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Organocatalytic Michael Addition of Aldehydes to γ-Keto-α,β-unsaturated Esters. An Efficient Entry to Versatile Chiral Building Blocks

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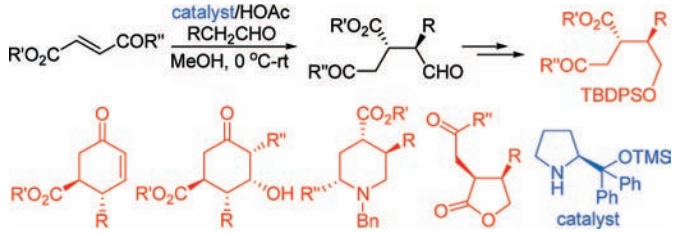
ABSTRACT



The diarylprolinol ether/HOAc-catalyzed Michael addition of aldehydes to γ-keto-α,β-unsaturated esters occurs in a highly regioselective and enantioselective manner. The adducts could easily be converted into synthetically useful cyclohexenones, cyclohexanones, piperidines, and γ-lactones.

Organocatalytic Michael addition of aldehydes to electron-deficient olefins is an attractive approach for organic synthesis because it can provide versatile chiral building blocks from conveniently available starting materials in an efficient manner.[1] This transformation normally requires highly reactive electron-deficient olefins as Michael acceptors to ensure good conversions.[1−6] These olefins include nitroalkenes,[2] 1,1-bis(benzenesulfonyl)ethylene,[3] maleimides,[4] alkylidenemalontes,[5] and α-keto-α,β-unsaturated esters.[6] For nitroalkenes, great progress has been made in developing effective catalytic systems and extending the reaction scope.[2] However, little attention has been directed to explore the possibility of using enones as substrates, although their products are more synthetically useful.[7] In 2003, Melchiorre and Jørgensen reported that chiral amines could catalyze the direct Michael addition of aldehydes to vinyl ketones.[7a] Gellman and co-workers subsequently discovered that diphenylprolinol methyl ether[7b] and MacMillan imidazolidinone catalyst[7c] provided better enantioselectivity. In their studies, only two enones, methyl vinyl ketone and ethyl vinyl ketone, gave the adducts with good yields.[7] More sterically hindered

(1) For a review, see: Vicario, J. L.; Badı´a, D.; Carrillo, L. *Synthesis* **2007**, 2065.

(2) For recent references, see: (a) Hayashi, Y. T.; Okano, T. S.; Aratake, S.; Hazelard, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 4922. (b) Zhu, S.; Yu, S.; Ma, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 545. (c) Wiesner, M.; Revell, J. D.; Wennemers, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 1871. (d) Chi, Y.; Guo, L.; Kopf, N. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2008**, *130*, 5608. (e) Wiesner, M.; Revell, J. D.; Tonazzi, S.; Wennemers, H. *J. Am. Chem. Soc.* **2008**, *130*, 5610. (f) García-García, P.; Ladépêche, A.; Halder, R.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 4719. (g) Hayashi, Y.; Itoh, T.; Ohkubo, M.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4722.

(3) Mossé, S.; Alexakis, A. *Org. Lett.* **2005**, *7*, 4361.

(4) Zhao, G.-L.; Xu, Y.; Sundén, H.; Eriksson, L.; Sayah, M.; Córdova, A. *Chem. Commun.* **2007**, 734.

(5) Wang, J.; Yu, F.; Zhang, X.; Ma, D. *Org. Lett.* **2008**, *10*, 3075. A hetero-Diels−Alder reaction mechanism is also possible for this reaction.

(6) Zhao, G.-L.; Vesely, J.; Sun, J.; Christensen, K. E.; Bonneau, C.; Córdova, A. *Adv. Synth. Catal.* **2008**, *350*, 657.

(7) (a) Melchiorre, P.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 4151. (b) Chi, Y.; Gellmann, S. H. *Org. Lett.* **2005**, *7*, 4253. (c) Peelen, T. J.; Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2005**, *127*, 11598.

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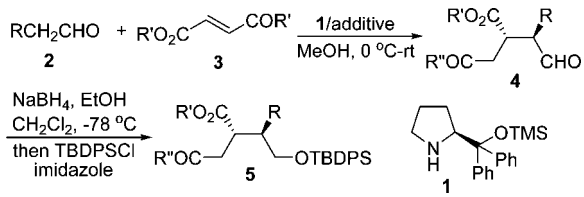
vinyl ketones and β-substituted enones were found as poor substrates, although they exhibited good reactivity in some intramolecular Michael addition.[8] Thus, it is highly desired to discover an alternative way to overcome this drawback.

