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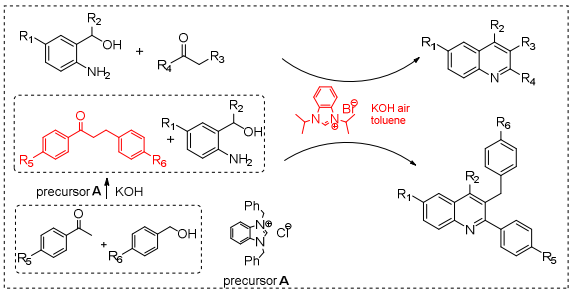
Graphical Abstract



Quinolines have been obtained through the indirect Friendländer annulation starting from 2-aminobenzyl alcohol and ketones catalyzed by *N*-heterocyclic carbene.

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A *N*-Heterocyclic Carbene - Catalyzed Approach to the indirect Friedländer Quinoline Synthesis

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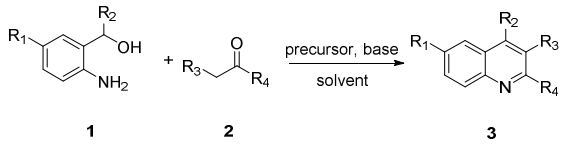
Quinolines have been obtained through the indirect Friendländer annulation starting from 2-aminobenzyl alcohol and ketones catalyzed by *N*-heterocyclic carbene, and the synthesis of polysubstituted quinolines through a one-pot, two-step tandem reaction starting from readily available ketones and alcohols via alpha-alkylation and indirect Friedländer annulation under air also has been presented.

The quinoline scaffold is one of the ubiquitous structures that exist in pharmaceuticals and biologicals. [1] 2-Arylquinoline scaffolds are of particular importance for the construction of a wide range of biologically active molecules, such as P-selectin antagonism, antimalarial, and antitumor activities. [2-6] Because of the diverse pharmacological value of quinolines, a variety of novel and expeditious approaches have been reported in recent years.

Conventional routes for the synthesis of quinolines, such as the Skraup, Doebner–von Miller, Conrad–Limpach, and Pfitzinger syntheses, suffer from harsh reaction conditions, low stereoselectivity or consist of multiple steps, resulting in low overall yields, limiting their applicability. [7] The Friendländer annulation starting from unstable 2-aminobenzaldehyde and ketones has proven to be one of the most simple, straightforward, and widely used ways to develop quinoline compounds. Despite some acids[8-16] have been employed for the reaction, these procedures often suffer from the unstable 2-aminobenzaldehyde[17] and the formation of side products as a result of the self-aldol condensation of the 2-aminoaryl carbonyls. [18]

In order to overcome the drawbacks mentioned before, the transition-metal catalyzed the indirect Friedländer annulation has obtained considerable attention as a useful tool for the synthesis of quinoline compounds, in which the indirect Friedländer reaction using 2-aminobenzyl alcohols instead of 2-aminoaryl carbonyls have emerged as a promising alternative.[19-21] However, this indirect method gave final products contaminated with traces of transition metals, which are limited in some industrial applications. Otherwise, base-mediated indirect Friedländer transformations can also afford quinoline compounds. In 2008, Yus and co-workers [17] reported the t-BuOK (1.0 equiv) catalyzed system with benzophenone (100 mol%) as hydride scavenger in dioxane at 90 °C under an argon atmosphere gave the expected 2-phenyl quinoline in an excellent yield (99%). In the same year, Verpoort and co-workers [22] demonstrated the same example in dioxane using t-BuOK (1.5 equiv) as the catalyst at 80 °C under air with the yield of 94%. And Liang et al. [23] reported this reaction proceed in toluene with t-BuOLi (2.0 equiv) as the catalyst at 110 °C under an argon atmosphere afforded the yield of 94% after 12 h. However, these approaches often suffer from excess bases, high temperature, and sometimes need an atmosphere of argon. Therefore, development of an alternative method for the indirect Friedländer transformations still remains a challenge.

