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Fast and convenient base-mediated synthesis of 3-substituted quinolines

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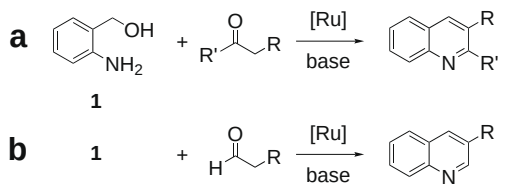
ABSTRACT

In a convenient method, 3-substituted quinolines are readily synthesized in a two-step process with initial oxazine formation and subsequent base-mediated cyclization.

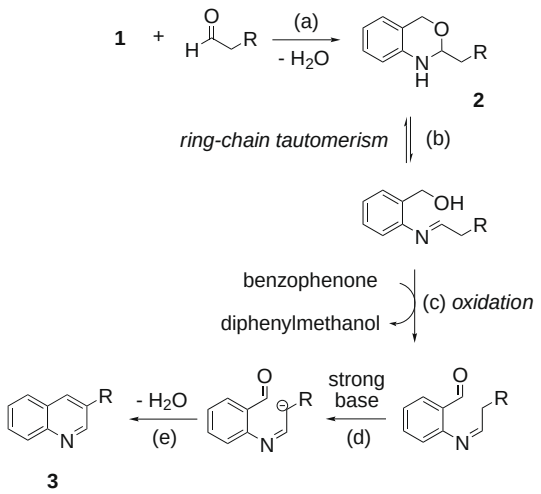
Compounds containing a quinoline framework exhibit a wide variety of pharmacological and biological activities.[1] During the last few decades, conventional named methods for their synthesis have been replaced by more efficient organometal-catalyzed approaches.[2] Our previous reports had surveyed a ruthenium-catalyzed modification of the Friedländer method in which 2-aminobenzylalcohol (**1**) is oxidatively cyclized with ketones in the presence of a base,[3] affording 2-substituted or 2,3-substituted quinolines (Scheme 1a). Recent investigations revealed that this coupling reaction also takes place in the presence of only a strong base without an expensive transition metal catalyst.[4]

Theoretically, the use of aldehydes instead of ketones should afford 3-substituted quinolines (Scheme 1b), but instead, a complex mixture of unwanted side-products was obtained, mostly as a result of the self-aldol reaction of the aldehyde. A report by Cho and Shim confirmed the difficulties in this approach.[5] They presented a step-by-step method, with an initial treatment of **1** in the presence of $RuCl_2(PPh_3)_3$ and KOH in dioxane for 15 h, followed by the addition of the aldehyde and by stirring for an additional 5 h. Even after long reaction times, only moderate quinoline yields ranging from 34% to 67% were reported. We now present a new fast and convenient method for the synthesis of 3-substituted quinolines in excellent yields. The general reaction mechanism is outlined in Scheme 2.

In a two-step procedure, first **1** is reacted with an aldehyde to form the 2-alkyl-2,4-dihydro-1*H*-benzo[d][1,3]oxazine **2**. This



Scheme 1. (a) Synthesis of 2- or 2,3-substituted quinolines from **1** and ketones; (b) Synthesis of 3-substituted quinolines from **1** and aldehydes.



Scheme 2. General reaction mechanism.

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Table 1
Optimization process[a]

Entry	Sieves	**1** (mmol)	Aldehyde[b] (mmol)	KO*t*Bu (mmol)	Benzophenone (mmol)	% Yield **3g**[c]
1	+	1.0	1.0	2.0	—	15
2	+	1.0	2.0	2.0	—	31
3	+	1.0	1.0	2.0	1.0	44
4	–	1.0	1.0	1.0	1.0	66
5	–	1.0	1.0	2.0	1.0	46
6	–	1.0	1.0	2.0	1.5	44
7	–	1.0	1.0	KOH, 2.0	1.0	6

[a] Reaction conditions: (i) **1** and aldehyde in 3 ml 1,4-dioxane, 1 h, 80 °C; (ii) **4**, base and benzophenone, 1 h, 80 °C.
[b] 3-Phenylbutyraldehyde.
[c] Determined by GC with dodecane as internal standard.

