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Copper-catalyzed aldol-type addition of ketones to aromatic nitriles: a simple approach to enaminone synthesis†

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An efficient method for the synthesis of enaminones is described. The aldol-type addition of ketones to aromatic nitriles proceeded smoothly in the presence of a simple copper catalyst system (CuI–2,2′-bipyridine–NaO^{t}Bu) in *N*,*N*-dimethylformamide. Enaminones in satisfactory to excellent yields were produced using this technique.

Enaminones are important synthetic intermediates and building blocks for drug development[1] and natural product synthesis.[2] For example, enaminones have been successfully used for synthesis of drugs (anticonvulsants,[3] anti-inflammatory agents,[4] and antitumor agents[5]) and bioactive heterocycles (pyridinones,[6a] quinolones,[6b] pyrroles,[6c] isoxazoles,[6d] indole,[6e] and polyazaheterocycles[6f]). Therefore, the development of convenient and efficient methods for the synthesis of enaminones has attracted considerable attention. Over the past decades, numerous techniques have been developed for the construction of enaminones, including the direct condensation reaction of 1,3-dicarbonyl compounds with amines or excess ammonium salts;[7–9] aldol-type addition reaction of 1,3-dicarbonyl compounds to activated nitrile compounds catalyzed by Lewis catalysts;[10] and others.[11] In addition, C–H activation has recently been successfully employed in the synthesis of enaminones.[12] Despite the success of these approaches in obtaining various enaminones, synthesis of enaminones frequently suffers from certain disadvantages such as harsh reaction conditions, unsatisfactory yields, and the need to use special starting materials.

To the best of our knowledge, the aldol-type addition reaction of ketones to aromatic nitriles to produce enaminones has not been systematically researched.[13] Poor reaction selectivity was found when a mixture of ketone and aromatic nitrile was treated in the presence of a Lewis acid catalyst under basic conditions; both self-condensation of ketone and aldol-type addition of ketone to aromatic nitrile were observed. The coordination ability of the cyano group to a Lewis acid catalyst was reportedly stronger than that of the carbonyl group.[12,14] We hypothesized that the reaction selectivity could be controlled by using an appropriate Lewis acid catalyst. The catalyst would be selectively coordinated to the cyano group to enhance the reactivity of the aromatic nitrile, thereby suppressing the self-condensation of ketone.

Several Lewis acid catalyst systems were investigated to test this hypothesis. The aldol-type addition reaction of acetophenone (**1a**) to benzonitrile (**2a**) was chosen as a model to optimize the reaction conditions. The results are summarized in Table 1. Lewis acid catalysts $ZnCl_2$, $CoCl_2$, $NiCl_2$, copper(II) trifluoromethanesulfonate [$Cu(OTf)_2$], copper(II) acetate [$Cu(OAc)_2$], CuCl, CuBr, and CuI were initially examined in the absence of a ligand by using NaO^{t}Bu as the base. Among these catalysts, CuI exhibited the highest catalytic selectivity (entry 8 *vs.* entries 1–7). Nitrogen-containing ligands pyridine (**L1**), ethane-1,2-diamine (**L2**), N^1,N^1,N^2,N^2-tetramethylethane-1,2-diamine (**L3**), 2,2′-bipyridine (**L4**), and 1,10-phenanthroline (**L5**) were then investigated using CuI as the Lewis acid catalyst (entries 9–13).[15] **L4** proved to be the best ligand for the selective synthesis of enaminone **3a**. Low yield or no formation of **3a** was observed when the bases NaOH, KOH, K_2CO_3, and Cs_2CO_3 were used instead of NaO^{t}Bu (entries 14–17). The solvent (entries 12, 18, and 19) and temperature (entries 12, 20, and 21) were finally screened. *N*,*N*-Dimethyl formamide (DMF) and 80 °C were identified as the best solvent and reaction temperature, respectively. Therefore, the subsequent aldol-type addition reactions of ketones to aromatic nitriles were performed in the presence of CuI and **L4** by using NaO^{t}Bu as the base in DMF at 80 °C for 12 h.

