Cobalt-Catalyzed Direct Alkenylation of 2-Methylquinolines with Aldehydes via C(sp^3)–H Functionalization in Water

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Abstract: The direct C(sp^3)–H alkenylation of 2-methylquinolines with aldehydes as a simple methodology to afford 2-alkenylated quinolines is reported. In the presence of catalytic $CoCl_2$ in water, the economically and ecologically sound transformation is proposed to proceed via the direct benzylic addition to the aldehyde followed by an elimination step to provide 2-alkenylated quinolines in good to excellent yield of up to 95%.

Key words: aldehydes, alkenylation, aza-arenes, C–H functionalization, cobalt

The aza-arenes are a privileged moiety that occur widely in pharmaceuticals and natural products as well as molecules with functional material properties.[1] Therefore, owning to their importance, research aimed at the development of expedient methodologies leading to functionalized aza-arenes is attracting a sizeable amount of attention.

Consequently, with the intense interest in direct C–H functionalization strategies,[2] recent developments have seen the emergence of reports on metal-catalyzed direct C(sp^2)–H functionalization of aza-arenes.[3] However, such developments come with a degree of complexity, notably, the use of aza-arene *N*-oxides which often require a final deoxygenation step. With regard to the less extensively explored direct C(sp^3)–H functionalization, reports in the context of elaborated aza-arene preparation have also emerged.[4] The key aspect of most of these reports is the utilization of Lewis acids for catalyzing the direct benzylic addition of alkyl-substituted aza-arenes via a proposed metal-enamide species.

The direct condensation of 2-methylquinolines with aldehydes represents a straightforward and convenient strategy to obtain alkenylated aza-arenes.[5] Recently, Huang et al. reported the alkenylation of 2-substituted aza-arenes with aldimines catalyzed by $Fe(OAc)_2$ via a C(sp^3)–H functionalization strategy.[4e] Despite the advantages of this protocol, some limitations nevertheless remain; typically the need to pre-synthesize the aldimines for optimal yields and the restriction to heteroaromatic substrates such as pyridyl aldehydes.

Hence, there is still a need to develop new and efficient strategies with a broad substrate scope that utilize cheap and sustainable Lewis acids for this class of reaction. With the potential of cobalt salts as economical and environmentally friendly Lewis acids,[6] we report herein the first cobalt-catalyzed direct C(sp^3)–H alkenylation of 2-methylquinolines with a wide array of aldehydes including heteroaromatic aldehydes in water.

Our approach towards developing the protocol began with the optimization of the reaction conditions for the alkenylation of **1a** with **2a** (Table 1) without any special precautions or prior preparation of substrates. Among the cobalt salts screened, $CoCl_2$ was found to be the best in promoting the reaction, whereby **3aa** was isolated in 78% yield (Table 1, entry 1). Analysis of the crude reaction mixture indicated that the olefinic geometry of **3aa** was of the *E* isomer only. Encouraged by these observations, we next attempted the reaction in water which led to the isolation of **3aa** in 95% yield (Table 1, entry 5). This result is an added advantage of this protocol, especially as water superior to other organic solvents screened (Table 1, entries 6–10).[7] However, as our optimization studies proceeded, we found that lower yields of **3aa** were isolated when the excess of **2a** was reduced to either 1.2 or 1.5 equivalents (Table 1, entries 11 and 12). Nonetheless, we were gratified to discover that lowering the temperature to 120 °C and catalyst loading to 2.0 mol% under more concentrated reaction conditions afforded the alkenylated product in an excellent yield of 90% (Table 1, entry 13).

Next, we applied the optimized protocol to the direct alkenylation of **1a** with a variety of aromatic aldehydes. Our initial results revealed excellent yields of the alkenylated products obtained from the reactions between **1a** and Cl-, Br-, and F-containing aromatic aldehydes (Table 2, entries 1–5). Notably, comparing **2b** and **2c** no steric effect was observed. With the biphenyl aldehyde **2h**, an impressive 95% product yield was isolated (Table 2, entry 7). However, with naphthalene-2-carboxaldehyde **2g**, only 68% of **3ag** was obtained (Table 2, entry 6).

