



## Inorganic ammonium salts as catalysts for direct aldol reactions in the presence of water

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### ABSTRACT

Inorganic ammonium salts catalyze the direct aldol reaction between unmodified ketones and aldehydes to furnish the corresponding  $\beta$ -hydroxy ketones in aqueous media. The reactions are highly chemoselective and operationally simple.

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The aldol reaction is a powerful method for forming carbon–carbon bonds.<sup>1,2</sup> The reaction is industrially relevant for the production of bulk chemicals, fine chemicals, and pharmaceuticals.<sup>3</sup> In Nature, aldolase enzymes catalyze the direct aldol reaction with excellent stereocontrol. Class I aldolases employ chiral enamines whereas class II aldolases utilize chiral Zn enolates as nucleophiles for the stereoselective addition of dihydroxyacetone phosphate (DHAP) to aldehydes.<sup>1</sup> Water is the reaction media for most enzymatic transformations in living systems. In organic synthesis, there are several methods for achieving catalytic aldol reactions.<sup>2,4</sup> However, methods for catalyzing aldol reactions in water are less developed and green methods are needed.<sup>5</sup> For example, organometallic complexes have been developed that catalyze the Mukaiyama-type aldol reaction between activated silyl enol ethers and aldehydes in aqueous media.<sup>6</sup> The development of procedures that have the advantages of incorporating ‘green chemistry’ parameters such as atom economy,<sup>7</sup> reduction of synthetic steps, and reduction of waste and solvents are of immense importance.<sup>8</sup> In this context, biocatalysts mediate the direct aldol reaction with unmodified carbonyl donors in aqueous buffers.<sup>1,9,10</sup> Amino acids, small peptides, and other small organic catalysts can also catalyze direct aldol reactions in aqueous media.<sup>11</sup> In addition, the direct aldol reaction is catalyzed by organic quaternary ammonium salts and tertiary amines.<sup>12</sup> The use of simple basic inorganic salts such as NaOH and  $K_2CO_3$  as catalysts is also possible but the reactions are hard to control due to competing  $\beta$ -elimination, Cannizzaro reaction or Tishchenko reaction.<sup>13,14</sup>

We recently discovered that inorganic ammonium salts catalyze the aldol condensation reaction of carbonyl compounds in aqueous media.<sup>15</sup> This reaction may be of relevance for the formation of secondary aerosols in the atmosphere. Intrigued by the simplicity of these catalysts, we wanted to investigate their potential application for aldol reactions in environmentally be-

nign reaction solvents such as water or other aqueous media. Herein, we report for the first time, to the best of our knowledge, that inorganic ammonium salts catalyze the aqueous aldol reaction between unmodified ketones and aldehydes to furnish the corresponding aldol products in moderate to high yields.

In initial experiments, we screened a variety of inorganic salts for their ability to catalyze the aldol reaction between cyclohexanone **1a** (4 mmol) and *p*-nitrobenzaldehyde (0.8 mmol) on water (0.26 mL) (Table 1).

To our delight, we found that all the inorganic salts investigated catalyzed the formation of the corresponding aldol product **3a**. In particular, inorganic ammonium salts were highly efficient, the best catalyst being  $NH_4OH$  (entry 17). Moreover,  $NH_4F$  and  $NH_4OAc$  salts gave the corresponding aldol product **3a** in high conversions at 60–80 °C (entries 2, 5–11, and 15). The  $NH_4F$ -catalyzed reactions were also efficient in the presence of organic solvents such as DMSO (entry 16) and could also be run neat (entry 11). The presence of water accelerated the reaction,<sup>16</sup> which possibly occurs at the water–organic phase boundary.<sup>17</sup> Moreover, the catalyst loading could be reduced to 10 mol % (entry 16). Based on these preliminary results, we decided to investigate the scope of the  $NH_4F$ - and  $NH_4OH$ -catalyzed direct aldol reactions on water (Table 2).<sup>18</sup>

The reactions between cyclohexanone **1a** and aldehydes **2a–g** were highly chemoselective and gave the corresponding aldol products **3a–g** in good to high yields. For example aldol products **3b** and **3g** were isolated in 93% and 51% yields, respectively (entries 2 and 7). We also performed one transformation on a two gram scale and were able to isolate the corresponding aldol product **2a** in 89% yield.

