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Secondary amine catalyzed *retro*-aldol reactions of enals and enones: one-pot conversion of enals to α-substituted derivatives

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ABSTRACT

A practical synthetic procedure to hydrolytically cleave the C,C-double bond of α,β-unsaturated aldehydes and ketones has been developed. Secondary amines are employed as organocatalysts for the *retro*-aldol process under simple and mild reaction conditions. Beside the generation of the parent aromatic aldehydes, the synthetic procedure has been successfully used in a one-pot reaction sequence to convert simple cinnamaldehydes into their α-aryl/alkyl substituted derivatives.

Benzaldehydes, an important class of carbonyl compounds, are valuable aromas in food, beverages, cosmetics, and pharmaceutical industries.[1,2] More importantly, benzaldehydes are synthetic starting materials for various families of structurally complex compounds. Hence, the production of benzaldehydes from natural and synthetic resources has always been in high demand.[1–4] Recently, the synthesis of benzaldehyde from natural cinnamon oil, which contains cinnamaldehyde, has drawn widespread attentions from synthetic chemists and industrial engineers.[5–11] Many production procedures have been developed to carry out this process, including critical-water hydrolysis,[5,6] alkaline hydrolysis,[7–12] hydrolysis on surfactants[7–10] or employment of natural catalysts such as cyclodextrins,[3,4] glycerine[1] and proline[12] to facilitate the hydrolysis of cinnamaldehyde to benzaldehyde. However, these processes have several drawbacks,[3,4] such as requiring very harsh conditions, incomplete conversion of cinnamaldehyde and low yield of benzaldehyde. Hence, it is still desirable to develop a new mild and simple method for the highly effective conversion of cinnamaldehyde to benzaldehyde. Herein, we would like to describe a practical synthetic approach to produce benzaldehydes from cinnamaldehydes under very mild reaction conditions, employing an iminium-catalytic process. The method could also be applied to other classes of α,β-unsaturated carbonyl compounds. Preliminary studies to use this synthetic approach in one-pot reaction sequences are reported.

Iminium catalysis is recognized as one of the most efficient modes of activation in organocatalysis.[13] The catalysts, normally secondary amines, react with the carbonyl compounds lacking a hydrogen atom at the α-position to form iminium ion species, thus activating the system for nucleophilic attacks.[13] The reversible formation of the iminium ion lowers the energy of the LUMO associated with the π-electron system and activates it for subsequent reactions, which include a wide variety of cycloaddition and conjugate addition reactions.[14] During the work in our group on iminium activation of α,β-unsaturated aldehydes by secondary amines, we noticed that conjugated C,C-double bonds were cleaved in the presence of water. We reasoned that water could act as a nucleophile to attack and hydrolyze the C,C-double bond of the iminium-activated species in a *retro*-aldol fashion. Although numerous examples of similar transformation have been reported to occur under harsh conditions using strong Brønsted bases,[7–12] a systematic method for organocatalyzed hydrolysis of the C,C-double bond of the α,β-unsaturated carbonyl compounds has never been fully developed.[15]

We started our investigation by screening different secondary amine catalysts for the *retro*-aldol reaction (Table 1). Cinnamaldehyde (**1**) was exposed to 0.5 equiv of secondary amine catalysts in THF solution in the presence of 2.0 equiv of water (Eq. 1, Table 1). For most of the catalysts tested, the reactions went smoothly at room temperature, giving benzaldehyde (**2**) in good yields (entries 1–5, Table 1). However, acyclic amines such as dibenzylamine and diisopropylamine showed poorer catalytic activity, and the reactions with these two amines were not complete within 1 day

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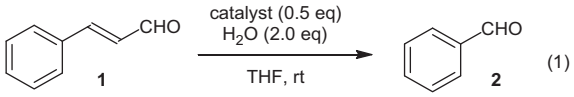
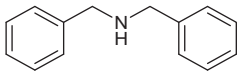
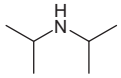
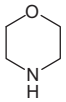
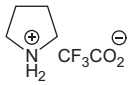
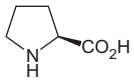
Table 1
Catalyst screening for the *retro*-aldol hydrolysis



Entry[a]	Catalyst	Reaction time (day)	Conversion[b] (%)	Yield **2**[c] (%)
1[d]		1	88	64
2[d]		1	90	69
3		1	100	73
4		1	100	70
5		1	100	81
6[e]		2	25	5
7[e]		2	17	3

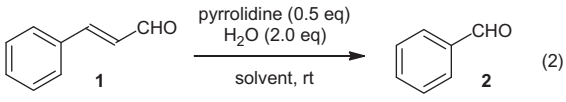
[a] Reaction conditions: 1 M THF solution, cinnamaldehyde (1.0 equiv), catalyst (0.5 equiv), water (2.0 equiv), rt.
[b] Determined by ^{1}H NMR with 1,3,5-triisopropylbenzene as internal standard.
[c] Yield of isolated benzaldehyde after column chromatography.
[d] After 1 day, the reaction was stopped.
[e] After 2 days, the reaction was stopped.

