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Iridium-Catalyzed Cascade Dehydrogenation, Ring-Closure Reaction Leading to 2,4,6-Triaryl-1,3,5-triazines[1]

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Abstract—An efficient iridium-catalyzed dehydrogenation, ring-closure reaction, has been developed via a cascade sequence, in which $[Cp^*IrI_2]_2$/Xantphos proved to be the most efficient catalyst for the synthesis of 2,4,6-triaryl-1,3,5-triazines from stable aryl-substituted alcohols and amidines. It was the first case of iridium catalyst successful application in such transformation.

Keywords: iridium catalysis, ring-closure reaction, dehydrogenation, 2,4,6-triaryl-1,3,5-triazines

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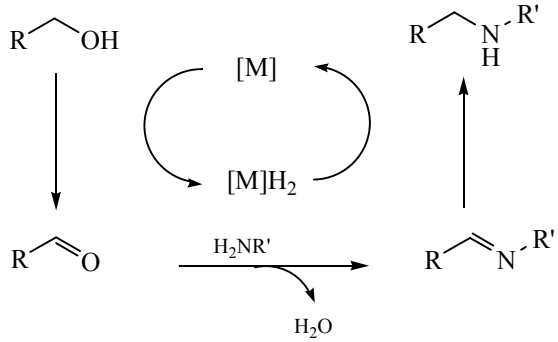
INTRODUCTION

The cascade reactions [1] are considered to be a powerful tool in organic chemistry as an efficient approach to desired or natural compounds based on relatively simple starting materials. A domino or cascade sequence can also lead to an increase in molecular complexity by combining a series of reactions in one synthetic procedure. Possibility of designing a "one-pot" sequence for constructing complex molecules is highly favorable for chemists. Among the reported methods, the Michael addition, the Henry reaction and/or aldol reaction are often used in a cascade manner for the purpose of obtaining the desired compounds.

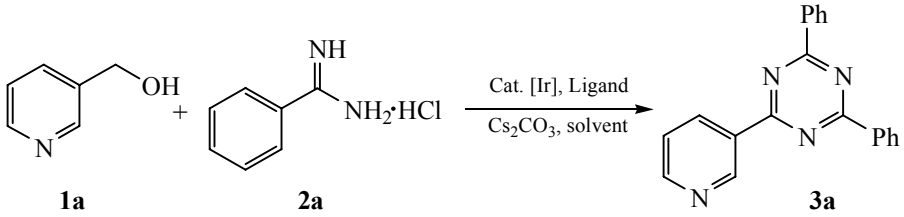
Recently, borrowing hydrogen strategy has attracted considerable attention because it provides an economically and environmentally sensible alternative to the conventional alkylation of amines [2]. Under the conditions of borrowing hydrogen methodology alcohols are easily converted *in situ* into aldehydes or ketones, that are more reactive than alcohols and easily react with amines (Scheme 1) [3]. Although borrowing hydrogen is considered to be a well-studied reaction, dehydrogenation, as its first step, might lead the reaction along a different reaction pathway if the coupling partner is changed. Given this possibility, we were encouraged to determine whether amidines could undergo such transformation being common commercially available compounds. Aryl-substituted 1,3,5-triazines are important heterocycles that exhibit diverse biological activity [4, 5]. In 2002 Díaz-Ortiz et al. [6] reported the synthesis of 1,3,5-triazines under solvent-free conditions catalyzed by silica-supported Lewis acids. Achelle et al. [7] synthesized 1,3,5-triazines with moderate yield via the Suzuki cross-coupling reaction. Such transformation to 1,3,5-triazines could also be performed from aldehydes [8]. The straightforward method of synthesis of 2,4,6-triaryl-1,3,5-triazines was carried out via copper-catalyzed cyclization of *N*-benzyl-benzamidine [9]. Recently, Xie et al. developed the ruthenium-catalyzed synthesis of

Scheme 1. Borrowing hydrogen reaction catalyzed by a transition metal.