In recent years, *N*-heterocyclic carbenes (NHCs) have received considerable attention as an important and powerful class of organocatalysts[24-26] with tremendous applications in a variety of synthetic transformations and as versatile ligands[27-29] in transition metal catalysis. However, the reaction catalyzed by NHCs employing other substrates was quite limited, [30-32] except aldehydes. [33-39] Herein, we wish to report the indirect Friedländer synthesis of quinolines from aminoalcohol and ketone using NHCs in the presence of a base, without any transition-metal catalyst. (Scheme 1).



Scheme 1. Synthesis of substituted quinolines from 2-aminobenzyl alcohol and ketones.

Our investigation began with the reaction of 2-aminobenzyl alcohol **1a** with acetophenone **2a** catalyzed by precursor **A** in the presence of KOH under air at 60 °C. To our delight, the target annulation product **3a** was obtained (Table 1, entry 1). Consequently, a series of other precursors (Fig.1) were evaluated, wherein precursor **B**

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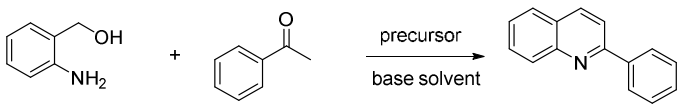
displayed the highest catalytic activity (Table 1, entry 2). Optimal amount of acetophenone **2a** was selected to be two equivalents to **1a** (Table 1, entries 2 and 5). The excess ketone may serve as a hydrogen acceptor, accelerating the oxidation of the alcohol function to an aldehyde. It was found that the bases drastically affected the reaction. An excellent yield (90%) of product **3a** can be achieved when KOH was used (Table 1, entry 2), while, using other weaker bases such as K_2CO_3, NEt_3 and Cs_2CO_3, no reaction occurred (Table 1, entries 6-8). In addition, decreased base dosage was found to afford unsatisfactory yield of **3a** (Table 1, entry 9). With the amount of precursor **B** decreased to 1 mol%, the yield dropped to 80% (Table 1, entry 10). Optimization of solvents for the synthesis of **3a** employing the precursor **B** was also undertaken and it was found that among toluene, DMF, CH_3Cl and dioxane (Table 1, entries 2, 11-13), the best solvent in terms of yield was toluene (Table 1, entry 2). Thus, nonpolar solvents, toluene, chloromethane were proven to be better effective than polar solvents on the reaction. Notably, performing the reaction in the absence of precursor **B** led to a low yield product **3a** (Table 1, entry 14). It should be noted that the indirect Friedländer synthesis of quinolines from aminoalcohol and ketones using NHC catalyst could be proceed readily at a lower temperature and under an atmosphere of air, as compared to those approaches that only using base as catalysts. [17, 22, 23]

Table 1. NHC-Catalyzed optimization of conditions for the reaction of **1a** with **2a**[a]



1a **2a** **3a**

Entry	Precursor	**1**:**2a**	Base (equiv)	Solvent	Isolated Yield[%]
1	**A**	1:2	KOH(1)	toluene	84
2	**B**	**1:2**	**KOH(1)**	**toluene**	**90**
3	**C**	1:2	KOH(1)	toluene	79
4	**D**	1:2	KOH(1)	toluene	82
5	**B**	1:1	KOH(1)	toluene	61
6	**B**	1:2	K_2CO_3(1)	toluene	nr
7	**B**	1:2	NEt_3(1)	toluene	nr
8	**B**	1:2	Cs_2CO_3(1)	toluene	nr
9	**B**	1:2	KOH(0.5)	toluene	69
10 [b]	**B**	1:2	KOH(1)	toluene	80
11	**B**	1:2	KOH(1)	DMF	43
12	**B**	1:2	KOH(1)	CH_3Cl	85
13	**B**	1:2	KOH(1)	dioxane	38
14	-	1:2	KOH(1)	toluene	38

[a] Reaction conditions: **1**, **2a** and precursor (2 mol%) were mixed together in toluene (2 ml） under air and finally base was added, 60 °C, for 1 h. [b] precursor (1mol%) was used.