(entries 2–3, Table 1). Among the cyclic amines that gave complete conversion after 24 h, pyrrolidine seemed to be the best catalyst for the currently studied conditions, yielding 81% of benzaldehyde (entry 5, Table 1).

As iminium activation is often carried out with a Brønsted acid co-catalyst,[13] we also studied the reaction with the trifluoroacetate ammonium salt of pyrrolidine (entry 6, Table 1) and L-proline (entry 7, Table 1). However, these catalysts gave unsatisfactory results, with incomplete conversion and low yields of benzaldehyde. We think that in these cases the pH of the reaction medium is low, disfavoring the nucleophilic addition of water to the C,C-double bond. It should be noted here that acetaldehyde (bp = 21 °C), the other product of the reaction, is volatile under the reaction conditions.

We continued to investigate the effect of solvents on the reaction (Eq. 2, Table 2). Cinnamaldehyde was again treated with 0.5 equiv of pyrrolidine and 2.0 equiv of water in various solvents. The initial study without adding any organic solvent to the reaction mixture gave very poor conversion and yield (entry 1, Table 2), so we chose several organic solvents that are miscible with water to facilitate the reaction. Out of the four solvents tested, tetrahydrofuran, acetonitrile and dimethylsulfoxide gave comparable results with clean reactions and high yields of benzaldehyde (entries 2, 4, 5, Table 2). The best yield of **2** was obtained in acetonitrile in 89%. On the other hand, methanol led to disappointing results with complex reaction mixtures and low yields of benzaldehyde (entry 3, Table 2). We presumed that the methanol solvent might interfere with the iminium ion formation process by forming a hemiacetal with cinnamaldehyde **1**. Although both of these processes are reversible, it is possible that the abundant nature of methanol limited the formation of iminium ions.

Table 2
Solvent screening for the *retro*-aldol hydrolysis

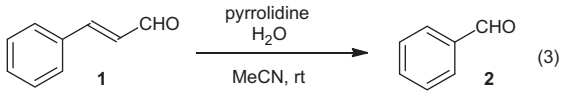


Entry[a]	Solvent	Reaction time (day)	Conversion[b] (%)	Yield **2**[c] (%)
1[d]	No solvent	2	10	Trace
2	THF	1	100	81
3	MeOH	1	67	5
4	DMSO	1	100	83
5	MeCN	1	100	89

[a] Reaction conditions: 1 M solution, cinnamaldehyde (1.0 equiv), pyrrolidine (0.5 equiv), water (2.0 equiv), rt.
[b] Determined by ^{1}H NMR with 1,3,5-triisopropylbenzene as internal standard.
[c] Yield of isolated benzaldehyde after column chromatography.
[d] No other organic solvent was added. After 2 days, the reaction was stopped.

After identifying the best catalyst and solvent for the *retro*-aldol reaction of cinnamaldehyde **1**, we decided to optimize the catalyst loading and amount of water added to the reaction (Eq. 3, Table 3). The amount of added pyrrolidine was varied from 0.1 to 1.0 equiv while keeping the amount of water constant at 2.0 equiv. The reaction time was prolonged more with less pyrrolidine as the catalyst (entries 1, 2, 4, 7, Table 3). However, 0.3 equiv of pyrrolidine was sufficient to catalyze the reaction to full conversion after 12 h at room temperature in a very good yield of benzaldehyde (entry 4, Table 3). Then, the amount of water added was varied from 1 to 10 equiv at 0.3 equiv catalyst loading (entries 3–6, Table 3). The re-

Table 3
Optimization of catalyst loading and amount of water



Entry[a]	Catalyst (equiv)	Water (equiv)	Reaction time[b] (h)	Yield **2**[c] (%)
1	1.0	2	6	84
2	0.5	2	8	91
3	0.3	1	18	85
4	0.3	2	12	88
5	0.3	4	12	86
6	0.3	10	12	76
7	0.1	2	84	53

[a] Reaction conditions: 1 M acetonitrile solution, cinnamaldehyde (1.0 equiv), pyrrolidine, water, rt.
[b] Reaction time for 100% conversion checked by TLC.
[c] Yield of isolated benzaldehyde after column chromatography.

