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A Novel Pyrrolidine Imide Catalyzed Direct Formation of α,β-Unsaturated Ketones from Unmodified Ketones and Aldehydes

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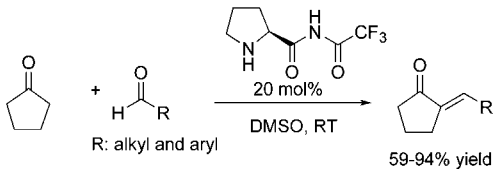
ABSTRACT



A method for direct, stereoselective preparation of (*E*)-α,β-unsaturated ketones from ketones and aldehydes, promoted by a novel pyrrolidine imide organocatalyst, has been developed in moderate to high yields. Unlike the Claisen–Schmidt condensation and Lewis acid catalyzed tandem aldol–dehydration processes, this method provides mild reaction conditions to access α,β-unsaturated ketones from simple, unmodified ketones.

The broad utility of α,β-unsaturated carbonyl compounds in organic synthesis has continued to attract considerable synthetic interest in developing new methods for their syntheses.[1] Generally, these compounds are prepared by the Claisen−Schmidt condensation from aromatic aldehydes and ketones.[2,3] However, this method suffers from several side reactions under relatively strong basic conditions and the narrow substrate diversity.[2,3] As an alternative, mild Lewis acid-catalyzed tandem Mukaiyama aldol−dehydration reactions have been described but require preformation of enolates from ketones.[4,5] In this paper, we wish to report a novel organocatalyst, an imide derivative of pyrrolidine, that can be used for direct, stereoselective synthesis of (*E*)-α,β-

(1) For reviews, see: (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Elsevier: Oxford, 1992; Chapters 2 and 3. (b) Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Elsevier: Oxford, 1991; Vol. 4, p 1. (c) Lee, V. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Elsevier: Oxford, 1991; Vol. 4, pp 69 and 139. (d) Kozlowski, J. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Elsevier: Oxford, 1991; Vol. 4, p 169. (e) Basavaiah, D.; Dharma Rao, P.; Suguna Hyma, R. *Tetrahedron* **1996**, *52*, 8001. (f) Ciganek, E. *Org. React.* **1997**, *51*, 201. (h) Basavaiah, D.; Jaganmohan Rao, A.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.

(2) For review, see: Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Elsevier: Oxford, 1991; Vol. 2, p 133.

(3) For recent examples of the Claisen−Schmidt condensation, see: (a) Mogilaiah, K.; Reddy, N. V. *Synth. Commun.* **2003**, *33*, 73. (b) Hatsuda, M.; Kuroda, T.; Seki, M. *Synth. Commun.* **2003**, *33*, 427. (c) Sensfuss, U. *Tetrahedron Lett.* **2003**, *44*, 2371. (d) Kreher, U. P.; Rosamilia, A. E.; Raston, C. L.; Scott, J. L.; Strauss, C. R. *Org. Lett.* **2003**, *5*, 3107. (e) Zhang, Z.; Dong, Y.-W.; Wang, G.-W. *Chem. Lett.* **2003**, 966. (f) Choudary, B. M.; Kantam, M. L.; Ranganath K. V. S.; Mahendar, K.; Sreedher, B. *J. Am. Chem. Soc.* **2004**, *126*, 3396. (g) Sabitha, G.; Reddy, G. S. K. K.; Reddy, K. B.; Yadav, J. S. *Synthesis* **2004**, 263. (h) Husson, J.; Migianu, E.; Beley, M.; Kirsch, G. *Synthesis* **2004**, 267. (i) Climent, M. J.; Corma, A.; Iborra, S.; Velty, A. *J. Catal.* **2004**, *221*, 474.

