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Highly Enantioselective Michael Addition of Cyclic 1,3-Dicarbonyl Compounds to β,γ-Unsaturated α-Keto Esters

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Abstract: A highly enantioselective Michael addition of cyclic 1,3-dicarbonyl compounds to β,γ-unsaturated α-keto esters catalyzed by amino acid-derived thiourea-tertiary-amine catalysts is presented. Using 5 mol% of a novel tyrosine-derived thiourea catalyst, a series of chiral coumarin derivatives were obtained in excellent yields (up to 99%) and with up to 96% *ee* under very mild conditions within a short reaction time.

Keywords: 1,3-dicarbonyl compounds; Michael addition; organocatalysts; thioureas; β,γ-unsaturated α-keto esters

Increased focus has recently been placed on the application of organocatalysis in reactions allowing the rapid construction of functionalized molecules from simple and readily available starting materials.[1] In this field, the asymmetric Michael addition of 1,3-cyclic dicarbonyl compounds to α,β-unsaturated carbonyl systems, which could provide many chiral compounds with biological and pharmaceutical activities such as *neo*-flavonoids and coumarins, has attracted much attention.[2] As a class of activated α,β-unsaturated carbonyl systems, β,γ-unsaturated α-keto esters sometimes are preferred electrophiles in this kind of reaction due to their high reactivity and the easy convertibility of the resultant products to other useful structures.[3] In 2003, Jørgensen et al. reported the enantioselective Michael addition of cyclic 1,3-dicarbonyl compounds to β,γ-unsaturated α-keto esters catalyzed by chiral bisoxazoline-copper(II) complexes with moderate to high enantioselectivities.[4] However, it was not until very recently that an similar organocatalyzed reaction between cyclic diketones and β,γ-unsaturated α-keto esters using *Cinchona* alkaloid-derived pyrimidines was reported by Calter et al.[5] In contrast, several organocatalysts have been developed for the Michael addition of cyclic diketones to α,β-unsaturated ketones, in which the "imine catalysis" usually controls the enantioselectivity.[6]

On the other hand, following the pioneering works of Jacobsen and Takemoto,[7] remarkable advances have been made in the development and application of bifunctional chiral thiourea catalysts in catalytic asymmetric reactions.[8] Recently, the use of inexpensive and readily available amino acids as the chiral scaffold to develop novel thiourea catalysts has attracted considerable interest and proved to be effective in several asymmetric reactions.[9] Our group has been interested in the development of organocatalytic reactions utilizing β,γ-unsaturated α-keto esters as a reaction partner to synthesize useful compounds.[10] We report herein the development of several amino acid-derived thiourea-tertiary amine catalysts and their applications to the asymmetric Michael addition of cyclic 1,3-dicarbonyl compounds to β,γ-unsaturated α-keto esters.

Using the reaction between (*E*)-methyl 2-oxo-4-phenylbut-3-enoate (**3a**) and 4-hydroxycoumarin (**4a**) as the model reaction, a series of thiourea-tertiary amine catalysts (Figure 1) was evaluated and the results are summarized in Table 1. Similar to Takemoto's catalyst **1**, all the amino acid-derived thiourea-tertiary amine catalysts **2a**–**2j** could catalyze the reaction efficiently to give excellent yields of the product **5a** in two hours at room temperature,[11] but the enantioselectivities were different. While catalysts **2a**–**2d** and **2e** and **2f** with several different amino acid skeletons

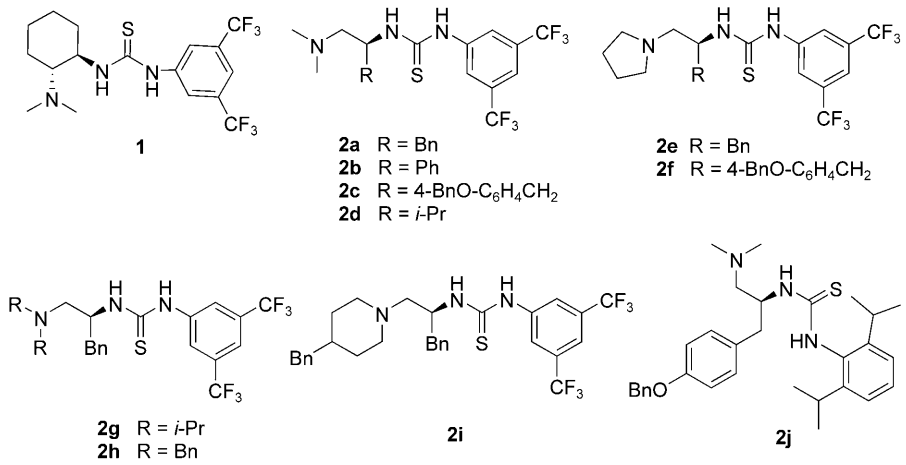
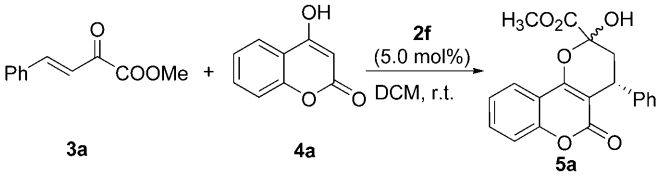


