

Enantioselective Synthesis of Polysubstituted Cyclopentanones by Organocatalytic Double Michael Addition Reactions

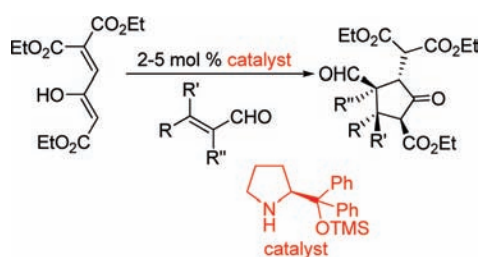
Anqi Ma and Dawei Ma*

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

Madw@mail.sioc.ac.cn

Received June 18, 2010

ABSTRACT



The *O*-TMS-protected diphenylprolinol-catalyzed cascade double Michael addition reactions of α,β -unsaturated aldehydes with a β -keto ester bearing a highly electron-deficient olefin unit occur smoothly to afford polysubstituted cyclopentanones. This process allows formation of four contiguous stereocenters in the cyclopentanone ring in one-step with excellent enantioselectivity.

Cyclopentane and cyclopentanone moieties have been frequently found in bioactive natural products.¹ This fact has stimulated a large number of investigations exploring new methodologies for asymmetric assembly of polysubstituted cyclopentanes and cyclopentanones.¹ In the field of organocatalysis, the Córdova group has found that 2,3,4-trisubstituted cyclopentanones could be assembled from 4-bromo β -ketoesters and α,β -unsaturated aldehydes via domino Michael addition/ α -alkylation reactions,² Wang et al. have reported the synthesis of highly functionalized cyclopentanes via double Michael additions,³ and Enders and co-workers have described a cascade Michael addition/ α -alkylation process to 1,1,2-

trisubstituted cyclopentanes.⁴ These achievements are additional examples that demonstrate the powerful application spectrum of organo-catalytic domino reactions in elaborating complex synthetic intermediates from simple precursors.^{5,6}

During the course of the development of organocatalytic Michael reactions,⁷ we became interested in exploring the possibility of assembling polysubstituted cyclopentanones via a cascade double Michael addition process of β -keto ester **1** and α,β -unsaturated aldehydes. As outlined in Scheme 1, we envisioned that after the Michael addition of an anion generated from **1** to iminium **5** through the transition state **A**, the newly formed enamine moiety in **6** would attack the highly electron-deficient olefin part to afford the intramo-

(1) For reviews, see: (a) Hudlicky, T.; Price, J. D. *Chem. Rev.* **1989**, *89*, 1467. (b) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293. (c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (d) Silva, L. F. *Tetrahedron* **2002**, *58*, 9137. (e) Helmchen, G.; Ernst, M.; Paradies, G. *Pure Appl. Chem.* **2004**, *76*, 495.

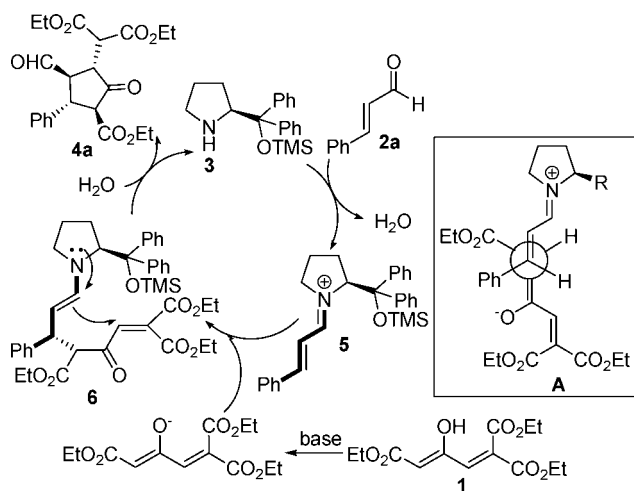
(2) Rios, R.; Vesely, J.; Sundén, H.; Ibrahim, I.; Zhao, G.-L.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 5835.

(3) Zu, L.; Li, H.; Xie, H.; Wang, J.; Jiang, W.; Tang, Y.; Wang, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3732.

(4) Enders, D.; Wang, C.; Bats, J. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 7539.

