CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200801749

VIP

Organocatalyzed Highly Enantioselective Michael Additions of Malonates to Enones by Using Novel Primary–Secondary Diamine Catalysts

Ying-Quan Yang[a] and Gang Zhao*[a, b]

The Michael reaction is one of the fundamental bond-forming processes in organic chemistry and its asymmetric version offers an extremely powerful tool for the synthesis of a variety of useful chiral functionalized organic molecules.[1] Particularly, the catalytic asymmetric addition reaction of malonates to α,β-unsaturated ketones would produce useful products which could be easily converted to synthetically useful optically active δ-ketoesters after simple decarboxylation procedures.[2] As a result, a variety of chiral metal catalysts[3] as well as organocatalysts[2,4] have been developed for this transformation. However, only very recently did Kobayashi et al. report the highest enantioselectivity (mostly >95% *ee*) for this reaction with di-*n*-propyl malonates and chalcones using a new strontium based catalysts.[5] In the field of organocatalysis, imidazoline catalyst,[2a] proline-derived tetrazole catalysts,[2b,c] phase-transfer catalysts,[6] and Cinchona alkaloid-derived chiral thioureas[7] have been introduced to catalyze this reaction. Nevertheless, these catalytic systems more or less suffer several drawbacks such as long reaction times (2–6 d), the need for a large excess of malonates, and unsatisfactory enantioselectivities (generally below 95% *ee*). Therefore, the development of a more efficient organocatalyst system is highly desirable in order to make this transformation more practical for use in organic synthesis.

On the other hand, chiral diamines, especially those bearing a primary amine moiety, have recently found many successful applications in organocatalysis.[8] Despite the recent inspiring successful applications of primary amine salts in the iminium catalysis of enones,[9] little examples have been reported for the use of primary–secondary diamine catalysts in the Michael addition reactions of enones. As part of our ongoing efforts in developing efficient organocatalysts for the asymmetric reactions of α,β-enones,[10] we report herein a novel primary–secondary diamine catalyst readily available from primary amino acids in three steps[11] for the Michael additions of malonates to α,β-unsaturated ketones.

Initially, the Michael reaction of dimethyl malonate **1a** with benzylideneacetone **2a** was selected as a model reaction for catalyst evaluation (Table 1). While catalyst **3a** (Figure 1) bearing two primary amino groups derived from

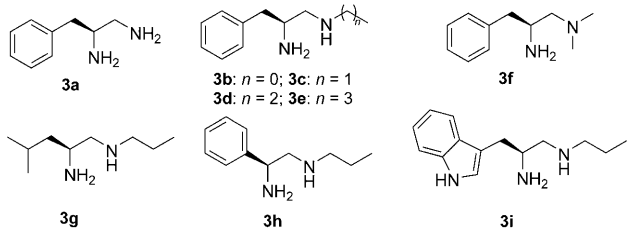


Figure 1. Structures of the catalysts studied.

L-phenylalanine promoted this reaction with poor yield and enantioselectivity, its monomethylated analogue **3b** provided much better results (Table 1, entries 1 and 2). The length of the alkyl chain was found to influence the catalytic abilities of the catalysts and the *n*-propylated catalyst **3d** gave the highest yield and *ee* value (Table 1, entry 4).[12] Surprisingly, the primary–tertiary **3f** exhibited very low activity in this reaction, which highlighted the importance of the secondary amine moiety in the catalyst (Table 1, entry 6). Moreover, variation of the benzyl group of **3d** yielded the optimum catalyst **3i** derived from L-tryptophan, which provided the desired product **4aa** with 91% *ee* (Table 1, entry 9). Next, we are pleased to find that decreasing the amount of **1a** to 2 equiv had little influence on both the yield and *ee*

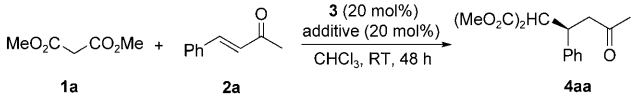
[a] Y.-Q. Yang, Prof. Dr. G. Zhao
Department of chemistry
University of Science and Technology of China
Hefei, Anhui 230026 (China)
Fax: (+86) 21-64166128
E-mail: zhaog@mail.sioc.ac.cn