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

Table 1. Screening of reaction conditions[a]



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

Entry no.	Catalyst	Ligand	Solvent	Yield[b], %	Entry no.	Catalyst	Ligand	Solvent	Yield[b], %
1	–	–	DMSO	<5	11	$[Cp^*IrI_2]_2$	**L1**	Dioxane	71
2	$IrCl_3$	–	DMSO	15	12	$[Cp^*IrI_2]_2$	**L2**	Dioxane	77
3	$[(COD)IrCl]_2$	–	DMSO	32	13	$[Cp^*IrI_2]_2$	**L3**	Dioxane	73
4	$[Cp^*IrCl_2]_2$	–	DMSO	46	14	$[Cp^*IrI_2]_2$	**L4**	Dioxane	81
5	$[Cp^*IrI_2]_2$	–	DMSO	58	15[c]	$[Cp^*IrI_2]_2$	**L4**	Dioxane	41
6	$[Cp^*IrI_2]_2$	–	Toluene	37	16[d]	$[Cp^*IrI_2]_2$	**L4**	Dioxane	69
7	$[Cp^*IrI_2]_2$	–	Xylene	35	17[e]	$[Cp^*IrI_2]_2$	**L4**	Dioxane	62
8	$[Cp^*IrI_2]_2$	–	DMF	47	18	$[Cp^*IrI_2]_2$	**L4**	TBME	21
9	$[Cp^*IrI_2]_2$	–	DMAc	49	19	$[Cp^*IrI_2]_2$	**L4**	THF	8
10	$[Cp^*IrI_2]_2$	–	Dioxane	66	20	$[Cp^*IrI_2]_2$	**L4**	Et_2O	<5

[a] Reaction conditions: **1a** (2.0 mmol), **2a** (1 mmol), Cat. [Ir] (1 mol %), ligand (2 mol %), Cs_2CO_3 (1 mmol), solvent (2 mL), 110°C or reflux, 20 h. [b] Isolated yield. [c] Reaction temperature 80°C. [d] Reaction temperature (140°C). [e] [Ir] (0.5 mol %).

2,4,6-triaryl-1,3,5-triazines [10a]. Here, we report the synthesis of aryl substituted 1,3,5-triazines via iridium-catalyzed dehydrogenation, ring-close cascade reaction giving mo-derate to high yields of products (Scheme 2).

RESULTS AND DISCUSSION

The cascade dehydrogenation, ring-close reaction of 3-pyridinemethanol (**1a**) was initiated by benz-amidine hydrochloride (**2a**) for testing the reaction activity upon catalysis by iridium (Table 1). The reaction was initially conducted by using 1 equiv. of Cs_2CO_3 in DMSO. Such procedure did not give even trace amounts of the expected product (Table 1, entry 1). The desired product was isolated with the yield 15% in case 1 mol % of $IrCl_3$ was introduced into the reaction (Table 1, entry 2). Subsequently, the iridium catalysts with DMSO as a solvent were tested. In that case

Scheme 2. Iridium-catalyzed cascade dehydrogenation ring-closure reaction.

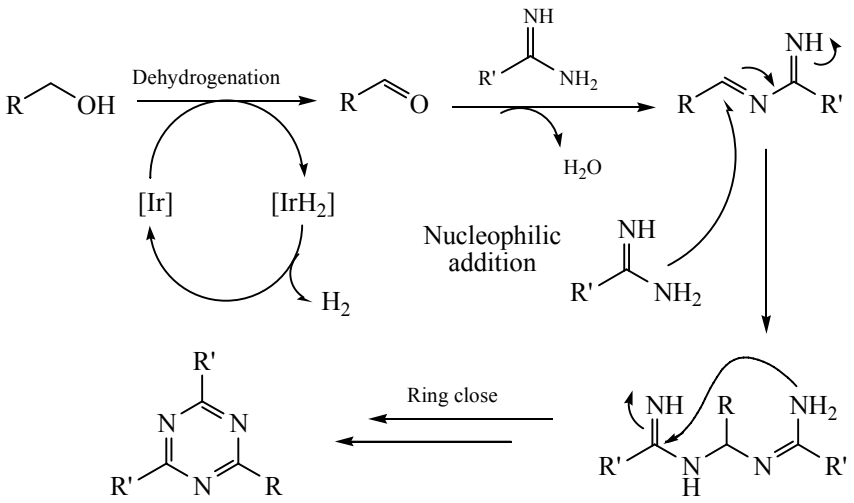
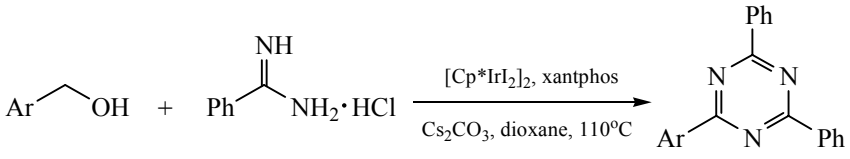
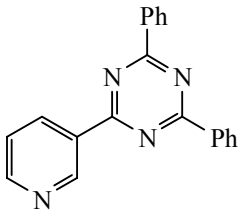
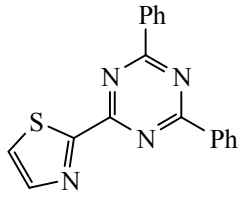
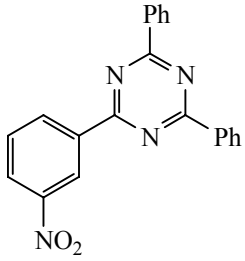
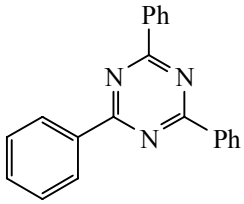
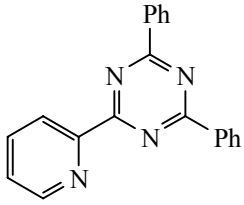
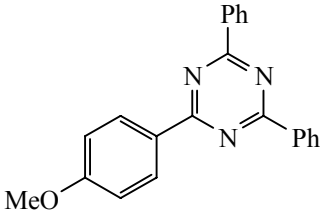
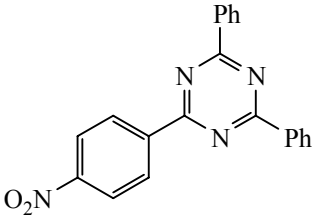
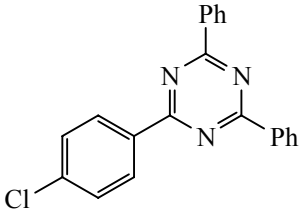
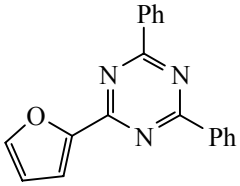