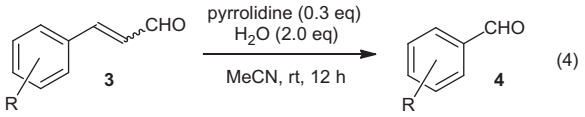
sults of these reactions revealed that 2.0 equiv are probably the optimal amount of water, as yields of **2** started to decrease when there was more than 4.0 equiv of water in the reaction mixture. This trend agrees well with the result of entry 1, Table 2 reported above.

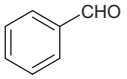
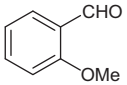
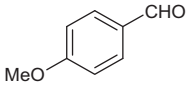
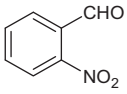
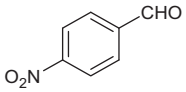
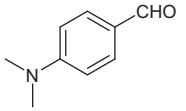
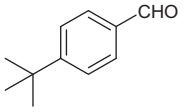
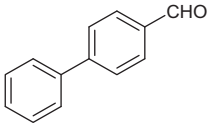
With the optimized reaction conditions for the *retro*-aldol hydrolysis of cinnamaldehyde **1** in hand, we then investigated the scope of this reaction on a series of substituted cinnamaldehydes **3a**–**h** (Eq. 4, Table 4). The reaction worked well on all of the substituted cinnamaldehydes tested (Table 4), giving high yields of aromatic aldehydes **4a**–**h**.[16] The mixture of *Z* and *E* (1:9) isomers of 4-*tert*-butylcinnamaldehyde and 4-phenylcinnamaldehyde also gave the related aldehydes in good yield (entries 7,8, Table 4). Thus, a catalytic amount of pyrrolidine could facilitate the hydrolysis of cinnamaldehydes to their corresponding aromatic aldehydes under mild reaction conditions.

We then tried to expand the scope of this *retro*-aldol hydrolysis further by examining several other classes of α,β-unsaturated carbonyl compounds (Eq. 5, Table 5). These included three aliphatic aldehydes and three chalcones (Table 5). The hydrolysis of the aliphatic aldehydes **5a**–**c** worked smoothly using the optimized reaction conditions developed above (entries 1–3, Table 5). However, the reactions with α,β-unsaturated ketones (chalcones **5d**–**f**, Table 5) were sluggish, so a small amount of trifluoroacetic acid was added and the temperature was elevated to facilitate the iminium ion formation (entries 4–6, Table 5).[17] With the Brønsted acid co-catalyst, hydrolysis of the chalcones proceeded well, giving a moderate yield of the products. It is possible that the inverse aldol condensation had affected the yield of the reaction with α,β-unsaturated ketones, different to that of α,β-unsaturated aldehydes where the acetaldehyde by-product is volatile. Yields of products **7d**–**f** were generally lower than that of **6e**–**f**, presumably due to the fact that they formed the homo aldol products under the reaction conditions.[18] In brief, although the *retro*-aldol hydrolysis did not work perfectly on α,β-unsaturated ketones, this synthetic procedure still gave encouraging results.

At this stage, we wanted to further extend the synthetic applications of the developed secondary amine catalyzed *retro*-aldol hydrolysis procedure of α,β-unsaturated carbonyl compounds. In a preliminary study, this process was successfully employed in a one-pot two-step reaction where cinnamaldehydes **8a**–**c** were converted into α-substituted cinnamaldehydes **11a**–**c** (Scheme 1). First, cinnamaldehydes **8a**–**c** were hydrolyzed to the aromatic aldehydes **9a**–**c** with pyrrolidine as the catalyst. Subsequently, aldehydes with two α-hydrogen atoms (**10a**–**c**) were added to the same reaction mixtures to react with **9a**–**c**

Table 4
Retro-aldol hydrolysis of cinnamaldehydes[16]



