

Note

A recyclable palladium-catalyzed modified Friedländer quinoline synthesis

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Abstract

2-Aminobenzyl alcohol reacts with an array of ketones in toluene/poly(ethylene glycol) (PEG-2000) at 100 °C in the presence of a palladium catalyst along with KOH under an atmosphere of air to give the corresponding quinolines in good yields. The catalytic system could be recovered and reused five times without any loss of catalytic activity.

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1. Introduction

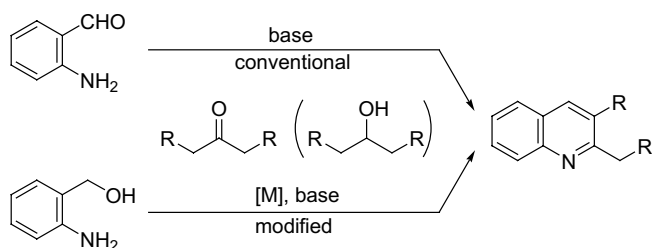
Besides conventional named quinoline routes such as Skraup, Döbner-von Miller, Conrad-Limpach, Friedländer and Pfitzinger syntheses [1], homogeneous transition metal-catalyzed reactions have also been developed as alternative methods for the construction of quinoline framework because of the facility and efficiency of reaction and the wide availability of substrate [2]. We also reported on several transition metal catalyzed routes for quinolines via ruthenium-catalyzed alkyl or alkanol group transfer from alkylamines or alkanolamines to N-atom of anilines (amine exchange reaction [3]) [2b,4] and palladium-catalyzed coupling, isomerization and cyclization between 2-iodoaniline and propargylic alcohols [5]. Furthermore, in connection with this report, during the course of our continuous studies on ruthenium-catalyzed carbon–carbon bond forming reactions between ketones (or secondary alcohols) and primary alcohols (or aldehydes) [6], we have also reported on ruthenium-catalyzed synthesis of quinolines via an oxidative cyclization of 2-aminobenzyl alcohol with ketones [7]

and secondary alcohols [8] (modified Friedländer quinoline synthesis) (Scheme 1) [9,10]. It was also disclosed that 2-aminobenzyl alcohol was found to be oxidatively coupled and cyclized with ketones and aldehydes in the presence of an inexpensive copper catalyst [11,12]. However, these protocols have some drawbacks requiring an expensive consumable transition metal catalyst. Under these circumstances, we have directed our attention to the discovery of a reusable catalyst for the synthesis of quinolines from 2-aminobenzyl alcohol and ketones. Herein, this report describes a recyclable palladium-catalyzed protocol for the modified Friedländer quinoline synthesis.

2. Results and discussion

Based on our recent report on ruthenium- and copper-catalyzed oxidative coupling and cyclization of 2-aminobenzyl alcohol (**1**) with ketones (**2**) and aldehydes [7,8,11], Table 1 shows several attempted results of reactions between **1** and acetophenone (**2a**) under various palladium catalytic systems. Treatment of **1** with 2 equiv of **2a** in toluene in the presence of a catalytic amount of Pd(OAc)₂ (2 mol%) along with KOH at 100 °C for 20 h afforded 2-phenylquinoline (**3a**) in 83% yield with concomitant

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Scheme 1. Friedlander quinoline synthesis.

Table 1
Palladium-catalyzed reaction of **1** with **2a** under several conditions^a

Entry	Palladium catalysts	Isolated yield (%)					
		1	2	3	4	5	6
1	Pd(OAc) ₂	83					
2	Nano-Pd	75	75	69	68	75	74
3	Pd(OAc) ₂ /PEG-2000 ^b	76	80	77	58	78	88
4	PdCl ₂ /PEG-2000 ^b	71	60	67	71	67	58
5	Pd/C/PEG-2000 ^b	50	71	66	74	53	72

^a Reaction conditions: **1** (1 mmol), **2a** (2 mmol), palladium catalyst (0.02 mmol), KOH (3 mmol), toluene (3 ml), 100 °C, 20 h.