Table 2. Substrate expansion experiment[a,b]



1 **2** **3**

Comp. no.	Formula	Yield, %	Comp. no.	Formula	Yield, %
3a		81	**3f**		71
3b		75	**3g**		85
3c		71	**3h**		88
3d		64	**3i**		81
3e		69			

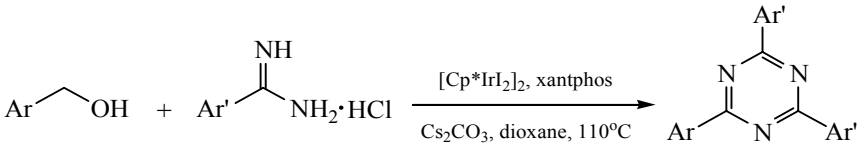
[a] Reaction conditions: **1** (2.0 mmol), **2** (1 mmol), $[Cp^*IrI_2]_2$ (1 mol %), xantphos (2 mol %), Cs_2CO_3 (1 mmol), Dioxane (2 mL), 110°C, 20 h. [b] Isolated yields.

catalysis by $[Cp^*IrI_2]_2$ gave slightly higher yield than other cationic Ir(III) compounds (Table 1, entries 3–5). Such solvents as toluene, xylene, DMF, and DMAc demonstrated no positive effect in the process. Yield of the process was increased up to 66% in the media of dioxane (Table 1, entries 6–10).

Yield of the reaction was increased significantly by application of phosphine ligands (Table 1, entries 11–14 and Scheme 3).

The scope of the reaction was studied with a series of aromatic alcohols and benzamidine hydrochloride

Table 3. Substrate expansion experiment[a,b]



