A recyclable copper catalysis in modified Friedländer quinoline synthesis

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ABSTRACT

2-Aminobenzyl alcohol reacts with ketones in dioxane at 100 °C in the presence of a catalytic amount of a copper catalyst along with KOH and MS 4A under O_2 atmosphere to afford the corresponding quinolines in good yields. The catalytic system could be recovered and reused 10 times without any loss of catalytic activity. A similar catalytic system using copper catalyst/PEG-2000 is also effective for this coupling and cyclization with a similar catalytic potential. 2-Aminobenzyl alcohol is also coupled and cyclized with secondary alcohols under the $CuCl_2$/MS 4A catalytic system to give quinolines in moderate to good yields.

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1. Introduction

During the course of our continuous studies on transition metal-catalyzed carbon–carbon bond forming reactions using alcohols as an electrophile, we recently disclosed on ruthenium- and palladium-catalyzed several coupling reactions between ketones (or secondary alcohols) and primary alcohols [1–5]. This type of carbon–carbon bond forming reaction could be applied to the synthesis of quinolines via a ruthenium-catalyzed oxidative cyclization of 2-aminobenzyl alcohol with ketones [6] and secondary alcohols [7] (modified Friedländer quinoline synthesis) [8–14]. This protocol is superior to the conventional Friedländer quinoline synthesis considering the price and stability of 2-aminobenzyl alcohol. Subsequent improved methods were also disclosed in order to overcome drawbacks such as the need for an expensive transition metal catalyst and a hydrogen acceptor (or the use of excess starting ketone to 2-aminobenzyl alcohol). 2-Aminobenzyl alcohol was found to be effectively coupled and cyclized with a nearly equimolar amount of ketones without a sacrificial hydrogen acceptor in the presence of an inexpensive copper catalyst [16]. A recyclable palladium-catalyzed protocol was also tested for this purpose [17]. Under these circumstances, we have directed our attention to the development of a recyclable copper catalytic system. Herein, we report a simple reusable copper catalytic system

for the modified Friedländer quinoline synthesis, oxidative cyclization of 2-aminobenzyl alcohol with ketones or secondary alcohols (Scheme 1) [18].

2. Experimental

2.1. General

^{1}H and ^{13}C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance Digital 400 spectrometer using TMS as an internal standard. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and were uncorrected. The isolation of pure products was carried out via thin layer (silica gel 60 GF_{254}, Merck) chromatography. Commercially available organic and inorganic compounds were used without further purification except for the solvent, which was distilled by known methods before use. Compounds **2n** and **2o** were prepared by alkylation of acetophenone with trialkylamines [19].

2.2. Typical experimental procedure for copper-catalyzed synthesis of quinolines from 2-aminobenzyl alcohol and ketones

A mixture of 2-aminobenzyl alcohol (**1**) (0.123 g, 1 mmol), acetophenone (**2a**) (0.144 g, 1.2 mmol), KOH (0.168 g, 3 mmol), $CuCl_2$ (0.007 g, 0.05 mmol) and powdered molecular sieves 4A (0.300 g) in dioxane (5 mL) was placed in an organic reactor (Radleys Discovery Technologies) and allowed to react at 100 °C for 20 h. After the reaction mixture was cooled to room temperature, the solid

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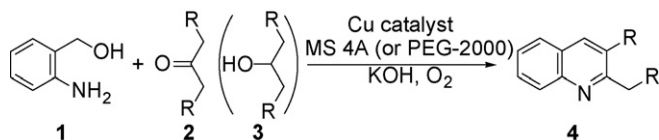
Scheme 1. Modified Friedländer quinoline synthesis.

was filtered out, washed with ethyl acetate, dried under vacuo and subjected to a second run by charging the reactor with **1**, **2a**, KOH and dioxane. Removal of the solvent from the filtrate left an oil, which was purified by thin layer chromatography (silica gel, ethyl acetate/hexane = 1/5) to give 2-phenylquinoline (**4a**) (0.185 g, 90%). Except for **4i**, **4j**, **4r** and **4u**–**w**, which were characterized spectroscopically as shown below, all quinolines exhibited characteristics identical to those previously synthesized by our recent reports [6,7,15,17].