(5) For reviews of organocatalytic cascade reactions, see: (a) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (b) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037. (c) Alba, A.-N.; Companyó, X.; Viciano, M.; Rios, R. *Curr. Org. Chem.* **2009**, *13*, 1432.

Scheme 1. Catalytic Cycle for Double Michael Addition Reactions of β -Keto Ester **1** and α,β -Unsaturated Aldehyde **2a**



lecular Michael adduct **4a**. Notably, this process would provide a product with diverse functional groups and up to four contiguous stereocenters in one step.

The β -keto ester **1** was prepared via Wittig olefination of diethyl 2-oxomalonate with the ylide generated from ethyl 4-chloro-3-oxobutanoate and Ph_3P (see Supporting Information for detailed procedure). Its reaction with cinnamaldehyde **2a** in the presence of 2 mol % *O*-TMS-protected diphenylprolinol **3** as a catalyst was selected as a model for screening suitable reaction conditions. It was found that the reaction worked well in water to provide **4a** in 62% yield and

(6) For selected examples of organocatalytic cascade reactions, see: (a) Bui, T.; Barbas, C. F., III. *Tetrahedron Lett.* **2000**, *41*, 6951. (b) Córdova, A.; Notz, W.; Barbas, C. F., III. *J. Org. Chem.* **2002**, *67*, 301. (c) Dudding, T.; Hafez, A. M.; Taggi, A. E.; Wagerle, T. R.; Lectka, T. *Org. Lett.* **2002**, *4*, 387. (d) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2003**, *42*, 4233. (e) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962. (f) Yang, J. W.; Fonseca, M. T. H.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036. (g) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (h) Brandau, S.; Maerten, E.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 14986. (i) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861. (j) Wang, B.; Wu, F.; Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 768. (k) Zu, L.-S.; Wang, J.; Li, H.; Xie, H.-X.; Jiang, W.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 1036. (l) Enders, D. M. R.; Hüttl, M.; Runsink, J.; Raabe, G.; Wendt, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 467. (m) Carlone, A.; Cabrera, S.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1101. (n) Wang, J.; Li, H.; Xie, H.; Zu, Li.; Shen, X.; Wang, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 9050. (o) Li, H.; Zu, L.; Xie, H.; Wang, J.; Jiang, W.; Wang, W. *Org. Lett.* **2007**, *9*, 1833. (p) Rueping, M.; Sugiono, E.; Merino, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3046. (q) Lu, L.-Q.; Cao, Y.-J.; Liu, X.-P.; An, J.; Yao, C.-J.; Ming, Z.-H.; Xiao, W.-J. *J. Am. Chem. Soc.* **2008**, *130*, 6946. (r) Tan, B.; Shi, Z.; Chua, P. J.; Zhong, G. *Org. Lett.* **2008**, *10*, 3425. (s) Bertelsen, S.; Johansen, R. L.; Jørgensen, K. A. *Chem. Commun.* **2008**, 3016. (t) Rueping, M.; Kuenkel, A.; Tato, F.; Bats, J. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 3699. (u) Schrader, W.; Handayani, P. P.; Zhou, J.; List, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 1463. (v) Galzerano, P.; Pescioli, F.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7892. (w) McGarrough, P. G.; Brenner, S. E. *Org. Lett.* **2009**, *11*, 5654.

(7) (a) Zhu, S.; Yu, S.; Ma, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 545. (b) Wang, J.; Yu, F.; Zhang, X.; Ma, D. *Org. Lett.* **2008**, *10*, 3075. (c) Wang, J.; Ma, A.; Ma, D. *Org. Lett.* **2008**, *10*, 5425. (d) Ma, A.; Zhu, S.; Ma, D. *Tetrahedron Lett.* **2008**, *49*, 3075. (e) Zhu, S.; Wang, Y.; Ma, D. *Adv. Syn. Catal.* **2009**, *351*, 2563. (f) Xu, D.; Zhang, Y.; Ma, D. *Tetrahedron Lett.* **2010**, *51*, 3827. (g) Zhu, S.; Yu, S.; Wang, Y.; Ma, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 4656.

satisfactory diastereoselectivity and enantioselectivity (Table 1, entry 1). Improved yields were observed by using some

Table 1. Condition Screening for the Formation of Cyclopentanone **4a** via Organocatalytic Double Michael Addition Reactions of **1** and **2a**^a

