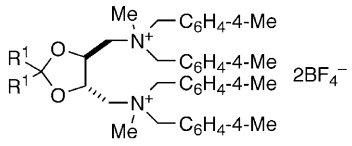
Phase-Transfer Catalysis

Enantio- and Diastereoselective Catalytic Mannich-Type Reaction of a Glycine Schiff Base Using a Chiral Two-Center Phase-Transfer Catalyst**

Akihiro Okada, Tomoyuki Shibuguchi, Takashi Ohshima, Hyuma Masu, Kentaro Yamaguchi, and Masakatsu Shibasaki**

α,β-Diamino acids are key structural components in molecules such as peptides and β-lactam antibiotics and in medicinally relevant compounds;[1,2] for example, 2,3-diamino-3-phenylpropanoic acid is used as an advanced alternative to the side chain of taxol to improve its water solubility.[3] Various methods for the preparation of optically active α,β-diamino acid derivatives have been reported. Almost all of them, however, require the use of stoichiometric amounts of chiral sources. One common method involves the displacement of the hydroxy group of serine derivatives with an azide moiety followed by reduction of the azide group,[1,4] and another is the addition of glycine ester derivatives to chiral *N*-sulfinyl imines.[5,6] Jørgensen and co-workers reported an efficient catalytic method that relies on the aza-Henry reaction of silyl nitronates with imines.[7] The catalytic asymmetric synthesis of chiral serine derivatives by the Sharpless asymmetric aminohydroxylation reaction is another useful method.[8] Recently, more direct and atom-economically favorable methods using a Mannich-type reaction of a glycine Schiff base with imines were reported by Jørgensen and co-workers[9] and Maruoka and co-workers.[10] Although these methods are highly enantioselective, there is still much room for improvement. For example, the removal of *para*-toluenesulfonate (tosyl) groups is difficult in the method of Jørgensen and co-workers, and low substrate generality is a problem in the method of Maruoka and co-workers. Both methods are also only moderately diastereoselective. Herein, we report a new direct method to access a variety of optically active *syn*-α,β-diamino acid derivatives by a Mannich-type reaction of a glycine Schiff base that uses a new chiral two-center phase-transfer catalyst. The selection of the imine-protecting group was pivotal to achieving high diastereoselectivity (up to 99:1). Moreover, the usefulness of the obtained products was successfully demonstrated by their transformation into a tripeptide and the key intermediate of CP-99,994 through chemoselective deprotection of the *N*-diphenylmethylene and *N*-*tert*-butoxycarbonyl (Boc) protecting groups.

To develop efficient methods for the synthesis of α,β-diamino acid derivatives, we used Mannich protocols under asymmetric phase-transfer reaction conditions because of the preparative advantages of the phase-transfer process, such as simple procedures and mild conditions.[11] Recently, we developed the tartrate-derived diammonium salt (TaDiAS) **1**, which efficiently catalyzes asymmetric phase-transfer alkylations and Michael reactions of a glycine Schiff base **2**.[12]



(*S*,*S*)-TaDiAS **1a**: R^1 = Pr
1b: R^1 = Bu

We initially examined a Mannich-type reaction of **2** using *N*-diphenylphosphinoyl (dpp) imine **3a** as an electrophile because the dpp group can be readily removed under mild conditions.[13] Under phase-transfer conditions using TaDiAS **1b**, which is a suitable catalyst for asymmetric phase-transfer Michael reactions,[12] and fluorobenzene and cesium carbonate were determined to be the best solvent and base, respectively; this reaction afforded the desired Mannich

[*] A. Okada, T. Shibuguchi, Dr. T. Ohshima, Prof. Dr. M. Shibasaki
Graduate School of Pharmaceutical Sciences
The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
Fax: (+81) 3-5684-5206
E-mail: ohshima@chem.es.osaka-u.ac.jp
mshibasa@mol.f.u-tokyo.ac.jp
Dr. H. Masu, Prof. Dr. K. Yamaguchi
Faculty of Pharmaceutical Sciences at Kagawa Campus
Tokushima Bunri University
Shido, Sanuki-city, Kagawa 769-2193 (Japan)

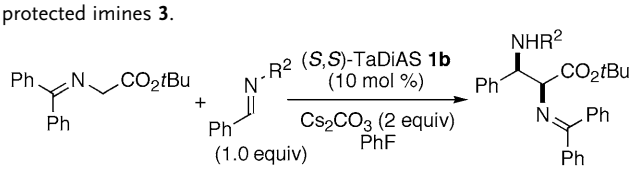
[**] This work was supported by RFTF, a Grant-in-Aid for the Encouragement of Young Scientists (A), and a Grant-in-Aid for Specially Promoted Research from the Japanese Society for the Promotion of Science (JSPS) and the Ministry of Education, Culture, Sports, Science, and Technology (MEXT).