[b] Prof. Dr. G. Zhao
Laboratory of modern synthetic chemistry
Shanghai institute of organic chemistry
354 Fenglin Road, Shanghai, 200032 (China)
Chinese Academy of Sciences

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200801749.

values (Table 1, entry 10). Our further optimizing efforts were shifted to the examination of the effect of several acid additives, which are well-documented to be beneficial for the formation of an iminium intermediate.[9] To our delight, the addition of acid additives not only improved the yield and *ee* values, but also decreased the reaction time significantly from 48 to 24 h (Table 1, entries 11–15). Thus, the reaction was best performed using a 1:1 combination of **3i**/TFA (trifluoro acetic acid) with 99% yield and 97% *ee* (Table 1, entry 13). The absolute configuration of the product **4aa** was determined by comparison of the specific optical rotation with that of the literature data.

Table 1. Screening of catalysts for the asymmetric Michael addition of dimethyl malonate **1a** to benzylideneacetone **2a**.[a]



1a 2a 4aa

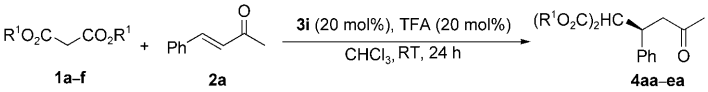
Entry	Catalyst **3**	Additive	Yield [%][b]	*ee* [%][c]
1	**3a**	none	27	36
2	**3b**	none	43	79
3	**3c**	none	51	81
4	**3d**	none	93	90
5	**3e**	none	85	87
6	**3f**	none	trace	–
7	**3g**	none	77	82
8	**3h**	none	55	36
9	**3i**	none	92	91
10[d]	**3i**	none	90	91
11[d,e]	**3i**	$PhCO_2H$	98	93
12[d,e]	**3i**	CH_3CO_2H	99	94
13[d,e]	**3i**	CF_3CO_2H	99	97
14[d,e]	**3i**	CF_3SO_3H	93	96
15[d,e]	**3i**	D-CSA	97	96

[a] Reaction conditions: **2a** (1.0 equiv), **1a** (10.0 equiv), **3** (20 mol%), $CHCl_3$ (1.0 mL). [b] Yield of the isolated product after column chromatography. [c] The *ee* value was determined by HPLC on a chiral phase. [d] Two equiv of **1a** was used. [e] The reaction was run for 24 h. D-CSA: D-camphor sulfonic acid.

Subsequently, the addition of a series of malonates **1** to enone **2a** was performed under the optimized conditions (Table 2). It seems that the reaction was quite sensitive to the steric hindrance on the malonates. While excellent yields and enantioselectivity were obtained for the less sterically demanding malonates **1a**, **b**, **d**, and **e**, a lower yield was observed for the diisopropyl malonate **1c** but still with up to >99% *ee* (Table 2, entry 3). The reaction even failed to proceed when the more sterically demanding di-*tert*-butyl malonates **1f** was employed (Table 2, entry 6). The use of dibenzyl malonate **1e** furnished the best results with up to 99% yield and *ee* value (Table 2, entry 5). Notably, it is favorable to use dimethyl or dibenzyl malonates for further useful conversions of the Michael adducts in organic synthesis.[2]

Then the scope of the addition of dibenzyl malonate to a variety of enones **2** was explored (Table 3). For 4-aryl-3-buten-2-ones **2a**–**j**, almost optically pure products could be obtained in excellent yields, irrespective of the electronic

Table 2. Examination of different malonates **1** with the **3i**/TFA combination.[a]



1a–f 2a 4aa–ea

Entry	**1**	R^1	Product	Yield [%][b]	*ee* [%][c]
1	**1a**	Me	**4aa**	99	97
2	**1b**	Et	**4ba**	97	98
3	**1c**	*i*Pr	**4ca**	72	>99
4	**1d**	allyl	**4da**	99	98
5	**1e**	Bn	**4ea**	99	99
6[d]	**1f**	*t*Bu	–	–	–