Next, the scope of the reaction was extended to aldehydes with varying electronic properties. Intriguingly, yields of only 68% and 70% were obtained from the activated aldehydes **2i** and **2j** with the former requiring an increased catalyst loading of 5.0 mol% (Table 2, entries 8 and 9). As for **2k** and **2l**, the corresponding products **3ak** and **3al** were obtained in 68% (Table 2, entry 10) and 47% yields, respectively, under the standard conditions. However, when the reaction was carried out in DMF, **3al** could be obtained in a significantly improved yield of 95% sug-

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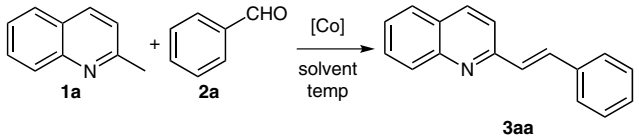
Table 1 Optimization Studies[a]



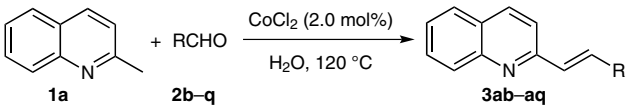
Entry	[Co]	Solvent	Temp (°C)	Yield (%)[b]
1	$CoCl_2$	THF	140	78
2	$Co(ClO_4)_2·6H_2O$	THF	140	53
3	$Co(acac)_2$	THF	140	62
4	$CoC_2O_4.2H_2O$	THF	140	trace
5	$CoCl_2$	H_2O	140	95
6	$CoCl_2$	toluene	140	84
7	$CoCl_2$	CH_2Cl_2	140	81
8	$CoCl_2$	DCE	140	86
9	$CoCl_2$	dioxane	140	78
10	$CoCl_2$	DMF	140	93
11	$CoCl_2$	H_2O	140	79[c]
12	$CoCl_2$	H_2O	140	81[d]
13	$CoCl_2$	H_2O	120	90[e]
14	–	H_2O	120	30

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (2.0 equiv), [Co] (10 mol%), solvent (0.6 mL), 24 h.
[b] Isolated yield.
[c] **2a** (1.2 equiv).
[d] **2a** (1.5 equiv).
[e] $CoCl_2$ (2.0 mol%), H_2O (0.3 mL).

gesting that solubility issue encountered with some aldehydes could affect the efficiency of the reaction (Table 2, entry 11). The weak electron-donating effect of 4-Me group in **2m** did not significantly affect the reaction and a good yield of 87% of **3am** was obtained (Table 2, entry 12). However, an extended reaction time (48 h) along with a higher catalyst loading (5.0 mol%) and temperature (140 °C) were required to afford **3an** in 80% yield (Table 2, entry 13).

Additionally, after several trials with aldehyde **2o**, a satisfactory yield of the 1,2-benzylic addition product **3ao** was eventually obtained (Table 2, entry 14). This was achievable in 65% yield under modified reaction conditions which were designed to limit the excess of **2o** so as to facilitate isolation of **3ao** by silica gel chromatography. Several aliphatic aldehydes were also tested under the conditions of 5.0 mol% $CoCl_2$ loading with 48 hours of reaction time. The best results were obtained with aldehydes **2p** and **2q** whereby 47% and 30% yields of the corresponding alkenylated products **3ap** and **3aq** were isolated (Table 2, entries 15 and 16).

Table 2 Scope of Aldehydes[a]