^b PEG-2000 (0.3 g).

formation of 1-phenylethanol by transfer hydrogenation of **2a** by **1** (58% yield based on **1** by GLC analysis of the crude mixture) (entry 1) [13]. Prompted by this result, we have directed our attention to the recyclable palladium catalytic system for the present cyclization. It is recently known that palladium nanoparticles (nano-Pd) can be prepared by treatment of poly(ethyleneglycol) (PEG) with Pd(OAc)₂ and are found to be a highly stable and reusable catalyst for Heck reaction [14]. Applying of this nano-Pd prepared from Pd(OAc)₂ and PEG-2000 to the present reaction resulted in 75% yield of **3a** and the recycling potential of the catalytic system could be reused five times without any loss of catalytic activity (entry 2). It is also reported by several groups that poly(ethylene glycol) (PEG) is used as a recyclable medium along with a transition metal catalyst [15]. The addition of PEG-2000 to the catalytic system of entry 1 resulted in 76% yield of **3a** and a palladium catalyst could be easily solidified along with PEG-2000 by cooling and separated by filtration (entry 3). The recovered palladium/PEG-2000 could also be reused five times without any loss of catalytic activity. The catalytic systems using palladium precursors such as PdCl₂ and Pd/C combined with PEG-2000 exhibited similar catalytic activity as Pd(OAc)₂/PEG-2000 system (entries 4 and 5).

Given these results, the reactions of **1** with various ketones **2** were screened using two sets of reaction conditions, nano-palladium (condition A) and Pd(OAc)₂/PEG-

2000 (condition B), and several representative results are summarized in Table 2. Various aryl(methyl) ketones (**2a–h**) having electron donating and withdrawing substituents on the aromatic ring were readily coupled and cyclized with **1** to give the corresponding quinolines (**3a–h**) along with minimal formation of aryl(methyl) carbinols as identifiable direct transfer hydrogenation products. Generally, the catalytic system using Pd(OAc)₂ combined with PEG-2000 (condition B) was superior to that using nano-palladium (condition A) toward the formation of **3**. Under condition A, the product yield was not significantly affected by the position of the substituent on the aromatic ring of **2a–h**, whereas the electronic nature of that had some relevance to the product yield. However, under condition B, quinolines were produced nearly invariable yields irrespective of the position and electronic nature of that. 2'-Acetonaphthone (**2i**) were also readily coupled and cyclized with **1** to afford 2-(2-naphthyl)quinoline (**3i**) in similar yields under both reaction conditions. With heteroaryl(methyl) ketone **2j**, the product yield was lower than that when aryl(methyl) ketones were used. Higher reaction rate and yield were observed with alkyl(aryl) ketones (**2k** and **2l**), which has only methylene reaction site. In the reaction of alkyl- (methyl) ketones (**2m** and **2n**) the corresponding quinolines were obtained as a regioisomeric mixture in similar yields and distributions under both reaction conditions, favoring cyclization at less-hindered position over α -methylene. With dialkyl ketone **2p** 3-butyl-2-pentylquinoline (**3p**) was also formed in 31% and 41% yields, respectively, under condition A and condition B and the product yield was lower than that when previously described ketones were used. Cyclic ketones such as 4-phenylcyclohexanone (**2q**) and 1-tetralone (**2r**) were also reacted with **1** to give 3-phenyl-1,2,3,4-tetrahydroacridine (**3q**) and 5,6-dihydrobenzo[*c*]acridine (**3r**) in 89% (94%) and 72% (79%) yields, respectively, under condition A (condition B).

Similar treatment of **1** with octyl aldehyde (**4**) under nano-Pd catalytic system afforded 3-hexylquinoline (**3s**) in 44% yield along with a considerable amount of oxazine **5** (9% yield) (Scheme 2). When the catalyst was reused, the yield of **3s** decreased from 44%, 34% (first reuse), to 24% (second reuse), while that of **5** increased from 9%, 22% (first reuse), to 30% (second reuse).

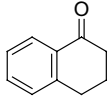
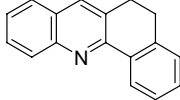
3. Conclusion

In summary, we have shown that 2-aminobenzyl alcohol undergoes oxidative cyclization with an array of ketones in the presence of a palladium catalyst combined with PEG-2000 along with KOH to give quinolines in good yields. The palladium/PEG-2000 catalytic system could be easily recovered from reaction mixture and reused five times without any loss of catalytic activity. To the best of our knowledge, this protocol is the first recyclable transition metal-catalyzed strategy for modified Friedländer quinoline synthesis.