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

  DOI: 10.1002/anie.200500927

product **4a** in high yield (95%) and moderate selectivity (*syn*/*anti* = 77:23, 51% *ee*; Table 1, entry 1).[14] Various N-protected imines were screened under the optimized conditions (Table 1, entries 2–5). Although the reaction did not proceed

Table 1: Catalytic asymmetric Mannich-type reaction with various *N*-protected imines **3**.



Entry	Imine **3**	R^2	*T* [°C]	*t* [h]	Yield [%]	d.r. [*syn*/*anti*][a]	*ee* [%][b]
1	**3a**	dpp	4	2	95	77:33	51
2	**3b**	$CHPh_2$	RT	72	n.r.[c]		
3	**3c**	CH_2Ph	RT	72	n.r.[c]		
4	**3d**	Boc	4	2	quant	>95:5	53
5	**3e**	tosyl	RT	2.5	97	70:30	0

[a] Determined by HPLC analysis. [b] The *ee* value of the *syn* product was determined by HPLC analysis. [c] n.r. = no reaction.

when diphenylmethyl imine **3b** (Table 1, entry 2) and benzyl imine **3c** (Table 1, entry 3) were used, *N*-Boc imine **3d** (Table 1, entry 4) gave the product **4d** in quantitative yield with high diastereoselectivity (*syn*/*anti* = >95:5) and moderate enantioselectivity (53% *ee*). These results suggested that the electron-withdrawing imine-protecting group plays an important role in the reactivity. On the other hand, the *N*-tosyl imine was less reactive and produced a low enantioselectivity (Table 1, entry 5). Thus, we chose the *N*-Boc imine **3d** as a substrate for further investigation because of these results and the fact that a Boc protecting group can be readily removed.

We next examined the structure of the catalyst to improve enantioselectivity. We had previously synthesized a variety of TaDiAS salts **1**, and they had been examined in catalytic asymmetric phase-transfer alkylations and Michael reactions. However, rational design of the catalyst was still difficult because of the lack of conformational information about **1**, except for preliminary computational analysis that suggested the formation of a tight ion complex between the two cation centers in **1** and the enolate of **2**. Thus, on the basis of the above analysis, we performed a conformational investigation of **1**. Although no useful information was obtained by NMR spectroscopy, the structure of **1a** was determined by X-ray crystallographic analysis. A tetrafluoroborate anion is situated very close to each of the ammonium units, thus creating an attractive C_2-symmetrical chiral environment (Figure 1). Another interesting fact is that the alkyl chains of the acetal moiety snake up in a direction perpendicular to the dioxolane ring. A previous examination of substituent effects in asymmetric phase-transfer catalysis revealed that both aromatic and acetal moieties strongly affected enantioselectivity. This unexpected substituent effect by the acetal moiety can be understood from the proximity of the counteranions to the

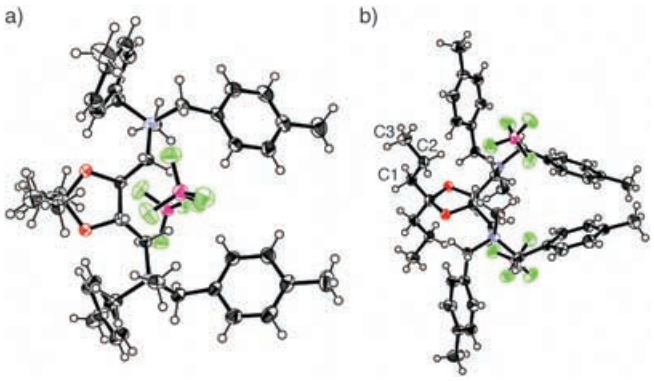
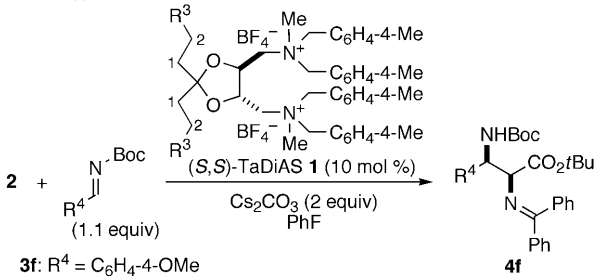


Figure 1. Crystal structure of (*S*,*S*)-TaDiAS (**1a**). a) Top view and b) side view.

acetal side chains, especially to the C2 and C3 positions (Figure 1b).