[a] Reaction conditions: **2a** (1.0 equiv), **1** (2.0 equiv), **3i**/TFA (20 mol%), $CHCl_3$ (1.0 mL). [b] Yield of the isolated product after column chromatography. [c] The *ee* value was determined by HPLC on a chiral phase. [d] No reaction was detected.

nature or positions of the substituents on the phenyl ring (Table 3, entries 1–10). Heterocyclic furan enone **2j** also performed well to give the desired product in 92% yield and 99% *ee* (Table 3, entry 11). No decrease in yield and *ee* value was observed for the slightly sterically hindered enone **2l** (Table 3, entry 12). Interestingly, chalcone **2m**, which was presumed to be a better Michael acceptor for this type of reaction,[4–7] was found to react rather slowly and a longer reaction time was required to obtain good yield, however, excellent enantioselectivity was still achieved (Table 3, entry 13). Poor reactivity was also observed for the alkyl-substituted enone **2n** and 2-cyclohexenone **2o**, in which only moderate yields were obtained while still in excellent enantioselectivities with prolonged reaction times (Table 3, entries 14 and 15).

A bifunctional iminium mechanism similar to those previously proposed for the primary amine salt catalysts in the iminium catalysis[9] of enone may be invoked to explain the observed enantioselectivity. We presume that the reaction may proceed via the iminium ion **I** (Figure 2), in which the primary amine moiety of the catalyst **3i** activates the enone **2** via the formation of an iminum ion while the secondary amine activates the nucleophile malonate **1**. The *Re* face of the enone in this pretransition state assembly **I** is shielded by the bulky indolyl group driving the malonate to attack the *Si* face of the enone **2**. The strong acid additives may facilitate the formation of the iminium ion and foster the regeneration of the catalyst in the hydrolysis of the enamine intermediate after the addition step. However, the exact existing or functioning forms of the strong acid additives in the reaction system are difficult to be determined.

In summary, we have developed a novel readily available primary–secondary diamine catalyst system for the Michael additions of malonates to enones. Excellent yields and enantioselectivities were achieved for a range of both malonates and enones. Efforts are being fo-

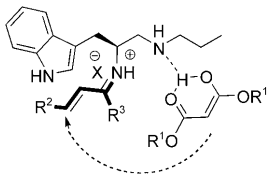
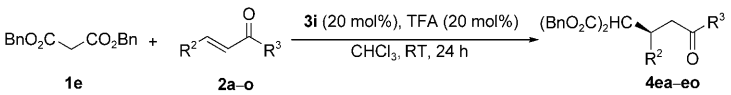


Figure 2. Pretransition state **I**.

Table 3. Enantioselective Michael addition of dibenzyl malonate **1e** to enones **2** catalyzed by the **3i**/TFA combination.[a]



1e **2a–o** **4ea–eo**

Entry	R^2	R^3	Product	Yield [%][b]	*ee* [%][c]
1	Ph	Me, **2a**	**4ea**	99	99
2	2-naphthyl	Me, **2b**	**4eb**	91	99
3	4-FC_6H_4	Me, **2c**	**4ec**	92	99
4	4-ClC_6H_4	Me, **2d**	**4ed**	91	>99
5	3-ClC_6H_4	Me, **2e**	**4ee**	90	99
6	2-ClC_6H_4	Me, **2f**	**4ef**	99	99
7	4-BrC_6H_4	Me, **2g**	**4eg**	96	99
8	4-MeC_6H_4	Me, **2h**	**4eh**	90	>99
9	4-$MeOC_6H_4$	Me, **2i**	**4ei**	93	>99
10	4-$NO_2C_6H_4$	Me, **2j**	**4ej**	96	99
11	2-furyl	Me, **2k**	**4ek**	92	99
12	Ph	Et, **2l**	**4el**	91	99
13[d]	Ph	Ph, **2m**	**4em**	82	>99
14[d]	*n*-C_4H_9	Me, **2n**	**4en**	66	98
15[e]	2-cyclohexenone (**2o**)		**4eo**	71	90

[a] Reaction conditions: **2** (1.0 equiv), **1e** (2.0 equiv), **3i**/TFA (20 mol%), $CHCl_3$ (1.0 mL). [b] Yield of the isolated product after column chromatography. [c] The *ee* value was determined by HPLC on a chiral phase. [d] The reaction was run for 120 h. [e] The reaction was run for 120 h at 0 °C.

cused on further application of the catalyst system to other related reactions as well as a more detailed mechanistic understanding of the reaction.