Figure 1. Organocatalysts tested in this study.

did not produce considerable changes in the enantioselectivity (Table 1, entries 2–7), catalysts **2g** and **2h** bearing increased steric hindrance at the tertiary amine moiety catalyzed the reaction with significantly reduced *ee* values (entries 8 and 9). In addition, changing the thiourea moiety to the electron-donating 2,6-diisopropylphenyl group (**2j**) also gave a much lower *ee* value (entry 11). Reducing the loading amount of the best catalyst **2f** to 1.0 mol%, 2.0 mol% or increasing the loading amount to 10 mol% have little influence on both the yield and enantioselectivity (entries 12–14).

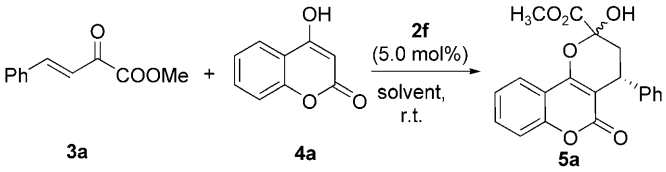
Table 1. The effect of catalysts on the reaction yield and selectivity[a]



Entry	Catalyst	Yield [%][b]	*ee* [%][c]
1	**1**	95	79
2	**2a**	99	78
3	**2b**	98	77
4	**2c**	99	82
5	**2d**	98	78
6	**2e**	98	80
7	**2f**	99	85
8	**2g**	97	45
9	**2h**	98	27
10	**2i**	98	81
11	**2j**	97	38
12[d]	**2f**	99	80
13[e]	**2f**	98	83
14[f]	**2f**	99	86

[a] Unless otherwise noted, the reaction was conducted with 0.1 mmol of **3a** and 0.11 mmol of **4a** in the presence of 5.0 mol% of catalyst in 2.0 mL of solvent at room temperature for 2 h.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis on a chiral column. The absolute configuration was determined by comparison with the literature (see ref.[4]).
[d] 1.0 mol% of **2f** was used.
[e] 2.0 mol% of **2f** were used.
[f] 10 mol% of **2f** were used.

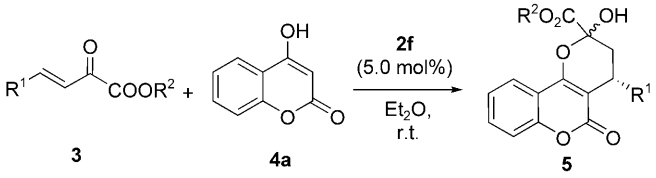
Table 2. Screening of solvents for the addition of **3a** to **4a** in the presence of **2f**.[a]



Entry	Solvent	Yield [%][b]	*ee* [%][c]
1	toluene	99	86
2	*n*-hexane	62	83
3	$CHCl_3$	98	83
4	Et_2O	99	93
5	THF	99	91
6	1,4-dioxane	99	83
7	MTBE	98	70
8	DME	98	92
9[d]	Et_2O	99	93
10[e]	Et_2O	99	94

[a] Unless otherwise noted, the reaction was conducted with 0.1 mmol of **3a** and 0.11 mmol of **4a** in the presence of 5.0 mol% of **2f** in 2.0 mL of solvent at room temperature for 2 h.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis on a chiral column. The absolute configuration was determined by comparison with the literature (see ref.[4]).
[d] The reaction was conducted at 0 °C for 3 h.
[e] The reaction was conducted at −25 °C for 15 h.

