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Synthesis of quinolines from amino alcohol and ketones catalyzed by $[IrCl(cod)]_2$ or $IrCl_3$ under solvent-free conditions

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Abstract—2-Aminobenzyl alcohol reacted with 2 equiv amount of ketones under the influence of $[IrCl(cod)]_2$ or $IrCl_3$ and KOH without any solvent, giving the corresponding quinoline derivatives in good yields.

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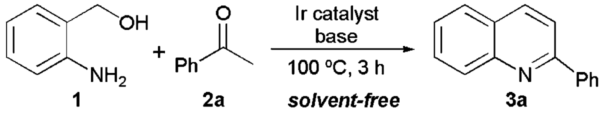
1. Introduction

The preparation of nitrogen-containing aromatic compounds such as quinolines and pyrroles has been extensively studied in synthetic organic chemistry, because these compounds are important as biologically active compounds.[1] Among several routes to quinoline syntheses, coupling of 2-aminobenzaldehyde with ketone, namely, the Friedländer reaction, is one of the most widely used methods due to high selectivity of the products.[2] Recently, the ruthenium-catalyzed modified Friedländer reaction has been reported by Cho and Shim et al. where 2-aminobenzyl alcohol, which is cheaper and more stable than 2-aminobenzaldehyde, is allowed to react with ketones or secondary alcohols in the presence of 1-dodecene as a hydrogen acceptor to form quinoline derivatives.[3] They showed that $RuCl_2(=CHPh)(PCy_3)_2$ is an efficient catalyst and that various quinolines can be synthesized in good yields. But, the reaction requires the use of both a stoichiometric amount of KOH and a solvent like dioxane which is a carcinogenic compound. Quite recently, Kaneda and co-workers reported a similar reaction of 2-aminobenzyl alcohol and ketones catalyzed by Ru-grafted hydrotalcite in toluene using dioxygen as a hydrogen acceptor under base-free conditions.[4]

Previously, we reported the high selective α-alkylation of ketones with alcohols catalyzed by an iridium complex.[5] This reaction is environmentally benign in a sense of green chemistry, since the reaction took place well without the solvent. Here, we would like to disclose that our reaction system could be applied to quinoline synthesis by the coupling reaction of 2-aminobenzyl alcohol with ketones in the presence of small amounts of $[IrCl(cod)]_2$ and a base under solvent-free conditions. It was found that even $IrCl_3$, which is a starting material for preparing $[IrCl(cod)]_2$, facilitated the coupling reaction. Additionally, pyrroles were synthesized by the reaction of 2-aminoethanols with ketones under the influence of an Ir complex as a catalyst.

The reaction of 2-aminobenzyl alcohol (**1**) with acetophenone (**2a**) was chosen as a model reaction and examined under selected conditions (Scheme 1, Table 1).

Treatment of **1** with 2 equiv of **2a** in the presence of catalytic amounts of $[IrCl(cod)]_2$ (1 mol%), PPh_3 (4 mol%) and KOH (20 mol%) at 100 °C for 3 h without a solvent gave 2-phenylquinoline (**3a**) in 90% yield (98% selectivity) at 92% conversion of **1** (run 1). In this reaction, a half-amount of **2a** used was found to be converted into 1-phenylethanol, indicating that **2a** acts as a hydrogen acceptor. In the absence of PPh_3, **3a** was obtained in slightly lower yield (run 2). Surprisingly, the reaction was catalyzed even by $IrCl_3$ which is a synthetic



Scheme 1. The modified Friedländer reaction.

Keywords: Iridium; Quinoline; Amino alcohol; Ketone.

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Table 1. Coupling reaction of **1** with **2a** to **3a** under selected reaction conditions[a]

