to the desired α-alkylated product **3a** by *in situ* generated hydrogen from the initial dehydrogenation of alcohol (Scheme 3).



Scheme 3 Plausible catalytic cycle for the Ni-catalyzed α-alkylation of 2-methyl-*N*-heteroaromatics.

In summary, an efficient strategy for the base-metal catalyzed dehydrogenative coupling of primary (benzylic, heterocyclic, and acyclic) and secondary alcohols with methyl-*N*-heteroaromatics is demonstrated for the first time. The reaction is enabled by commercially available $NiBr_2$ as the catalyst and TMEDA as the ligand system. The reaction proceeded through α-olefination and provided an atom-economical route for the synthesis of C_2-alkylated *N*-heteroaromatics. We believe that the developed catalytic protocol can open a new avenue for dehydrogenation and related reactions.

Conflicts of interest

There are no conflicts to declare.

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