Experimental Section

Typical procedure: To a mixture of enone **2a** (0.5 mmol), catalyst **3i** (0.1 mmol) and TFA (0.1 mmol) in $CHCl_3$ (1.0 mL) was added dibenzyl malonate **1e** (1.0 mmol) at ambient temperature. After 24 h of stirring, the reaction mixture was quenched with 1 M aqueous HCl, and extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated and purified by flash column chromatography on silica gel (petroleum ether/Et_2O 10:1) to afford the Michael adduct **4ea**[2a] (213 mg, 99%) as a white solid.

Acknowledgements

The generous financial support from the National Natural Science Foundation of China, QT Program, Shanghai Natural Science Council, and Excellent Young Scholars Foundation of NNSF are gratefully acknowledged.

Keywords: asymmetric catalysis · enones · malonates · Michael addition · organocatalysis

[1] a) P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Pergamon Press, Oxford, **1992**; b) N. Krause, A. Hoffman-Roder, *Synthesis* **2001**, 171; c) M. Sibi, S. Manyem, *Tetrahedron* **2000**, *56*, 8033; d) M. Kanai, M. Shibasaki, in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), 2nd ed., Wiley, New York, **2000**, p. 569; e) K. Tomioka, Y. Nagaoka, in *Comprehensive Asymmetric Catalysis, Vol. 3* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, Chapter 31.1; f) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701; g) J. L. Vicario, D. Badía, L. Carrillo, *Synthesis* **2007**, 2065; h) D. Almaşi, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry* **2007**, *18*, 299.

[2] a) N. Halland, P. S. Abured, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 685; *Angew. Chem. Int. Ed.* **2003**, *42*, 661; b) V. Wascholowski, K. R. Knudsen, C. E. T. Mitchell, S. V. Ley, *Chem. Eur. J.* **2008**, *14*, 6155; c) K. R. Knudsen, C. E. T. Mitchell, S. V. Ley, *Chem. Commun.* **2006**, 66.

[3] For recent examples: a) S.-Y. Park, H. Morimoto, S. Matsunaga, M. Shibasaki, *Tetrahedron Lett.* **2007**, *48*, 2815; b) C. Chen, S.-F. Zhu, X.-Y. Wu, Q.-L. Zhou, *Tetrahedron: Asymmetry* **2006**, *17*, 2761; c) G. Kumaraswamy, N. Jena, M. N. V. Sastry, G. V. Rao, K. Ankamma, *J. Mol. Catal. A* **2005**, *230*, 59.

[4] a) Z. Wang, Q. Wang, Y. Zhang, W. Bao, *Tetrahedron Lett.* **2005**, *46*, 4657; b) M. Yamaguchi, T. Shiraishi, M. Hirama, *J. Org. Chem.* **1996**, *61*, 3520; c) M. Yamaguchi, T. Shiraishi, M. Hirama, *Angew. Chem.* **1993**, *105*, 1243; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1176.

[5] M. Agostinho, S. Kobayashi, *J. Am. Chem. Soc.* **2008**, *130*, 2430.

[6] a) T. Ooi, D. Ohara, K. Fukumoto, K. Maruoka, *Org. Lett.* **2005**, *7*, 3195; b) R. T. Dere, R. R. Pal, P. S. Patil, M. M. Salunkhe, *Tetrahedron Lett.* **2003**, *44*, 5351; c) D. Y. Kim, S. C. Hunh, S. M. Kim, *Tetrahedron Lett.* **2001**, *42*, 6299.