Table 2
Recyclable palladium-catalyzed synthesis of quinolines **3** from **1** and **2^a**

Ketones 2	Quinolines 3	Yield (%)	
		Condition A ^b	Condition B ^c
2a R = Ph	3a R = Ph	75	76
2b R = 4-MeC ₆ H ₄	3b R = 4-MeC ₆ H ₄	58	80
2c R = 3-MeC ₆ H ₄	3c R = 3-MeC ₆ H ₄	78	85
2d R = 2-MeC ₆ H ₄	3d R = 2-MeC ₆ H ₄	68	70
2e R = 4-MeOC ₆ H ₄	3e R = 4-MeOC ₆ H ₄	60	76
2f R = 3-MeOC ₆ H ₄	3f R = 3-MeOC ₆ H ₄	75	85
2g R = 2-MeOC ₆ H ₄	3g R = 2-MeOC ₆ H ₄	73	87
2h R = 3-CF ₃ C ₆ H ₄	3h R = 3-CF ₃ C ₆ H ₄	47	78
2i R = 2-naphthyl	3i R = 2-naphthyl	61	78
2j R = 2-thienyl	3j R = 2-thienyl	38	35
		85	88
2k	3k		
		69	79
2l	3l		
		47 ^d	49 ^f
2m	3m		
		47 ^e	49 ^g
2n	3n		
		58	65
2o	3o		
		31	41
2p	3p		
		89	94
2q	3q		

Table 2 (continued)

Ketones 2	Quinolines 3	Yield (%)	
		Condition A ^b	Condition B ^c
		72	79
2r	3r		

^a Reaction conditions: **1** (1 mmol), **2** (2 mmol), palladium (0.02 mmol), KOH (3 mmol), toluene (3 ml), 100 °C, for 20 h.

^b Nano-Pd (0.02 mmol).

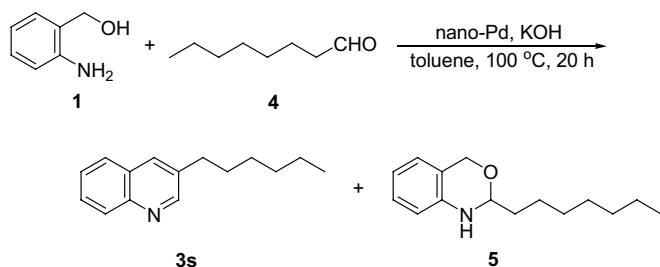
^c Pd(OAc)₂ (0.02 mmol), PEG-2000 (0.3 g).

^d 3-Benzyl-2-methylquinoline was also formed in 18% yield.

^e 3-Butyl-2-methylquinoline was also formed in 23% yield.

^f 3-Benzyl-2-methylquinoline was also formed in 28% yield.

^g 3-Butyl-2-methylquinoline was also formed in 15% yield.



4. Experimental

¹H and ¹³C 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. GLC analyses were carried out with a Shimadzu GC-17A instrument equipped with a CBP10-S25-050 column (Shimadzu, fused silica capillary column, 0.33 mm × 25 m, 0.25 μm film thickness) using nitrogen as carrier gas. The isolation of pure products was carried out via column chromatography (silica gel 60, 70–230 mesh, Merck) and thin layer chromatography (silica gel 60 GF₂₅₄, Merck). Nano-Pd catalyst was prepared from Pd(OAc)₂ and PEG-2000 [poly(ethylene glycol-2000)] by the reported method [14]. Commercially available organic and inorganic compounds were used without further purification except for toluene, which was distilled by known method before use.