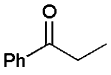
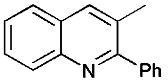
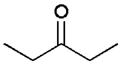
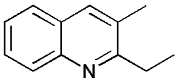
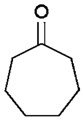
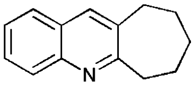
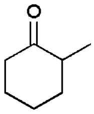
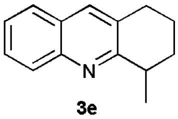
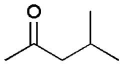
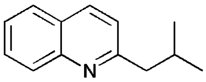
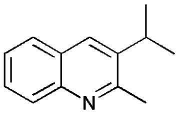
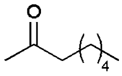
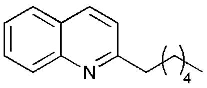
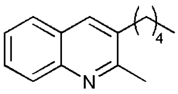
Run	Catalyst	Base	Conv. (%)[b]	Yield[b] (%)
1	$[IrCl(cod)]_2$	KOH	92	90
2[c]	$[IrCl(cod)]_2$	KOH	85	82
3[c]	$IrCl_3$	KOH	89	85
4[c]	$[IrCl(coe)_2]_2$	KOH	80	75
5[c]	$[Cp^*IrCl_2]_2$	KOH	82	74
6[c]	$[IrCOCl(PPh_3)_2]$	KOH	76	73
7	$[IrCl(cod)]_2$	K_2CO_3	11	8
8	$[IrCl(cod)]_2$	Cs_2CO_3	51	47

[a] Compound **1** (2 mmol) was allowed to react with **2a** (4 mmol) in the presence of catalyst (0.04 mmol Ir), PPh_3 (0.08 mmol) and base (0.4 mmol) at 100 °C for 3 h under solvent-free conditions.

[b] Based on **1** used.

[c] Without PPh_3.

Table 2. Ir-catalyzed coupling reaction of **1** with several ketones **2b–g** under solvent-free conditions[a]

Run	Ketone	Product	Conv. (%)[b]	Yields[b] (%)
1	 **2b**	 **3b**	86 (80)	80 (74)
2	 **2c**	 **3c**	85 (61)	76 (53)
3	 **2d**	 **3d**	91 (81)[c]	91 (77)[c]
4	 **2e**	 **3e**	82 (79)[c]	78 (72)[c]
5	 **2f**	 **3f**	82 (80)[c]	74 (75)[c]
		 **3′f**		6 (4)[c]
6	 **2g**	 **3g**	85 (79)	63 (56)
		 **3′g**		22 (23)

[a] Compound **1** (2 mmol) was allowed to react with ketone **2b–g** (4 mmol) in the presence of $[IrCl(cod)]_2$ (0.02 mmol), PPh_3 (0.08 mmol) and KOH (0.4 mmol) at 100 °C for 3 h under solvent-free conditions.

[b] Based on **1** used. Numbers in parentheses show the conversion and yield using $IrCl_3$ (0.04 mmol) in place of $[IrCl(cod)]_2$ without PPh_3.

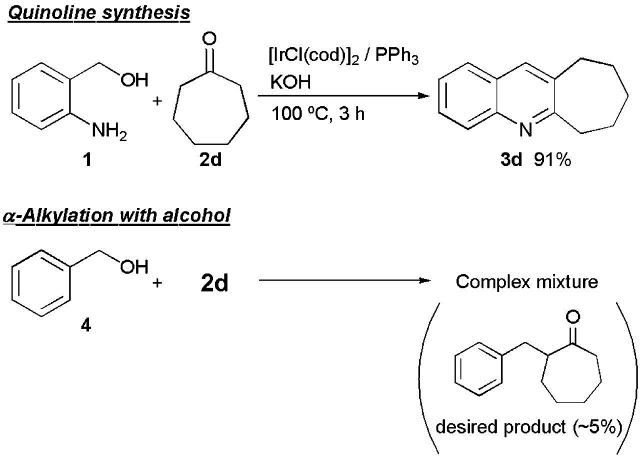
[c] In the case of the reaction catalyzed by $IrCl_3$, the reaction was performed at 115 °C.

precursor of $[IrCl(cod)]_2$. When **1** was allowed to react with **2a** in the presence of $IrCl_3$ (2 mol%) and KOH (20 mol%), **3a** was obtained in satisfactory yield without a solvent (run 3). Although the ruthenium-catalyzed modified Friedländer reaction reported by Cho et al.[3] or Kaneda and co-workers[4] required the use of more complicated ruthenium compounds as catalysts, the present reaction proceeded by employing a commercially available iridium salt such as $IrCl_3$ without any further treatment under solvent-free conditions. Therefore, the present work provides an operationally simple methodology for quinoline synthesis.

