Asymmetric Synthesis

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The Direct Asymmetric Vinylogous Aldol Reaction of Furanones with α-Ketoesters: Access to Chiral γ-Butenolides and Glycerol Derivatives**

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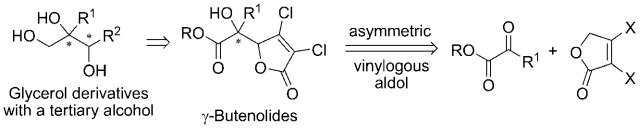
The creation of quaternary stereogenic centers is still a challenge in organic synthesis even though significant progress has been made in the past few decades.[1] As part of our ongoing research efforts towards the efficient generation of quaternary stereogenic centers,[2] we were interested in organic molecules containing a tertiary hydroxy group. Structures that contain tertiary alcohols are very important in the biological sciences and pharmaceutical industry.[3] In particular, enantiomerically pure glycerol derivatives having a quaternary center are key chiral structural motifs that are present in many pharmaceuticals, and they are also versatile synthetic intermediates.[4] Although many excellent methods have been devised for the synthesis of chiral tertiary alcohols,[5] the asymmetric preparation of glycerol derivatives having a quaternary center is still a formidable task. To the best of our knowledge, only two examples have been reported in the literature. In 1992, Harada, Oku, and co-workers reported a synthetic approach utilizing menthone as a chiral auxiliary.[6] Very recently, Kang and co-workers elegantly employed chiral copper complexes to carry out the enantioselective desymmetrization of *meso*-2-substituted glycerols, and obtained 2-substituted 1,2,3-propanetriols with excellent enantioselectivity.[7] It is thus our goal to develop an efficient organocatalytic variant to allow easy access to 2-substituted chiral glycerol derivatives.

We focused on the vinylogous aldol reaction between furanones and α-ketoesters (Scheme 1). The γ-butenolides that would result from these reactions are common structural motifs in bioactive molecules.[8] Moreover, they can be readily converted into tertiary-alcohol-containing glycerol derivatives. The vinylogous aldol reaction has been investigated intensively in the past few decades,[9] and although it is commonplace to employ 2-silyloxyfurans as nucleophiles,[10] the direct utilization of 2-furanone derivatives in the vinylogous aldol reactions is rare, probably because of their low reactivity. Zhang and co-workers first utilized α,β-dichloro-γ-butenolides in the direct vinylogous aldol reaction.[11] Recently, Terada and co-workers reported an enantioselective vinylogous aldol reaction of furanone derivatives with aldehydes catalyzed by a chiral guanidine.[12] Feng and co-workers subsequently disclosed a thiourea-catalyzed direct vinylogous aldol reaction of furanones with aldehydes.[13] Herein, we document the first direct asymmetric vinylogous aldol reaction of 3,4-dichlorofuran-2(5*H*)-one with α-ketoesters, catalyzed by an L-tryptophan-derived bifunctional catalyst, that leads to an efficient synthesis of chiral γ-butenolides and 2-substituted glycerol derivatives.



Scheme 1. Construction of γ-butenolides and glycerol derivatives through the vinylogous aldol reaction.

We recently introduced a novel tertiary amine/thiourea bifunctional catalyst derived from L-tryptophan, and showed its effectiveness in the Mannich reaction of fluorinated ketoesters.[2b] To extend the applications of these amino-acid-based bifunctional catalysts,[14] we prepared a number of L-tryptophan-derived organic catalysts and examined their catalytic effects in the vinylogous aldol reaction of 3,4-dichlorofuran-2(5*H*)-one (**1a**) with the phenylglyoxylates **2** (Table 1). The reaction was quite slow in the presence of **Trp-1** alone (Table 1, entry 1), but the rate of the reaction could be substantially improved with the addition of molecular sieves (4 Å; Table 1, entry 2). An examination of the ester moieties in the different α-ketoesters revealed that *tert*-butyl phenylglyoxylate (**2c**) offered the best diastereoselectivity and enantioselectivity (Table 1, entry 4). Changing the concentration of the reaction mixture yielded the product with a 91% *ee* (Table 1, entry 6). Notably, in contrast to the high stereoselectivity induced by the tryptophan-derived organic catalysts, quinidine **QD-1**, 6′-demethylated quinidine **QD-2**,[15] quinidine-derived sulfonamide **QD-3**,[16] and quinidine-