The aldol-type addition reactions of ketones **1a–1m** to **2a** were performed under optimized conditions to determine the scope of ketone substrates. The results are summarized in Table 2. The desired product enaminone **3a** was isolated in 72% yield from the reaction of **1a** with **2a** (entry 1). Satisfactory yields similar to that of **3a** were observed when 1-(*p*-tolyl)ethanone (**1b**), 1-(*o*-tolyl)ethanone (**1c**), 1-(4-methoxyphenyl)ethanone (**1d**), 1-(4-(dimethylamino)phenyl)ethanone (**1e**), and 1-(4-(butylamino)phenyl)ethanone (**1f**) were tested under optimized reaction conditions (entries 2–6 *vs.* entry 1, 65–82%). However, the reactions of 1-(4-fluorophenyl)ethanone (**1g**) and 1-(4-chlorophenyl)ethanone (**1h**)

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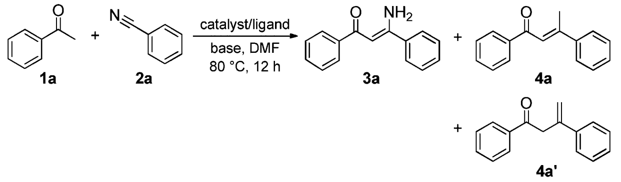
† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for isolated compounds. See DOI: 10.1039/c3cc40466h

Table 1 Reaction condition screening[a]



Entry	Catalyst	Ligand	Base	Yield^b (%) 3a	Yield^c (%) 4a + 4a′
1	$ZnCl_2$	None	NaO^{t}Bu	25	57
2	$CoCl_2$	None	NaO^{t}Bu	15	38
3	$NiCl_2$	None	NaO^{t}Bu	4	24
4	$Cu(OTf)_2$	None	NaO^{t}Bu	58	39
5	$Cu(OAc)_2$	None	NaO^{t}Bu	62	37
6	CuCl	None	NaO^{t}Bu	49	43
7	CuBr	None	NaO^{t}Bu	62	37
8	CuI	None	NaO^{t}Bu	70	31
9	CuI	**L1**	NaO^{t}Bu	55	45
10	CuI	**L2**	NaO^{t}Bu	56	52
11	CuI	**L3**	NaO^{t}Bu	60	41
12	CuI	**L4**	NaO^{t}Bu	83	12
13	CuI	**L5**	NaO^{t}Bu	50	36
14	CuI	**L4**	NaOH	12	Trace
15	CuI	**L4**	KOH	13	Trace
16	CuI	**L4**	K_2CO_3	ND^d	ND^d
17	CuI	**L4**	Cs_2CO_3	ND^d	Trace
18^e	CuI	**L4**	NaO^{t}Bu	50	43
19^f	CuI	**L4**	NaO^{t}Bu	69	14
20^g	CuI	**L4**	NaO^{t}Bu	79	27
21^h	CuI	**L4**	NaO^{t}Bu	85	24

[a] Reaction conditions: Lewis acid catalyst (10 mol%), ligand (11 mol%), acetophenone (**1a**, 0.6 mmol, 72.0 mg), benzonitrile (**2a**, 0.5 mmol, 51.5 mg), and base (2.0 mmol) in DMF (1.0 mL) at 80 °C for 12 h. [b] GC yield based on **2a**. (*E*)-4-Phenylbut-3-en-2-one was used as an internal standard. [c] GC yield based on **1a**. (*E*)-4-Phenylbut-3-en-2-one was used as an internal standard. [d] Not determined. [e] THF was used as the solvent. [f] Dioxane was used as the solvent. [g] The reaction was conducted at 70 °C. [h] The reaction was conducted at 90 °C.

