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Iridium-Catalyzed Synthesis of Quinolines from 2-Aminobenzyl Alcohols with Secondary Alcohols[1]

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Abstract—The quinoline derivatives were synthesized from 2-aminobenzyl alcohols and secondary alcohols by the direct one-step synthesis using the iridium complexes as catalyst. This efficient and easy method is suitable for all kinds of substituted quinolines.

Keywords: iridium, quinolines, secondary alcohols, 2-aminobenzyl alcohols

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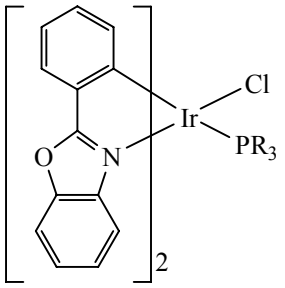
INTRODUCTION

The quinoline derivatives are typical biologically active N-heterocyclic compounds widely used in practice as building block for the synthesis of organic intermediates and molecules and in the modern pharmaceutical and agrochemical industries [1–5]. A straightforward and widely used method of their synthesis is the Friedländer annulation reaction. However, most of these reactions proceed at high temperatures and under harsh conditions [6–9]. In 2003, Cho et al. [10] showed that quinoline derivatives can be synthesized by ruthenium-catalyzed coupling of 2-aminobenzyl alcohol and secondary alcohols by the borrowing hydrogen strategy [11–15]. In 2006, Ramón and Yus also reported $RuCl_2(DMSO)_4$-catalyzed alkylation of secondary alcohols with primary alcohols to synthesize quinolines [16]. Later, they renewed this methodology for the synthesis of polysubstituted quinolines [17]. In 2013, Srimani et al. [18] described the synthesis of pyridines and quinolines by coupling of γ-amino-alcohols with secondary alcohols with liberation of hydrogen in the presence of ruthenium pincer complexes as catalyst. In 2014, Ruch et al. [19] found that iridium can also catalyze this transformation to synthesize quinoline derivatives in moderate to good yield.

Recently, we developed several iridium complexes with the tridentate ligand CNP, which binds with iridium through carbon, nitrogen, and phosphine atoms [20, 21]. These complexes, especially the system benzoxazolyl Ir(III)–CNP complex/$AgNTf_2$, showed good catalytic activities in the C–N and C–C coupling reactions via the borrowing hydrogen strategy (Scheme 2) [22]. Herein, we found that these complexes could also

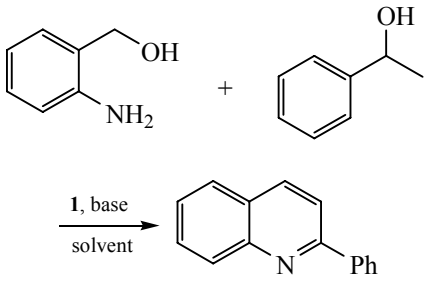
Scheme 1. Several benzoxazolyl Ir(III)-CNP complexes.



1a–1d

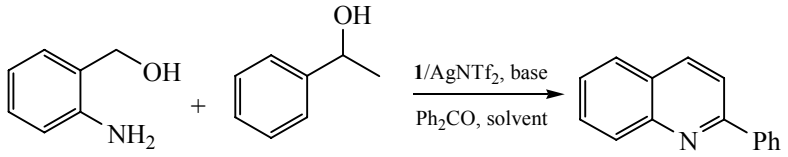
R = Ph (**a**), *p*-tolyl (**b**), *p*-methoxphenyl (**c**), *n*-butyl (**d**).

Scheme 2. Ir-catalyzed coupling of 2-aminobenzyl alcohols and secondary alcohols.



[1] The text was submitted by the authors in English.

Table 1. Screening of reaction conditions[a]



2a **3a** **4a**

Run no.	Iridium	Base	Solvent	Yield[b], %	Run no.	Iridium	Base	Solvent	Yield[b], %
1	**1a**	Cs_2CO_3	Toluene	68	9	**1d**	Cs_2CO_3	Xylene	74
2	**1a**	Cs_2CO_3	THF	61	10	**1a**	NEt_3	Xylene	<5
3	**1a**	Cs_2CO_3	1,4-dioxane	54	11	**1a**	K_2CO_3	Xylene	15
4	**1a**	Cs_2CO_3	Benzene	61	12	**1a**	Na_2CO_3	Xylene	8
5	**1a**	Cs_2CO_3	DCM	66	13	**1a**	KOH	Xylene	47
6	**1a**	Cs_2CO_3	Xylene	72	14	**1a**	*t*-BuONa	Xylene	68
7	**1b**	Cs_2CO_3	Xylene	70	15	**1a**	*t*-BuOK	Xylene	70
8	**1c**	Cs_2CO_3	Xylene	68	16	**1a**	–	Xylene	<5