2-(2-Bromophenyl)quinoline (**4i**): Solid; mp 69–71 °C (hexane–chloroform) (lit. [20] 69–71 °C); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.27–7.32 (m, 1H), 7.45 (dt, J = 1.0 and 7.5 Hz, 1H), 7.56–7.60 (m, 1H), 7.64 (dd, J = 1.5 and 7.5 Hz, 1H), 7.70 (d, J = 8.5 Hz, 2H), 7.72–7.77 (m, 1H), 7.87 (dd, J = 1.0 and 8.0 Hz, 1H), 8.18 (d, J = 8.5 Hz, 1H), 8.21 (d, J = 9.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 122.25, 123.12, 127.20, 127.53, 127.97, 128.11, 130.07, 130.13, 130.40, 131.97, 133.66, 136.08, 142.06, 148.32, 159.14.

2-(1,1′-Biphenyl)-4-ylquinoline (**4j**) [21]: Solid; mp 176–177 °C (hexane–chloroform); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.36–7.40 (m, 1H), 7.46–7.50 (m, 2H), 7.51–7.55 (m, 1H), 7.67–7.69 (m, 2H), 7.71–7.77 (m, 3H), 7.83 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H), 8.18–8.27 (m, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 119.30, 126.70, 127.55, 127.62, 127.89, 127.96, 128.00, 128.37, 129.26, 130.12, 137.21, 138.93, 140.99, 142.46, 148.74, 157.30.

2-^{t}Butylquinoline (**4r**) [22]: Oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.47 (s, 9H), 7.44–7.48 (m, 1H), 7.51 (d, J = 8.5 Hz, 1H), 7.63–7.67 (m, 1H), 7.74 (dd, J = 1.0 and 8.0 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 30.56, 38.53, 118.63, 126.02, 126.84, 127.63, 129.38, 129.82, 136.26, 147.83, 169.66.

7,8,9,10-Tetrahydro-6*H*-cyclohepta[*b*]quinoline (**4u**): Solid; mp 90–91 °C (hexane–chloroform) (lit. [23] 90–91.5 °C); ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.74–1.82 (m, 4H), 1.87–1.93 (m, 2H), 2.92–2.95 (m, 2H), 3.20–3.22 (m, 2H), 7.43–7.47 (m, 1H), 7.59–7.64 (m, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.80 (s, 1H), 8.00 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 27.41, 29.25, 32.65, 35.85, 40.46, 126.15, 127.21, 127.74, 128.80, 128.87, 135.01, 136.93, 146.60, 165.11.

6,7,8,9,10,11-Hexahydrocycloocta[*b*]quinoline (**4v**) [24]: Solid; mp 56–57 °C (hexane–chloroform); ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.37–1.43 (m, 4H), 1.74–1.77 (m, 2H), 1.86–1.90 (m, 2H), 2.92–2.96 (m, 2H), 3.14–3.18 (m, 2H), 7.41–7.46 (m, 1H), 7.59–7.63 (m, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.82 (s, 1H), 8.03 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 26.30, 26.44, 31.36, 32.47, 33.10, 35.64, 125.92, 127.23, 128.01, 128.76, 128.87, 135.37, 135.51, 147.36, 163.57.

6,7,8,9,10,11,12,13,14,15-Decahydrocyclododeca[*b*]quinoline (**4w**) [25]: Solid; mp 75–76 °C (hexane–chloroform); ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.42–1.56 (m, 12H), 1.77–1.83 (m, 2H), 1.93–1.99 (m, 2H), 2.80–2.84 (m, 2H), 3.00–3.04 (m, 2H), 7.41–7.45 (m, 1H), 7.58–7.62 (m, 1H), 7.70 (d, J = 8.5 Hz, 1H), 7.89 (s, 1H), 8.00 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 23.43, 23.51, 25.86, 26.43, 26.89, 27.13, 28.89, 30.07, 30.16, 33.11, 125.94, 127.21, 127.56, 128.77, 128.81, 135.27, 136.18, 146.97, 163.11.