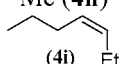
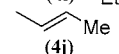
entry	solvent	<i>t</i> (h)	yield (%) ^b	dr ^c	ee (%) ^d
1	H ₂ O	2.5	62	19:1	99.4
2	MeCN	4	66	21:1	97.1
3	THF	8	71	16:1	99.6
4	CH ₂ Cl ₂	3	71	20:1	99.1
5	Cl(CH ₂) ₂ Cl	1	77	18:1	99.9
6	toluene	1	77	21:1	>99.9
7 ^e	toluene	1	82	20:1	>99

^a Reaction conditions: **1** (0.12 mmol), **2a** (0.15 mmol), 2 mol % catalyst **3**, 0.2 mL of solvent, 0 °C for 1 h, then rt if the reaction is not finished. ^b Isolated yield. ^c Determined by ¹H NMR measurements performed on the isolated product. ^d Determined by chiral-phase HPLC analysis of the corresponding alcohol obtained by reduction of the aldehyde moiety. ^e **2a** (0.13 mmol) was used.

organic solvents (entries 2–6), and toluene was found to be the best reaction media (entry 6). The highest yield could be obtained by reducing the molar ratio of **2a** and **1** from 1.25:1 to 1.08:1 (entry 7).

Having the optimized conditions in hand, the scope of the cascade process was examined by varying α,β -unsaturated aldehydes. The results are summarized in Table 2. In all

Table 2. Asymmetric Double Michael Addition Reactions of **1** with β -Monosubstituted α,β -Unsaturated Aldehydes^a

entry	R (product)	yield (%) ^b	dr ^c	ee (%) ^d
1	4-MeOC ₆ H ₄ (4b)	79	23:1	>99
2	4-BrC ₆ H ₄ (4c)	75	10:1	>99
3	4-FC ₆ H ₄ (4d)	83	16:1	99
4	2-MeOC ₆ H ₄ (4e)	95	16:1	>99
5	2-BrC ₆ H ₄ (4f)	78	4:1	99
6	2-Furyl (4g)	89	15:1	98
7	Me (4h)	86 ^{e,f}	19:1	95
8	 (4i)	70 ^f	27:1	98
9	 (4j)	76 ^{e,f}	4:1	99 ^g

^a Reaction conditions: **1** (0.12 mmol), **2** (0.13 mmol), 2 mol % catalyst **3**, toluene (0.2 mL), 0 °C for 1 h, then rt for about 1 h. ^b Isolated yield. ^c Determined by ¹H NMR after purification. ^d Determined by chiral-phase HPLC analysis of the corresponding alcohol obtained by reduction of the aldehyde moiety. ^e Reaction was carried out at -20 °C for 1 h. ^f Reaction was carried out with 5 mol % catalyst **3**. ^g Determined by chiral-phase HPLC analysis of the corresponding *p*-bromobenzoate derivative of the alcohol.

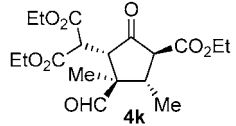
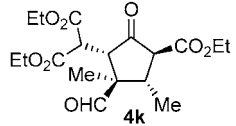
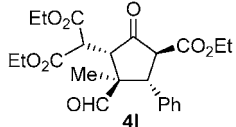
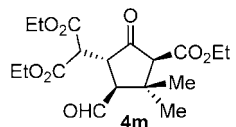
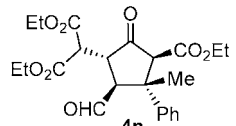
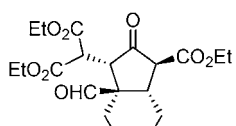
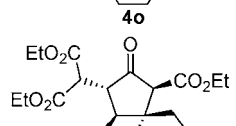
cases, only two diastereomers were determined by HPLC, and their structures were established (see discussion below) as **4** and **7**. For aromatic α,β -unsaturated aldehydes, their electronic nature seemed to have little influence on the cascade reaction process, as is evident from the observation that the substrates bearing both electron-rich and electron-deficient aromatic groups all gave the corresponding cyclopentanones in good yields and diastereoselectivity with excellent enantioselectivity (entries 1–4, 6). In case of the 2-bromophenyl substituted α,β -unsaturated aldehyde, diastereoselectivity dropped to 4:1 (entry 5), although the reason for this phenomenon was not clear. When less-reactive aliphatic α,β -unsaturated aldehydes were employed, increasing the catalytic loading from 2 to 5 mol % was required to ensure the complete conversion within 1–2 h (entries 7–9). It seemed that steric hindrance of the α,β -unsaturated aldehydes has a slight influence on enantioselectivity (compare entries 7 with 8). The product **4h** is a promising intermediate for synthesizing brasoside and littoralisone,⁸ natural products with neuroprotection activity, while the olefin part in the products **4i** and **4j** would allow further transformations to elaborate more complex molecules.

