# Tartaric acid-zinc nitrate as an efficient Brønsted acid-assisted Lewis acid catalyst for the Mannich reaction

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Tartaric acid-zinc nitrate has been found to be an efficient Brønsted acid-assisted Lewis acid catalytic system for the facile synthesis of  $\beta$ -amino carbonyl compounds through the one-pot Mannich reaction of aldehydes, aromatic amines and ketones in ethanol at room temperature. Remarkable enhancement of reactivity by tartaric acid (Brønsted acid) was observed in these reactions in the presence of anhydrous zinc nitrate (Lewis acid), due to coordination of the tartaric acid ligand to zinc ions increasing the acidity of the system. This procedure shows some advantages such as mild reaction conditions, short reaction times and high yields.

Keywords: Mannich reaction, anhydrous zinc nitrate, tartaric acid, Lewis acid catalysis

Multicomponent reactions represent a very interesting organic synthetic methodology due to their advantages, such as one-pot and easy operating conditions, atom economy, high chemical yields and cheap substrates.<sup>1</sup> β-Amino carbonyl compounds are important intermediates for various pharmaceuticals and natural products, and are usually synthesised via the one-pot three-component Mannich reaction.<sup>1,2</sup> This reaction can be catalysed by many acidic catalysts, such as ionic liquids,<sup>3,4</sup> Lewis acids, Brønsted acids, heteropolyacids, supported acids as well as copper nanotubes or nanoparticles.<sup>5</sup> Also, Zetchi et al. reported that the Mannich reaction can be carried out in high yields within shorter reaction times using PEG-600 as a safer catalyst under solvent-free conditions at room temperature.<sup>6</sup> Most of the above strategies suffer from several shortcomings, including the high cost of catalyst, low activities,<sup>7</sup> long reaction times or the use of environmentally unfriendly solvents.<sup>4</sup> Thus, there is high interest in developing a new readily available and efficient catalyst for the Mannich reaction.

Brønsted acid-assisted Lewis acid (BLA) catalytic systems can be formed by mixing an inactive metal salt and an organic acid inactive towards a specific reaction, which becomes active *via* the enhancement of the Brønsted acidity.<sup>8</sup> Recently, much attention has been focused on BLA catalytic systems, which have been used as the combined catalyst in reactions such as the Fries rearrangement,<sup>9</sup> aldol reactions,<sup>10</sup> the Diels–Alder reaction,<sup>11</sup> allylation,<sup>12</sup> diacetylation<sup>13</sup> and tetrahydropyranylation.<sup>14</sup> The discovery and development of new BLAs is therefore in demand.

Tartaric acid is a common natural product that is found in many plants, particularly grapes. It can be used as a juice additive and antioxidant, and is also an important chiral ligand.<sup>15</sup> Tartaric acid contains six oxygen atoms, and binds easily with metal atoms as a mono-, bi- or tridentate ligand.<sup>16,17</sup> As a result, dimeric or polymeric structures can be formed via the interaction of the hydroxyl and carboxyl groups of the ligand with different metal atoms.<sup>18</sup> Thus, we decided to examine the feasibility of the mixture of tartaric acid and metal salts as a promising BLA catalyst. Furthermore, Eshghi et al. reported that enantioselective ring opening by using  $Zn(NO_2)_2/(+)$ -tartaric acid was an efficient alternative short route with simple work up and high enantiomeric excess for the synthesis of (S)-propranolol.<sup>19</sup> Following our research work on catalysis,<sup>20,21</sup> the mixture of zinc nitrate and tartaric acid as a new BLA catalytic system for the Mannich reaction is investigated in this work. We find it exhibits enhanced catalytic activity with short reaction times and a high yield.