In the reaction, the enolate of **2** was expected to be replaced with the BF_4^- ion and form a tight complex with the cationic centers of **1**. Therefore, we assumed that longer or more sterically congested acetal substituents would prevent an unfavorable approach by the imines to the enolate of **2**. On the basis of this hypothesis, the substituent effects of the acetal moiety were examined (Table 2).[15] As expected, the

Table 2: Optimization of the catalyst structure for the asymmetric Mannich-type reaction.



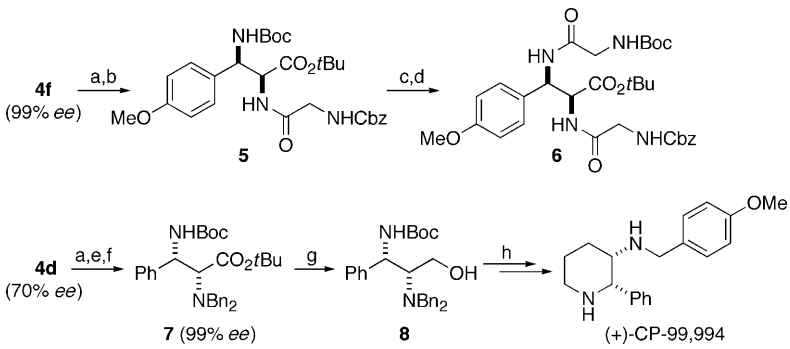
Entry	Cat. **1**	R^3	*T* [°C]	*t* [h]	Yield [%]	d.r. [*syn*/*anti*][a]	*ee* [%][b]
1	**1a**	H	4	1	96	>95:5	58
2	**1b**	Me	4	1	quant	>95:5	59
3	**1c**	Ph	4	0.5	quant	98:2	62
4	**1d**	CH_2Ph	4	0.5	quant	>95:5	57
5	**1e**	4-*t*BuC_6H_4	4	0.5	quant	98:2	60
6	**1f**	2,4,6-$Me_3C_6H_2$	4	0.5	97	98:2	48
7	**1g**	4-FC_6H_4	4	0.5	99	97:3	65
8[c]	**1g**	4-FC_6H_4	−45	48	95	95:5	82

[a] Determined by HPLC analysis. [b] The *ee* value of the *syn* product was determined by HPLC analysis. [c] Solvent was PhF/pentane (4:1).

introduction of an aromatic ring at the C2 positions of the acetal side chains improved the enantioselectivity (Table 2, entry 3). On the other hand, the introduction of a benzyl group at C2, which results in an aromatic ring at the C3 position (Table 2, entry 4), and a bulky substituent at C2 (Table 2, entry 6) gave only moderate enantioselectivity. Finally, the best results were obtained from the use of the 4-fluorophenyl-substituted catalyst **1g** (Table 2, entry 7), which

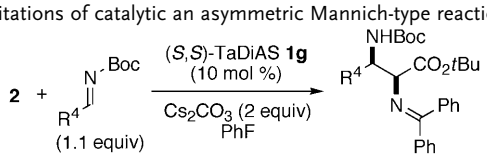
suggests the possibility of π–π interactions.[16] Performing the latter reaction at lower temperature (−45 °C) further improved the enantioselectivity to 82 % *ee* (Table 2, entry 8).

We examined the scope and limitations of the reaction under the optimized conditions using various *N*-Boc imines. As summarized in Table 3, all the asymmetric Mannich-type reactions proceeded in high yield with high diastereoselectivity (*syn*/*anti* = 95:5–99:1) when 10 mol % of TaDiAS **1g** was used with Cs_2CO_3 in fluorobenzene. In terms of enantioselectivity, *C*-phenyl imine derivatives with an electron-donating group at the 4-position were suitable substrates (Table 3, entries 2 and 3). On the other hand, 4-chlorophenyl and 2-naphthyl substituents (Table 3, entries 7 and 8) were only moderately enantioselective.