[a] Conditions: **2a** (1.0 mmol), **3a** (1.1 mmol), **1** (1.0 mol %), $AgNTf_2$ (1.2 mol %), base (2.0 mmol), Ph_2CO (3.0 mmol), solvent (5 mL), 150°C or reflux, 16 h. [b] Isolated yield.

be used in the synthesis of quinoline derivatives with moderate to good yield.

RESULTS AND DISCUSSION

Because the system Ir(III)–CNP complex/$AgNTf_2$ has good catalytic activity in the C–N and C–C coupling reactions [22], we used it to synthesize heterocyclic compounds. 2-aminobenzyl alcohol and 1-phenylethanol were selected as the model substrates for the optimization of catalytic activity. The reaction proceeded in the presence of cesium carbonate as base and benzophenone as hydride scavenger.

The experiment showed that the desired product was separated in 68% yield (Table 1, run no. 1). Results obtained in screening the reaction conditions are summarized in Table 1. It was found in the experiment that the best solvent is xylene. For all iridium complexes the results were the same, whereas complex **1d** was somewhat better than the other complexes. Next, it was found that cesium carbonate is superior to other bases by yield.

With the best reaction conditions in hand, we studied the reaction scope of all kinds of 2-aminobenzyl alcohols and secondary alcohols. In general, the experiments showed that the reaction could carry on smoothly. The results are summarized in Table 2. In most cases, moderate to good yields were obtained under the above optimal conditions. The change in the substituent group on secondary alcohols did not virtually affect the reaction. The best yield of up to 81% was obtained with the methoxy group in 2-aminobenzyl alcohols.

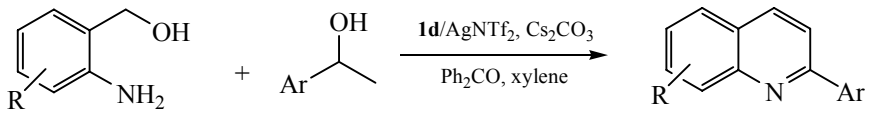
EXPERIMENTAL

Typical procedure for the synthesis of 4a. To a solution of **2d** (1 mol %) in xylene (5 mL), $AgNTf_2$ (1.2 mol %) was added and the mixture was stirred for 5 min. Then, 2-aminobenzyl alcohol (1 mmol), 1-phenylethanol (1.1 mmol), cesium carbonate (2.0 mmol), and benzophenone (3 mmol) were added. The mixture was heated under reflux for 16 h and then cooled to room temperature. The resulting solution was directly purified by column chromatography with petroleum ether–ethyl acetate (5 : 1) as eluent to give the desired product.

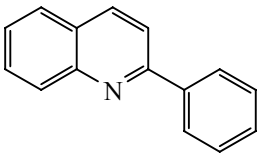
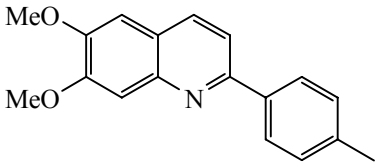
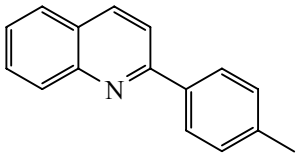
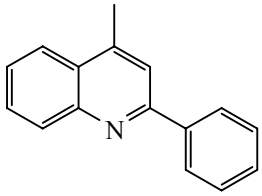
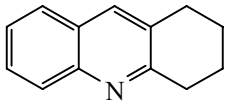
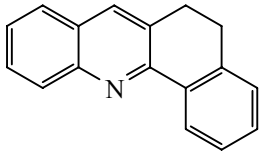
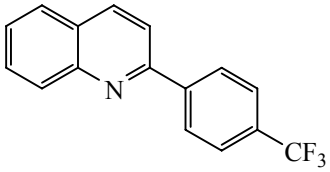
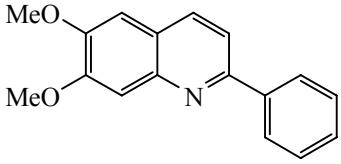
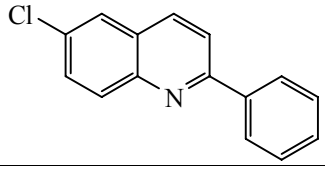
2-Phenylquinoline (4a). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 8.11 m (4H), 7.76 m (2H), 7.62 t (1H, J = 7.8 Hz), 7.51–7.29 m (4H).