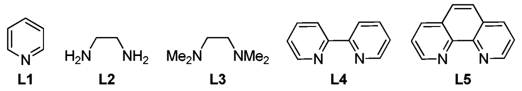
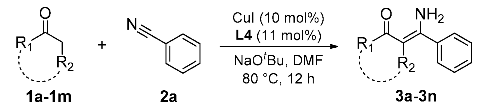
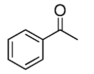
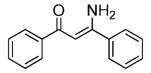
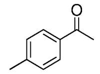
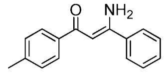
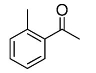
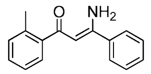
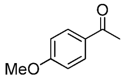
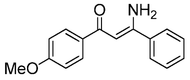
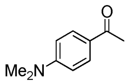
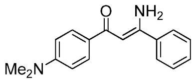
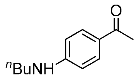
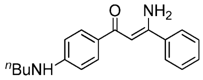
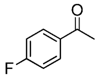
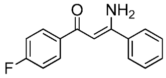
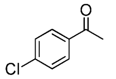
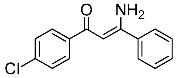
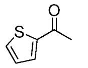
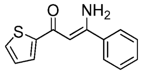
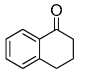
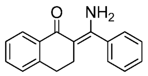
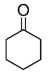
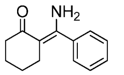
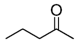
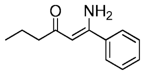
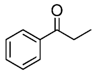
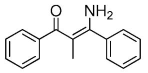


Table 2 Copper-catalyzed aldol-type addition of various ketones to benzonitrile[a]



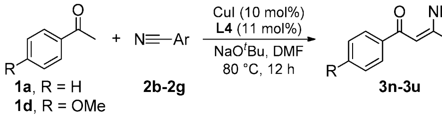
Entry	Ketone **1**		Product **3**		Yield^b (%)
1		**1a**		**3a**	72
2		**1b**		**3b**	82
3		**1c**		**3c**	71
4		**1d**		**3d**	74
5		**1e**		**3e**	75
6		**1f**		**3f**	65
7		**1g**		**3g**	67^c
8		**1h**		**3h**	65^c
9		**1i**		**3i**	30
10		**1j**		**3j**	65
11		**1k**		**3k**	51
12		**1l**		**3l**	53^c
13		**1m**		**3m**	NR^d

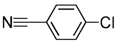
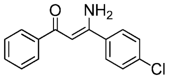
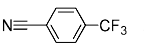
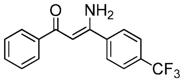
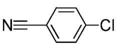
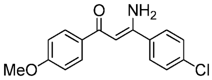
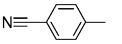
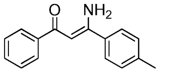
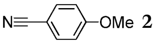
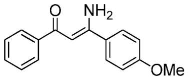
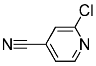
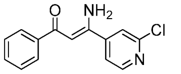
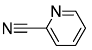
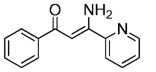
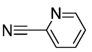
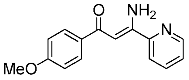
[a] Reaction conditions: CuI (10 mol%, 9.5 mg), **L4** (11 mol%, 9.5 mg), ketone (**1**, 0.6 mmol, 1.2 equiv.), benzonitrile (**2a**, 0.5 mmol, 51.5 mg), NaO^{t}Bu (2.0 mmol, 96.0 mg) in 1 mL of DMF at 80 °C for 12 h. [b] Isolated yield. [c] Reaction conditions: CuI (20 mol%, 19.0 mg), **L4** (22 mol%, 19 mg), benzonitrile (**2a**, 0.5 mmol, 51.5 mg), ketone (**1**, 1.0 mmol, 2 equiv.), NaO^{t}Bu (3.3 mmol, 160 mg) in 1.5 mL of DMF at 80 °C for 24 h. [d] No reaction.

required an extended time (24 h) to complete despite increases in catalyst loading and the amount of ketone substrate to 20 mol% and two equivalents, respectively (entries 7 and 8, 67% and 65% yields). These results indicate that the reactivity of aromatic ketones should be lowered by an electron-withdrawing group linked to a benzene ring. Although the ketone substrate 1-(thiophen-2-yl)ethanone (**1i**) disappeared within 12 h, the desired product enaminone **3i** was isolated in only 30% yield (entry 9). Enaminone **3j** was obtained in a moderate yield when 3,4-dihydronaphthalen-1(2*H*)-one (**1j**) was tested (entry 10, 65% yield). Aliphatic ketones, cyclohexanone (**1k**) and pentan-2-one (**1l**), were then used in the addition reaction. Enaminones **3k** and **3l** were obtained in 51% and 53% yields, respectively (entries 11 and 12). The reaction of unsymmetrical ketone **3l** regioselectively occurred on the less sterically hindered α-carbon atom. As expected, no reaction was observed when propiophenone (**1m**) was examined (entry 13).