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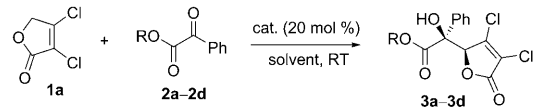
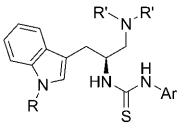
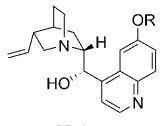
Table 1: Catalyst screening for the asymmetric vinylogous aldol reaction of **1a** with **2**.[a]



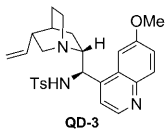
2a: R = Me; **2b**: R = Et;
2c: R = *t*Bu; **2d**: R = Ph



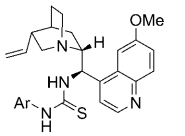
Trp-1: R = Me, R' = Et, Ar = 3,5-$CF_3C_6H_3$
Trp-2: R = H, R' = Et, Ar = 3,5-$CF_3C_6H_3$
Trp-3: R = H, R' = Me, Ar = 3,5-$CF_3C_6H_3$
Trp-4: R = H, R' = $(CH_2)_4$, Ar = 3,5-$CF_3C_6H_3$
Trp-5: R = H, R' = Et, Ar = 4-FC_6H_4
Trp-6: R = H, R' = Et, Ar =(1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol



QD-1: R = Me
QD-2: R = H



QD-3

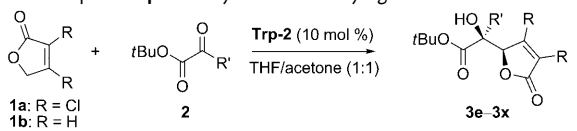


QD-4: Ar = 3,5-$CF_3C_6H_3$

Entry	Cat.	R	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1[e]	**Trp-1**	Me (**3a**)	48	<50	82:18	75
2	**Trp-1**	Me (**3a**)	15	83	80:20	74
3	**Trp-1**	Et (**3b**)	24	89	81:19	82
4	**Trp-1**	*t*Bu (**3c**)	24	92	>91:9	87
5	**Trp-1**	Ph (**3d**)	24	79	91:9	61
6[f]	**Trp-1**	*t*Bu (**3c**)	24	85	>91:9	91
7[f]	**QD-1**	*t*Bu (**3c**)	24	84	>91:9	−11
8[f]	**QD-2**	*t*Bu (**3c**)	24	85	>91:9	12
9[f]	**QD-3**	*t*Bu (**3c**)	24	<50	>91:9	0
10[f]	**QD-4**	*t*Bu (**3c**)	24	92	>91:9	−65
11[f]	**Trp-2**	*t*Bu (**3c**)	24	91	>91:9	92
12[f]	**Trp-3**	*t*Bu (**3c**)	24	87	>91:9	80
13[f]	**Trp-4**	*t*Bu (**3c**)	24	89	>91:9	71
14[f]	**Trp-5**	*t*Bu (**3c**)	24	84	>91:9	65
15[f]	**Trp-6**	*t*Bu (**3c**)	24	87	>91:9	29
16[f,g]	**Trp-2**	*t*Bu (**3c**)	40	83	95:5	90
17[g,h]	**Trp-2**	*t*Bu (**3c**)	24	89	94:6	88
18[g,i]	**Trp-2**	*t*Bu (**3c**)	24	88	97:3	93
19[g,j]	**Trp-2**	*t*Bu (**3c**)	40	73	97:3	93

[a] Reaction conditions: **1** (0.1 mmol), **2** (0.05 mmol), the catalyst (0.01 mmol), molecular sieves (4 Å), THF (0.35 mL), room temperature. [b] Yield of the isolated product. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis on a chiral stationary phase. [e] Without molecular sieves (4 Å). [f] Reaction was performed in 0.5 mL of solvent. [g] With 10 mol% catalyst. [h] Reaction was performed in 0.2 mL of THF. [i] Reaction was performed in 0.2 mL of acetone/THF (1:1). [j] Reaction was performed in 0.2 mL of acetone. Ts = p-toluenesulfonyl

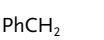
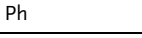
Table 2: Scope of **Trp-2**-catalyzed direct vinylogous aldol reaction.[a]