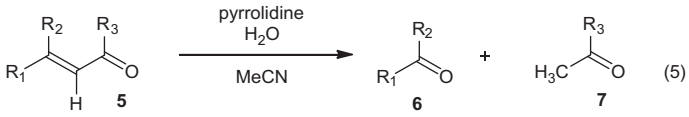
Entry[a]	**3**,**4**	R	Product **4**	Yield[b] **4** (%)
1	**a**	H		88
2	**b**	*o*-MeO		83
3	**c**	*p*-MeO		77
4	**d**	*o*-NO_2		84
5	**e**	*p*-NO_2		79
6	**f**	*p*-NMe_2		91
7	**g**	*p*-^{t}Bu *Z*:*E* = 1:9		83
8	**h**	*p*-Ph *Z*:*E* = 1:9		86

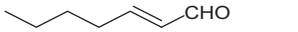
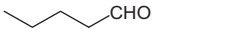
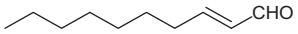
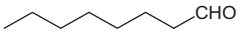
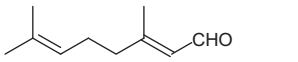
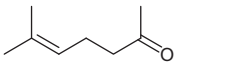
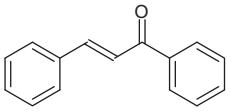
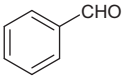
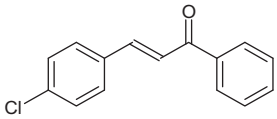
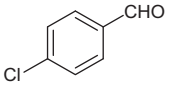
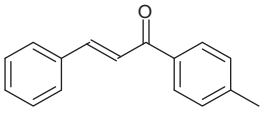
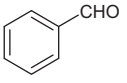
[a] Reaction conditions: 1 M acetonitrile solution, cinnamaldehyde (**3**, 1.0 equiv), pyrrolidine (0.3 equiv), water (2.0 equiv), rt, 12 h.
[b] Yield of isolated aldehyde **4** after column chromatography.

to form **11a**–**c** under pyrrolidine catalysis.[19] Three examples, where R was a methyl or phenyl group, have been carried out with moderate to good overall yields.[20] The final outcome of this one-pot two-step reaction is equivalent to an alkylation/arylation at the α-position of cinnamaldehydes **8**. Thus, the developed *retro*-aldol hydrolysis procedure could be utilized to facilitate an interesting chemical transformation that would be difficult by other means.[21] Work on further synthetic applications of this procedure is currently in progress.

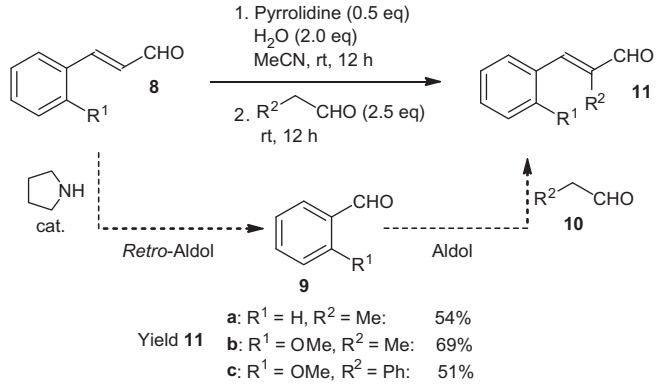
In conclusion, a practical synthetic procedure to hydrolytically cleave the C,C-double bond of α,β-unsaturated aldehydes and ketones has been developed. It employs the secondary amines as organocatalysts for a *retro*-aldol process under simple and mild reaction conditions. Several classes of α,β-unsaturated carbonyl compounds have been successfully transformed using this procedure, including the valuable cinnamaldehydes. This synthetic procedure has been successfully employed in a one-pot reaction sequence to convert cinnamaldehydes into α-aryl/alkyl substituted cinnamaldehydes. Future directions to develop the reported chemistry will focus on optimizing catalyst/reaction conditions for α,β-unsaturated ketones and α-substituted α,β-unsaturated aldehydes and including this synthetic transformation in further organocatalytic cascade sequences.