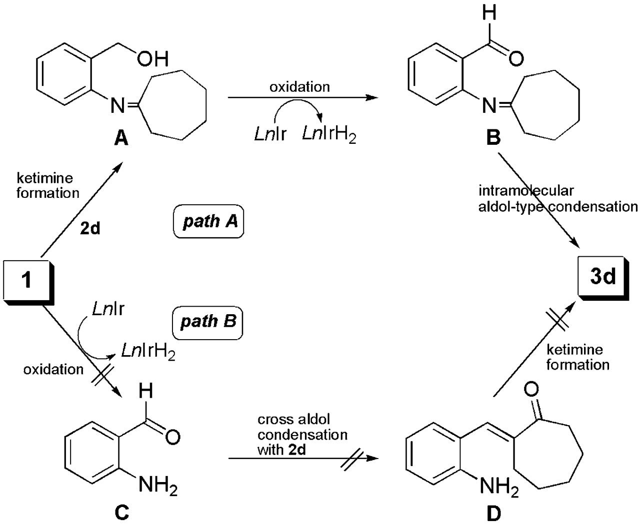
Other iridium complexes such as $[IrCl(coe)_2]_2$, $[Cp^*IrCl_2]_2$ and $[IrCOCl(PPh_3)_2]$ were also effective for the modified Friedländer reaction affording **3a** in 73–75% yields (runs 4–6). The use of K_2CO_3 in place of KOH resulted in low conversion of **1**, whereas Cs_2CO_3 led to **3a** in moderate yield (runs 7 and 8).

Next, the iridium-catalyzed coupling of **1** with several ketones was carried out under solvent-free conditions (Table 2). In a similar manner as the reaction of **1** with **2a**, it was found that propiophenone (**2b**), diethyl ketone (**2c**), cycloheptanone (**2d**), and 2-methylcyclohexanone (**2e**) reacted with **1** to give the corresponding quinoline derivatives (**3b–e**) in good yields (runs 1–4). Notably, $IrCl_3$ and $[IrCl(cod)]_2$ indicated high catalytic activity for the modified Friedländer reaction. The coupling of **1** with 4-methyl-2-pentanone (**2f**) or 2-octanone (**2g**) was difficult to carry out regioselectively to afford a regioisomeric mixture of the corresponding quinoline derivatives (runs 5 and 6).

It is noteworthy that the coupling reaction of **1** with cycloheptanone (**2d**) was smoothly catalyzed by an iridium complex forming **3d** in excellent yield (Table 2, run 3 and Scheme 2). We previously reported the α-alkylation of ketone with alcohol catalyzed by $[IrCl(cod)]_2$ in the presence of a small amount of KOH,[5] but the reaction of benzyl alcohol (**4**) with **2d** failed to proceed selectively to lead to a complex mixture involving α-benzylcycloheptanone and some undesired self-aldol condensation products of **2d**, etc. (Scheme 2). These results may suggest that **3d** is formed through the following reaction pathway (Scheme 3). The reaction is initiated by the formation of ketimine (**A**) from **1** and **2d** (path A), and **A** thus formed is oxidized under the influence of an Ir catalyst and **2d** which serves as a hydrogen acceptor giving the corresponding aldehyde **B**, which is eventually converted into **3d** through intramolecular aldol-type condensation. As another possible pathway, it may be assumed that the hydroxyl group of **1** is first oxidized to 2-aminobenzaldehyde (**C**), followed by the cross-aldol condensation between **C** and **2d** to generate **D**, which then is transformed into **3d** (path



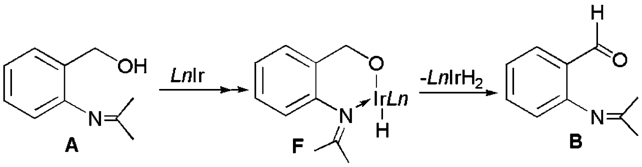
Scheme 2. Ir-catalyzed reaction of 2-aminobenzyl alcohol (**1**) or benzyl alcohol (**4**) with **2d**.



Scheme 3. A possible reaction pathway for the Ir-catalyzed reaction of **1** with **2d**.

B). If the dehydrogenation of an alcohol function to aldehyde followed by the cross-aldol condensation with **2d** easily takes place, the reaction of **4** with **2d** is expected to occur smoothly. However, the reaction is difficult to proceed as shown in Scheme 2. Therefore, we assume that path A is preferable to path B in the reaction of **1** with **2d** and that the initial formation of ketimine **A** from **1** and **2d** is an important factor.