Entry	Aldehyde **2**, R	Product	Yield (%)[b]
1	**2b**, 4-ClC_6H_4	**3ab**	90
2	**2c**, 2-ClC_6H_4	**3ac**	90
3	**2d**, 4-BrC_6H_4	**3ad**	91
4	**2e**, 4-FC_6H_4	**3ae**	90
5	**2f**, 4-$F_3CC_6H_4$	**3af**	93
6	**2g**, 2-naphthyl	**3ag**	68
7	**2h**, 4-PhC_6H_4	**3ah**	95
8	**2i**, 4-NCC_6H_4	**3ai**	68[c]
9	**2j**, 4-$O_2NC_6H_4$	**3aj**	70
10	**2k**, 3-$O_2NC_6H_4$	**3ak**	68
11	**2l**, 2-$O_2NC_6H_4$	**3al**	95[d]
12	**2m**, 4-MeC_6H_4	**3am**	87
13	**2n**, 4-$MeOC_6H_4$	**3an**	80[e]
14	**2o**, (*E*)-PhCH=CH	**3ao**	65[f]
15	**2p**, C_6H_{11}	**3ap**	47[g]
16	**2q**, $(CH_2)_7Me$	**3aq**	30[g]

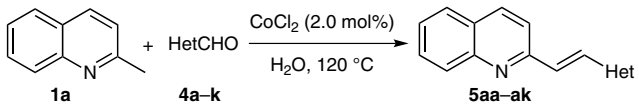
[a] Reaction conditions: **1a** (0.5 mmol), aldehyde (2.0 equiv), $CoCl_2$ (2.0 mol%), H_2O (0.3 mL), 24 h, 120 °C.
[b] Isolated yield.
[c] $CoCl_2$ (5.0 mol%).
[d] DMF (0.3 mL).
[e] $CoCl_2$ (5.0 mol%), 48 h, 140 °C.
[f] **1a** (2.0 equiv), **2o** (0.5 mmol), $CoCl_2$ (5.0 mol%), 48 h.
[g] $CoCl_2$ (5.0 mol%), 48 h.

With heteroaromatic aldehydes, initial efforts revealed that both **5aa** and **5ab** could be readily isolated in yields of 68% and 75%, respectively (Table 3, entries 1 and 2).

However, due to the importance of the pyridine structural subunit,[8] pyridinecarboxaldehydes formed the bulk of the aldehydes examined whereby under the standard reaction conditions, **4c** and **4d** proved to be good substrates, affording the corresponding products in 80% and 86% yield, respectively (Table 3, entries 3 and 4). Compound **4e** was unreactive under the standard reaction conditions but reacted efficiently in DMF to afford **5ae** in 86% yield (Table 3, entry 5). Encouraged by the reactivity of **4c** and **4d**, several 2- and 3-pyridinecarboxaldehydes were also attempted which led to product yields ranging from 74–90% (Table 3, entries 6–11).

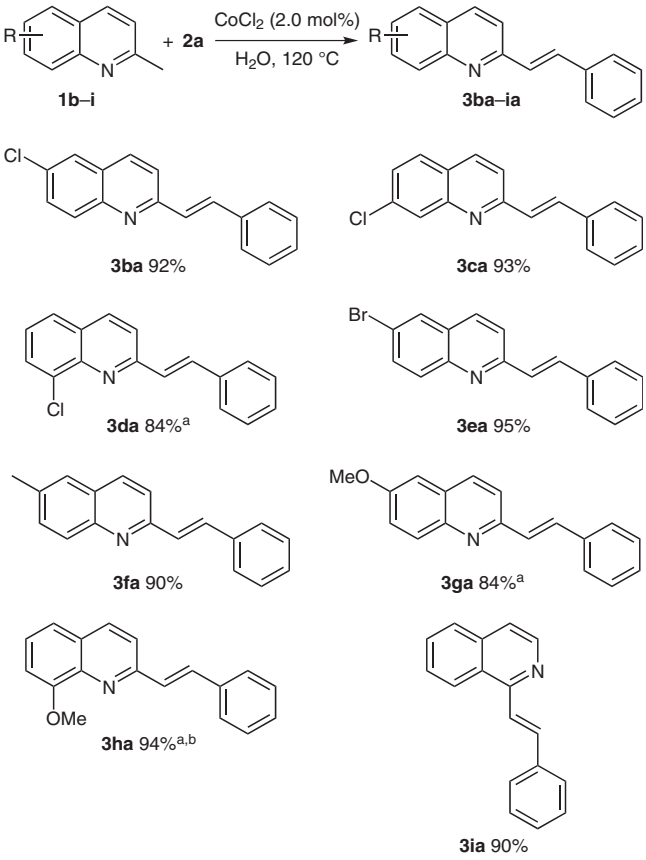
Having tested the generality of the protocol on various aldehydes, our attention was next focused on the alkenyl-