(4) (a) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A. Yamamoto, H., Eds.; Springer-Verlag: Berlin, Germany, 1999; Vol. III, p 997. (b) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. (c) Mukaiyama, T. *Org. React.* **1982**, *28*, 203. (d) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, *9*, 1011. (e) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. (f) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392. (g) Yamamoto, Y.; Maruyama, K. *Tetrahedron Lett.* **1980**, *21*, 4607. (h) Denmark, S. E.; Wong, K.-T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333. (i) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432. (j) Denmark, S. E.; Wong, K.-T.; Stavenger, R. A.; Su, X. *J. Am. Chem. Soc.* **1999**, *121*, 4982.

(5) (a) Ishihara, K.; Kurihara, H.; Yamamoto, H. *Synlett* **1997**, 597. (b) Yanagisawa, A.; Goudu, R.; Arai, T. *Org. Lett.* **2004**, *6*, 4281.

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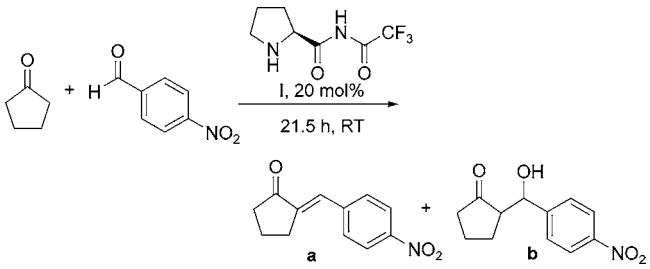
unsaturated ketones in moderate to good yields from unmodified ketones and aldehydes under mild reaction conditions.

In recent years, small organic molecule-based organocatalysis has received considerable attention in organic synthesis.[6] One of the extensively studied oragnocatalyst-catalyzed reactions is the aldol condensation of aldehydes and ketones.[7−11] In seeking new organocatalysts with structural diversity for catalyzing aldol reactions, we have designed and prepared a novel organocatalyst pyrrolidine imide **I** (Table 1).[12,13] This bifunctional molecule having a basic pyrrolidine and a significantly acidic imide moiety could function the same way as L-proline does for promoting reactions. In an initial study using 20 mol % of **I** for an aldol condensation, the reaction of cyclopentanone with *p*-nitrobenzaldehyde in DMSO, surprisingly, did not result in the formation of the desired condensation product **b** (Table 1, entry 1). In contrast, the dehydration product, an α,β-unsaturated ketone **a**, with (*E*) configuration was obtained stereoselectively as the major product in high yield (93%) (Table 1, entry 1). Based on the observation, we envisioned that the compound **I** could serve as an effective catalyst for direct preparation of the synthetically useful α,β-unsaturated carbonyl compounds from simple aldehydes and ketones.

An initial investigation of a variety of reaction media for the process revealed that reaction solvents played a significant role in the formation of α,β-unsaturated ketone **a** and condensation product **b**. It is noted that in DMSO, dehydration product **a** was produced exclusively in 93% yield without aldol product **b** (Table 1, entry 1). However, in the other eight solvents tested, both products were formed, and in many cases, the aldol product **b** was the major one (Table 1, entries 3−9). The results of the study prompted us to select DMSO as reaction medium for the subsequent investigation (Table 1, entry 3).

Table 1. Effect of Solvents on Dehydration Reaction of Cyclopentanone with *p*-Nitrobenzaldehyde[a]

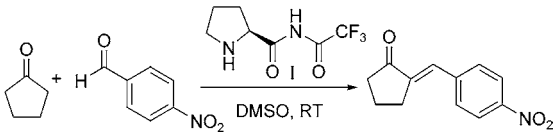


entry	solvent	yield (%) for product **a**[b]	yield (%) for product **b**[b,c]
1	DMSO	93	
2	DMF	71	28
3	CH_2Cl_2	43	54
4	$CHCl_3$	37	61
5	1,4-dioxane	33	65
6	EtOAc	32	66
7	*i*-PrOH	32	53
8	THF	31	68
9	CH_3CN	31	47

[a] Reaction conditions: A mixture of aldehyde (0.15 mmol), ketone (0.30 mmol), and catalyst **I** (0.03 mmol) in 0.5 mL of anhydrous DMSO was vigorously stirred for 21.5 h. The resulting mixture was then directly purified by silica gel chromatography to provide a solid or clear oil. [b] Isolated yield. [c] Stereoselectivity not determined.