Again, the present quinoline synthesis from **1** with various ketones was successfully achieved even by the use of $IrCl_3$ as a catalyst, while almost no reaction of α-alkylation of ketone with alcohols took place by $IrCl_3$.[5] In the reaction of **1** with ketones catalyzed by an Ir compound, the formation of a six-membered iridium hydride complex **F**, in which a ketimine group of **A** generated from 2-aminobenzyl alcohol (**1**) and ketone coordinates to an iridium species, seems to be the driving force as shown in Scheme 4. The β-hydride elimination from **F** would afford the corresponding aldehyde **B** and iridium dihydride. Thus, the coupling reaction of **1** with ketone could proceed even by the use of $IrCl_3$ as a catalyst.

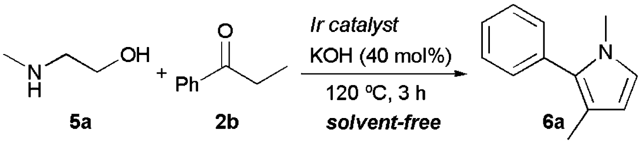


Scheme 4. A possible route for the formation of **B** from **A** by an Ir compound.

Finally, it was found that the present catalytic system could be applied to pyrrole synthesis. *N*-Methyl-3-methyl-2-phenylpyrrole (**6a**) was prepared by the reaction of *N*-methyl-2-aminoethanol (**5a**) with **2b** in the presence of small amounts of an iridium compound and a base under solvent-free conditions. Choice of the ligand was found to be important for this reaction, and the best result was obtained when **5a** was allowed to react with **2b** catalyzed by $[IrCl(cod)]_2$ combined with 2-(diphenylphosphino)ferrocene (dppf) and KOH at 120 °C for 3 h, forming **6a** in 70% yield (Scheme 5).

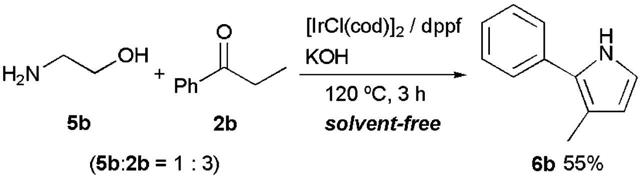
Similarly, treatment of 2-aminoethanol (**5b**) with **2b** afforded 3-methyl-2-phenylpyrrole (**6b**) in 55% yield (Scheme 6).

In summary, we have shown that the oxidative coupling of 2-aminobenzyl alcohol with ketones was promoted in



Ir-catalyst	yield (%)
$[IrCl(cod)]_2$ / PPh_3	48
$[IrCl(cod)]_2$ / PCy_3	55
$[IrCl(cod)]_2$ / dppf	70
$[IrCl(cod)]_2$	39
$IrCl_3$ / dppf	35
$IrCl_3$	40

Scheme 5. Reaction of **5a** with **2b**. Compound **5a** (2 mmol) was allowed to react with **2b** (4 mmol) in the presence of catalyst (0.03 mmol Ir) and KOH (0.8 mmol) at 120 °C for 3 h under solvent-free conditions. PPh_3 (0.12 mmol), PCy_3 (0.12 mmol) or dppf (0.06 mmol) was used, respectively.



Scheme 6. Reaction of **5b** with **2b**.

the presence of catalytic amounts of an iridium complex such as $[IrCl(cod)]_2$ and $IrCl_3$ and KOH under solvent-free conditions. The present catalytic system could apply to the synthesis of pyrrole from β-aminoalcohol and ketone.

2. Experimental section

All starting materials were commercially available and used without any purification. GLC analysis was performed with a flame ionization detector using a 0.2 mm × 25 m capillary column (OV-1). ^1H and ^{13}C NMR were measured at 270 or 400 MHz and 67.5 MHz, respectively, in $CDCl_3$ with Me_4Si as an internal standard.

2.1. General procedure for reaction of 1 with 2a

To a mixture of $[IrCl(cod)]_2$ (0.02 mmol), PPh_3 (0.08 mmol) and KOH (0.4 mmol) were added **1** (2 mmol) and **2a** (4 mmol) under Ar. The reaction mixture was stirred at 100 °C for 3 h. The product was isolated by column chromatography (230–400 mesh silica gel, *n*-hexane–ethyl acetate = 20:1). The yields of the products were estimated from the peak areas based on the internal standard technique using GC.

Acknowledgments

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