3. Results and discussion

Initial attempts for the oxidative cyclization of 2-aminobenzyl alcohol (**1**) with acetophenone (**2a**) were carried out under several copper catalytic systems and the results are listed in Table 1. We recently reported that **1** reacts with **2a** in dioxane at 100 °C in the presence of a catalytic amount of CuCl$_2$ along with KOH under O$_2$ atmosphere to afford 2-phenylquinoline (**4a**) in 79% yield (run 1). When the reaction was carried out with molecular sieve 4A (MS 4A) added to the copper catalytic system, **4a** was obtained in 90% isolated yield and the copper catalytic system could be easily recovered by simple filtration from the reaction mixture. No Cu in the filtrate was observed by ICP-AES (inductively coupled plasma-atomic emission spectroscopy) determination. The recovered CuCl$_2$/MS 4A could be reused 10 times without any loss of catalytic activity (run 2). Other copper catalyst such as CuCl and CuBr combined with MS 4A exhibited similar catalytic activity with similar recycling potential to the CuCl$_2$/MS 4A system (runs 3 and 4). It has been recently reported that poly(ethylene glycol) (PEG) can be used as a catalyst recyclable medium in transition metal-catalyzed reactions [26–33]. We also recently used PEG-2000 as a recyclable medium for a palladium catalyst in modified Friedländer quinoline synthesis [17]. Several copper catalysts combined with PEG-2000 also could be used as a recyclable catalytic system (runs 5–7). However, the yield of **4a** was lower than under the Cu/MS 4A catalytic systems (runs 5–7). As a result, among copper catalysts combined with a recyclable medium examined, in terms of

Table 1
Copper-catalyzed reaction of **1** with **2a** under several conditions.
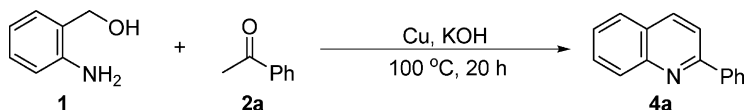
Run	Copper catalysts	Solvents	Isolated yield (%)										
			1	2	3	4	5	6	7	8	9	10	11
1	CuCl$_2$[a]	Dioxane	79										
2	CuCl$_2$/MS 4A[b]	Dioxane	90	92	88	88	88	89	89	88	85	89	92
3	CuCl/MS 4A[b]	Dioxane	86	86	87	80	87	82	83	89	88	84	80
4	CuBr/MS 4A[b]	Dioxane	82	85	86								
5	CuCl$_2$/PEG-2000[c]	Toluene	68	78	75	73	75	80					
6	CuCl/PEG-2000[c]	Toluene	73[d]	70[d]	68[d]	68[d]	80[d]	79[d]					
7	CuBr/PEG-2000[c]	Toluene	75[d]	72[d]	73[d]	71[d]	75[d]	80[d]					

Reaction conditions: **1** (1 mmol), **2a** (1.2 mmol), copper catalyst (0.05 mmol), KOH (3 mmol), solvent (5 mL), 100 °C, 20 h, O$_2$ (1 atm).

[a] 0.01 mmol.
[b] MS 4A (0.3 g).
[c] PEG-2000 (0.3 g).
[d] Average of two times.

Table 2
Recyclable copper-catalyzed synthesis of quinolines **4** from **1** and **2**.

Ketones **2**	Quinolines **4**	Yield (%)
2a Ar = Ph	**4a** Ar = Ph	90
2b Ar = 4-MeC$_6$H$_4$	**4b** Ar = 4-MeC$_6$H$_4$	92
2c Ar = 3-MeC$_6$H$_4$	**4c** Ar = 3-MeC$_6$H$_4$	89
2d Ar = 2-MeC$_6$H$_4$	**4d** Ar = 2-MeC$_6$H$_4$	85
2e Ar = 4-MeOC$_6$H$_4$	**4e** Ar = 4-MeOC$_6$H$_4$	97
2f Ar = 3-MeOC$_6$H$_4$	**4f** Ar = 3-MeOC$_6$H$_4$	97
2g Ar = 2-MeOC$_6$H$_4$	**4g** Ar = 2-MeOC$_6$H$_4$	90
2h Ar = 3-CF$_3$C$_6$H$_4$	**4h** Ar = 3-CF$_3$C$_6$H$_4$	84
2i Ar = 2-BrC$_6$H$_4$	**4i** Ar = 2-BrC$_6$H$_4$	58
2j Ar = 4-PhC$_6$H$_4$	**4j** Ar = 4-PhC$_6$H$_4$	94
2k Ar = 2-naphthyl	**4k** Ar = 2-naphthyl	80
2l Ar = 2-thienyl	**4l** Ar = 2-thienyl	86
2m R = Me	**4m** R = Me	67
2n R = butyl	**4n** R = butyl	65
2o R = benzyl	**4o** R = benzyl	60
		47[a]
2p	**4p**	
		42
2q	**4q**	
		44
2r	**4r**	
		47
2s	**4s**	
2t n = 1	**4t** n = 1	66
2u n = 2	**4u** n = 2	91
2v n = 3	**4v** n = 3	90
2w n = 7	**4w** n = 7	47

Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), CuCl$_2$ (0.05 mmol), MS 4A (0.3 g), KOH (3 mmol), dioxane (5 mL), O$_2$ (1 atm), 100 °C, for 20 h.