Comparing with many Michael addition reactions of α,β -unsaturated aldehydes catalyzed by secondary amines,⁹ this double Michael addition process requires less catalyst and proceeds significantly faster. The high efficiency may come from the robust activity of the β -keto ester **1** and prompted us to try the construction of quaternary carbon centers^{10–12} by using α,β - or β,β -disubstituted α,β -unsaturated aldehydes. This is a challenging task, because the additional alkyl group makes α,β -unsaturated aldehydes much less reactive by increasing both steric hindrance and electronic density of the C–C double bond.^{11,13} To the best of our knowledge, only one example using an α,β -disubstituted α,β -unsaturated aldehyde as the Michael acceptor has been described.¹³ However, in this case, no quaternary carbon center was formed.

With this idea in mind, the reaction of β -keto ester **1** with (*E*)-2-methylbut-2-enal was conducted under our standard conditions. It was found that at room temperature the reaction

proceeded quite slowly, but the desired product **4k** was isolated in 70% yield after 120 h (Table 3, entry 1). To

Table 3. Asymmetric Double Michael Addition Reactions of **1** with α,β - and β,β -Disubstituted α,β -Unsaturated Aldehydes^a

entry	product	<i>t</i> (h)	yield (%) ^b	dr ^c	ee (%) ^d
1		120	70	23:1	-
2		20	70 ^e	25:1	90
3		24	67 ^e	10:1	95 (91)
4		2	90	5:2:1	>99 (95)
5		12	82 ^f	1.6:1	>99 (99)
6		24	81 ^f	3:1	99 ^{g,h} (97)
7		2	90 ^f	11:3:1:1	>99 (98)

^a Reaction conditions: **1** (0.12 mmol), **2** (0.13 mmol), 2 mol % catalyst **3**, toluene (0.2 mL), 0 °C for 1 h, then rt. ^b Isolated yield. ^c Determined by ¹H NMR measurements after purification. ^d Determined by chiral-phase HPLC analysis of the corresponding alcohol obtained by reduction of the aldehyde moiety. The data in parentheses is the ee value for the minor diastereoisomer. ^e Reaction was carried out at 45 °C for the indicated time. ^f Reaction was carried out with 5 mol % catalyst **3**. ^g Determined by chiral-phase HPLC analysis of **4o**.

(8) (a) Mangion, I. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3696. (b) Li, Y.-S.; Matsunaga, K.; Ishibashi, M.; Ohizumi, Y. *J. Org. Chem.* **2001**, *66*, 2165.

(9) For recent reviews, see: (a) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638. (b) Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2007**, 2065.

(10) For recent reviews on quaternary stereogenic centers, see: (a) Douglas, C. J.; Overmann, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (b) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688. (c) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (d) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473. (e) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (f) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969.

(11) For a review on the organocatalytic formation of quaternary stereocenters, see: Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583.

(12) For selected recent examples regarding the formation of an all-carbon-substituted quaternary stereocenter in chiral amine-catalyzed domino reactions, see: (a) Rios, R.; Sundén, H.; Vesely, J.; Zhao, G.-L.; Dziedzic, P.; Cordova, A. *Adv. Synth. Catal.* **2007**, *349*, 1028. (b) Penon, O.; Carlone, A.; Mazzanti, A.; Locatelli, M.; Sambri, L.; Bartoli, G.; Melchiorre, P. *Chem.–Eur. J.* **2008**, *14*, 4788. (c) Tan, B.; Chua, P. J.; Li, Y.; Zhong, G. *Org. Lett.* **2008**, *10*, 2437.