1 **2** **3**

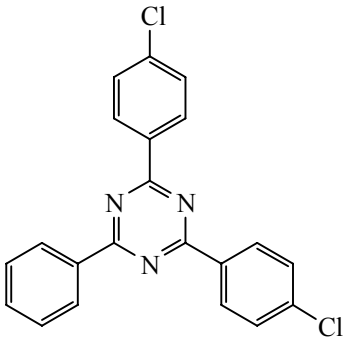
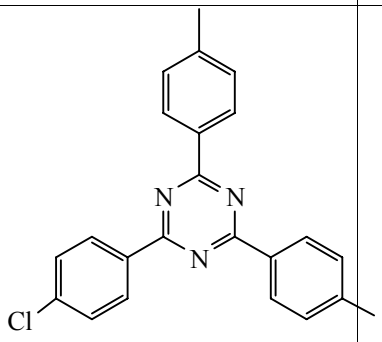
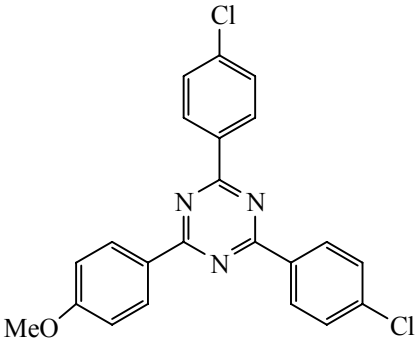
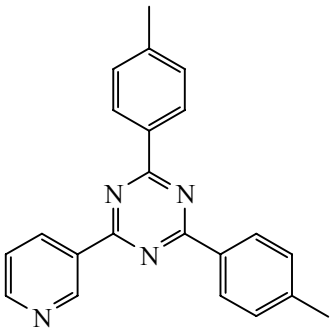
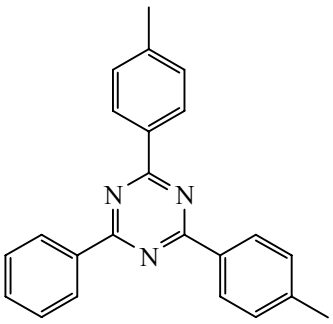
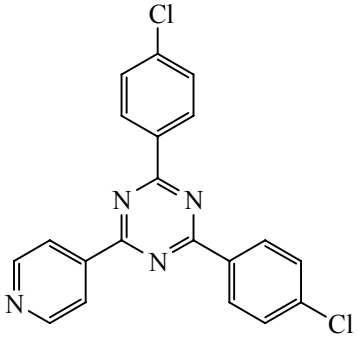
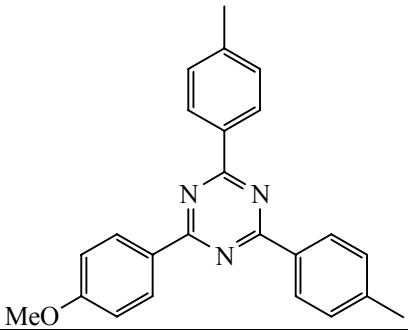
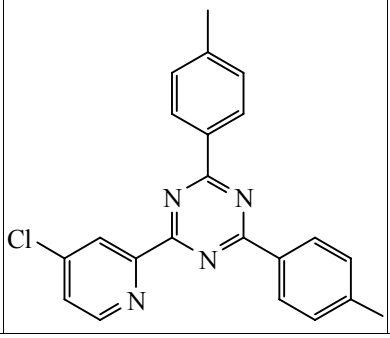
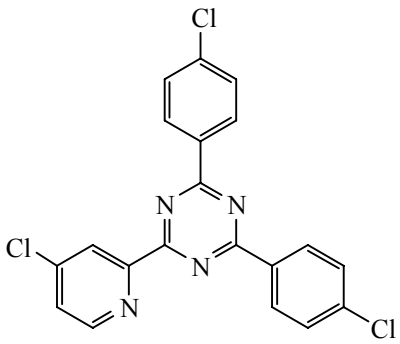
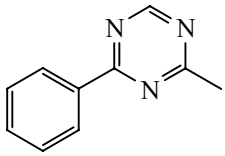
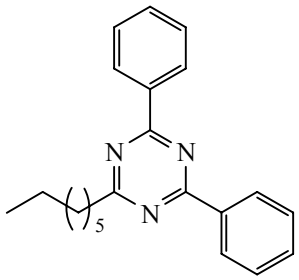
Comp. no.	Formula	Yield, %	Comp. no.	Formula	Yield, %
3j		69	**3n**		61
3k		75	**3o**		56
3l		66	**3p**		63
3m		71	**3q**		58

Table 3. (Contd.)

Comp. no.	Formula	Yield, %	Comp. no.	Formula	Yield, %
3r		66	**3t**		<5
3s		<5			

[a] Reaction conditions: **1** (2.0 mmol), **2** (1 mmol), $[Cp^*IrI_2]_2$ (1 mol %), xantphos (2 mol%), Cs_2CO_3 (1 mmol), dioxane (2 mL), 110°C, 20 h. [b] Isolated yields.