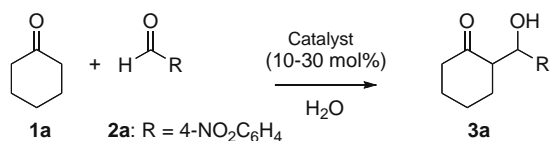
The aldol reactions between various ketones **1** and aldehyde **2a** were next investigated (Table 3).<sup>19</sup> The ammonium salt-catalyzed reactions were productive for both linear and cyclic ketones **1a–f** giving access to the corresponding aldols **3a** and **3h–l** typically in high yield. Notably, in two cases, the reaction was stereoselective

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**Table 1**

Examples of screened catalysts for the direct asymmetric intermolecular aldol reaction between **1a** and *p*-nitrobenzaldehyde on water<sup>a</sup>



Entry	Catalyst	H <sub>2</sub> O (μL)	Temp (°C)	Time (h)	Conv. <sup>a</sup> (%)
1	—	260	80	24	17
2	NH <sub>4</sub> F <sup>b</sup>	260	80	24	99
3	KF <sup>b</sup>	260	80	24	33
4	KAc <sup>b</sup>	260	80	24	29
5	NH <sub>4</sub> F <sup>c</sup>	260	80	24	98
6	NH <sub>4</sub> F <sup>b</sup>	260	60	18	99
7	NH <sub>4</sub> F <sup>c</sup>	260	60	48	99
8	NH <sub>4</sub> F <sup>d</sup>	150	60	18	98
9	NH <sub>4</sub> F <sup>d</sup>	50	60	18	98
10	NH <sub>4</sub> F <sup>d</sup>	10	60	18	95
11	NH <sub>4</sub> F <sup>d</sup>	0	60	24	92
12	NH <sub>4</sub> Cl <sup>d</sup>	150	60	120	50
13	NH <sub>4</sub> Br <sup>d</sup>	150	60	120	56
14	(NH <sub>4</sub> ) <sub>2</sub> SO <sub>4</sub> <sup>d</sup>	150	60	120	32
15	NH <sub>4</sub> Ac <sup>d</sup>	150	60	18	99
16	NH <sub>4</sub> F <sup>c</sup>	50 <sup>e</sup>	60	18	99
17	NH <sub>4</sub> OH <sup>d</sup>	150	60	1	99
18	NH <sub>4</sub> F <sup>d</sup>	150	60	72	76

<sup>a</sup> Conversion determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. The dr was 50:50 in all cases.

<sup>b</sup> 30 mol % of catalyst was employed.

<sup>c</sup> 10 mol % of catalyst was employed.

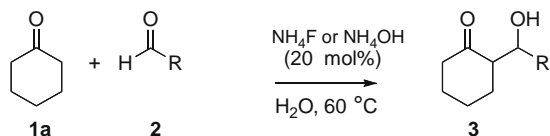
<sup>d</sup> 20 mol % of catalyst was employed.

<sup>e</sup> 150 mL of DMSO was also added.

affording dihydroxyacetone **1b** derived sugar-like product **3h** and cycloheptanone-derived product **3k**, respectively, with good *syn*-diastereoselectivity (entries 2 and 5). It was also possible to employ the cyclic  $\alpha,\beta$ -unsaturated ketone **1d** as a donor (entry 4). The ammonium salt catalysis should also be applicable to the synthesis of tertiary aldol products. In fact, the reaction between

**Table 2**

The ammonium fluoride-catalyzed direct intermolecular aldol reaction between **1a** and various aldehydes **2**



Entry	R	Product	Time (h)	Yield <sup>a</sup> (%)
1	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>3a</b>	18 <sup>b</sup>	88
2	4-NCC <sub>6</sub> H <sub>4</sub>	<b>3b</b>	24 <sup>b</sup>	93
3	3-ClC <sub>6</sub> H <sub>4</sub>	<b>3c</b>	26 <sup>b</sup>	75
4	4-ClC <sub>6</sub> H <sub>4</sub>	<b>3d</b>	26 <sup>b</sup>	68
5	4-BrC <sub>6</sub> H <sub>4</sub>	<b>3e</b>	28 <sup>b</sup>	58
6	Naphth	<b>3f</b>	96 <sup>c</sup>	51
7	CO <sub>2</sub> Et	<b>3g</b>	24 <sup>c</sup>	51
8	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>3a</b>	72 <sup>c</sup>	65 <sup>d</sup>
9	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>3a</b>	1 <sup>c,e</sup>	90
10	4-NCC <sub>6</sub> H <sub>4</sub>	<b>3b</b>	1 <sup>c,e</sup>	82
11	Naphth	<b>3f</b>	3 <sup>c,e</sup>	74

<sup>a</sup> Isolated yield after silica gel column chromatography. The dr was 50:50 in all cases.

<sup>b</sup> Reaction run in 0.26 mL of H<sub>2</sub>O.

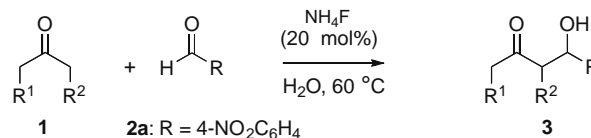
<sup>c</sup> Reaction run in 0.15 mL of H<sub>2</sub>O.

<sup>d</sup> Reaction run at room temperature.