Scheme 1. Syntheses of tripeptide **6** and the key intermediate **8** of CP-99,994. Reagents and conditions: a) 0.5 M citric acid, THF, RT; b) *N*-Cbz-gly, WSC, HOBt, CH_2Cl_2, 4 °C (90 % over 2 steps); c) 2 N HCl, MeOH, RT; d) *N*-Boc-gly, WSC, HOBt, CH_2Cl_2, 4 °C (92 % over 2 steps); e) BnBr, K_2CO_3, THF, reflux; f) recrystallization from EtOAc/hexane (42 % over 3 steps, 99 % *ee*); g) $LiAlH_4$, 4 → 40 °C (91 %); h) see ref. [19] Cbz = carbobenzoxy, Bn = benzyl, gly = glycine, HOBt = 1-hydroxybenzotriazole, WSC = *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide.

Table 3: Scope and limitations of catalytic an asymmetric Mannich-type reaction.



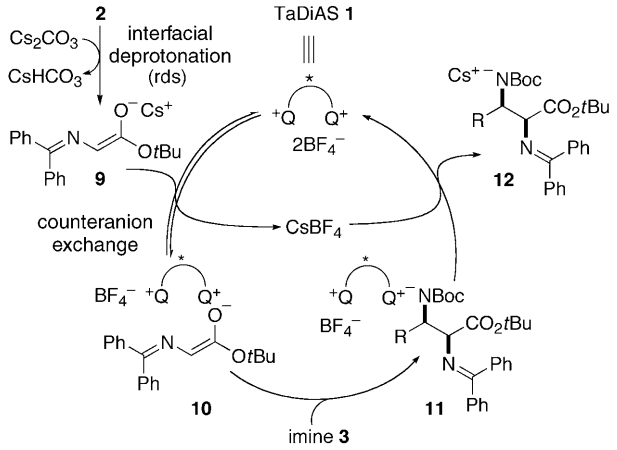
Entry	Imine **3**	R^4	*T* [°C]	*t* [h]	Yield [%]	d.r. [*syn*/*anti*][a]	*ee* [%][b]
1	**3d**	Ph	−30	19	98	99:1	70
2[c]	**3f**	4-OMe-C_6H_4	−45	48	95	95:5	82 (99)[d]
3	**3g**	4-Me-C_6H_4	−40	48	98	98:2	80
4[c]	**3h**	3-Me-C_6H_4	−45	72	96	95:5	70
5	**3i**	2-Me-C_6H_4	−20	66	99	97:3	68
6	**3j**	4-F-C_6H_4	−40	48	99	98:2	72
7	**3k**	4-Cl-C_6H_4	−20	20	87	98:2	58
8	**3l**	2-naphthyl	−20	72	87	> 95:5	60
9	**3m**	2-thiophenyl	−40	48	98	98:2	80
10	**3n**	(*E*)-PhCH=CH_2	−30	48	86	98:2	66

[a] Determined by HPLC analysis. [b] The *ee* value of the *syn* product was determined by HPLC analysis. [c] Solvent was PhF/pentane (4:1). [d] The *ee* value after a single recrystallization.

Although *N*-Boc C-aliphatic imines could not be applied because of the difficulties in synthesizing them, the use of α,β-unsaturated imines for the Mannich-type reaction followed by hydrogenation is an alternative method (Table 3, entry 10). Another beneficial feature of this process is that most of the products were obtained as crystalline solids, and in fact a single recrystallization of **4f** (82 % *ee*) provided an optically pure compound in 74 % yield. Although the enantioselectivity of the reaction was not very satisfactory, to the best of our knowledge, this diastereoselectivity is the highest reported for a catalytic Mannich-type reaction of a glycine Schiff base **2** with imines.

The synthetic utility of the resulting optically active α,β-diamino acid derivatives was demonstrated by straightforward transformations into tripeptide **6** and key intermediate **8** for the synthesis of the selective and potent neurokinin substance P antagonist (+)-CP-99,994[17–19] through deprotection of the *N*-diphenylmethylene and *N*-Boc groups (Scheme 1, top). Highly chemoselective deprotection of the *N*-diphenylmethylene group of **4f** by aqueous citric acid, followed by a subsequent peptide-coupling reaction gave dipeptide **5**. Next, the *N*-Boc group was readily deprotected with a 2 N solution of HCl in methanol to afford, after another peptide-coupling reaction, the optically pure tripeptide **6** in good yield. Moreover, the protected α,β-diamino ester **4d**, which was synthesized by using (*R*,*R*)-TaDiAS **1g**, was successfully converted into the key intermediate **8**[19] in an optically pure form (Scheme 1, bottom).