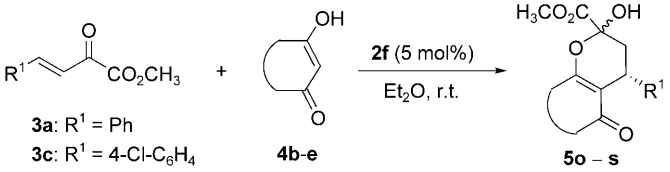
Table 3. Examination of the generality of the reaction with different β,γ-unsaturated α-keto esters **3** and **4a**.[a]



Entry	R^1, R^2	5	Yield [%][b]	*ee* [%][c]
1	Ph, Me (**3a**)	**5a**	99	93
2	4-F-C_6H_4, Me (**3b**)	**5b**	98	92
3	4-Cl-C_6H_4, Me (**3c**)	**5c**	99	90
4	4-Br-C_6H_4, Me (**3d**)	**5d**	96	92
5	4-NO_2-C_6H_4, Me (**3e**)	**5e**	99	96
6	4-CH_3-C_6H_4, Me (**3f**)	**5f**	95	92
7	4-EtO-C_6H_4, Me (**3g**)	**5g**	92	90
8	2-Br-C_6H_4, Me (**3h**)	**5h**	94	90
9	2-Furyl, Me (**3i**)	**5i**	97	93
10	Ph, Et (**3j**)	**5j**	91	91
11	Ph, *i*-Pr (**3k**)	**5k**	97	90
12	Ph, Bn (**3l**)	**5l**	93	92
13	$PhCH_2CH_2$, Et (**3m**)	**5m**	78	84
14[d]	*n*-Bu, Me (**3n**)	–	–	–

[a] Unless otherwise noted, the reaction was conducted with 0.1 mmol of **3** and 0.11 mmol of **4a** in the presence of 5.0 mol% of **2f** in 2.0 mL of Et_2O at room temperature for 2 h.
[b] Isolated yields.
[c] Determined by HPLC analysis on a chiral column.
[d] A complicated mixture was obtained.

Table 4. Scope of the reaction with different 1,3-dicarbonyl compounds as donors.[a]



Entry	3	4[14]	Product	*t* (h)	Yield [%][b]	*ee* [%][c]
1	**3a**	**4b**	**5o**	1	99	94
2	**3c**	**4b**	**5p**	1	99	93
3	**3a**	**4c**	**5q**	5	98	90
4	**3a**	**4d**	**5r**	5	99	91
5	**3a**	**4e**	**5s**	8	96	77

[a] Unless otherwise noted, the reaction was conducted with 0.1 mmol of **3** and 0.11 mmol of **4** in the presence of 5.0 mol% of **2f** in 2.0 mL of Et_2O at room temperature.
[b] Isolated yields.
[c] Determined by HPLC analysis on a chiral column

As a compromise between catalyst amount and enantioselectivity, 5.0 mol% of the newly developed catalyst **2f** was used for further screening of solvents and reaction temperature (Table 2). In general, the reactions proceeded well in the solvents examined giving the desired **5a** in excellent yields except for *n*-hexane, which may be ascribed to the poor solubility of the reactants in this solvent. The highest *ee* value of 93% was obtained in diethyl ether with up to 99% yield (entry 4). However, no obvious improvement in enantioselectivity was observed when reducing the reaction temperature to 0 °C or −25 °C, except that prolonged reaction times were required (entries 9 and 10). To conclude, the present reaction is best performed with 5 mol% of **2f** in diethyl ether at room temperature.

With the optimal reaction conditions achieved above, we subsequently examined the reaction of **4a** with a range of β,γ-unsaturated α-keto esters **3** to explore the generality of this reaction, and the results are summarized in Table 3. High yields and enantioselectivities were achieved with β,γ-unsaturated α-keto esters bearing various γ-aryl substituents, irrespective of their electronic nature or steric hindrance (entries 1–9). Substrates **3j–3l** with bulkier substituents at the ester moiety (R^2) also gave good results (entries 10–12). However, less satisfactory results were obtained with aliphatic substrates **3m** and **3n**: decreased yield and *ee* value with **3m** and only a complicated mixture were obtained in the case of **3n** (entries 14 and 15).