1a: R = Cl
1b: R = H

2

3e–3x

Entry	**1**	R′		*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**1a**	4-PhC_6H_4	**3e**	24	92	96:4	93
2	**1a**	2-naphthyl	**3f**	40	86	94:6	94
3[e]	**1a**	4-MeC_6H_4	**3g**	48	86	95:5	95
4[e]	**1a**	3-MeC_6H_4	**3h**	48	81	96:4	94
5[e]	**1a**	4-*t*BuC_6H_4	**3i**	72	80	95:5	94
6[e]	**1a**	4-OMeC_6H_4	**3j**	72	76	94:6	95
7	**1a**	4-ClC_6H_4	**3k**	24	85	97:3	92
8	**1a**	3-ClC_6H_4	**3l**	24	84	93:7	88
9	**1a**	4-BrC_6H_4	**3m**	24	93	95:5	90
10	**1a**	4-FC_6H_4	**3n**	36	81	94:6	92
11[f]	**1a**	4-CNC_6H_4	**3o**	20	93	92:8	82
12[f]	**1a**	4-CO_2MeC_6H_4	**3p**	20	86	97:3	87
13	**1a**		**3q**	20	86	92:8	85
14	**1a**		**3r**	20	87	90:10	81
15[g]	**1a**		**3s**	10	41	88:12	90
16	**1a**		**3t**	12	73	89:11	88
17	**1a**	$PhCH_2$	**3u**	8	61	85:15	80
18	**1a**	$PhCH_2CH_2$	**3v**	5	53	86:14	85
19	**1a**		**3w**	12	70	87:13	80
20	**1b**	Ph	**3x**	144	69	91:9	82

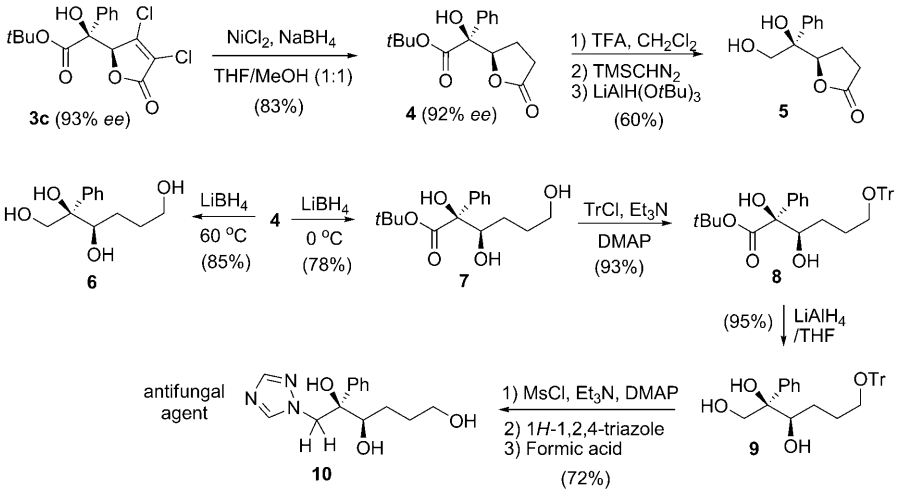
[a] Reaction conditions: **1** (0.1 mmol), **2** (0.05 mmol), **Trp-2** (0.005 mmol), molecular sieves (4 Å), 1:1 mixture of THF/acetone (0.2 mL), room temperature. [b] Yield of the isolated product. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis on a chiral stationary phase. [e] With 20 mol% of catalyst. [f] The reaction was performed in 0.35 mL of solvent. [g] The double bond in the allyl group was shifted to yield the 2-methyl-vinyl-substituted product.

derived thiourea **QD-4**[17] were all found to be poor catalysts (Table 1, entries 7–10). Among the various tryptophan-based catalysts, **Trp-2** gave the best results (Table 1, entry 11). To make the method more practical, the catalyst loading was lowered to 10 mol%, and under the optimized reaction conditions, the desired vinylogous aldol product could be obtained in excellent yield and with 97:3 d.r. and 93% *ee* (Table 1, entry 18).

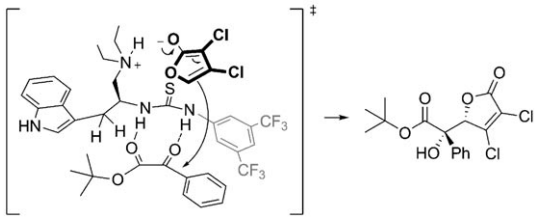
With these optimized reaction conditions in hand, the reaction scope was studied next (Table 2). Consistently high diastereo- and enantioselectivities were observed for a wide range of aromatic-substituted α-ketoesters (Table 2, entries 1–12). Vinylic substituents on the α-ketoesters were well-tolerated, and high d.r. and *ee* values were attainable (Table 2, entries 13–14). Alkyl-substituted ketoesters were suitable substrates as well, and stereoselectivities were maintained (Table 2, entries 16–19). The nonhalogenated furanone could also be used, although a much longer reaction time was required (Table 2, entry 20).