Information about the reaction mechanism is essential to improve the efficiency of the catalyst, TaDiAS **1**. Despite the value of mechanistic investigations in catalyst development, however, only limited mechanistic studies on asymmetric phase-transfer catalysis have been reported.[20] To gain insight into the mechanism of this asymmetric phase-transfer catalytic reaction, we performed initial rate kinetic studies.[21] First-order dependency was observed for the glycine Schiff base **2** and Cs_2CO_3, whereas the reaction rate had zero-order dependency for the imine **3** and the catalyst **1**. These results indicated that the rate-determining step of the Mannich-type reaction is deprotonation of **2** by Cs_2CO_3; unexpectedly, **1** was not involved in this step. On the basis of these results, we propose a catalytic cycle for the asymmetric Mannich-type reaction (Scheme 2). Deprotonation of **2** by Cs_2CO_3 at the interface between the liquid and solid phase followed by counteranion exchange with the catalyst **1** gives complex **10**.[22] An asymmetric C–C bond-forming reaction of **10** with the imine **3** gives the Mannich product **11**. Finally, counteranion exchange between **11** and the resulting $CsBF_4$ provides **12** and generates **1**. The very low reaction efficiency that results from the use of a catalytic amount of Cs_2CO_3 indicates that the formation of **10** through direct deprotonation of **2** in



Scheme 2. Proposed catalytic cycle of the asymmetric Mannich-type reaction. rds = rate-determining step.

the liquid phase with **11** or a hydroxide complex of the chiral ammonium cation is slow, thus making the interfacial deprotonation (**2**→**9**) the rate-determining step.

In summary, we have developed a highly efficient (up to quantitative yield) and *syn*-selective (up to 99:1) enantio- and diastereoselective catalytic Mannich-type reaction of a glycine Schiff base **2** with *N*-Boc imines **3** using the newly designed phase-transfer catalyst **1g**. Moreover, we have demonstrated the synthetic utility of the α,β-diamino acid products. Further mechanistic studies and investigations to improve the enantioselectivity are in progress.

Received: March 14, 2005
Published online: June 14, 2005

Keywords: amino acids · asymmetric catalysis · Mannich reaction · phase-transfer catalysis · Schiff bases

