Synthesis of *β*-Amino Ketones by Iridium(III)-catalyzed Direct-Mannich Reaction

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The direct-Mannich reaction of ketones **1**, aldehydes **2**, and anilines **3** was studied using catalytic amount of transition-metal complexes. The trivalent iridium complex, $[IrCl_2(H)(cod)]_2$, catalyzed the direct-Mannich reaction effectively to give various β-amino kenotes in good yields under mild conditions.

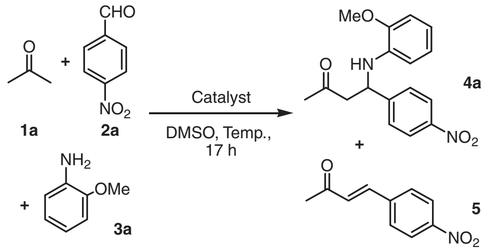
Carbon–carbon bond forming reactions utilizing transition-metal catalysts which proceed under mild conditions are useful tools for production of organic compounds in environmentally benign way. In recent years, multicomponent coupling reactions (MCRs) have attracted much attention because the complex molecules form in one pot and chemical diversity can be achieved with ease.[1] Reaction of amines and carbonyl compounds known as the Mannich reaction involving the sequential formation of C–N bond and C–C bond is one of the most useful multicomponent coupling reactions.[2] However, to execute the reaction for complicated organic compounds fine tunings of reaction conditions are necessary. So far several reactions, which are promoted or catalyzed by Lewis acids,[3] lanthanides,[4] early transition metals,[5] and organocatalysts,[6] are developed. However, late transition metals or noble metals,[7] which tolerate a wide variety of organic compounds having functional groups, are recognized to be inactive as catalysts for the Mannich reaction. Recently, Xia et al. reported $AuCl_3$–PPh_3 is effective for N-protected β-amino ketone synthesis.[8] In our study to develop transition metal-catalyzed reactions, we have found a trivalent Ir complex catalyzed the Mannich reaction although most of the late transition metals are not effective including Ir(I) complex.

At first, reaction of acetone (**1a**), *p*-nitrobenzaldehyde (**2a**), and *o*-anisidine (**3a**) was studied using catalytic amount of transition-metal complexes. In a typical experiment, to a mixture of the catalyst (0.025 mmol), **2a** (0.5 mmol), and **3a** (0.55 mmol) in DMSO (2 mL) was added **1a** (3 mL) and the mixture was stirred for 17 h. The phosphate buffer saline was added to the mixture and the product was extracted with ethyl acetate and purified by column chromatography. As representative results of the reactions are shown in Table 1, when $[Rh(cod)Cl]_2$ and $[Ru(cod)Cl_2]_2$ (cod = cyclooctadiene) were used as catalysts β-amino ketone **4a** was obtained in 21 and 18% yields, respectively. $[Ir(cod)Cl]_2$ and $[Ir(cod)(OMe)]_2$ scarcely have catalytic activity. However, the reaction using the trivalent iridium complex, $[IrCl_2(H)(cod)]_2$, proceeded smoothly to give **4a** in 64% yield although $IrCl_3$ and $Ir(acac)_3$ (acac = acetylacetonato) are inactive. Ytterbium triflate did not give a satisfactory result.[4]

Furthermore, $TiCl_4$, a typically used Lewis acid, gave β-amino ketone **4a** in 48% yield, but the undesired enone **5** by aldol condensation was obtained in 14% yield. When conc. HCl was used, the enone **5** was obtained as the major product.

The reaction with $[IrCl_2(H)(cod)]_2$ proceeded at 0 °C in 57% yield, but in the reaction at 90 °C the yield of **4a** decreased dramatically and the enone **5** was obtained in 54% yield. In the absence of catalyst the reaction of **1**, **2a**, and **3a** proceeded at 90 °C to give the enone **5** in 55% yield. The role of the catalyst is ambiguous. However, it should be noted that the Ir(III) catalyst is not strong enough to catalyze the aldol reaction but the imine was readily activated with an Ir(III) complex. Indeed, reaction of **1** and **2a** was carried out with $[IrCl_2(H)(cod)]_2$, no formation of **5** was observed.

Table 1. Activity of catalysts for direct-Mannich reaction



Catalyst (mol % based on **2a**)	Temp./°C	Yield/%[a]	
		4a	**5**
$[Rh(cod)Cl]_2$ (5.0)	rt	21	—[b]
$[Ru(cod)Cl_2]_2$ (5.0)	rt	18	—[b]
$[Ir(cod)Cl]_2$ (5.0)	rt	—[b]	—[b]
$[Ir(cod)(OMe)]_2$ (5.0)	rt	0	—[b]
$IrCl_3$ (10)	rt	6	—[b]
$Ir(acac)_3$ (10)	rt	7	—[b]
$[IrCl_2(H)(cod)]_2$ (5.0)	0	57	—[b]
	rt	64	9
	90	0	54
$Yb(OTf)_3$ (10)	rt	39	—[b]
$TiCl_4$ (10)	rt	48	14
conc. HCl	rt	15	37
Blank	90	16	55