Table 3 Scope of Heteroaromatic Aldehydes[a]



Entry	Aldehyde **4**, Het	Product	Yield (%)[b]
1	**4a**, 2-thienyl	**5aa**	68[c]
2	**4b**, 2-furyl	**5ab**	75
3	**4c**, 2-pyridyl	**5ac**	80
4	**4d**, 3-pyridyl	**5ad**	86
5	**4e**, 4-pyridyl	**5ae**	86[d]
6	**4f**, 6-Br-2-pyridyl	**5af**	76[e]
7	**4g**, 5-Br-2-pyridyl	**5ag**	76
8	**4h**, 2-Br-3-pyridyl	**5ah**	78
9	**4i**, 5-Br-3-pyridyl	**5ai**	74[e]
10	**4j**, 6-Br-3-pyridyl	**5aj**	82
11	**4k**, 2-Cl-3-pyridyl	**5ak**	90

[a] Reaction conditions: **1a** (0.5 mmol), aldehyde (2.0 equiv), $CoCl_2$ (2.0 mol%), H_2O (0.3 mL), 24 h, 120 °C.
[b] Isolated yield.
[c] **1a** (2.0 equiv), **4a** (0.5 mmol), $CoCl_2$ (5.0 mol%), 48 h.
[d] $CoCl_2$ (5.0 mol%), DMF (0.3 mL), 48 h, 140 °C.
[e] $CoCl_2$ (5.0 mol%).



Scheme 1 Scope of 2-methylquinolines. [a] $CoCl_2$ (2.0 mol%), 48 h, 140 °C. [b] Reaction was carried out on 0.3 mmol scale.

ation of various 2-methylquinolines (**1b**–**h**) with **2a** (Scheme 1).

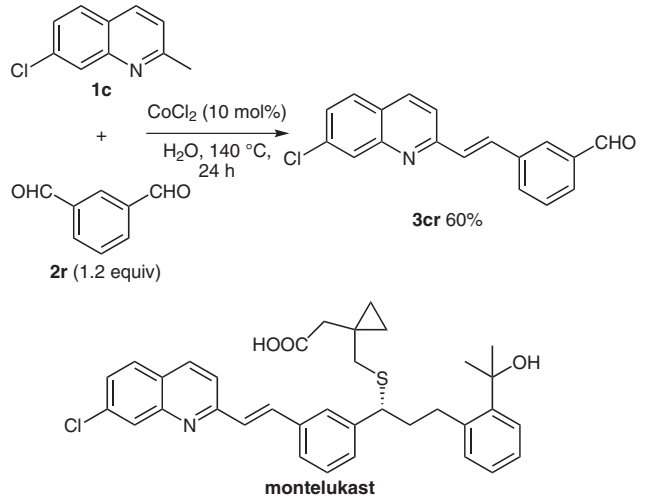
Good to excellent yields were isolated, albeit with modifications to the standard reaction conditions for some substrates, in particular eight- and/or methoxy-substituted 2-methylquinolines. These modifications were possibly necessary due to steric effects near the reactive site of the eight-substituted 2-methylquinolines (**1d** and **1h**) as well as the electron-rich nature of the quinoline core in the methoxy-substituted 2-methylquinolines (**1g** and **1h**).

Apart from quinolines, the scope of aza-arene substrates was also extended to the isoquinoline core whereby an excellent yield of 90% of the alkenylated product **3ia** was isolated with 1-methylisoquinoline (**1i**). However, no alkenylated products were formed from either 2-picoline or 2,6-lutidine under the standard reaction conditions.

In order to demonstrate the synthetic utility of our endeavors, preparation of the key intermediate for the synthesis of montelukast, a leukotriene receptor antagonist used for the treatment of asthma, was hence initiated (Scheme 2).