To further extend the scope of the present reaction, several other cyclic 1,3-dicarbonyl compounds **4b–4e** were also studied as the Michael donors and the results are listed in Table 4. To our delight, all the substrates underwent the reaction smoothly to give the desired products **5o–5s** in excellent yields and high *ee* values. The electronic nature of the substrates seemed to have an influence on the reaction rate: a longer reaction time of 5 h was required for substrates **4c** and **4d** with all-carbon skeletons and 8 h were needed in the case of substrate **4e** bearing an additional electron-withdrawing carbonyl group (entries 3–5). It is worth mentioning that a much longer reaction time

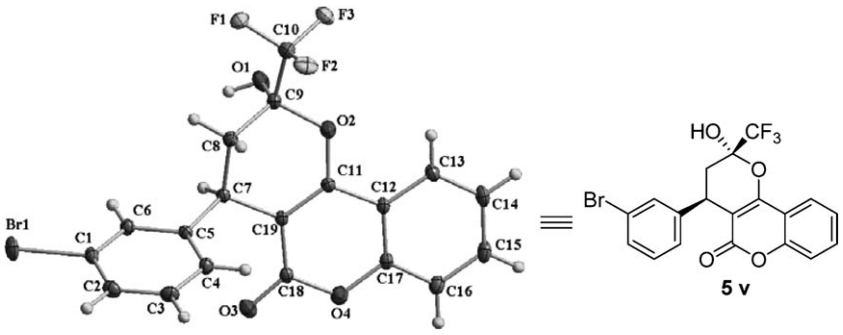
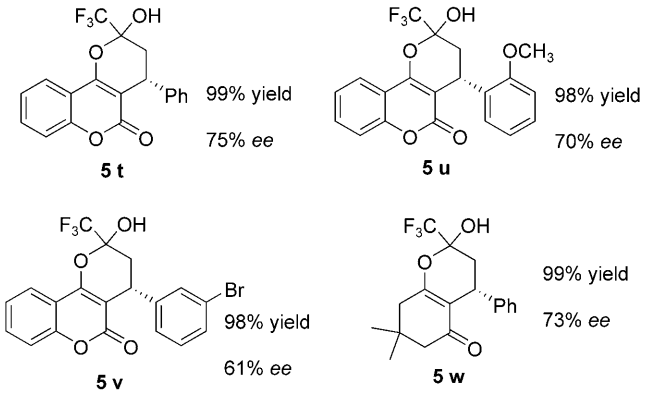


Figure 2. X-ray structure of **5v**.

(24 h) was required for the reaction of **4c** and **4d** with **3a** in Calter's system.[5]

Warfarin and its derivatives are widely used as anticoagulant drugs and their fluorine-containing counterparts may have interesting biological activities. Herein the Michael addition of cyclic 1,3-dicarbonyl compounds to α,β-unsaturated trifluoromethyl ketones was further investigated.[12] A model reaction between **4a** and (*E*)-1,1,1-trifluoro-4-phenylbut-3-en-2-one showed that good results could be obtained in toluene in the presence of **2f** (5 mol%) within 5 h. The generality of this reaction was also extended to other substrates (Scheme 1), which gave the CF_3-containing products in high yields (98–99%) and moderate enantioselectivities (61–75% *ee*). The *ee* value of product **5v** could be improved to up to 99.9% after a single recrystallization from hexane/ethyl acetate (5:1, v/v).[13] The absolute configurations of **5t**–**5w** were determined according to the X-ray structure of **5v** (Figure 2).



Scheme 1. Michael addtion between cyclic 1,3-dicarbonyl compounds and α,β-unsaturated trifluoromethyl ketones.

In conclusion, we have accomplished a highly enantioselective Michael addition of cyclic 1,3-dicarbonyl compounds to β,γ-unsaturated α-keto esters using amino acid-derived thiourea-tertiary amine catalysts under mild conditions. With 5 mol% of the best catalyst, a broad range of adducts was obtained in high yields and with up to 96% *ee*. Further elaboration of the products to other useful compounds and the application of the catalysts in other reaction systems are now under investigation in our laboratory.