[7] J. Wang, H. Li, L. Zu, H. Xie, W. Duan, W. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 12652.

[8] For reviews: a) L. Ai, J. C. Xiao, X.-M. Shen, C. Zhang, *Chin. J. Org. Chem.* **2005**, *25*, 1319; b) S. Saito, H. Yamamoto, *Acc. Chem. Res.* **2004**, *37*, 570; c) M. Nakadai, S. Saito, H. Yamamoto, *Tetrahedron* **2002**, *58*, 8167; for recent examples: d) J. Liu, Z. Yang, Z. Wang, F. Wang, X. Chen, X. Liu, X. Feng, Z. Su, C. Hu, *J. Am. Chem. Soc.* **2008**, *130*, 5654; e) B. Jiang, J. J. Dong, Y. G. Si, X. L. Zhao, Z. G. Huang, M. Xu, *Adv. Synth. Catal.* **2008**, *350*, 1360; f) S. Luo, H. Xu, J. Li, J.-P. Cheng, *Org. Lett.* **2008**, *10*, 1775; g) S. Luo, J. Li, L. Zhang, H. Xu, J.-P. Cheng, *Chem. Eur. J.* **2008**, *14*, 1273; h) S. Luo, H. Xu, J. Li, L. Zhang, J.-P. Cheng, *Org. Lett.* **2008**, *10*, 653; i) T. Kano, Y. Tanaka, K. Maruoka, *Chem. Asian J.* **2007**, *2*, 1161; j) S. Luo, H. Xu, J. Li, L. Zhang, J.-P. Cheng, *J. Am. Chem. Soc.* **2007**, *129*, 3074; k) Vishnumaya, V. K. Singh, *Org. Lett.* **2007**, *9*, 1117; l) S. V. Pansare, K. Pandaya, *J. Am. Chem. Soc.* **2006**, *128*, 9624; m) K. H. Kim, S. Lee, D. W. Lee, D.-H. Ko, D.-C. Ha, *Tetrahedron Lett.* **2005**, *46*, 5991.

[9] a) X. Lu, Y. Liu, B. Sun, B. Cindric, L. Deng, *J. Am. Chem. Soc.* **2008**, *130*, 8134; b) X. Wang, C. M. Reisinger, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 6070; c) R. P. Singh, K. Bartelson, Y. Wang, H. Su, X. Lu, L. Deng, *J. Am. Chem. Soc.* **2008**, *130*, 2422; d) J. Xie, W. Chen, R. Li, M. Zeng, W. Du, Y. Chen, J.-G. Deng, *Angew. Chem.* **2007**, *119*, 393; *Angew. Chem. Int. Ed.* **2007**, *46*, 389; e) G. Bartoli, M. Bosco, A. Carlone, F. Pesciaioli, L. Sambri, P. Melchiorre, *Org. Lett.* **2007**, *9*, 1403; f) W. Chen, W. Du, Y. Duan, Y. Wu, S. Yang, Y. Chen, *Angew. Chem.* **2007**, *119*, 7811; *Angew. Chem. Int. Ed.* **2007**, *46*, 7667; g) N. J. A. Martin, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 13368.

[10] a) X. Liu, Y. Li, G. Wang, Z. Chai, Y. Wu, G. Zhao, *Tetrahedron: Asymmetry* **2006**, *17*, 750; b) Y. Li, X. Liu, Y. Yang, G. Zhao, *J. Org.*

Chem. **2007**, *72*, 288; c) H. Cui, Y. Li, C. Zheng, G. Zhao, S. Zhu, *J. Fluorine Chem.* **2008**, *129*, 45.

[11] See the Supporting Information for details.

[12] Several other solvents were also screened for catalyst **3d** with inferior results: DMF (94% yield, 66% *ee*), THF (85% yield, 83% *ee*), toluene (95% yield, 83% *ee*), *n*-hexane (93% yield, 80% *ee*), CH_2Cl_2 (84% yield, 88% *ee*).

Received: August 23, 2008
Published online: November 10, 2008