Table 5
Scope of the *retro*-aldol hydrolysis of α,β-unsaturated carbonyl compounds[17]



Entry		Substrate	Additive	Reaction time (h)		Product **6**	Yield **6**[a] (%)	Yield **7**[a] (%)
Aliphatic α,β-unsaturated aldehydes								
1[b]	**a**		—	12	**a**		62[c]	n.d.
2[b]	**b**		—	12	**b**		79	n.d.
3[b]	**c**		—	12	**c**		90	n.d.
Chalcones								
4[d]	**d**		TFA	48	**d**		49	36
5[d]	**e**		TFA	48	**e**		53	41
6[d]	**f**		TFA	48	**f**		51	39

[a] Yield of isolated product after column chromatography, unless otherwise noted.
[b] Reaction conditions: 1 M acetonitrile solution, unsaturated carbonyl compound (**5**, 1.0 equiv), pyrrolidine (0.3 equiv), water (2.0 equiv), rt.
[c] The reaction was performed in *d3*-acetonitrile; yield determined by crude ^{1}H NMR with 1,3,5-triisopropylbenzene as internal standard
[d] Reaction conditions: 1 M acetonitrile solution, unsaturated carbonyl compound (**5**, 1.0 equiv), pyrrolidine (0.5 equiv), water (3.0 equiv), trifluoroaceticacid (TFA, 0.1 equiv), 50 °C.



Scheme 1. One-pot *retro*-aldol/aldol condensation to convert cinnamaldehydes **8** to α-substituted cinnamaldehydes **11**.

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15. See for example Ref. 1,3,4,12 on the hydrolysis using organic compounds such as cyclodextrin, proline and glycine as reagents or catalysts. However, these examples either involve the use of inorganic Brønsted bases or are ineffective. On the other hand, there have been several literature examples describing organocatalyzed *retro*-aldol reactions of β-hydroxy carbonyl compounds: Flock, A. M.; Reucher, C. M. M.; Bolm, C. *Chem. Eur. J.* **2010**, *16*, 3918–3921; Luo, S.; Zhou, P.; Li, J.; Cheng, J. P. *Chem. Eur. J.* **2010**, *16*, 4457–4461.
16. General procedure for the *retro*-aldol reaction of cinnamaldehydes: To a solution of cinnamaldehyde (**3**, 1 mmol, 1.0 equiv) in acetonitrile (1 mL) were added water (2 mmol, 2.0 equiv) and pyrrolidine (0.3 mmol, 0.3 equiv). The reaction mixture was stirred at room temperature for 12 h under argon, after which it was filtered through a short pad of $MgSO_4$ and washed with dry dichloromethane. The solvent of the filtrate was removed in vacuo and the residue was chromatographed on silica gel (dichloromethane/hexane; 7:3) to give the aromatic aldehyde **4**. All aldehydes **3a–h** and **4a–h** are either commercially available or have been described previously, and their analytical data match literature values.
17. General procedure for the *retro*-aldol reaction of chalcones: To a solution of chalcone (**5**, 1 mmol, 1.0 equiv) in acetonitrile (1 mL) were added water (3 mmol, 3.0 equiv), pyrrolidine (0.5 mmol, 0.5 equiv) and trifluoroacetic acid (0.1 mmol, 0.1 equiv). The reaction mixture was stirred at 50 °C for 48 h under argon, after which it was cooled to rt and quenched with aqueous saturated NH_4Cl solution. The organic products were extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (dichloromethane/hexane; 7:3) to give the aromatic aldehyde **6** and aromatic ketone **7**. All of the products **6d–f** and **7d–f** are either commercially available or have been described previously, and their analytical data match literature values.
18. Traces of dimerized products of 7 could be found in the reaction mixture.

19. General procedure for the *retro*-aldol/aldol one-pot condensation of cinnamaldehydes: To a solution of cinnamaldehyde (**8**, 1 mmol, 1.0 equiv) in acetonitrile (1 mL) were added water (2 mmol, 2.0 equiv) and pyrrolidine (0.5 mmol, 0.5 equiv). The reaction mixture was stirred at room temperature for 12 h under argon and aldehyde **10** (2.5 mmol, 2.5 equiv) was subsequently added. After another 12 h at rt, the reaction mixture was filtered through a short pad of $MgSO_4$ and washed with dry dichloromethane. The solvent of the filtrate was removed in vacuo and the residue was chromatographed on silica gel (dichloromethane/hexane; 7:3) to give the α-substituted cinnamaldehyde **11**. Compounds **11a–c** are either commercially available or have been described previously, and their analytical data match the literature values.
20. The backward *retro*-aldol hydrolysis of **11**–**9** did not seem to occur, probably because α-substituted α,β-unsaturated aldehydes are much less activated by iminium catalysis due to steric hindrance: Yang, J. W.; Fonseca, M. T. H.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 6660–6662.
21. Arylation/alkylation at this position could possibly be carried out via recently developed Heck-type coupling chemistry, see review: Arpad, M. *Chem. Rev.* **2011**, *111*, 2251–2320 and references therein