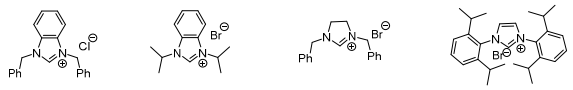
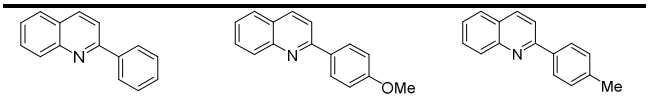


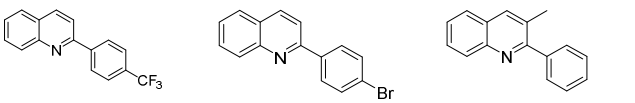
Fig. 1 N-heterocyclic carbene precursors used in the reaction

With the optimized reaction conditions in hand, we set out to explore the substrate scope of this process. In all cases, moderate to excellent yields could be achieved. Both electron-donating substituents including methyl and methoxy groups as well as electron-withdrawing substituents such as bromo and trifluoromethyl groups on the aromatic ring of acetophenone were well tolerated in this reaction (Table 2, **3a-3e**). The quinolines using other aryl ketones with longer chains also could be obtained in excellent yields (**3f**, **3g** in Table 2). In addition, the protocol could be employed also with aliphatic ketones, with similar excellent results (**3h-3l** in Table 2). 2-Acetylpyridine was well tolerated in this reaction to give **3m** in moderate yield. 2-Aminobenzyl alcohols with methyl on the alpha-position also finished the desired products **3n** in good yield. 2-Aminobenzyl alcohol with electron-donating and electron-withdrawing groups on the aromatic ring gave excellent yields of products (**3o**, **3p** in Table 2).

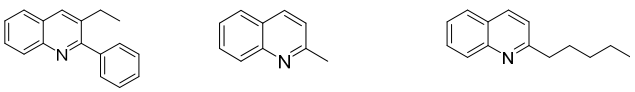
Table 2. Synthesis of quinolines from (2-aminophenyl) methanol and ketones[a]



3a 90% yield **3b** 95% yield **3c** 90% yield



3d 83% yield **3e** 86% yield **3f** 85% yield



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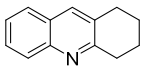
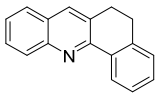
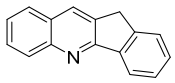
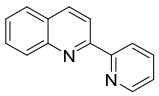
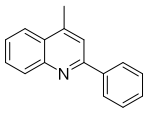
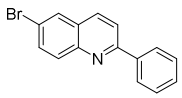
3g 87% yield 

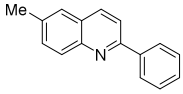
3h 85% yield 

3i 70% yield 

3j 93% yield 

3k 84% yield 

3l 82% yield 

3m 65% yield 

3n 62% yield

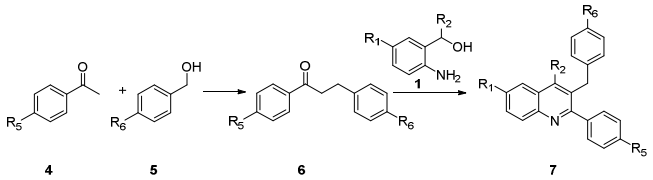
3o 79% yield

3p 95% yield

[a] Reaction conditions: 2-aminobenzyl alcohol (0.5 mmol), **2** (1.0 mmol), precursor **B** (2 mol%), KOH (0.5 mmol), toluene (2 mL), 60 °C, for 1 h, under air. Isolated yield based on 2-aminobenzyl alcohol.

Encouraged by upon results we then envisioned that the use of alpha-alkylation of ketones with alcohols in conjunction with the indirect Friedländer synthesis would be suitable for creating more complicated quinoline compounds. To our delight, this reaction proceeded very smoothly, afforded the corresponding products in moderate to excellent yields. When **4a** was reacted with **5a** in the presence of 0.2 mol % of precursor **A** and 1.0 equiv of KOH at 110 °C (bath temp) for 5 h, the desired α-alkylated ketone **6a** was formed in 98% yield. For the second step, substrates **6a** and 2-aminobenzyl alcohol were reacted at 60 °C for 1 h with the precursor **B** and 1 equiv of KOH to form the product quinoline **7a** in 46 % yield. When **6a** was allowed to react with 2-aminobenzyl alcohol at 80 °C for 4 h, **7a** was produced in 85% yield. After establishing ideal conditions for the one-pot reaction, we investigated the scope of this two-step tandem reaction with various ketones and alcohols catalyzed by NHC. The electronic effect had an obvious influence on this reaction (Table 3, **7a**-**7e**). Electron-rich benzyl ketones and benzyl alcohols have a relatively higher reactivity, affording the corresponding products in good yields (Table 3, **7b**, **7d**). 2-Aminobenzyl alcohol with electron-withdrawing groups on the aromatic ring and methyl on the alpha-position also finished the desired products in good yields (Table 3, **7f**, **7g**). It should be noted that the indirect Friedländer synthesis of quinolines through a one-pot, two-step tandem reaction using NHC catalyst could be proceed readily at a lower temperature and under an atmosphere of air, as compared to the approach.[21]