In connection with our interest in development of organocatalytic reactions,[2b,6] we found that γ-keto-α,β-unsaturated esters **3**, the enones with a β-carboxylate ester, could easily react with aldehydes to give Michael adducts **4** (Scheme 1) with good yields and diastereoselectivity and excellent enantioselectivity. Upon simple treatments, these adducts could be converted into substituted cyclohexenones, cyclohexanones, piperidines, and γ-lactones that are useful chiral building blocks for assembly of some complex natural products. Herein we wish to detail our results.

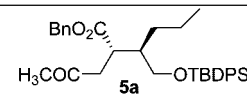
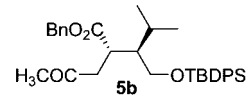
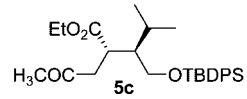
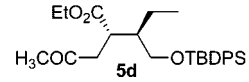
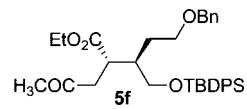
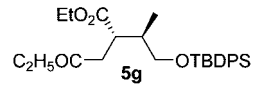
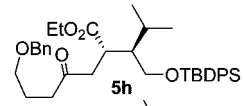
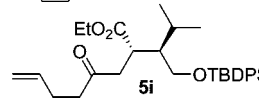
Scheme 1



The required enones **3** can easily be prepared by a simple Wittig reaction of ethyl glyoxylate with ketone derived ylides or by ng Nozaki's method.[9] Initially, the reaction of benzyl 4-oxopent-2-enoate **3a** with *n*-pentanal was explored as a model transformation. As indicated in Table 1, it was found that Michael addition gave adduct **4a** (entry 1) under our previous conditions (10 mol % of catalyst **1**, 50 mol % of $PhCO_2H$, water as the solvent).[2b] However, both yield and diastereoselectivity were unsatisfactory. Reducing the catalytic loading gave a slight improvement (entry 2). A better result was obtained by changing the solvent to methanol (entry 3). Further improvement was achieved when the additive was switched to acetic acid (entry 4). It is noteworthy that epimerization occurred rapidly during the purification of the crude adduct **4a**; therefore, it was converted into the silyl ether **5a** for both NMR and chiral HPLC analysis.

Using this three-step transformation as a benchmark, we examined a series of aldehydes and enones in order to establish the scope and limits of this Michael addition. Generally, the adducts were obtained in good yield and diastereoselectivity and excellent enantioselectivity (entries 5−9). Besides the simple alkyl substituents, benzoxy- and olefin-embodied substrates were compatible with these conditions, giving more functionalized products (entries 9, 11, and 12). The size of the aldehydes seemed to have a slight influence on both enantioselectivity and diastereoselectivity being evident from the fact that relatively low stereoselectivity was observed when using propionaldehyde as a Michael donor (entries 8 and 10).

Table 1. Synthesis of Substituted γ-Keto Esters **5**[a]

entry	product	*syn*/*anti*[b]	yield (%)[c]	ee (%)[d]
1	 **5a**	1.3:1	45[e,f]	-
2		3:1	55[f]	-
3		4:1	56	95
4		10:1	72	99
5	 **5b**	11:1	74	98
6	 **5c**	10:1	71	97
7	 **5d**	11:1	71	97
8		9:1	64	96
9	 **5f**	7:1	63	98
10	 **5g**	6:1	63	93
11	 **5h**	7:1	50	>99
12	 **5i**	9:1	55	96

[a] Reaction conditions for cycloaddition: **1** (0.0125 mmol), aldehyde **2** (0.5 mmol), enone **3** (0.25 mmol), HOAc (or $PhCO_2H$ for entries 1−3, 0.0125 mmol), MeOH (0.5 mL), 0 °C to rt. [b] Determined by ^1H NMR of the crude adducts. [c] Isolated yield for three steps, [d] Determined by chiral-phase HPLC analysis. [e] 10 mol % of **1** and 50 mol % of $PhCO_2H$ were used. [f] Isolated yield for reduction products, while water was used as the solvent.