(13) King, H. D.; Meng, Z.; Denhart, D.; Mattson, R.; Kimura, R.; Wu, D.; Gao, Q.; Macor, J. E. *Org. Lett.* **2005**, *7*, 3437.

accelerate the reaction, we tried to heat the reaction mixture and were pleased to find that the reaction was completed after 20 h at 45 °C (entry 2). To our delight, enantioselectivity only slightly dropped under these heating conditions, probably due to great asymmetric induction ability of the amine catalyst.¹⁴ (*E*)-2-Methyl-3-phenyl-acrylaldehyde could also be converted under these conditions giving cyclopentanone **4l** in 67% yield (entry 3). Its reduced derivative **8** is crystalline, thereby giving us the opportunity to establish the relative configuration of the polysubstituted cyclopentanones **4** via X-ray analysis as indicated in Figure 1.

The β,β -disubstituted α,β -unsaturated aldehydes are more reactive than α,β -disubstituted α,β -unsaturated aldehydes for

(14) For a review, see: Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876.

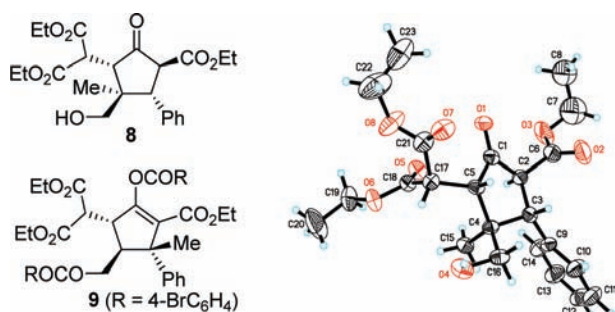


Figure 1. Structures of the alcohol **8** and the enol ether **9** and the X-ray structure of **8**.

this process, as is evident from the reaction of **1** with 3-methylbut-2-enal, which was completed at room temperature in 2 h to give **4m** in 90% yield (entry 4). In this case, the diastereoselectivity was only moderate (5:2:1 for three isomers), mainly because of the increased steric hindrance at the *ortho* position of the 2-ester group. However, the major diastereomer has over 99% ee. A similar phenomenon was observed in the case of (*E*)-3-phenylbut-2-enal as a substrate (entry 5). Next, we moved our attention to build fused and spiro rings by employing cyclic α,β -unsaturated aldehydes. Gratifyingly, starting from 1-cyclohexene-1-carbaldehyde, we could isolate bicyclo-[4.3.0]nonanone **4o** in 81% yield with a diastereoselectivity of 3:1 and an excellent ee (>99% major, 97% minor) (entry 6). When 2-cyclohexylideneacetaldehyde was used, the reaction was finished in 2 h to afford spiro[4.5]decanone **4p** in 90% yield (entry 7). In this case, four diastereomers were determined, presumably due to the increased steric hindrance caused by the spiro ring. The ratio for these isomers was about 11:3:1:1, and the two major ones

gave determinable ee values (>99% for major component, 98% for minor component).

The minor diastereomer in most cases was assumed to be the 2-epimer of **4**. To prove this hypothesis, a mixture of the reduced derivative of **4n** and its isomer was treated with 4-bromobenzoyl chloride and trimethylamine. Only one isomer **9** (Figure 1) was isolated from this reaction, indicating that the 2-position is the one most likely to isomerize in the cascade reaction process.

In conclusion, we have developed a highly efficient cascade double Michael addition process to assemble polysubstituted cyclopentanones, in which four contiguous stereocenters in the cyclopentanone ring were generated in one-step with excellent enantioselectivity. The diverse functional groups in the products will permit further manipulation to synthesize bioactive natural products. Most importantly, our result provides the first example for the creation of an all-carbon-substituted quaternary stereogenic center by using less-reactive α,β - or β,β -disubstituted α,β -unsaturated aldehydes as Michael acceptors in organocatalytic reactions, which will stimulate further investigations to extend the scope of organocatalytic Michael addition reactions.

Acknowledgment. We are grateful to the Ministry of Science and Technology (grant 2009ZX09501-00), Chinese Academy of Sciences, and National Natural Science Foundation of China (grant 20632050 & 20921091) for their financial support.

Supporting Information Available: Experimental procedures and copies of ^1H NMR and ^{13}C NMR spectra for all new products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL101414B