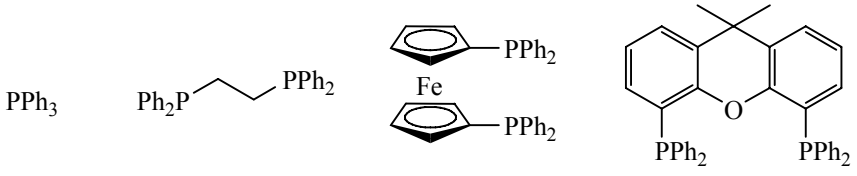
under optimized conditions. The substituents on pyridyl methanol substrates had little impact on formation of the desired products (Table 2, see **3a**–**3d**). The effect of substituents on the aromatic ring of alcohols was studied. Benzamidine hydrochloride with benzyl alcohols having electron-donating or electron-withdrawing substituents produced moderate to high yields (Table 2, see **3j**–**3l**). Furyl- and thiazolyl- heterocyclic alcohols reacted under the optimized conditions with satisfactory yields (Table 2, see **3e**–**3f**).

The reaction of substituted benzamidines with aryl methanols (Table 3) catalyzed by $[Cp^*IrI_2]_2$ gave the corresponding 2,4,6-triaryl-1,3,5-triazines in high yields. Generally, the reaction had high substituent tolerance. Substituents with different electronic properties on the aryl ring of benzamidines significantly affected the reaction. Benzamidines possessing electron-poor groups led to corresponding products in higher yields than the electron-donating ones. The reaction of *n*-octyl alcohol with benzamidine and alkyl amidines did not run probably due to decomposition that took place prior to dehydrogenation of alcohols [10a].

EXPERIMENTAL

Typical procedure for the synthesis of 3a. $[Cp^*IrI_2]_2$ (1 mol %, 0.01 mmol), xantphos (2 mol %, 0.02 mmol) and dioxane (2 mL) were stirred shortly in a Schlenk tube at room temperature. Subsequently, 3-pyridinemethanol (2.0 mmol), benzamidine hydrochloride (1.0 mmol), and cesium carbonate (1.0 mmol) were added. The mixture was heated under 110°C for 20 h and then cooled down to room temperature. The

Scheme 3. Ligands used in screening of reaction conditions.



L1 **L2** **L3** **L4**

resulting solution was purified by column chromatography with petroleum ether–ethyl acetate (10 : 1) as an eluent to give 2,4-diphenyl-6-(pyridin-3-yl)-1,3,5-triazine (**3a**) as a white solid.

Thus synthesized compounds were tested by ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and mass-spectrometry. The accumulated data correlated well with those presented earlier for the same compounds in the following publications: 4-di-phenyl-6-(pyridin-3-yl)-1,3,5-triazine (**3a**) [10a], 2-(4-nitrophenyl)-4,6-diphenyl-1,3,5-triazine (**3b**) [11],

2,4-Diphenyl-6-(pyridin-2-yl)-1,3,5-triazine (**3c**) [10a], 2-(3-nitrophenyl)-4,6-diphenyl-1,3,5-triazine (**3d**) [12], 2,4-diphenyl-6-(thiazol-2-yl)-1,3,5-triazine (**3f**) [10a], 2,4,6-triphenyl-1,3,5-triazine (**3g**) [13], 2-(4-methoxyphenyl)-4,6-diphenyl-1,3,5-triazine (**3h**) [12], 2-(4-chlorophenyl)-4,6-diphenyl-1,3,5-triazine (**3i**) [14], 2,4-bis(4-chlorophenyl)-6-phenyl-1,3,5-triazine (**3j**) [13], 2,4-bis(4-chlorophenyl)-6-(4-methoxyphenyl)-1,3,5-triazine (**3k**) [10a], 2-phenyl-4,6-di-*p*-tolyl-1,3,5-triazine (**3l**) [10a], 2-(4-methoxyphenyl)-4,6-di-*p*-tolyl-1,3,5-triazine (**3m**) [10a], 2-(4-chlorophenyl)-4,6-di-*p*-tolyl-1,3,5-triazine (**3n**) [11], 2-(pyridin-3-yl)-4,6-di-*p*-tolyl-1,3,5-triazine (**3o**) [10a], 2,4-bis(4-chlorophenyl)-6-(pyridin-4-yl)-1,3,5-triazine (**3p**) [10a], 2-(4-chloropyridin-2-yl)-4,6-di-*p*-tolyl-1,3,5-triazine (**3q**) [10a], 2-(4-chloropyridin-2-yl)-4,6-bis(4-chlorophenyl)-1,3,5-triazine (**3r**) [10a].

CONCLUSIONS

2,4,6-Triaryl-1,3,5-triazines were synthesized efficiently in iridium-catalyzed dehydrogenation, ring-close reaction with the use of commercially available $[Cp^*IrI_2]_2$–xantphos as a catalyst system. The reaction of aryl amidines in combination with different substituted benzylic alcohols proceeded smoothly, furnishing the desired products in moderate to high yields.

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