In the presence of 10 mol% $CoCl_2$ at 140 °C, the product **3cr** was obtained in 60% yield with the additional aldehyde moiety remained intact for further manipulation towards montelukast and other related molecules.[9]

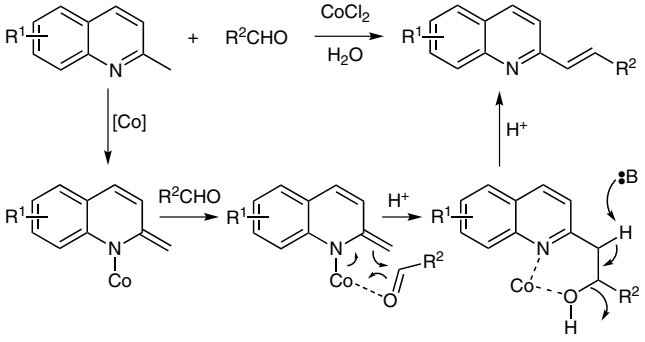
Attempts towards understanding the reaction pathway were also performed by means of deuterium-exchange ex-



Scheme 2 Preparation of the key intermediate for montelukast synthesis

periments. After heating **1a** in D_2O at 120 °C for 24 hours, 91% deuterium incorporation was observed when the experiment was carried out in the presence of 2.0 mol% $CoCl_2$. On the contrary, only 16% incorporation was observed for the control experiment in the absence of $CoCl_2$ (see Supporting Information). These observations are

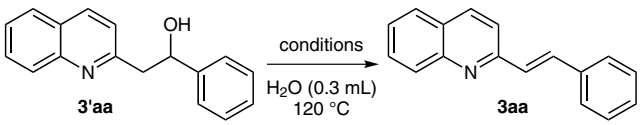
consistent with the acidity enhancement of the methyl protons of **1a** by $CoCl_2$ to effect a rapid exchange reaction with deuterium. Therefore, it was proposed that the $CoCl_2$ acts as a Lewis acid catalyst through coordination to the N atom of aza-arene leading to C(sp^3)–H bond cleavage and formation of a cobalt-enamide species. In the presence of an aldehyde as the electrophilic acceptor, benzylic addition to the carbonyl then proceeds to afford an alcohol intermediate that undergoes elimination to yield the alkenylated product (Scheme 3).



Scheme 3 Proposed reaction mechanism

Several experiments with the proposed alcohol intermediate **3′aa** were also performed. Along with **3aa**, **3′aa** could also be obtained when the reaction between **1a** and **2a** was performed under cobalt-free conditions. With regard to the proposed mechanism, this observation in turn suggests the intermediacy of the alcohol and role of $CoCl_2$ as a Lewis acid catalyst for the final elimination step. Indeed, when **3′aa** was subjected to the cobalt-catalyzed conditions (Table 4, entry 1), a 40% yield of **3aa** was isolated as opposed to only traces observed for the reaction conducted under cobalt-free conditions.

Table 4 Experiments Performed with **3′aa**



Entry	Conditions	Yield (%)
1	$CoCl_2$ (2.0 mol%), 18 h	40
2	no Co catalyst, 18 h	trace
3	$CoCl_2$ (2.0 mol%), **2a** (1.0 equiv), 2 h	61

In both cases, analysis of the crude mixtures indicated the presence of **1a** and **2a** which suggested that the initial benzylic addition is a reversible step. Therefore, it was hypothesized that the presence of excess **2a** under our standard reaction conditions was critical in maintaining the equilibrium and suppressing this reversible reaction.

In order to test this hypothesis, the reaction using **3′aa** under the cobalt-catalyzed conditions was modified with the addition of 1.0 equivalent of **2a** (Table 4, entry 3). A complete conversion of **3′aa** was indeed achieved after two hours along with a higher yield of **3aa** (61%). The shorter reaction time for the conversion further suggested that the Lewis acidity of $CoCl_2$ is effective in facilitating the elimination step. This was also shown by ^{1}H NMR analysis of the crude reaction mixtures involving **1a** and **2a** under standard conditions which demonstrated that no intermediate accumulation occurred during the reaction. This experiment indicated that the appearance of **3′aa** was preceded by its initial coexistence with **3aa** and eventual disappearance during the first four hours of the reaction (see Supporting Information).