4.1. Typical experimental procedure

A mixture of 2-aminobenzyl alcohol (**1**) (0.123 g, 1 mmol), acetophenone (**2a**) (0.240 g, 2 mmol), KOH (0.168 g, 3 mmol), Pd(OAc)₂ (0.0045 g, 0.02 mmol) and PEG-2000 (0.300 g) in toluene (3 ml) was placed in a 5 ml screw-capped vial and allowed to react at 100 °C for 20 h. After the brown black solution was cooled in refrig-

erator, the solidified Pd/PEG-2000 was filtered, washed with dry ether, dried under vacuo and subjected to a second run by charging with **1**, **2a**, KOH and toluene [18]. Removal of the solvent of the filtrate left an oil, which was purified by thin-layer chromatography (silica gel, ethyl acetate/hexane = 1/5) to give 2-phenylquinoline (**3a**) (0.155 g, 75%).

Except for **3l**, **3o**, **3s** and **5**, all quinolines prepared by the above procedure were characterized by GLC and spectroscopic comparison with authentic samples synthesized by our recent reports [7,8,16,17].

4.1.1. 3-Benzyl-2-phenylquinoline (**3l**)

Solid, m.p. 91–92 °C (from hexane–CHCl₃) (lit. [19] 84–88 °C); ¹H NMR (CDCl₃): δ 4.12 (s, 2H), 6.99 (d, *J* = 6.5 Hz, 2H), 7.16–7.25 (m, 3H), 7.40–7.52 (m, 6H), 7.65–7.69 (m, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.91 (s, 1H), 8.14 (d, *J* = 8.5 Hz, 1H); ¹³C NMR (CDCl₃): δ 39.49, 126.65, 126.87, 127.50, 127.91, 128.57, 128.67, 128.87, 129.24, 129.39, 129.53, 129.70, 132.89, 137.39, 140.34, 141.03, 147.03, 161.13.

4.1.2. 2-Isopropyl-3-phenylquinoline (**3o**)

Solid, m.p. 87–88 °C (from hexane–CHCl₃) (lit. [20] 194–195 °C (picrate)) ¹H NMR (CDCl₃): δ 1.29 (d, *J* = 7.0 Hz, 6H), 3.21–3.24 (sp, 1H), 7.37–7.49 (m, 6H), 7.65–7.69 (m, 1H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.90 (s, 1H), 8.10 (d, *J* = 8.5 Hz, 1H); ¹³C NMR (CDCl₃): δ 22.87, 32.56, 126.27, 126.84, 127.76, 127.78, 128.67, 129.36, 129.77, 135.50, 136.65, 140.68, 147.92, 165.82.

4.1.3. 3-Hexylquinoline (**3s**) [12a]

Oil; ¹H NMR (CDCl₃): δ 0.89 (t, *J* = 6.6 Hz, 3H), 1.29–1.40 (m, 6H), 1.68–1.75 (m, 2H), 2.79 (t, *J* = 7.8 Hz, 2H), 7.49–7.53 (m, 1H), 7.63–7.67 (m, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 1.0 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 8.78 (d, *J* = 2.0 Hz, 1H); ¹³C NMR (CDCl₃): δ 14.04, 22.54, 28.83, 31.07, 31.61, 33.17, 126.46, 127.25, 128.16, 128.44, 129.10, 134.05, 135.35, 146.71, 152.10.

4.1.4. 2-Heptyl-2,4-dihydro-1H-benzo[d][1,3]oxazine (5)

Oil; ^1H NMR (CDCl_3): δ 0.89 (t, $J = 6.8$ Hz, 3H), 1.29–1.34 (m, 8H), 1.43–1.57 (m, 2H), 1.63–1.79 (m, 2H), 4.54 (t, $J = 5.5$ Hz, 1H), 4.80 (d, $J = 14.6$ Hz, 1H), 4.94 (d, $J = 14.6$ Hz, 1H), 6.66 (d, $J = 8.0$ Hz, 1H), 6.79 (t, $J = 7.5$ Hz, 1H), 6.91 (d, $J = 7.5$ Hz, 1H), 7.06 (t, $J = 7.5$ Hz, 1H); ^{13}C NMR (CDCl_3): δ 14.48, 23.04, 24.91, 29.58, 29.87, 32.16, 35.60, 68.06, 84.79, 117.60, 120.02, 123.00, 125.38, 127.71, 141.98. Anal. Calcd for $\text{C}_{15}\text{H}_{23}\text{NO}$: C, 77.21; H, 9.93; N, 6.00. Found: C, 77.37; H, 9.85; N, 5.91%.

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