<sup>e</sup> NH<sub>4</sub>OH (20 mol %) was used as the catalyst.

**Table 3**

The ammonium fluoride-catalyzed direct intermolecular aldol reaction between various ketones **1** and aldehyde **2a**



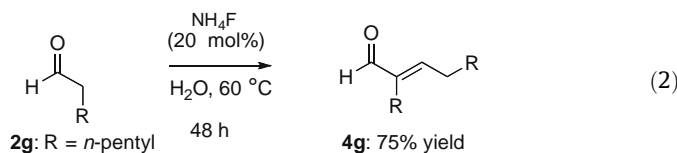
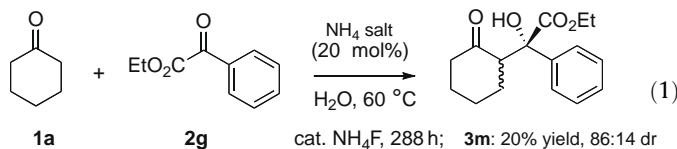
Entry	Ketone	Product	Time (h)	dr <sup>a</sup>	Yield <sup>b</sup> (%)
1	<b>1a</b>	<b>3a</b>	18	50:50	88
2	<b>1b</b>	<b>3h</b>	300 <sup>c</sup>	75:25	26
3	<b>1c</b>	<b>3i</b>	22	—	71
4	<b>1d</b>	<b>3j</b>	288	50:50	68
5	<b>1e</b>	<b>3k</b>	48	67:33	68
6	<b>1f</b>	<b>3l</b>	26	50:50	59

<sup>a</sup> *syn:anti* ratio as determined by NMR analysis of the crude product.

<sup>b</sup> Isolated yield after silica gel column chromatography.

<sup>c</sup> The reaction was performed at room temperature using 30 mol % of NH<sub>4</sub>F and 150 μL of DMSO.

ketone **1a** and  $\alpha$ -ketoester **2g** was highly stereoselective and gave the corresponding tertiary aldol product **3m**<sup>20</sup> in up to 86:14 dr (Eq. 1). Thus, even the simplest amine catalyst can in some cases control the stereoselectivity in the C–C bond-forming step. The NH<sub>4</sub>F salt was also able to catalyze the self-aldol reaction of heptanal **2g** to afford **4g** in high yield (Eq. 2).



To account for the product formation by ammonium salt catalysis, we propose the enamine mechanism shown in Figure 1.

Thus, equilibrium of the ammonium salt generates ammonia, which is followed by the formation of the nucleophilic enamine intermediate by reaction of the ketone and ammonia via an initial

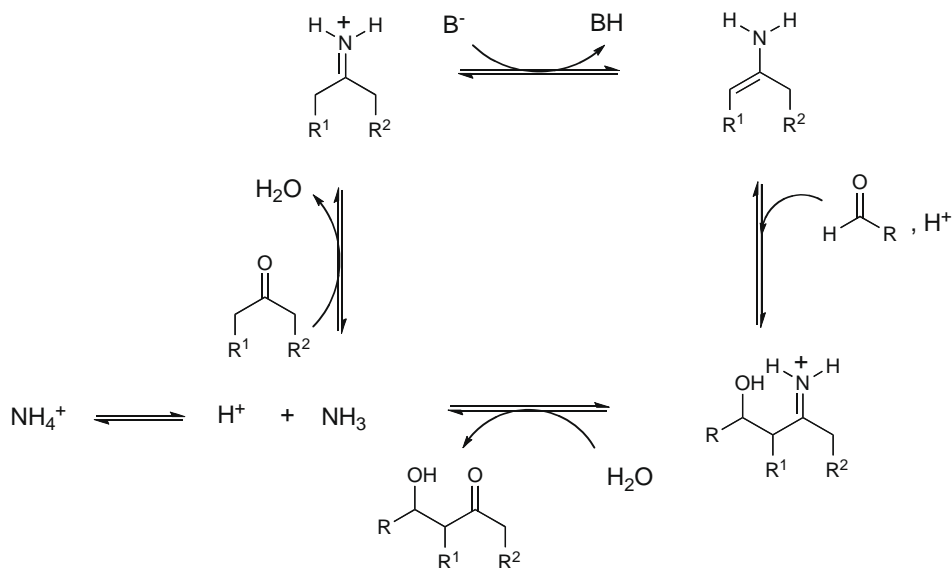


Figure 1. Proposed reaction mechanism.