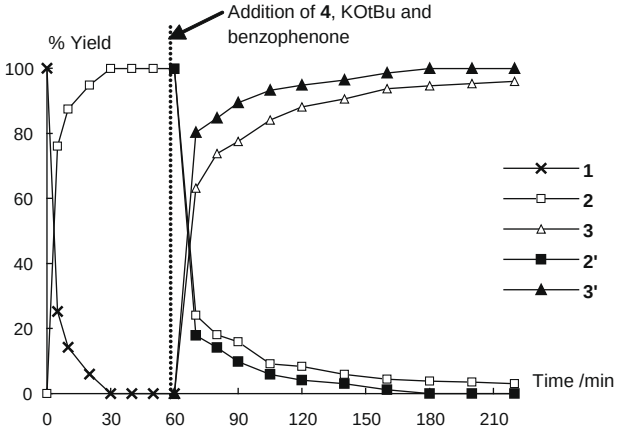


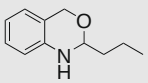
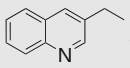
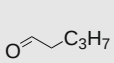
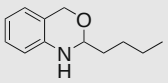
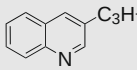
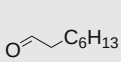
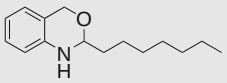
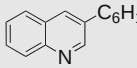
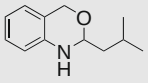
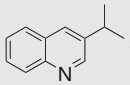
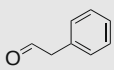
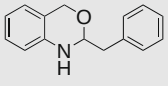
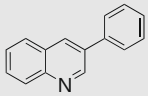
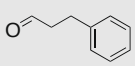
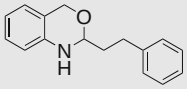
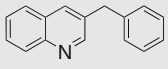
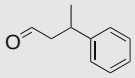
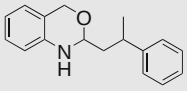
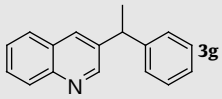
Figure 1. Progression of the reaction with butanal as the aldehyde.

oxazine is at equilibrium with the corresponding imine via a ring-chain tautomerism that has been well studied and described by others.[6] Upon addition of $(H_2IMes)(PCy_3)Cl_2Ru$ = CHPh (**4**), the second generation Grubbs catalyst, the benzylic alcohol of the imine is oxidized to an aldehyde. The strong base abstracts a proton of the α-carbon next to the imine, and an intramolecular aldol-type cyclocondensation then affords the 3-substituted quinoline **3**.

In our initial experiments, 2 equiv of aldehyde were used: one equivalent for the reaction with **1** and the other as hydrogen acceptor in the hydrogen transfer reaction. However, only low quinoline yields of 16–40% were obtained and self-aldol products from the aldehyde were found. This self-aldol reaction lowers the amount of necessary hydrogen acceptor, lowering the final quinoline yield as a consequence. Furthermore, **1** was present at the end of the reaction, even though it was completely consumed in the initial oxazine formation (verified by GC). Possibly **2** is decomposed again by water in the reaction mixture. Therefore, an optimization process was performed, and the most important results are summarized in Table 1.