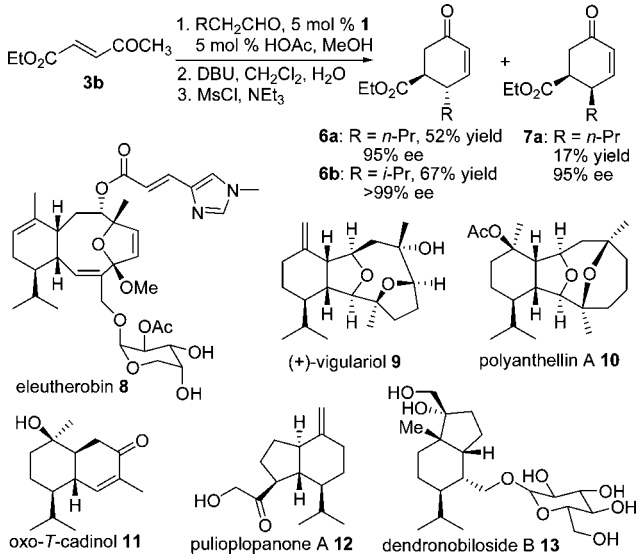
This encouraging result prompted us to explore the synthetic applications of the Michael adducts. As shown in Scheme 2, DBU-mediated intramolecular aldol reaction of the adducts followed by treatment with mesyl chloride and triethylamine produced 4,5-disubstituted cyclohexenones. In the case of *n*-pentanal, both *trans*-isomer **6a** and *cis*-isomer **7a** were isolated in a ratio of 3:1. The low diastereoselectivity should result from epimerization of the aldehyde under aldol reaction conditions. However, starting from 3-methylbutanal, only *trans*-isomer **6b** was obtained with 67% yield and 99% ee, indicating that steric hindrance has an important effect on the diastereo-selectivity during the aldol reaction. Possibly, enone **6b** can be employed for the synthesis of natural

(8) (a) Fonseca, M. T. H.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3958. (b) Yang, J. W.; Fonseca, M. T. H.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036. (c) Hayashi, Y.; Gotoh, H.; Tamura, T.; Yamaguchi, H.; Masui, R.; Shoji, M. *J. Am. Chem. Soc.* **2005**, *127*, 16028. (d) Vo, N. T.; Pace, R. D. M.; O'Hara, F.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 404.

(9) Nozaki, Y.; Tamura, T.; Kaji, A. *Synthesis* **1983**, 134.

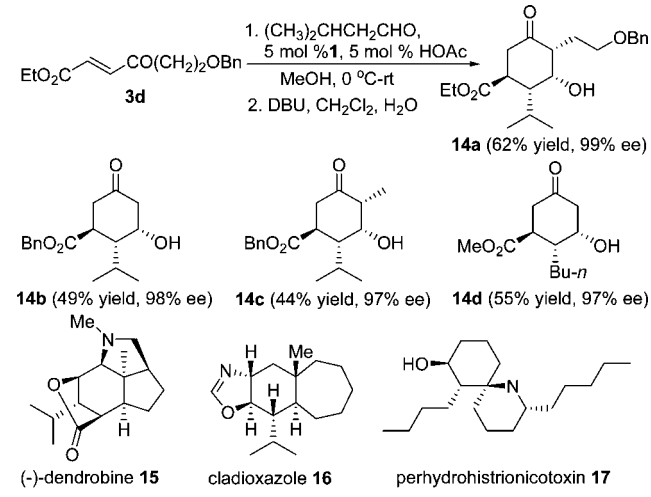
products such as cytotoxic marine diterpenes eleutherobin **8**,[10] (+)-vigulariol **9**,[11] and polyanthellin A **10**,[12] calcium channel antagonist oxo-T-cadinol **11**,[13] cytotoxic sesquiterpenoid pulioplopanone A **12**,[14] and the immunomodulator **13**.[15] The diterpenes **8**−**10** belong to a growing family of nontaxane-based microtubule stabilizers that have received great attention for synthetic and SAR studies during the past decade.[16] Many successful protocols rely on using natural (+)-carvone[10b−d] or (−)-cryptone[12b] as the starting material. Our easy assess to both enantiomers of **6b** will open a new avenue to access these biologically important molecules.