Experimental Section

Typical Procedure

To a solution of β,γ-unsaturated α-keto ester **3a** (0.10 mmol) and 4-hydroxy-2*H*-chromen-2-one 4 (0.11 mmol) in 2.0 mL of diethyl ether (Et_2O), **2f** (0.005 mmol) was added. The mixture was stirred at room temperature for 2 h. Then the crude product was purified directly by column chromatography on silica gel (hexane/acetate = 5:1) to afford the corresponding product **5a** as a white solid; yield: 99%; mp 88–89 °C; $[\alpha]_D^{24.7}$: −22.36 (*c* 1.0, DCM). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.81$ (dd, $J = 8.4$, 7.8 Hz, 0.92 H), 7.48–7.56 (m, 1 H), 7.22–7.36 (m, 7 H), 4.98 (br s, 0.57 H), 4.73 (br s, 0.26 H), 4.28 (d, $J = 7.8$ Hz, 0.32 H), 4.17 (t, $J = 7.7$ Hz, 1.15 H), 3.92 (s, 0.96 H), 3.89 (s, 2.04 H), 2.79 (dd, $J = 7.2$, 7.8 Hz, 0.31 H), 2.44 (m, 1.68 H), enantiomeric excess: 93%, determined by HPLC (Chiralpak ADH column, hexane/*i*-PrOH = 80:20, flow rate 0.75 mL min^{-1}, $t_{major} = 16.4$ min, $t_{minor} = 28.3$ min, $\lambda = 254$ nm).

Acknowledgements

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References

[1] For reviews on organocatalysts, see: a) P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840; *Angew. Chem. Int. Ed.* **2001**, *40*, 3726; b) M. Benaglia, A. Puglisi, F. Cozzi, *Chem. Rev.* **2003**, *103*, 3401; c) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; d) J. Seayad, B. List, *Org.*

Biomol. Chem. **2005**, *3*, 719; e) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701; f) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713; g) H. Pellissier, *Tetrahedron* **2007**, *63*, 9267; h) C. F. Barbas, III, *Angew. Chem.* **2008**, *120*, 44; *Angew. Chem. Int. Ed.* **2008**, *47*, 42.

[2] a) N. Halland, T. Hansen, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 5105; *Angew. Chem. Int. Ed.* **2003**, *42*, 4955; b) M. Rueping, E. Sugiono, E. Merino, *Angew. Chem.* **2008**, *120*, 3089; *Angew. Chem. Int. Ed.* **2008**, *47*, 3046; c) M. Rueping, E. Merino, E. Sugiono, *Adv. Synth. Catal.* **2008**, *350*, 2127; d) M. Rueping, E. Sugiono, E. Merino, *Chem. Eur. J.* **2008**, *14*, 6329; e) Y. Tsuchiya, Y. Hamashima, M. Sodeoka, *Org. Lett.* **2006**, *8*, 4851; f) E. Melliou, P. Magiatis, S. Mitaku, A. L. Skaltsounis, E. Chinou, I. Chinou, *J. Nat. Prod.* **2005**, *68*, 78; g) L. Xie, Y. Takeuchi, L. M. Cosentino, K. H. Lee, *J. Med. Chem.* **1999**, *42*, 2662; h) L. Xie, Y. Takeuchi, L. M. Cosentino, A. T. McPhail, K. H. Lee, *J. Med. Chem.* **2001**, *44*, 664.

[3] For reactions utilizing β,γ-unsaturated α-keto esters as electrophiles, see: a) S. Kanemasa, Y. Oderaotoshi, S. Sakaguchi, H. Yamamoto, J. Tanaka, E. Wada, D. P. Curran, *J. Am. Chem. Soc.* **1998**, *120*, 3074; b) S. Leconte, G. Dujardin, E. Brown, *Eur. J. Org. Chem.* **2000**, 639; c) J. Zhou, Y. Tang, *Org. Biomol. Chem.* **2004**, *2*, 429; d) S. Tardy, A. Tatibouët, P. Rollin, G. Dujardin, *Synlett* **2006**, *9*, 1425; e) G. Desimoni, G. Faita, M. Mella, F. Piccinini, M. Toscanini, *Eur. J. Org. Chem.* **2007**, 1529; f) F. Gohier, K. Bouhadjera, D. Faye, C. Gaulon, V. Maisonneuve, G. Dujardin, R. Dhal, *Org. Lett.* **2007**, *9*, 211; g) K. B. Jensen, J. Thorhauge, R. G. Hazell, K. A. Jørgensen, *Angew. Chem.* **2001**, *113*, 164; *Angew. Chem. Int. Ed.* **2001**, *40*, 160; h) K. A. Jørgensen, *Synthesis* **2003**, 1117; i) C. Ünaleroglu, B. Temelli, A. S. Demir, *Synthesis* **2004**, 2574; j) R. P. Herrera, D. Monge, M. Z. Eloísa, R. Fernández, J. M. Lassaletta, *Org. Lett.* **2007**, *9*, 3303.