## **Results and discussion**

In multicomponent condensation reactions, three or more reactants come together in a single reaction vessel to form the products containing portions of all the components. However, the sequence of additions sometimes plays an important role in these reactions.<sup>22</sup> In this work, the reaction of benzaldehyde, aniline and acetophenone was selected as a model to investigate the effect of the addition sequence. As shown in Table 1 (entries 2 and 3), the sequence has an obvious effect on the catalytic activity for the Mannich reaction. The reaction time was long with low yield when three components were added simultaneously. However, if acetophenone and the catalyst (tartaric acid-zinc nitrate) were added 10 min after the addition of benzaldehyde and aniline, the reaction proceeded smoothly in a short time with high yield. Hence, the ketones were treated with aldehydes and aromatic amines with the latter method in the following tests.

Furthermore, several different catalysts were examined for the model reaction. When tartaric acid was used alone as the catalyst, no product was obtained even after 24 h (Table 1, entry 1). Similarly, the catalytic activities of metal nitrates alone were inferior (Table 1, entries 2–6). However, the yields were improved markedly when tartaric acid was used together with metal nitrates. Among them, tartaric acid–zinc nitrate was the best with a yield of 92% after 6 h (Table 1, entry 2). In addition, several different zinc salts were also investigated for this Mannich reaction (Table 1, entries 7–9). Whether they were used alone or combined with tartaric acid, the activities were poorer than that of tartaric acid–zinc nitrate. In short, in view of the excellent catalytic activity and low cost, tartaric acid–zinc nitrate was found to be the best catalytic system for this Mannich reaction.

The effect of the molar ratio of the tartaric acid–zinc nitrate catalyst system on the Mannich reaction was investigated, and the results are shown in Table 2. First, the amount of  $Zn(NO_3)_2$  was fixed at 10 mol%, and a significant enhancement was observed when the amount of tartaric acid was increased from 1 to 10 mol% (Table 2, entries 1–3), while, an excess amount of tartaric acid (15 mol%) did not lead to further improvement of the yield (Table 2, entry 4). However, when the amount of zinc nitrate was increased, there was no increment in the yield (Table 2, entries 5–7). Therefore, the optimum molar ratio of tartaric acid–zinc nitrate was 1:1, and the selective amounts of the ware both 10 mol%. In addition, the molar ratio of the tartaric acid–zinc nitrate can affect the coordination modes of

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#### Table 1 Screening of catalysts for the Mannich reaction<sup>a</sup>



Fata	MAX		Yield (%) <sup>b</sup>			
спи у	MX <sub>n</sub>	Time (n)	Catalyst: MX <sub>n</sub>	Catalyst: MX <sub>n</sub> + TA		
1	-	24	_c	0		
2	Zn(NO <sub>3</sub> ) <sub>2</sub>	24	_c	62 <sup>d</sup>		
3	$Zn(NO_3)_2$	6	37	92°		
4	Cu(NO <sub>3</sub> ) <sub>3</sub> ·3H <sub>2</sub> O	8	52	87		
5	Fe(NO <sub>3</sub> ) <sub>3</sub> ·9H <sub>2</sub> O	24	39	70		
6	$Ni(NO_3)_2 \cdot 6H_2O$	6	21	65		
7	Co(NO <sub>3</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	24	43	78		
8	ZnCl <sub>2</sub>	20	0	86		
9	ZnSO <sub>4</sub> ·7H <sub>2</sub> 0	30	0	24		
10	Zn(0Ac) <sub>2</sub> ·2H <sub>2</sub> 0	16	0	Trace		

<sup>a</sup>Reaction conditions: 20 mmol benzaldehyde, 20 mmol aniline, 20 mmol acetophenone, 2 mmol tartaric acid, 2 mmol metal salt, 5 mL ethanol, room temperature. <sup>b</sup>Isolated yield.

°Not done in this work.

<sup>d</sup>Addition sequence: benzaldehyde, aniline and acetophenone were added simultaneously.

<sup>e</sup>Addition sequence: benzaldehyde and aniline reacted for 10 min, after that acetophenone was added to the above mixture for the further reaction.