The vinylogous aldol reaction described here represents a novel asymmetric preparation of biologically important γ-substituted butenolides.[8] Furthermore, these aldol products are versatile chiral building blocks as is demonstrated in Scheme 2. Reduction of the γ-substituted butenolide **3c** afforded the chiral γ-butyrolactone[18] **4**, and subsequent selective reduction of the *tert*-butyl ester using LiAl-(O*t*Bu)$_3$H[19] yielded lactone **5**, which contains an adjacent tertiary hydroxy group. Chiral glycerol derivatives were accessed by treating **4** with $LiBH_4$ at 60 °C to effect a global reduction and give the 2-substituted glycerol derivative **6**. Alternatively, exposing **4** to $LiBH_4$ at 0 °C selectively reduced the lactone to triol **7**, which could be elaborated to yield the antifungal agent **10**.[20]

To account for the stereochemical outcome of the vinylogous aldol reaction, a plausible transition-state model is proposed in Scheme 3. The tertiary amine of the catalyst deprotonates the dichlorofuranone to yield an ammonium ion and an enolate. Hydrogen-bonding interactions between the ketoester and the thiourea moiety play a key role in the

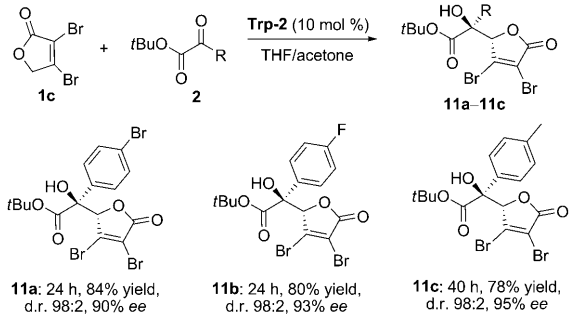


Scheme 2. Preparation of chiral γ-substituted butenolides and 2-substituted glycerol derivatives. DMAP = 4-dimethylaminopyridine, Ms = methanesulfonyl, TFA = trifluoroacetic acid, TMS = trimethylsilyl, Tr = trityl.



Scheme 3. Proposed transition-state model.

substrate binding. The attack of enolate from the Si face of the ketone leads to the formation of the major stereoisomer. The presence of the two chlorine atoms is believed to contribute significantly to the observed high diastereoselectivity. If the chlorine atoms were replaced by the more bulky bromine atoms, an increase in diastereoselectivity would be anticipated. Moreover, the introduction of bromine atoms to the furanones would result in the formation of a tighter ion pair as a result of the higher electron density on the enolate oxygen atom, therefore leading to aldol products with improved diastereoselectivity. Additional experiments, illustrated in Scheme 4, supported this proposal. When 3,4-dibromofuranone (**1c**) was employed in the vinylogous aldol reaction under otherwise identical reaction conditions, a 98:2 d.r. was observed, as compared to a 95:5 d.r. with 3,4-dichlorofuranone (**1a**).



Scheme 4. Vinylogous aldol reaction employing 3,4-dibromofuran-2(5*H*)-one.

In conclusion, we have developed the first highly diastereo- and enantioselective direct vinylogous aldol reactions between furanones and α-ketoesters catalyzed by a tryptophan-derived bifunctional organic catalyst. The synthetic method reported provides easy access to biologically important γ-substituted butenolides and chiral glycerol derivatives containing a tertiary alcohol moiety. Investigations into the extension of this method to other asymmetric vinylogous reactions are ongoing and will be reported in due course.

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[1] For a recent book, see: *Quaternary Stereocenters* (Eds.: J. Christoffers, A. Baro), Wiley-VCH, Weinheim, **2005**.