The effect of catalyst loading on the reaction efficiency was evaluated next (Table 2). Reactions with 10 and 5 mol % catalyst **I** took place much slower, and a large amount of starting materials remained. Therefore, the use of 20 mol % of pyrrolidine imide **I** was optimal to ensure high reaction efficiency (93% yield) while maintaining a reasonable reaction time (Table 2, entry 1).

Table 2. Effect of Catalyst Loading on Dehydration Reaction of Cyclopentanone with *p*-Nitrobenzaldehyde[a]



entry	catalyst (mol %)	time	% yield[b]
1	20	21.5 h	93
2	10	7 d	70
3	5	7 d	31

[a] Reaction conditions (see footnote a in Table 1). [b] Isolated yield.

Having established optimal reaction conditions, we probed the generality of the process (Table 3). The reaction between

(6) For selected recent organocatalysis reviews, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (c) List, B. *Synlett* **2001**, 1675. (d) List, B. *Tetrahedron* **2002**, *58*, 5573. (e) Special issue: Asymmetric Organocatalysis. *Acc. Chem. Res.* **2004**, *37*, 487.

(7) For L-proline-catalyzed aldol reactions, see: (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573. (c) Pidathala, D.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 2785. (d) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (e) Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 3541. (f) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798. (g) Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 2152. (h) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752. (i) Pan, Q.; Zou, B.; Wang, Y.; Ma, D. *Org. Lett.* **2004**, *6*, 1009.

(8) For diamine catalyzed aldol reactions, see: (a) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2004**, *43*, 2420. (b) Saito, S.; Nakadai, M.; Yamamoto, H. *Synlett* **2001**, 1245. (c) Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8167.

(9) For amino alcohol catalyzed aldol reactions, see: (a) Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262. (b) Tang, Z.; Jiang, F.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5755. (c) Zhong, G.; Fan, J.; Barbas, C. F., III. *Tetrahedron Lett.* **2004**, *45*, 5681.

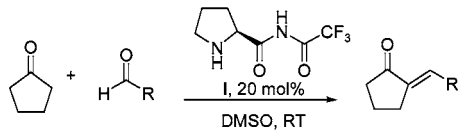
(10) For peptide-catalyzed aldol reactions, see: Tang, Z.; Yang, Z.-H.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Org. Lett.* **2004**, *6*, 2285.

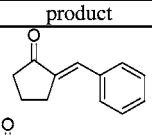
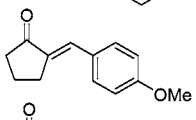
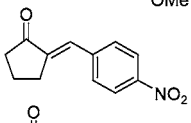
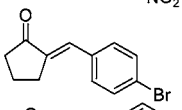
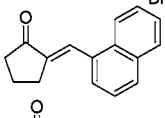
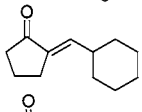
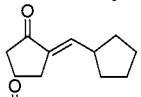
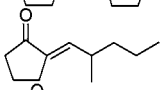
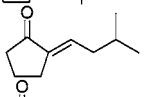
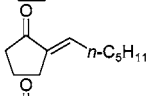
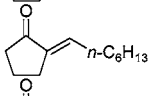
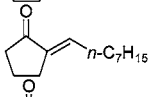
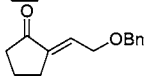
(11) For pyrrolidine tetrazole catalyzed aldol reactions, see: Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983.

(12) For the preparation of catalyst **I**, see the Supporting Information.

(13) Recently, we have found pyrrolidine sulfonamide/amide as effective catalysts for asymmetric organic transformations, see: Michael addition: (a) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2004**, in press. α-Aminoxylation: (b) Wang, W.; Wang, J.; Li, H.; Liao, L.-X. *Tetrahedron Lett.*, **2004**, *45*, 7235. Mannich-type reaction: (c) Wang, W.; Wang, J.; Li, H. *Tetrahedron Lett.* **2004**, *45*, 7243. α-Selenenylation: (d) Wang, W.; Wang, J.; Li, H. *Org. Lett.* **2004**, *6*, 2817. α-Sulfenylation: (e) Wang, W.; Li, H.; Wang, J.; Liao, L.-X. *Tetrahedron Lett.* **2004**, *45*, 8229.