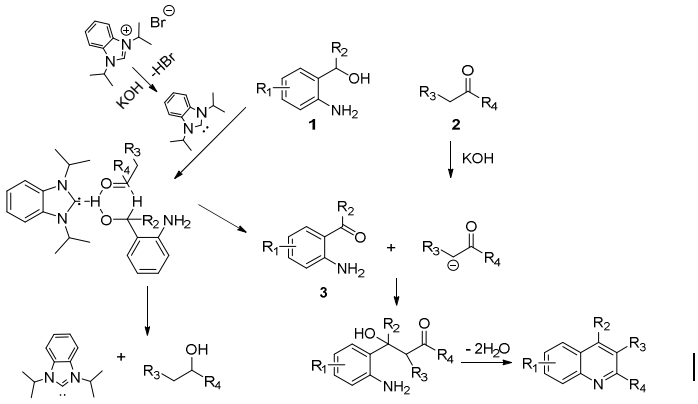
Table 3. NHC-catalyzed coupling of various alcohols with ketones and subsequent addition of 2-aminobenzyl alcohol or derivatives from it to produce quinolines.[a]



Entry	R_1	R_2	R_5	R_6	Quinoline	Isolated yield [%]
1	H	H	H	H	**7a**	85 (46)[b]
2	H	H	H	OMe	**7b**	83
3	H	H	H	Br	**7c**	65
4	H	H	OMe	H	**7d**	81
5	H	H	CF_3	H	**7e**	63
6	H	CH_3	H	H	**7f**	68
7	Br	H	H	H	**7g**	72

[a] Reaction conditions: **5** (0.6 mmol), **4** (0.5 mmol), precursor **A** (0.2 mol%), KOH (0.5 mmol), toluene (1.5 mL), 110 °C, 5 h. This was followed by the addition of 2-aminobenzyl alcohol (0.25 mmol), precursor **B** (2 mol%), KOH (0.25 mmol), 80 °C, 4 h; [b] Reaction conditions: **5** (0.6 mmol), **4** (0.5 mmol), precursor **A** (0.2 mol%), KOH (0.5 mmol), toluene (1.5 mL), 110 °C, 5 h. This was followed by the addition of 2-aminobenzyl alcohol (0.25 mmol), precursor **B** (2 mol %), KOH (0.25 mmol), 60 °C, 4 h.

The proposed mechanism for the reaction is presented in Scheme 2. The base deprotonates *N*-heterocyclic carbene salt to generate a free carbene. The role of NHC may be to assist both proton and hydride transfer from **1** to **2**, forming the intermediate. One equivalent of **2** acts as hydrogen acceptor and is converted to the corresponding alcohol in the oxidation process of **1**. A cross aldol reaction between the **3** and deprotonated ketone, followed by a cyclization step, leads to the quinoline.



Scheme 2. Proposed reaction mechanism and cyclic intermediate.

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Conclusions

We have developed a metal-free NHC-catalyzed indirect Friedländer annulation of ketones with 2-aminobenzyl alcohol to furnish functionalized quinolines in good to excellent yields and the synthesis of 2, 3-substituted quinolines has been achieved through a one-pot, two-step tandem reaction. With its multiple bond-forming ability the present tandem reaction represents an attractive option for the rapid construction of 2, 3-substituted quinolines library based on small organic molecules. The method can avoid products containing toxic metals, makes it a choice for the pharmaceutical and chemical industries.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures and characterization of new products.

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