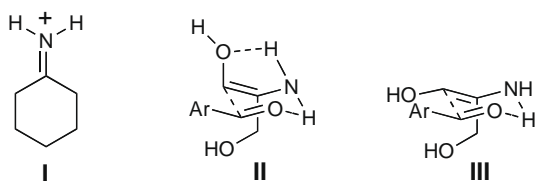


Figure 2. Iminium ion I, *cis*-enamine intermediate II and *trans*-enamine intermediate III.

iminium intermediate. Subsequent C–C bond formation followed by hydrolysis of the iminium intermediate gives the corresponding aldol product as well as the ammonium ion. The formation of the iminium intermediate I (Fig. 2) from the reaction between cyclohexanone 1a and  $\text{NH}_4\text{F}$  was established by HRMS analysis. The counter ion of the inorganic ammonium salt was important contributing to the pH of the reaction media,<sup>15d</sup> which controlled the rate of reaction. Thus, for the  $\text{NH}_4\text{OH}$ -catalyzed transformation, a base-mediated aldol reaction mechanism is also likely to contribute. The ability of the ammonium salt to control the stereoselectivity in some cases can be explained by the fact that one of the possible enamine intermediate confirmations was preferred in the transition state. Thus, in Table 2 entry 2, the *cis*-enamine intermediate II is preferred over the *trans*-enamine intermediate III due to hydrogen bonding (Fig. 2). In the case of the aldol reactions with ketones as donors, the aldol reaction pathway (Fig. 1) is faster compared to the possible enamine pathway.<sup>15c</sup> However, for aldol reactions with aldehydes as donors this is reversed and the aldol condensation reaction proceeds (Eq. 2) via the faster enamine reaction pathway.<sup>15c</sup>

In summary, we have reported that inexpensive and simple inorganic ammonium salts catalyze direct aldol reactions in aqueous media. The corresponding aldol products are formed in moderate to high conversions under environmentally benign reaction conditions. In some cases, the reaction exhibited high diastereoselectivity. Moreover, the ability of naturally occurring inorganic ammonium salts to catalyze the aldol reaction and for formation of sugar molecules in aqueous media is of potential significance to prebiotic chemical processes.<sup>21</sup> Ammonium salt catalyzed-aldol reactions may also occur in the atmosphere.<sup>15</sup> Further develop-

ment of environmentally benign asymmetric C–C bond-forming reactions and mechanistic studies of ammonium catalysis is ongoing.

#### Acknowledgments

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#### Supplementary data

Supplementary data associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.014.

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18. Typical experimental procedure for the NH<sub>4</sub>F-catalyzed direct aldol reactions in aqueous media (Table 2). A catalytic amount of NH<sub>4</sub>F (20 mol %) was added to a vial containing aldehyde **2** (0.8 mmol), cyclohexanone **1a** (4.0 mmol, 427 μL) in H<sub>2</sub>O (150 or 260 μL). After stirring the reaction mixture for the time shown in Table 2 at 60 °C it was loaded directly onto a silica gel column. The crude aldol product was purified by silica gel column chromatography (EtOAc-pentane mixtures) to furnish the desired aldol product **3**.
19. Typical experimental procedure for the NH<sub>4</sub>F-catalyzed direct aldol reactions in aqueous media (Table 3). A catalytic amount of NH<sub>4</sub>F (20 mol %) was added to a vial containing 4-nitrobenzaldehyde **2a** (0.8 mmol) and ketone **1** (4.0 mmol) in H<sub>2</sub>O (150 μL). After stirring the reaction mixture for the time shown in Table 3 at 60 °C it was loaded directly onto a silica gel column. The crude aldol product was purified by silica gel column chromatography (EtOAc-pentane mixtures) to furnish the desired aldol product **3**.
20. **Compound 3m**: Major diastereomer. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 1.28 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.55–1.88 (m, 4H) 1.90 (m, 1H), 2.06 (m, 1H), 2.29–2.44 (m, 2H), 3.18 (dd, *J* = 5.5, 12.7 Hz, 1H), 4.16 (s, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 7.26–7.36 (m, 3H, ArH), 7.50 (d, *J* = 7.2 Hz, 2H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm): 14.3, 25.6, 28.0, 30.8, 30.8, 43.2, 53.9, 62.1, 73.4, 125.8, 128.1, 128.5, 128.7, 140.6, 173.2, 212.7. Minor diastereomer. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 1.23 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.52–1.75 (m, 4H) 1.87 (m, 1H), 2.07 (m, 1H), 2.31–2.45 (m, 2H), 3.40 (dd, *J* = 6.1, 12.9 Hz, 1H), 3.87 (s, 1H), 4.11–4.25 (m, 2H), 7.27–7.37 (m, 3H, ArH), 7.58 (d, *J* = 7.9 Hz, 2H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm): 14.2, 25.1, 27.5, 27.8, 42.6, 59.0, 62.2, 77.8, 125.5, 127.9, 128.5, 139.2, 174.8, 213.0.
21. Weber, A. *Orig. Life Evol. Biosph.* **2007**, *37*, 105. In preliminary experiments, we also found that the ammonium salt catalyzed the formation of sugars by aldol reactions with dihydroxyacetone or glycolaldehyde in water.