To eliminate the presence of water, several experiments were carried out with molecular sieves, but with no beneficial effect (entry 3 vs entry 5). Apparently, the presence of water in the reaction mixture is not a major issue, but rather the self-aldol reaction poses the biggest problem. Without an additional hydrogen acceptor (entry 1), the reaction does hardly proceed at all, and the use of a second equivalent of the aldehyde seriously limits the yield because of the aldol side reaction (entry 2). Benzophenone is found to be the ideal 'inert' hydrogen acceptor that does not undergo self-condensation, nor cross aldol-reactions with the aldehyde. Equimolar amounts of reagents produced the best results (entry

Table 2
Synthesis of 3-substituted quinolines from **1** and aldehydes[a]

Entry	Aldehyde	Oxazine	Quinoline	% Yield [Ru]	% Yield[b] MPVO
1		 **2a**	 **3a**	94	97
2		 **2b**	 **3b**	95	>99
3		 **2c**	 **3c**	>99	>99 (92)
4		 **2d**	 **3d**	>99	>99
5		 **2e**	 **3e**	84	78 (73)
6		 **2f**	 **3f**	85	95
7		 **2g**	 **3g**	71	98

[a] Reaction conditions: (i) **1** (1.0 mmol) and aldehyde (1.0 mmol) in 3 ml 1,4-dioxane, 1 h, 80 °C; (ii) **4** and/or KO*t*Bu (1.2 mmol) and benzophenone (1.1 mmol), 2 h, 80 °C. Yields determined by GC with dodecane as internal standard.
[b] Isolated yields of selected compounds in parentheses.

4). The reaction proceeds much slower, when the weaker base KOH is used instead of KO*t*Bu (entry 7).

Figure 1 shows the progression of the reaction. The formation of **2** proceeds smoothly, but the conversion to **3** quickly slows down after the addition of **4**, KO*t*Bu and benzophenone. This is probably caused by the reaction of KO*t*Bu with water that is released during the reaction (Scheme 1, step e). The resulting KOH is a weaker base, and as a consequence, the reaction continues at a slower rate. When slightly higher amounts of KO*t*Bu and benzophenone were used, the reaction was completed faster, as shown by the filled shape curves 2′ and 3′ in Figure 1. A further increase in the amount of KO*t*Bu had no additional effect.

A variety of aldehydes were subjected to this reaction, and the results are presented in Table 2.[7,8] In this ruthenium-catalyzed procedure, good to excellent quinoline yields were achieved for all aldehydes, although the presence of an aromatic ring resulted in lower yields (Table 2, entries 5–7). Recently, we have found that the oxidation reaction can also be mediated by only a strong base such as KO*t*Bu, without the presence of a ruthenium catalyst.[4] This oxidation process presumably follows the Meerwein-Ponndorf-Verley-Oppenauer mechanism (MPVO). The same reactions were performed with only KO*t*Bu, and nearly quantitative quinoline yields were obtained for all aldehydes except phenylacetaldehyde.

In conclusion, we have developed a fast and convenient base-mediated method that affords 3-substituted quinolines in excellent yields. In a two-step procedure, first, 2-aminobenzylalcohol is reacted with an aldehyde to form an oxazine. Subsequent addition of KO*t*Bu and benzophenone then results in a MPVO oxidation and aldol-type cyclization reaction affording the quinoline.