Scheme 2



of water is helpful to avoid racemization during the Aldol for a slight decrease in ee values was observed if dry methylene chloride was used. Similarly, ketones **14b**-**d** were prepared from the corresponding enones and aldehydes. The stereochemistry of the present products was established by NOESY studies of the ketone **14c**, which can be explained using a chairlike transition state model. These compounds may also be useful building blocks for the assembly of natural products. From the enantiomer of **14b**, for example, antipyretic alkaloid dendrobine **15**[17] and sesquiterpene cladioxazole **16**[18] could be elaborated, while an analogue of **14d** has been used for synthesis of perhydrohistrionicotoxin **17**.[19]

Scheme 3



The aldol reaction of our Michael adducts has the potential to give more functionalized cyclohexanones by changing the substituents of the enone part. Accordingly, the Michael adduct of 3-methylbutanal and enone **3d** was treated with DBU in methylene chloride (Scheme 3). It was gratifying to observe that under these reaction conditions 2,3,4,5-tetrasubstituted cyclohexanone **14a** was isolated as a single isomer with 62% yield and 99% ee. It was found that a trace

We then explored the possibility of preparing heterocycles from our Michael adducts, and were pleased to observe that direct reductive amination of the adduct of enone **3a** and *n*-pentanal with benzylamine and $NaBH(OAc)_3$ provided 1,2,4,5-tetrasubstituted piperidine **18a** with 74% yield and 97% ee. Variation at the 2,4 and 5 positions is possible as indicated by formation of piperidines[20] **18b**−**e**. In these cases other minor isomers were isolated in less than 20% yield and the stereochemistry of these major isomers was established by NOESY studies of **18a**. The stereoselectivity in the reductive amination step can be rationalized by a stereoelectronic control model as indicated in Scheme 4.

Scheme 5 illustrates our effort toward the construction of γ-lactones. Reduction of the Michael adduct of 4-benzoxybutanal with **3a** at −78 °C gave rise to semiacetal **19** in 80% yield, which was treated with TsOH in benzene to afford lactone **20** in excellent yield. Importantly, *cis*-3,4-disubsti-

(10) Isolation: (a) Lindel, T.; Jensen, P. R.; Fenical, W.; Long, B. H.; Casazza, A. M.; Carboni, J.; Fairchild, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 8744. Synthesis: (b) Nicolaou, K. C.; Ohshima, T.; Hosokawa, S.; van Delft, F. L.; Vourloumis, D.; Xu, J. Y.; Pfefferkorn, J.; Kim, S. *J. Am. Chem. Soc.* **1998**, *120*, 8674. (c) Chen, X.; Zhou, B.; Bhattacharya, S. K.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 789. (d) Castoldi, D.; Caggiano, L.; Panigada, L.; Sharon, O.; Costa, A. M.; Gennari, C. *Chem.—Eur. J.* **2006**, *12*, 51.

(11) Isolation: (a) Su, J.-H.; Huang, H.-C.; Chao, C.-H.; Yan, L.-Y.; Wu, Y.-C.; Sheu, J.-H. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 877. Synthesis: (b) Becker, J.; Bergander, K.; Fröhlich, R.; Hoppe, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1654.

(12) Isolation: (a) Ospina, C. A.; Rodrigueza, A. D.; Ortega-Barria, E.; Capson, T. L. *J. Nat. Prod.* **2003**, *66*, 357. Synthesis: (b) Kim, H.; Lee, H.; Kim, J.; Kim, S.; Kim, D. *J. Am. Chem. Soc.* **2006**, *128*, 15851.

(13) Taber, D. F.; Christos, T. E. *J. Org. Chem.* **1996**, *61*, 2081.

(14) Triana, J.; López, M.; Pérez, F. J.; González-Platas, J.; Quintana, J.; Estévez, F.; León, F.; Bermejo, J. *J. Nat. Prod.* **2005**, *68*, 523.

(15) Zhao, W.; Ye, Q.; Tan, X.; Jiang, H.; Li, X.; Chen, K.; Kinghorn, A. D. *J. Nat. Prod.* **2001**, *64*, 1196.

(16) Busch, T.; Kirschning, A. *Nat. Prod. Rep.* **2008**, *25*, 318.

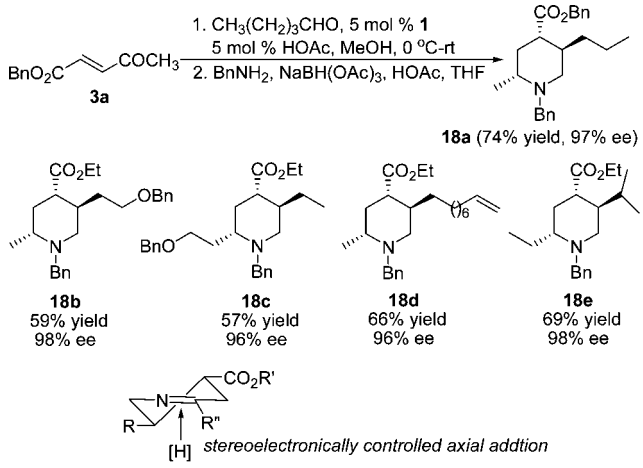
(17) Sha, C.-K.; Chiu, R.-T.; Yang, C.-F.; Yao, N.-T.; Tseng, W.-H.; Liao, F.-L.; Wang, S.-L. *J. Am. Chem. Soc.* **1997**, *119*, 4130.