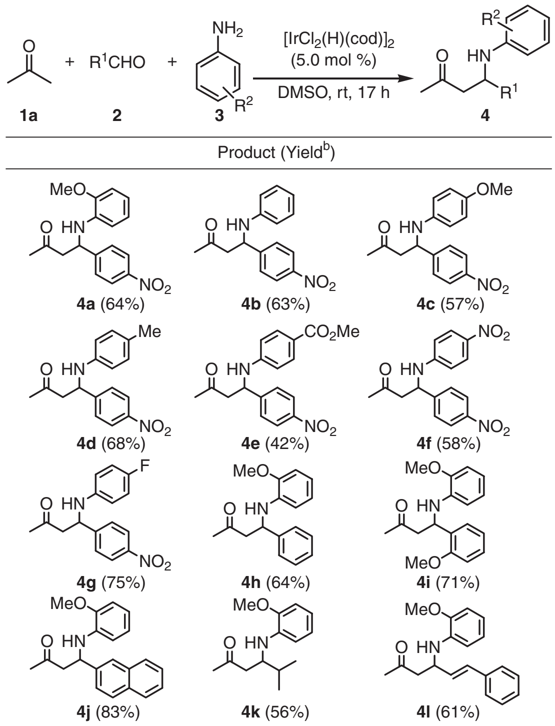
[a]Yield based on **2a**. [b]Not isolated, only detected by TLC.

Various solvents can be used for this reaction at 0 °C. Polar solvents such as DMSO, THF, and acetonitrile, are suitable for smooth reaction, and the product **4a** was obtained in 57, 43, and 41%, respectively. However, less polar solvent such as dichloromethane (26%) and toluene (24%) did not give satisfactory results. Acetone was used not only as the substrate but as solvent in this case to give the product in 46% yield.

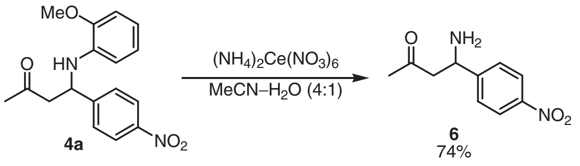
The generality of the reaction to prepare β-amino ketones was examined using several substrates having a variety of functional groups (Table 2). 4-amino-4-Aryl-2-butanones, **4a**–**4l** were obtained in moderate to good yields in one pot starting from acetone and the corresponding aldehydes **2** and aromatic amines **3**. When aliphatic amines, such as cyclohexylamine, piperidine, and phenethylamine, were used as amine components, the reaction did not proceed.

Various aromatic amines were prepared in this reaction. The primary amine can be obtained by removal of the *o*-methoxyphenyl group (OMP). As shown in Scheme 1, the OMP was removed oxidatively with treatment of cerium ammonium nitrate

Table 2. Results of Ir-catalyzed direct-Mannich reaction[a]



[a] **1a** (3 mL), **2** (0.5 mmol), **3a** (0.55 mmol), and DMSO (2 mL) were used. [b] Yield based on **2**.



Scheme 1. Removal of OMP group with treatment of CAN.

(CAN) to give **6** in 74% yield.

The reaction with 2-butanone or hydroxyacetone instead of acetone was carried out (Table 3). The regioisomers, **4m** and **4n**, were obtained in the 3:1 ratio in the case of 2-butanone. The major ketone **4m** was found to be a 2:3 mixture of syn and anti diastereomers. But in the reaction of hydroxyacetone the α-hydoxy-β-amino ketone was obtained as a 7:5 diastereo mixture of syn and anti isomers without the regioisomer.

In conclusion, we have found the iridium complexes as new catalysts for the direct-Mannich reaction. $[IrCl_2(H)(cod)]_2$ is the most suitable catalyst in DMSO and the variety of β-amino ketones are obtained under mild conditions.

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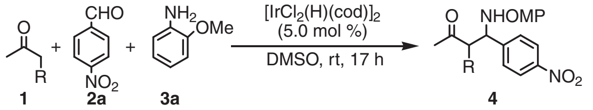
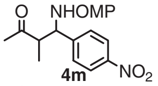
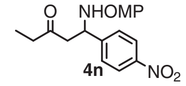
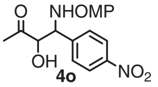
Table 3. Ir-catalyzed direct-Mannich reaction with methyl ketones[a] (OMP = *o*-methoxyphenyl)



Entry	R	Product	Yield/%[b]	Dr syn:anti[c]
1	Me	 **4m**  **4n**	50 (**4m**:**4n** = 3:1)[d]	2:3
2	OH	 **4o**	75	7:5

[a] **1** (1 mL), **2a** (0.5 mmol), **3a** (0.55 mmol), and DMSO (4 mL) were used. [b] Yield based on **2a**. [c] Determined by ^{1}H NMR. [d] Determined by GC/MS.

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