Table 3. Pyrrolidine Imide I Catalyzed Dehydration Reactions of Cyclopentanone with Aldehydes[a]

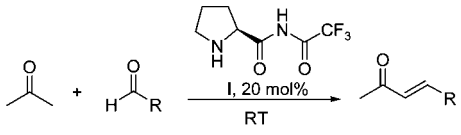


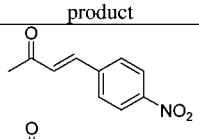
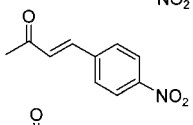
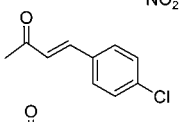
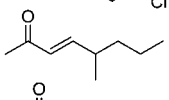
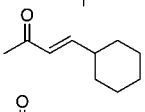
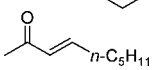
entry	product	t (h)	% yield[b]
1		10	84
2		40	94
3		21.5	93
4		40	88
5		132	85
6		40	82
7		6	61
8		72	69
9		47	71
10		47	79
11		47	64
12		47	59
13[c]		107	66

[a] Reaction conditions (see footnote a in Table 1). [b] Isolated yield. [c] Ratio of 5:1 for ketone to aldehyde was used.

cyclopentanone (0.15 mmol) and an aldehyde (0.3 mmol) in DMSO (0.5 mL) at room temperature in the presence of 20 mol % pyrrolidine imide **I** was conducted. The processes proceeded smoothly and stereoselectively to afford (*E*) α,*β*-unsaturated ketones in good to high yields (59−94%). The pyrrolidine imide **I** promoted reactions were applicable to a variety of aldehydes with different structural features including aromatic (Table 3, entries 1−5) and aliphatic (entries 6−13) systems. It was found that electronic effect on the reactions was very limited (Table 3, entries 2 and 3). For example, benzaldehydes having electron-donating (Table 3, entry 2) and -withdrawing (entry 3) groups afforded both

Table 4. Pyrrolidine Imide I Catalyzed Dehydration Reactions of Acetone with Aldehydes[a]



entry	product	t (h)	% yield[b]
1[c]		46	61
2		10	95
3		46	89
4		46	41
5		46	60
6		46	67

[a] Reaction conditions: A mixture of aldehyde (0.15 mmol) and catalyst **I** (0.03 mmol) in 0.5 mL of acetone was vigorously stirred for 10 or 46 h. The resulting mixture was then directly purified by silica gel chromatography, and fractions were collected and concentrated in vacuo to provide a solid or clear oil. [b] Isolated yield. [c] Ratio of 2:1 for ketone to aldehyde in DMSO was used.

products in high yields (94 and 93%, respectively). On the other hand, a pronounced steric effect is evident in the case of 1-naphthaldehyde (Table, entry 5 vs entries 1−4). The variations in chains of aliphatic aldehydes (Table 3, entries 6−9) resulted in comparable reaction yields (82, 61, 69, and 71%, respectively).

The catalyst **I** catalyzed reactions were tolerant of not only cyclic ketones, but also acylic systems (Table 4). When the same reaction conditions were employed for reaction of acetone with *p*-nitrobenzaldehye in 2:1 molar ratio in DMSO, a relatively low reaction yield (61%, Table 4, entry 1) was obtained. However, when acetone was used as a solvent and reagent, significant improvement for the reaction was made with a much higher yield (95%, Table 4, entry 2). Consequently, the reactions between acetone and aldehydes (0.15 mmol) were carried out in acetone (0.5 mL) in the presence of 20 mol % catalyst **I**. The reactions were general to both aromatic and aliphatic aldehydes and the α,*β*-unsaturated ketones were produced in good yields. Unfortunately, under the same reaction conditions, reactions with other ketone substrates proceeded very slowly in low yields and a large amount of the unreacted starting materials were recovered.