(18) Ata, A.; Ackerman, J.; Radhika, P. *Tetrahedron Lett.* **2003**, *44*, 6951.

(19) Ibuka, T.; Mitsui, Y.; Hayashi, K.; Taga, T.; Inubushi, Y. *Tetrahedron Lett.* **1981**, *22*, 4425.

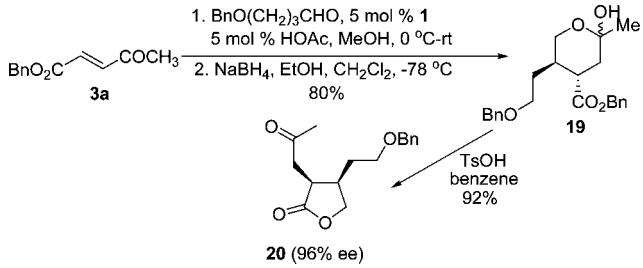
(20) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953.

Scheme 4



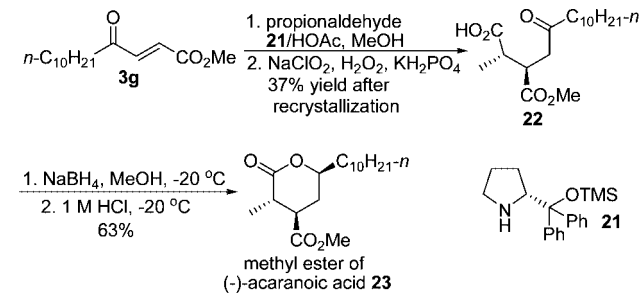
tuted-γ-lactone was selectively formed, which is not easily obtained using ordinary methods like stereocontrolled alkylation.

Scheme 5



(−)-Acaranoic acid is a natural δ-lactone that was isolated from lichen *Acarospora chlorophana*.[21] Its structure was revised by chemical transformation studies[22] but has not been synthesized from commercially available compounds. Using the present method, we developed a simple route to its methyl ester. As outlined in Scheme 6, Michael addition of propionaldehyde to enone **3g** proceeded smoothly to afford crude adduct, which was oxidized to give acid **22** and its 2-epimer in a ratio of 4:1. After recrystallization, the acid **22** was obtained with 37% overall yield and about 95% purity. Reduction of **22** with $NaBH_4$ at −20 °C delivered an alcohol, which was treated under acidic conditions to produce **23** in 63% yield, together with its 6-epimer in 26% yield. The NMR data were identical to those reported in the literature, and the optical rotation ($[\alpha]^{25}_D$ −30 (*c* 1.3 $CHCl_3$)) was close to the reported value ($[\alpha]^{25}_D$ −31 (*c* 1.595 $CHCl_3$)). Thus, this synthesis also confirmed the stereochemistry of the present adducts which was originally proposed by analyzing the enamine transition state.[23]

Scheme 6



In conclusion, we have found that γ-keto-α,β-unsaturated esters are very reactive Michael acceptors toward organocatalytic Michael addition with aldehydes. The reaction took place in a highly regioselective and enantioselective manner to give adducts which could easily be converted into some useful chiral building blocks such as 4,5-disubstituted cyclohexenones, polysubstituted cyclohexanones, and *cis*-3,4-disubstituted γ-lactones. Our results will stimulate further exploration of new Michael acceptors for organocatalytic reactions. The synthetic usefulness of the present method has been demonstrated by the synthesis of (−)-acaranoic acid methyl ester and will be applied in the total synthesis of other complex natural products. Further investigations on this novel synthetic process are actively pursued in our laboratory and will be reported in due course.

Acknowledgment. We are grateful to National Natural Science Foundation of China (Grant No. 20621062) for their financial support.

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

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(21) (a) Zopf, W. *Liebigs Ann. Chem.* **1895**, *284*, 107. (b) Santesson, J. *Acta Chem. Scand.* **1967**, *21*, 1993.

(22) Huneck, S.; Höfle, G. *Phytochemistry* **1980**, *19*, 2713.

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