[a] 3-Butyl-2-methylquinoline was also formed in 17% yield.

product **4a** yield and recycling potential, CuCl$_2$/MS 4A revealed to be the catalytic system of choice.

After the reaction conditions have been established, various ketones **2** were subjected to the reaction with **1** in order to investigate the reaction scope and several representative results are summarized in Table 2. With aryl(methyl) ketones (**2a**–**j**), the corresponding quinolines (**4a**–**j**) were formed in the range of 58–97% yields without any identifiable side products. The position and electronic nature of the substituent on the aromatic ring of aryl(methyl) ketones had no relevance to the quinoline yield except for 2′-bromoacetophenone (**2i**). The catalytic activity using CuCl$_2$ combined with MS 4A as recyclable medium was superior to that using only CuCl$_2$ toward the formation of 2-arylquinolines [16]. The reaction proceeds likewise with 2′-acetonaphthone (**2k**) and heteroaryl(methyl) ketone **2l** to give the corresponding quinolines (**4k** and **4l**) in similar yields. With alkyl(aryl) ketones (**2m**–**o**), which have only a methylene reaction site, the product yield was lower than when aryl(methyl) ketones were used. Lower reaction rates and yields were observed with alkyl(methyl) ketones (**2p**–**r**). Prolonging the reaction time (40 h) resulted in a slightly increased yield (**4q**: 47%; **4r**: 55%). In the reaction of alkyl(methyl) ketone **2p**, quinolines were obtained as a regioisomeric mixture, favoring cyclization at a less-hindered methyl position over α-methylene. With dialkyl ketone **2s** having only methylene reaction site, quinoline **4s** was

Table 3
Recyclable copper-catalyzed synthesis of quinolines **4** from **1** and **3**.

Secondary alcohols **3**	Quinolines **4**	Isolated yield (%)										
		1	2	3	4	5	6	7	8	9	10	11
3a Ar = Ph	**4a**	54	63	69	57	57	57	56	56	61	59	70
3b Ar = 4-MeC$_6$H$_4$	**4b**	49										
3c Ar = 3-MeC$_6$H$_4$	**4c**	40										
3d Ar = 4-MeOC$_6$H$_4$	**4e**	47										
3e Ar = 3-CF$_3$C$_6$H$_4$	**4h**	69										
3f Ar = 2-thienyl	**4l**	69										
3g	**4m**	34										
3h	**4u**	41										

Reaction conditions: **1** (1 mmol), **3** (1.2 mmol), CuCl$_2$ (0.05 mmol), MS 4A (0.3 g), KOH (3 mmol), dioxane (5 mL), O$_2$ (1 atm), 100 °C, for 40 h.

formed in 47% yield. Cyclic ketones (**2t**–**w**) were also coupled and cyclized with **1** to give the corresponding quinolines in yields in the range of 47–91% and the ring size of **2t**–**w** had no relevance to quinoline yield.

Similar treatment of **1** with 1-phenylethanol (**3a**) under the CuCl$_2$/MS 4A catalytic system afforded **4a** in 54% yield along with acetophenone (**2a**) (10% yield) as sole identifiable byproduct (Table 3). The recovered copper catalytic system could be reused 10 times without any loss of catalytic activity. With several aryl- and heteroaryl(methyl) carbinols (**3b**–**f**) having electron-donating and withdrawing substituents on the aromatic ring of **3b**–**f** the oxidative coupling and cyclization products were formed in 40–69% yields. The reaction of 1-phenyl-1-propanol (**3g**) with **1** also proceeds to give quinoline **4m**. Cyclic carbinol **3h** was also reacted with **1** to give **4u**. However, the quinoline yield was generally lower than when ketones were used.

4. Conclusion

In summary, we have shown that 2-aminobenzyl alcohol undergoes oxidation followed by coupling and cyclization with various ketones and secondary alcohols in the presence of a copper catalyst combined with MS 4A or PEG-2000 along with KOH to give quinolines in good yields. The copper catalytic system could be easily recovered from the reaction mixture and reused 10 times without any loss of catalytic activity. The present reaction provides a cheaper catalytic route for modified Friedländer quinoline synthesis and further study of synthetic applications using the present recyclable copper catalytic system is currently under investigation.

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