Table	2	Effect	of	molar	ratio	of	zinc	nitrate	and	tartaric	acid	on	the
Manni	ch	reaction	ona										

<b>F</b> .	Amoun		
Entry	$Zn(NO_3)_2$	Tartaric acid	Yield (%) <sup>5</sup>
1	10	1	42
2	10	5	75
3	10	10	92
4	10	15	92
5	20	10	92
6	30	10	92
7	40	10	91

<sup>a</sup>Reaction conditions: 20 mmol benzaldehyde, 20 mmol aniline, 20 mmol acetophenone, 5 mL ethanol, room temperature, 6 h.

<sup>b</sup>Isolated yield.

ligand tartaric acid and metal ions.<sup>23</sup> Lin *et al.* have reported that Zn ions had a six-coordinate distorted octahedron geometry with tartaric acid adopted *via* two different coordinated modes in { $[Zn(C_4H_4O_6)(H_2O)]_2 \cdot 3H_2O$ }, when the molar ratio of tartaric acid and zinc ions is  $2:1.^{24}$  In this work, the molar ratio of tartaric acid and zinc ion was 1:1, and two possible coordination modes are shown in Fig. 1. As can be seen, the Lewis acid Zn<sup>2+</sup> coordinated with two hydroxyl groups and two H<sup>+</sup> were released, which increases the acidity of the system. In all, the above results clearly showed that tartaric acid-assisted zinc nitrate formed a new BLA synergistic catalytic system that catalysed the Mannich reaction efficiently.

Encouraged by the above results, a variety of aromatic aldehydes, amines and ketones were also examined, and the results are shown in Table 3. In the investigation of various aldehydes, both electron-withdrawing and electron-donating substituents resulted in excellent yields, indicating the high generality of the aldehydes in this reaction (Table 3, entries 1–4). However, aliphatic aldehydes, such as butyraldehyde, did not favour the formation of the desired product, because the enamine was formed (Table 3, entry 5).<sup>25</sup> When *para*- or



Fig. 1 Two possible coordination modes of the tartaric acid ligand and zinc ions with a molar ratio of 1:1.

*ortho*-substituted aniline was used as substrate, the reaction time is very long, possibly because of the steric hindrance of *para*- or *ortho*-substituent, or other factors (Table 3, entries 6–7). Furthermore, cyclohexanone was also used under these conditions (Table 3, entries 8–10). Compared with acetophenone, cyclohexanone showed higher activity, which may be because its enol formation was much faster than that of acetophenone. Moreover, the great efficiency of tartaric acid–zinc nitrate catalyst system as a novel catalyst compared with data reported in the literature for the Mannich reaction is shown in Table 4. As can be seen, the tartaric acid–zinc nitrate catalyst system shows high activity, short reaction time, high purity, simple work-up and green solvent, which further indicates that this catalytic system is an efficient catalyst for the Mannich reaction.

## Conclusions

We have shown tartaric acid-zinc nitrate as a new Brønsted acid-assisted Lewis acid catalytic system for the Mannich reaction in ethanol at room temperature. The combined catalyst is highly efficient because the coordination of ligand tartaric Table 3 Catalytic activities of tartaric acid and zinc nitrate for the Mannich reaction<sup>a</sup>



⁼aryl	R <sub>2</sub> =aryl	R <sub>3</sub> =H	R <sub>4</sub> =Ph
alkyl		-(CI	$(H_2)_4$