2-(*p*-Tolyl)quinoline (4b). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 8.11 t (2H, J = 7.9 Hz), 7.98 d (2H, J = 7.8 Hz), 7.75 d.d (2H, J = 16.2, 8.1 Hz), 7.64 t (1H, J = 7.9 Hz), 7.43 t (1H, J = 7.8 Hz), 7.26 d (2H, J = 8.0 Hz), 2.34 s (3H).

Table 2. Substrate expansion experiments[a,b]



2 **3** **4**

Comp. no.	Formula	Yield, %	Comp. no.	Formula	Yield, %
4a		74	**4f**		73
4b		63	**4g**		62
4c		71	**4h**		53
4d		67	**4i**		81
4e		64			

[a] Conditions: **2** (1.0 mmol), **3** (1.1 mmol), **1d** (1.0 mol %), $AgNTf_2$ (1.2 mol %), base (2.0 mmol), Ph_2CO (3.0 mmol), xylene (5 mL), 150°C, 16 h. [b] Isolated yield based on **2**.

1,2,3,4-Tetrahydroacridine (4c). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.91 d (1H, *J* = 7.8 Hz), 7.71 s (1H), 7.62 d (1H, *J* = 8.0 Hz), 7.53 t (1H, *J* = 7.8 Hz), 7.35 t (1H, *J* = 7.9 Hz), 3.04 t (2H, *J* = 8.0 Hz), 2.89 t (2H, *J* = 7.8 Hz), 1.93–1.86 m (2H), 1.83–1.78 m (2H).

2-[4-(Trifluoromethyl)phenyl]quinoline (4d). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 8.25–8.07 m (4H), 7.76 t (2H, *J* = 7.8 Hz), 7.67 t (3H, *J* = 7.8 Hz), 7.47 t (1H, *J* = 8.1 Hz).

6-Chloro-2-phenylquinoline (4e). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 8.12–7.96 m (4H), 7.75 d (1H, *J* = 8.0 Hz), 7.68 s (1H), 7.53 d (1H, *J* = 8.0 Hz), 7.41 m (3H).

6,7-Dimethoxy-2-(*p*-tolyl)quinoline (4f). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.96–7.86 m (3H), 7.59 d (1H, *J* = 7.8 Hz), 7.41 s (1H), 7.21 d (2H, *J* = 8.0 Hz), 6.92 s (1H), 3.95 s (3H), 3.91 s (3H), 2.33 s (3H).

4-Methyl-2-phenylquinoline (4g). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 8.09 d.d (3H, *J* = 12.0, 8.0 Hz), 7.93 d (1H, *J* = 7.8 Hz), 7.63 d (2H, *J* = 8.0 Hz), 7.51–7.37 m (4H), 2.68 s (3H).

5,6-Dihydrobenzo[*c*]acridine (4h). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 8.49 d (1H, *J* = 7.8 Hz), 8.04 d (1H, *J* = 8.0 Hz), 7.78 s (1H), 7.62 d (1H, *J* = 7.8 Hz), 7.54 t (1H, *J* = 8.1 Hz), 7.39–7.24 m (3H), 7.19–7.14 m (1H), 3.03–2.94 m (2H), 2.93–2.85 m (2H).

6,7-Dimethoxy-2-phenylquinoline (4i). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 8.03 d (2H, *J* = 8.0 Hz), 7.90 d (1H, *J* = 7.8 Hz), 7.61 d (1H, *J* = 7.9 Hz), 7.41 t (3H, *J* = 7.8 Hz), 7.33 t (1H, *J* = 7.8 Hz, 6.93 s (1H), 3.96 s (3H), 3.91 s (3H).

CONCLUSIONS

In conclusion, an efficient method for synthesizing quinolines from 2-aminobenzyl alcohols and secondary alcohols was developed. The reaction proceeds actively in the presence of the system Ir(III)–CNP complex/$AgNTf_2$ with moderate to good yield. This methodology provides alternative method to prepare quinoline derivatives.

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