Two possible reaction mechanisms for the formation of α,*β*-unsaturated ketones have been proposed (Figure 1).[7b,8c,14,15] One route is the generation of *β*-hydroxyketone through an

(14) Ishikawa, T.; Uedo, E.; Okada, S.; Saito, S. *Synlett* **1999**, 450.

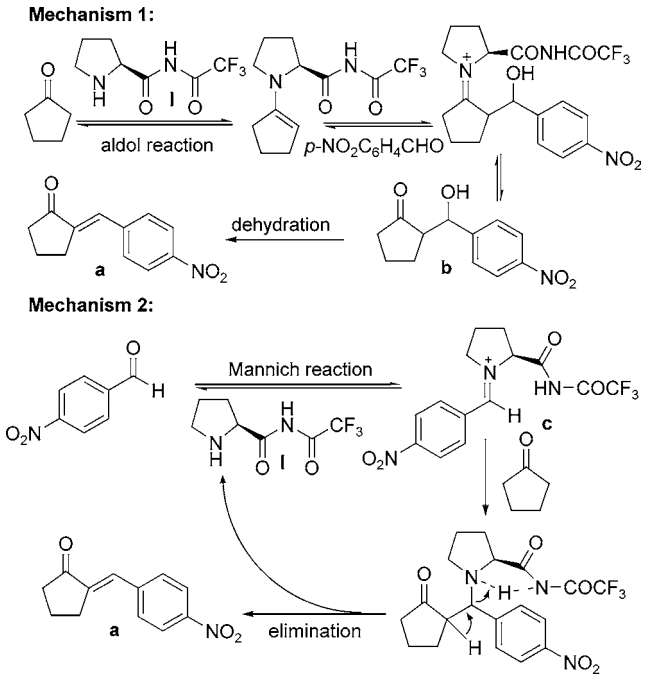


Figure 1. Two possible reaction pathways for formation of α,*β*-unsaturated ketones.

aldol condensation reaction, which then undergoes a dehydration process to afford the α,*β*-unsaturated ketone (Figure 1, mechanism 1).[5,7b,8c] It is known that a Lewis acid catalyzed tandem aldol condensation and dehydration process has been used for formation of α,*β*-unsaturated ketones.[5] Careful monitoring of the course of the reaction of cyclopentanone with *p*-nitrobenzaldehyde with 20 mol % **I** in DMSO by TLC revealed that the aldol condensation product was not observed. On the basis of this observation, we hypothesized the generation of α,*β*-unsaturated ketone may go through a Mannich-elimination sequence (Figure 1, mechanism 2).[14,15] This presumption was confirmed by a controlled study. Reaction of pure aldol product **b** in the presence of 20 mol % **I** in DMSO did not result in dehydration product **a** after 12 h by TLC analysis. We believe that the stronger acidic imide in **I** may play a critical role in facilitating the Mannich reaction over the aldol reaction. Moreover, the reactive charged aldimine species **c** was significantly stabilized in polar solvent such as DMSO or DMF, and thus high-yielding α,*β*-unsaturated ketone was generated, whereas in less polar solvents such as CH_2Cl_2 and $CHCl_3$, the aldol product was formed as major product (Table 1). However, more studies are needed to verify the proposed mechanism.

In summary, we have uncovered a mild and efficient method for preparation of α,*β*-unsaturated ketones from readily available, simple aldehydes and ketones, which takes advantage of the novel pyrrolidine imide organocatalyst **I**. This reaction is applicable to a wide range of aldehydes in good yields. A preliminary mechanistic study reveals that the reaction proceeds via a Mannich-elimination process. The full scope and reaction mechanism of the study will be reported in due course.

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Supporting Information Available: Experimental procedures and ^1H, ^{13}C NMR and/or MS data for catalyst **I** and dehydration products. This material is available free of charge via the Internet at http://pubs.acs.org.

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