In summary, a simple cobalt-catalyzed protocol for the direct C(sp^3)–H alkenylation of 2-methylquinolines with aldehydes has been successfully developed.[10] This protocol offers major advantages in terms of both cost effectiveness and mildness whereby good to excellent yields of the alkenylated products can be obtained from 2-methylquinolines and aldehydes. Studies to expand the scope of coupling partners for the direct C(sp^3)–H functionalization of alkyl aza-arenes are currently ongoing in our laboratory.

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Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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(10) **General Procedure**

To an 8 mL screw-capped reaction vial equipped with a magnetic stirrer bar, $CoCl_2$ (1.3 mg, 2.0 mol%), 2-methylquinoline (0.5 mmol), aldehyde (1.0 mmol), and H_2O (0.3 mL) were added. The resulting mixture was placed into a preheated oil bath at 120 °C with vigorous stirring. After 24 h, the reaction mixture was removed from the oil bath, allowed to cool to r.t. and poured into H_2O (10 mL). The mixture was then extracted with EtOAc (3 × 20 mL), washed with brine (40 mL), dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The crude product was then loaded onto a column of silica gel suspended in hexane. Purification by flash chromatography (hexane–EtOAc = 95:5, v/v) then gave the pure alkenylation product.

(*E*)-2-(4-Bromostyryl)quinoline (3ad)

Pale yellow solid in 91% yield (141.8 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.4 Hz, 2 H), 7.76 (d, *J* = 8.0 Hz, 1 H), 7.70 (t, *J* = 7.62 Hz, 1 H), 7.62–7.58 (m, 2 H), 7.51–7.45 (m, 5 H), 7.35 (d, *J* = 16.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.6, 148.3, 136.5, 135.5, 133.1, 132.0, 129.9, 129.7, 129.3, 128.7, 127.5, 127.4, 126.3, 122.6, 119.4. ESI-HRMS: *m*/*z* calcd for $C_{17}H_{13}BrN$ [M + H]: 310.0231; found: 310.0234.

(*E*)-2-[2-(Pyridin-3-yl)vinyl]quinoline (5ad)

Pale yellow solid in 86% yield (100.2 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.83 (s, 1 H), 8.54 (s, 1 H), 8.10 (dd, J_1 = 8.4 Hz, J_2 = 12.2 Hz, 2 H), 7.92 (d, *J* = 8.0 Hz, 1 H), 7.78–7.61 (m, 4 H), 7.50 (t, *J* = 7.4 Hz, 1 H), 7.42 (d, *J* = 16.4 Hz, 1 H), 7.30 (dd, J_1 = 5.2 Hz, J_2 = 8.0 Hz 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.2, 149.4, 149.2, 148.2, 136.6, 133.3, 132.3, 130.9, 130.6, 129.9, 129.3, 127.55, 127.52, 126.5, 123.7, 119.4. ESI-HRMS: *m*/*z* calcd for $C_{16}H_{13}N_2$ [M + H]: 233.1078; found: 233.1075.

(*E*)-8-Chloro-2-styrylquinoline (3da)

This compound was prepared in a similar procedure to the general procedure with 5.0 mol% $CoCl_2$ at 140 °C for 48 h to afford a pale yellow solid in 84% yield (111.3 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.8 Hz, 1 H), 7.81 (dd, J_1 = 1.0 Hz, J_2 = 7.4 Hz, 1 H), 7.75 (d, *J* = 16.4 Hz, 1 H), 7.70–7.64 (m, 4 H), 7.48–7.32 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.6, 144.4, 136.6, 136.3, 135.3, 133.3, 129.8, 128.8, 128.75, 128.73, 128.5, 127.4, 126.6, 125.9, 120.0. ESI-HRMS: *m*/*z* calcd for $C_{17}H_{13}ClN$ [M + H]: 266.0736; found: 266.0739.