[2] For our recent examples of the synthesis of quaternary stereocenters, see: a) Q. Zhu, Y. Lu, *Angew. Chem.* **2010**, *122*, 7919; *Angew. Chem. Int. Ed.* **2010**, *49*, 7753; b) X. Han, J. Kwiatkowski, F. Xue, K.-W. Huang, Y. Lu, *Angew. Chem.* **2009**, *121*, 7740; *Angew. Chem. Int. Ed.* **2009**, *48*, 7604; c) Q. Zhu, Y. Lu, *Chem. Commun.* **2010**, *46*, 2235; d) X. Han, J. Luo, C. Liu, Y. Lu, *Chem. Commun.* **2009**, 2044; e) J. Luo, L.-W. Xu, R. A. S. Hay, Y. Lu, *Org. Lett.* **2009**, *11*, 437; f) Z. Jiang, Y. Lu, *Tetrahedron Lett.* **2010**, *51*, 1884; g) X. Han, F. Zhong, Y. Lu, *Adv. Synth. Catal.* **2010**, *352*, 2778; h) F. Zhong, G.-Y. Chen, Y. Lu, *Org. Lett.* **2011**, *13*, 82.

[3] a) Y. Hayashi, H. Yamaguchi, M. Toyoshima, K. Okado, T. Toyo, M. Shoji, *Chem. Eur. J.* **2010**, *16*, 10150; b) D. A. Nicewicz, A. D. Satterfield, D. C. Schimitt, J. S. Johnson, *J. Am. Chem. Soc.* **2008**, *130*, 17281; c) A. N. Cuzzupe, R. D. Florio, J. M. White, M. A. Rizzacasa, *Org. Biomol. Chem.* **2003**, *1*, 3572; d) K. Narasaka, T. Sakakura, T. Uchimaru, D. G. Vuong, *J. Am. Chem. Soc.* **1984**, *106*, 2954.

[4] a) A. C. Pasqualotto, K. O. Thiele, L. Z. Goldani, *Curr. Opin. Invest. Drugs* **2010**, *11*, 165; b) J. J. Partridge, S.-J. Shiuey, N. K. Chadha, E. G. Blount, J. F. Baggiolini, M. R. Uskokovic, *J. Am. Chem. Soc.* **1981**, *103*, 1253; c) X. Wu, P. Öhrngren, J. K. Ekegren, J. Unge, T. Unge, H. Wallberg, B. Samuelsson, A. Hallberg, M. Larhed, *J. Med. Chem.* **2008**, *51*, 1053.

[5] For selected examples, see: a) R. Shintani, K. Takatsu, T. Hayashi, *Org. Lett.* **2008**, *10*, 1191; b) J. L. Stymiest, V. Bagutski, R. M. French, V. K. Aggarwal, *Nature* **2008**, *456*, 778; c) P. I. Dosa, G. C. Fu, *J. Am. Chem. Soc.* **1998**, *120*, 445; d) K. Oisaki, D. Zhao, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 7164; e) M. Rueping, T. Theissmann, A. Kuenkel, R. M. Koenigs, *Angew. Chem.* **2008**, *120*, 6903; *Angew. Chem. Int. Ed.* **2008**, *47*,

6798; f) H. Li, B. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 732; g) B. Török, M. Abid, G. London, J. Esquibel, M. Török, S. C. Mhadgut, P. Yan, G. K. S. Prakash, *Angew. Chem.* **2005**, *117*, 3146; *Angew. Chem. Int. Ed.* **2005**, *44*, 3086; h) S. Ogawa, N. Shibata, J. Inagaki, S. Nakamura, T. Toru, M. Shiro, *Angew. Chem.* **2007**, *119*, 8820; *Angew. Chem. Int. Ed.* **2007**, *46*, 8666.

[6] T. Harada, H. Nakajima, T. Ohnishi, M. Takeuchi, A. Oku, *J. Org. Chem.* **1992**, *57*, 720.

[7] a) B. Jung, M. S. Hong, S. H. Kang, *Angew. Chem.* **2007**, *119*, 2670; *Angew. Chem. Int. Ed.* **2007**, *46*, 2616; b) B. Jung, S. H. Kang, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 1471.

[8] a) A. D. Rodríguez, *Tetrahedron* **1995**, *51*, 4571; b) F. W. Alali, X.-X. Liu, J. L. McLaughlin, *J. Nat. Prod.* **1999**, *62*, 504; c) X. J. Smith, D. Abbanat, V. S. Bernan, W. M. Maiese, M. Greenstin, J. Jompa, A. Tahir, C. M. Ireland, *J. Nat. Prod.* **1999**, *63*, 142; d) R.-T. Li, Q.-B. Han, Y.-T. Zheng, R.-R. Wang, L.-M. Yang, Y. Lu, S.-Q. Sang, Q.-T. Zheng, Q.-S. Zhao, H.-D. Sun, *Chem. Commun.* **2005**, 2936; e) Y. S. Rao, *Chem. Rev.* **1976**, *76*, 625; f) H. M. C. Ferraz, L. S. Longo, Jr., M. V. A. Grazini, *Synthesis* **2002**, 2155.