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6. Fulop, F.; Pihlaja, K.; Mattinen, J.; Bernath, G. *J. Org. Chem.* **1987**, *52*, 3821–3825.
7. General experimental procedure for the base-mediated process: Compound **1** (0.1232 g, 1.0 mmol), aldehyde (1.0 mmol) and dodecane (0.0426 g, 0.25 mmol) were dissolved in 3 ml of 1,4-dioxane and were stirred at 80 °C for 1 h. Then, benzophenone (0.2004 g, 1.1 mmol) and KO*t*Bu (0.1347 g, 1.2 mmol) were added, and the solution was allowed to react for 2 h at 80 °C. 30 μl of the solution was passed through a short silica gel column (ethyl acetate) to remove inorganic salts, and the resulting solution was analyzed by GC to determine the yield. Dodecane was used as internal standard. All quinolines were isolated and purified by an acidic/basic extraction as described previously.[3a] Isolated yields were typically 5–10% lower than GC yields.
8. The oxazines and quinolines were characterized by ^{1}H and ^{13}C NMR spectroscopy on a Varian Unity 300 spectrometer: *2-propyl-2,4-dihydro-1H-benzo[d][1,3]oxazine* (**2a**): ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.06 (t, 1H), 6.90 (d, 1H), 6.80 (t, 1H), 6.67 (d, 1H), 4.93 (d, 1H), 4.80 (d, 1H), 4.54 (t, 1H), 1.70 (m, 2H), 1.54 (m, 2H), 0.98 (t, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 141.8, 127.6, 125.2, 122.9, 119.9, 117.5, 84.4, 67.9, 37.5, 18.1, 14.2; *2-butyl-2,4-dihydro-1H-benzo[d][1,3]-oxazine* (**2b**). ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.06 (t, 1H), 6.90 (d, 1H), 6.79 (t, 1H), 6.66 (d, 1H), 4.93 (d, 1H), 4.80 (d, 1H), 4.53 (t, 1H), 1.72 (m, 2H), 1.50 (m, 2H), 1.39 (m, 2H), 0.94 (t, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 141.8, 127.6, 125.2, 122.8, 119.9, 117.5, 84.6, 67.9, 35.1, 26.9, 22.8, 14.2; *2-heptyl-2,4-dihydro-1H-benzo[d][1,3]oxazine* (**2c**). ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.05 (t, 1H), 6.90 (d, 1H), 6.78 (t, 1H), 6.65 (d, 1H), 4.93 (d, 1H), 4.79 (d, 1H), 4.52 (t, 1H), 1.72 (m, 2H), 1.50 (m, 2H), 1.35-1.20 (m, 8H), 0.89 (t, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 141.9, 127.6, 125.2, 122.8, 119.9, 117.5, 84.7, 67.9, 35.4, 32.0, 29.7, 29.4, 24.8, 22.9, 14.3; *2-isobutyl-2,4-dihydro-1H-benzo[d][1,3]oxazine* (**2d**). ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.09 (t, 1H), 6.93 (d, 1H), 6.83 (t, 1H), 6.69 (d, 1H), 4.96 (d, 1H), 4.82 (d, 1H), 4.61 (t, 1H), 1.94 (m, 1H), 1.71 (m, 1H), 1.54 (m, 1H), 1.01 (d, 6H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 141.8, 127.6, 125.3, 123.0, 120.0, 117.7, 83.4, 67.9, 44.4, 24.5, 23.3, 22.9; *2-benzyl-2,4-dihydro-1H-benzo[d][1,3]oxazine* (**2e**). ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.40–7.15 (m, 5H), 7.01 (t, 1H), 6.86 (d, 1H), 6.75 (t, 1H), 6.56 (d, 1H), 4.90 (d, 1H), 4.79 (d, 1H), 4.57 (t, 1H), 3.10 (d, 1H), 2.94 (d, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 141.8, 136.3, 129.9, 129.0, 128.4, 127.6, 127.2, 125.2, 122.9, 119.9, 117.2, 84.7, 67.9, 41.8; *2-phenethyl-2,4-dihydro-1H-benzo[d][1,3]oxazine* (**2f**). ^{1}H NMR (300 MHz; $CDCl_3$) δ.30–7.09 (m, 5H), 7.04 (t, 1H), 6.88 (d, 1H), 6.78 (t, 1H), 6.62 (d, 1H), 4.85 (d+d, 2H), 4.51 (t, 1H), 2.92–2.75 (m, 2H), 2.02 (m, 2H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 141.8, 128.9 (2 C), 128.8 (2 C), 127.7, 126.6, 126.4, 125.3, 122.9, 120.1, 117.6, 83.9, 67.9, 36.9, 31.0; *2-(2-phenylpropyl)-2,4-dihydro-1H-benzo[d][1,3]oxazine* (**2g**). ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.29–7.18 (m, 5H), 7.02 (t, 1H), 6.84 (d, 1H), 6.77 (t, 1H), 6.68 (d, 1H), 4.79 (m, 2H), 4.23 (t, 1H), 3.09 (m, 1H), 2.12–1.90 (m, 2H), 1.31 (d, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 146.5, 141.9, 128.8 (2 C), 127.5, 127.3 (2 C), 126.6, 125.2, 123.0, 120.0, 117.6, 83.2, 67.8, 43.9, 36.2, 23.1; *3-Ethylquinoline* (**3a**). Pale yellow oil; ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.79 (s, 1H), 8.07 (d, 1H), 7.92 (s, 1H), 7.76 (d, 1H), 7.65 (t, 1H), 7.51 (t, 1H), 2.85 (q, 2H), 1.36 (t, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 152.1, 146.9, 136.9, 133.6, 129.4, 128.7, 128.5, 127.5, 126.8, 26.5, 15.5; *3-Propylquinoline* (**3b**). Pale yellow oil; ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.76 (s, 1H), 8.07 (d, 1H), 7.89 (s, 1H), 7.75 (d, 1H), 7.64 (t, 1H), 7.49 (t, 1H), 2.75 (t, 2H), 1.72 (m, 2H), 0.98 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 152.3, 146.9, 135.4, 134.5, 129.3, 128.8, 128.4, 127.6, 126.8, 35.5, 24.5, 13.9; *3-Hexylquinoline* (**3c**). Pale yellow oil; ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.77 (s, 1H), 8.08 (d, 1H), 7.92 (s, 1H), 7.76 (d, 1H), 7.65 (t, 1H), 7.52 (t, 1H), 2.78 (t, 2H), 1.70 (m, 2H), 1.32 (m, 6H), 0.88 (t, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 152.0, 146.5, 135.7, 129.3, 128.9, 128.5, 127.5, 126.9, 33.4, 31.9, 29.1, 22.8, 14.3; *3-Isopropylquinoline* (**3d**). Pale yellow oil; ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.82 (s, 1H), 8.08 (d, 1H), 7.93 (s, 1H), 7.76 (d, 1H), 7.65 (t, 1H), 7.51 (t, 1H), 3.13 (m, 1H), 1.36 (m, 6H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 151.2, 146.9, 141.4, 132.3, 129.1, 128.8, 128.5, 127.7, 126.8, 32.1, 23.9; *3-Phenylquinoline* (**3e**). Pale yellow solid; ^{1}H NMR (300 MHz; $CDCl_3$) δ 9.17 (s, 1H), 8.24 (s, 1H), 8.14 (d, 1H), 7.83 (d, 1H), 7.71–7.66 (m, 3H), 7.56–7.47 (m, 3H), 7.42 (d, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 150.2, 147.6, 138.1, 134.0, 133.3, 129.6, 129.5, 129.4, 128.6, 128.4, 128.3, 127.7, 127.2; *3-Benzylquinoline* (**3f**). Light brown oil; ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.81 (s, 1H), 8.07 (d, 1H), 7.87 (s, 1H), 7.72 (d, 1H), 7.65 (t, 1H), 7.50 (t, 1H), 7.34–7.21 (m, 5H), 4.15 (s, 2H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 152.4, 147.1, 139.9, 135.1, 134.1, 129.4, 129.2, 129.1, 129.0, 128.6, 127.7, 127.0, 126.8, 39.5; *3-(1-phenylethyl)quinoline* (**3g**). Light brown solid; ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.80 (s, 1H), 8.07 (d, 1H), 7.93 (s, 1H), 7.75 (d, 1H), 7.65 (t, 1H), 7.51 (t, 1H), 7.33–7.20 (m, 5H), 4.36 (q, 1H), 1.75 (d, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 152.0, 146.9, 145.1, 139.2, 133.4, 129.2, 129.1, 128.9, 128.3, 127.9, 127.8, 126.9, 126.8, 42.8, 21.9.