Entry	Aldehyde	Amine	Ket	Ketone			Mp (°C)		
	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	$R_4$	l ime (h)	Yield (%) <sup>b</sup>	Found	Reported	Ket.
1	Ph	Ph	Н	Ph	6	92	167-169	167–169	26
2	4-CIC <sub>6</sub> H <sub>4</sub>	Ph	Н	Ph	8	97	131-132	130–132	26
3	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	Ph	Н	Ph	6	96	128-130	129–130	5
4	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	Ph	Н	Ph	7	99	148–149	148–150	26
5	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub>	Ph	Н	Ph	24	0	-	-	-
6	Ph	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	Н	Ph	12	95	170–171	170–171	27
7	Ph	2-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	Н	Ph	24	0	-	-	-
8	Ph	Ph	-(CI	H <sub>2</sub> ) <sub>4</sub> -	1	93	138–140	137–139	26
9	4-CIC <sub>6</sub> H <sub>4</sub>	Ph	-(CI	$H_{2})_{4}$ –	6	94	118–120	117–118	5
10	Ph	4-CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	-(CI	H_),-	10	90	118-120	118–119	27

<sup>a</sup>Reaction conditions: 20 mmol aldehyde, 20 mmol aromatic amine, 20 mmol ketone, 2 mmol tartaric acid, 2 mmol zinc nitrate, 5 mL ethanol, room temperature. <sup>b</sup>Isolated yield.

Table 4 Comparison of different catalytic systems used for the Mannich reaction in literature



Entry	Catalyst	Amount of catalyst (mol%)	Solvent	Time (h)	Yield (%)	Ref.
1	Tartaric acid–zinc nitrate	10	EtOH	6	92	This work
2	[bmim][OH] ionic liquid	10	EtOH	10	85	28
3	[DDPA][HSO]] ionic liquid	10	H <sub>2</sub> 0	6	90	29
4	[Hmim]⁺Tfa⁻ ionic liquid	2.5 g	IL	12	83	3
5	Cu nanoparticles	10	MeOH	8	93	5
6	Benzenedisulfonimide	5	Neat	24	99	30
7	Dodecylbenzene-sulfonic acid	10	H <sub>2</sub> 0	12	69	7
8	MSI <sub>3</sub> PW	5	BMI.NTf <sub>2</sub>	20	95	4
9	NbCl <sub>5</sub>	10	EtOH	12	95	31
10	BiCl <sub>3</sub>	5	EtOH	11	95	8
11	Ph <sub>2</sub> IOTF	10	Neat	24	93	32
12	Polyacrylic acid	7.5	H <sub>2</sub> 0	12	92	33
13	Bi(OTf) <sub>3</sub>	5	H,0	7	84	34
14	HNMPCI/ZnCl <sub>2</sub> /SBA-15	30 mg	EtOH	5 (60 °C)	95	35

acid and zinc ions can increase the acidity of the system, which is crucial for this reaction. This work sheds light on the design of catalysts for acid-catalysed organic synthesis.

# Experimental

All the chemicals with analytical grade were purchased from Sinopharm Chemical Reagent Co. Ltd, China, and used without further treatment. All reagents were purchased and used without further purification. Melting points were determined by using XT-4 micromelting point apparatus (Beijing Taike Instrument Company,

# General procedure for Mannich reaction

IR and <sup>1</sup>H NMR with those reported in the literature.

Aldehyde (20 mmol) and aromatic amine (20 mmol) in anhydrous ethanol (5 mL) were added and stirred in a 50 mL round-bottomed

China). The Fourier-transform infrared spectra (FTIR) were taken on a Nicolet 380 Fourier Transform-Infrared spectrophotometer (Thermo

Electron Corporation, USA) in the range of 400-4000 cm<sup>-1</sup>. <sup>1</sup>H NMR

spectra were taken on an EFT-60 NMR spectrometer (Anasazi Instruments, USA) using CDCl<sub>3</sub> as solvent and TMS as the internal

standard. All products are known compounds and identified by m.p.,

flask at room temperature for 10 min. Then, acetophenone or cyclohexanone (20 mmol), tartaric acid (2 mmol) and anhydrous zinc nitrate (2 mmol) were added successively, and the reaction mixture was further stirred for the specified time (see Table 3). After completion of the reaction, the mixture was treated with saturated NaHCO<sub>3</sub> solution (10 mL). The product was filtered and washed with water several times, and recrystallised from ethanol and acetone (1:1) to afford the pure product.

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