The reactions of the ketone substrates **1a** and **1d** with the aromatic nitriles **2b**–**2g** were then examined to explore the scope of nitrile substrates. The results are shown in Table 3. As expected, the reactions of **1a** with 4-chlorobenzonitrile (**2b**) or 4-(trifluoromethyl)benzonitrile (**2c**) proceeded smoothly to produce the enaminones **3n** and **3o** in excellent yields (entries 1 and 2; 89% and 95%, respectively). The desired product **3p** was also obtained in excellent yield (93%) from the reaction of **1d** with **2b** (entry 3). Nitrile substrates, 4-methylbenzonitrile (**2d**) and 4-methoxybenzonitrile (**2e**), exhibited low reactivities in this type of addition reaction. Moderate yields of the enaminones **3q** and **3r** were observed in the reactions of **1a** with either **2d** or **2e**

Table 3 Copper-catalyzed aldol-type addition of aromatic ketones **1a** and **1b** to various aromatic nitriles[a]



Entry	Ketone **1**	Nitrile **2**		Product **3**		Yield[b] (%)
1	**1a**		**2b**		**3n**	89
2	**1a**		**2c**		**3o**	95
3	**1d**		**2b**		**3p**	93
4	**1a**		**2d**		**3q**	61[c]
5	**1a**		**2e**		**3r**	70[c]
6	**1a**		**2f**		**3s**	73
7	**1a**		**2g**		**3t**	85
8	**1d**		**2g**		**3u**	87

[a] Reaction conditions: CuI (10 mol%, 9.5 mg), **L4** (11 mol%, 9.5 mg), ketone (**1a** or **1d**, 0.6 mmol, 1.2 equiv., 72.0 mg or 90.0 mg), aromatic nitrile (**2**, 0.5 mmol), NaO^{t}Bu (2.0 mmol, 96.0 mg) in 1 mL of DMF at 80 °C for 12 h. [b] Isolated yield. [c] Reaction conditions: CuI (20 mol%, 19 mg), **L4** (22 mol%, 19 mg), aromatic nitrile (**2**, 0.5 mmol), acetophenone (**1a**, 1.0 mmol, 2 equiv., 120.1 mg), NaO^{t}Bu (3.3 mmol, 160 mg) in 1.5 mL of DMF at 80 °C for 24 h.

(entries 4 and 5; 61% and 70% yields, respectively). These results suggest that the reactivity of the nitrile substrate was remarkably influenced by the electronic property of the substituent linked to the benzene ring of nitrile. Enaminones **3n**, **3q**, and **3r** are isomers of enaminones **3h**, **3b**, and **3d**, respectively. These isomers were selectively synthesized by the present method. Reactions of heteroaryl nitriles, 2-chloroisonicotinonitrile (**2f**) and picolinonitrile (**2g**), were finally examined. The enaminone products **3s**–**3u** were obtained in 73%, 85%, and 87% yields, respectively (entries 6–8).

In summary, a general method for synthesis of enaminones was developed using simple and readily available starting materials, namely, ketones and aromatic nitriles. The copper-catalyzed aldol-type addition of ketones to aromatic nitriles proceeded smoothly under mild conditions and produced enaminones in satisfactory to excellent yields. The affordability of the catalyst, wide availability of the starting materials, mild reaction conditions, and simplicity of the procedure render the present methodology more useful in organic synthesis. The use of 2,2′-bipyridine as a ligand plays a key role in the control of reaction selectivity.

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