[1] Y. Luo, M. A. Blaskovich, G. A. Lajoie, *J. Org. Chem.* **1999**, *64*, 6106, and references therein.
[2] a) N. Subasinghe, M. Shulte, R. J. Roon, J. F. Koerner, R. L. Johnson, *J. Med. Chem.* **1992**, *35*, 4602; b) M. Wang, S. J. Gould, *J. Org. Chem.* **1993**, *58*, 5176; c) E. S. Lee, J. Jurayj, M. Cushman, *Tetrahedron* **1994**, *50*, 9873.
[3] F. M. Rossi, E. T. Powers, R. Yoon, L. Rosenberg, J. Meinwald, *Tetrahedron* **1996**, *52*, 10279.
[4] a) O. Mitsunobu, *Synthesis* **1981**, 1; b) M. Otsuka, A. Kittaka, T. Iimori, H. Yamashita, S. Kobayashi, M. Ohno, *Chem. Pharm. Bull.* **1985**, *33*, 509.
[5] a) A. Viso, R. Fernández de la Pradilla, C. Guerrero-Strachan, M. Alonso, M. Martínez-Ripoll, I. André, *J. Org. Chem.* **1997**, *62*, 2316; b) A. Viso, R. Fernández de la Pradilla, A. García, C. Guerrero-Strachan, M. Alonso, M. Tortosa, A. Flores, M. Martínez-Ripoll, I. Fonseca, I. André, A. Rodríguez, *Chem. Eur. J.* **2003**, *9*, 2867; c) A. Viso, R. Fernández de la Pradilla, M. L. López-Rodríguez, A. García, A. Flores, M. Alonso, *J. Org. Chem.* **2004**, *69*, 1542.
[6] F. A. Davis, J. Deng, *Org. Lett.* **2004**, *6*, 2789.
[7] K. R. Knudsen, T. Risgaard, N. Nishiwaki, K. V. Gothelf, K. A. Jørgensen, *J. Am. Chem. Soc.* **2001**, *123*, 5843.
[8] a) H. Han, J. Yoon, K. D. Janda, *J. Org. Chem.* **1998**, *63*, 2045; b) S.-H. Lee, J. Yoon, S.-H. Chung, Y.-S. Lee, *Tetrahedron* **2001**, *57*, 2139.
[9] L. Bernardi, A. S. Gothelf, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2003**, *68*, 2583.
[10] T. Ooi, M. Kameda, J. Fujii, K. Maruoka, *Org. Lett.* **2004**, *6*, 2397.
[11] For recent reviews of asymmetric phase-transfer catalysis, see: a) M. J. O'Donnell, *Aldrichimica Acta* **2001**, *34*, 3; b) K. Maruoka, T. Ooi, *Chem. Rev.* **2003**, *103*, 3013; c) M. J. O'Donnell, *Acc. Chem. Res.* **2004**, *37*, 506; d) B. Lygo, B. I. Andrews, *Acc. Chem. Res.* **2004**, *37*, 518.
[12] a) T. Shibuguchi, Y. Fukuta, Y. Akachi, A. Sekine, T. Ohshima, M. Shibasaki, *Tetrahedron Lett.* **2002**, *43*, 9539; b) T. Ohshima, T. Shibuguchi, Y. Fukuta, M. Shibasaki, *Tetrahedron* **2004**, *60*, 7743; for application of the TaDiAS-catalyzed phase-transfer reaction to the synthesis of aeruginosins, see: c) T. Ohshima, V. Gnanadesikan, T. Shibuguchi, Y. Fukuta, T. Nemoto, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 11206; d) Y. Fukuta, T. Ohshima, V. Gnanadesikan, T. Shibuguchi, T. Nemoto, T. Kisugi, T. Okino, M. Shibasaki, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5433.
[13] a) R. Ramage, D. Hopton, M. J. Parrott, G. W. Kenner, G. A. Moore, *J. Chem. Soc. Perkin Trans. 1* **1984**, 1357; b) R. Ramage, B. Atrash, D. Hopton, M. J. Parrott, *J. Chem. Soc. Perkin Trans. 1* **1985**, 1217; c) H. M. I. Osborn, J. B. Sweeney, *Synlett* **1994**, 145.
[14] The absolute configuration of **4a** was determined to be the *S* enantiomer by optical rotation studies of the cyclic urea derived from **4a**; see ref. [5b] and the Supporting Information for details.
[15] Modification of the aromatic moiety gave only unsatisfactory results.
[16] a) U.-H. Dolling, P. Davis, E. J. J. Grabowski, *J. Am. Chem. Soc.* **1984**, *106*, 446; b) S.-S. Jew, Mi.-S. Yoon, B.-S. Jeong II, Y. Park, H.-G. Park, *Org. Lett.* **2002**, *4*, 4245; c) C. A. Hunter, K. R. Lawson, J. Perkins, C. J. Urch, *J. Chem. Soc. Perkin Trans. 2* **2001**, 651.
[17] M. C. Desai, S. L. Lefkowiz, P. F. Thadeio, K. P. Longo, R. M. Snider, *J. Med. Chem.* **1992**, *35*, 4911.
[18] For recent total syntheses of (+)-CP-99,994, see: a) N. Tsuritani, K. Yamada, N. Yoshikawa, M. Shibasaki, *Chem. Lett.* **2002**, 276; b) N. Yamazaki, M. Atobe, C. Kibayashi, *Tetrahedron Lett.* **2002**, *43*, 7979; c) P. -Q. Huang, L. -X. Liu, B.-G. Wei, Y.-P. Ruan, *Org. Lett.* **2003**, *5*, 1927; d) M.-R. Tsai, B.-F. Chen, C.-C. Cheng, N.-C. Chang, *J. Org. Chem.* **2005**, *70*, 1780.
[19] For the transformation of **8** into CP-99,994, see: S. Chandrasekhar, P. K. Mohanty, *Tetrahedron Lett.* **1999**, *40*, 5071.
[20] a) D. L. Hughes, U.-H. Dolling, K. M. Ryan, E. F. Schoenewaldt, E. J. J. Grabowski, *J. Org. Chem.* **1987**, *52*, 4745; b) K. B. Lipkowitz, M. W. Cavanaugh, B. Baker, M. J. O'Donnell, *J. Org. Chem.* **1991**, *56*, 5181; c) I. A. Esikova, M. J. O'Donnell in *ACS Symposium Series 659*, *Phase-Transfer Catalysis* (Ed.: M. E. Halpern), American Chemical Society, Washington, DC, **1997**, chap. 7.
[21] See the Supporting Information.
[22] The precise geometry of enolate **10** remains unclear despite extensive attempts, although we assume that the reaction proceeds through the *Z* enolate of **10**; see ref. [12b].