[9] For reviews, see: a) G. Casiraghi, F. Zanardi, G. Appendino, G. Rassu, *Chem. Rev.* **2000**, *100*, 1929; b) S. E. Denmark, J. R. Heemstra, Jr., G. L. Beutner, *Angew. Chem.* **2005**, *117*, 4760; *Angew. Chem. Int. Ed.* **2005**, *44*, 4682; c) M. Kalesse, *Top. Curr. Chem.* **2005**, *244*, 43.

[10] For enantioselective vinylogous aldol reactions using 2-silyloxyfurans, see: a) D. A. Evans, M. C. Kozlowski, J. A. Murry, C. S. Burgey, K. R. Campos, B. T. Connell, R. J. Staples, *J. Am. Chem. Soc.* **1999**, *121*, 669; b) M. Szlosek, B. Figadère, *Angew. Chem.* **2000**, *112*, 1869; *Angew. Chem. Int. Ed.* **2000**, *39*, 1799; c) S. P. Brown, N. C. Goodwin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 1192; d) Y. Matsuoka, R. Irie, T. Katsuki, *Chem. Lett.* **2003**, *32*, 584; e) J. Sedelmeier, T. Hammerer, C. Bolm, *Org. Lett.* **2008**, *10*, 917; f) R. P. Singh, B. M. Foxman, L. Deng, *J. Am. Chem. Soc.* **2010**, *132*, 9558.

[11] K. D. Sarma, J. Zhang, T. T. Curran, *J. Org. Chem.* **2007**, *72*, 3311.

[12] H. Ube, N. Shimada, M. Terada, *Angew. Chem.* **2010**, *122*, 1902; *Angew. Chem. Int. Ed.* **2010**, *49*, 1858.

[13] Y. Yang, K. Zheng, J. Zhao, J. Shi, L. Lin, X. Liu, X. Feng, *J. Org. Chem.* **2010**, *75*, 5382.

[14] For reviews on asymmetric catalysis mediated by amino acids and synthetic peptides, see: a) L.-W. Xu, J. Luo, Y. Lu, *Chem. Commun.* **2009**, 1807; b) L.-W. Xu, Y. Lu, *Org. Biomol. Chem.* **2008**, *6*, 2047; c) E. A. C. Davie, S. M. Mennen, Y. Xu, S. J. Miller, *Chem. Rev.* **2007**, *107*, 5759.

[15] a) H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906; b) T. Marcelli, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem.* **2006**, *118*, 7658; *Angew. Chem. Int. Ed.* **2006**, *45*, 7496.

[16] J. Luo, L.-W. Xu, R. A. S. Hay, Y. Lu, *Org. Lett.* **2009**, *11*, 437.

[17] For reviews, see: a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289; b) H. Yamamoto, K. Futatsugi, *Angew. Chem.* **2005**, *117*, 1958; *Angew. Chem. Int. Ed.* **2005**, *44*, 1924; c) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999; d) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; e) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713; f) X. Yu, W. Wang, *Chem. Asian J.* **2008**, *3*, 516; g) S. J. Connon, *Chem. Commun.* **2008**, 2499.

[18] a) A. Kamal, M. Sandbhor, A. A. Shaik, *Tetrahedron: Asymmetry* **2003**, *14*, 1575; b) S.-H. Lee, O.-J. Park, *Appl. Microbiol. Biotechnol.* **2009**, *84*, 817.

[19] a) D. S. Reddy, N. Shibata, J. Nagai, S. Nakamura, T. Toru, *Angew. Chem.* **2009**, *121*, 817; *Angew. Chem. Int. Ed.* **2009**, *48*, 803; b) T. A. Ayers, *Tetrahedron Lett.* **1999**, *40*, 5467.

[20] M. Ogata, H. Matsumoto, K. Takahashi, S. Shimizu, S. Kida, A. Murabayashi, M. Shiro, K. Tawara, *J. Med. Chem.* **1987**, *30*, 1054.