[4] N. Halland, T. Velgaard, K. A. Jørgensen, *J. Org. Chem.* **2003**, *68*, 5067.

[5] M. A. Calter, J. Wang, *Org. Lett.* **2009**, *11* , 2205.

[6] a) J. W. Xie, L. Yue, W. Chen, W. Du, J. Zhu, J. G. Deng, Y. C. Chen, *Org. Lett.* **2007**, *9* , 413; b) H. Kim, C. Yen, P. Preston, J. Chin, *Org. Lett*, **2006**, *8*, 5239; c) T . Kristensen, K. Vestli, F. Hansen, T. Hansen, *Eur. J. Org. Chem.* **2009**, *30*, 5185; d) Z. H. Dong, L. J. Wang, X. H. Chen, X. H. Liu, L. L. Lin, X. M. Feng, *Eur. J. Org. Chem.* **2009**, *30*, 5192.

[7] a) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901; b) P. Vachal, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 867; c) M. S. Sigman, P. Vachal, E. Jacobsen, *Angew. Chem.* **2000**, *112*, 1336; *Angew. Chem. Int. Ed.* **2000**, *39*, 1279; d) P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012; e) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672; f) G. D. Joly, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 4102; g) T. Okino, S. Nakamura, T. Furukawa, Y. Takemoto, *Org. Lett.* **2004**, *6*, 625; h) Y. ohtome, A. Tanatani, Y. Hashimoto, K. Nagasawa, *Tetrahedron Lett.* **2004**, *45*, 5589; i) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119; j) T. P. Yoon, E. N. Jacobsen, *Angew. Chem.* **2005**, *117*, 470; *Angew. Chem. Int. Ed.* **2005**, *44*, 466.

[8] a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289; b) P. M. Pihko, *Angew. Chem.* **2004**, *116*, 2110; *Angew. Chem. Int. Ed.* **2004**, *43*, 2062; c) Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299; d) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; e) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418; f) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999; g) Y. J. Takemoto, *J. Synth. Org. Chem. Jpn.* **2006**, *64*, 1139; h) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713.

[9] a) C. G. Kokotos, G. Kokotos, *Adv. Synth. Catal.* **2009**, *351*, 1355; b) J. M. Andrés, R. M. Anzano, R. Pedrosa, *Chem. Eur. J.* **2008**, *14*, 5116; c) E. A. Peterson, E. N. Jacobsen, *Angew. Chem.* **2009**, *121*, 6446; *Angew. Chem. Int. Ed.* **2009**, *48*, 6328; d) J. Z. Stephan, P. C. Matthew, P. L. Mathieu, E. N. Jacobsen, *Nature* **2009**, *461*, 968; e) J. Z. Stephan, E. N. Jacobsen, *J. Am. Chem. Soc.* **2009**, *131*, 15358.

[10] a) H. F. Wang, C. W. Zheng, Y. Q. Yang, Z. Chai, G. Zhao, *Tetrahedron: Asymmetry* **2008**, *19*, 2608; b) X. S. Wang, C. W. Zheng, S. L. Zhao, Z. Chai, G. Zhao, G. S. Yang, *Tetrahedron: Asymmetry* **2008**, *19*, 2699; c) C. W. Zheng, Y. Y. Wu, X. S. Wang, G. Zhao, *Adv. Synth. Catal.* **2008**, *350*, 2690; d) S. L. Zhao, C. W. Zheng, G. Zhao, *Tetrahedron: Asymmetry* **2009**, *20*, 1046; e) C. W. Zheng, Y. W. Li, Y. Q. Yang, H. F. Wang, H. F. Cui, J. K. Zhang, G. Zhao, *Adv. Synth. Catal.* **2009**, *351*, 1685; f) S. L. Zhao, C. W. Zheng, H. F. Wang, G. Zhao, *Adv. Synth. Catal.* **2009**, *351*, 2811.

[11] Compounds **5** were found to exist as mixtures of anomers in solution, see Supporting Information for details.

[12] P. Li, Z. Chai, S. L. Zhao, Y. Q. Yang, H. F. Wang, C. W. Zheng, G. Zhao, S. Z. Zhu, Y. P. Cai, *Chem. Commun.* **2009**, *47*, 7369.

[13] CCDC 762027 (**5v**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[14] Two acyclic 1,3-dicarbonyl compounds were also tested but with inferior results: acetylacetone (48 h, 41% yield, 83% *ee*) and ethyl acetoacetate (48 h, trace conversion).

