Asymmetric Synthesis

Catalytic Asymmetric Addition of β-Ketoesters to Various Imines by Using Chiral Palladium Complexes**

*Yoshitaka Hamashima, Naoki Sasamoto, Daido Hotta, Hidenori Somei, Natsuko Umebayashi, and Mikiko Sodeoka**

Addition reactions of metal enolates of carbonyl compounds to imines, the so-called Mannich-type reaction, represent an important class of carbon–carbon bond-forming reactions.[1] Reflecting the potential utility of the Mannich adducts in the synthesis of nitrogen-containing compounds,[2] we[3] and others[4] have reported efficient methods for catalytic enantioselective Mannich-type reactions.[5] In our previous reports, however, the pre-activation of ketones to form silyl enol ethers was necessary. To meet the present need for atom-economical processes, the direct addition of pronucleophiles to imines is highly desirable.[6]

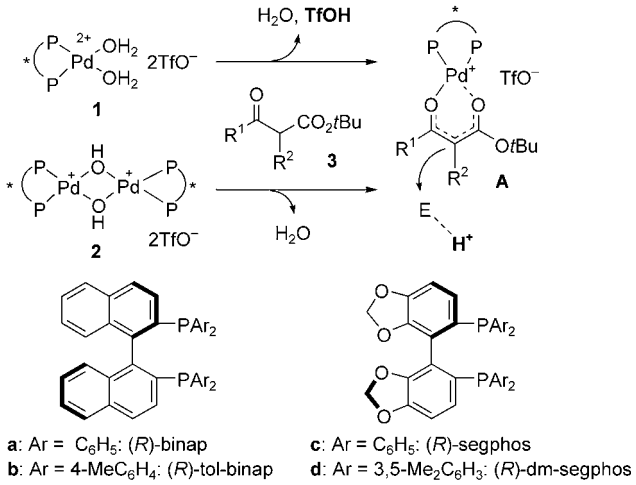
Recently we reported that chiral Pd complexes **1** and **2** reacted with 1,3-dicarbonyl compounds, such as β-ketoesters, to give chiral Pd enolates (Scheme 1).[7] Using this Pd enolate chemistry, an efficient catalytic enantioselective Michael reaction with enones was developed.[7a] Interestingly, the chiral enolate **A** derived from **1** underwent the Michael reaction smoothly, whereas the corresponding Pd enolate derived from **2** was completely inactive. These results indicated that the strong protic acid, trifluoromethanesulfonic acid (TfOH), formed concomitantly with the Pd enolate from **1** and activated the enone to act cooperatively with the Pd enolate **A**, thereby promoting the C–C bond-forming reaction. Provided that the reactivity of imines is greatly enhanced by protonation, the above-mentioned Pd enolate chemistry would be applicable to the Mannich-type reaction. To our knowledge there has been only one reported example of the use of β-ketoesters in a catalytic asymmetric Mannich-type reaction, where Jørgensen and co-workers[8] achieved excellent enantioselectivities of more than 90% *ee*. However, only the imine tested was a highly reactive *N*-*p*-toluenesulfonyl-protected imino ester and the scope of the available

[*] Dr. Y. Hamashima, N. Sasamoto, D. Hotta, Dr. H. Somei, N. Umebayashi, Prof. Dr. M. Sodeoka
Institute of Multidisciplinary Research for Advanced Materials (IMRAM)
Tohoku University
Katahira, Sendai, Miyagi 980-8577 (Japan)
and
PRESTO, Japan Science and Technology Agency (JST)
Fax: (+81) 22-217-5601
E-mail: sodeoka@tagen.tohoku.ac.jp

[**] This work was supported in part by a Grant-in-Aid for Encouragement of Young Scientists (B) from JSPS. We thank Dr. T. Saito of Takasago International Corp. for providing the chiral phosphine ligands.

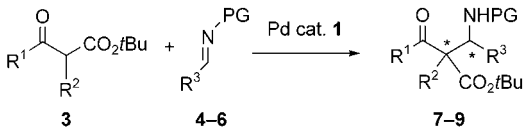
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

 DOI: 10.1002/anie.200462202



Scheme 1. Top: Reaction of chiral Pd complexes **1** and **2** with 1,3-dicarbonyl compounds **3** to afford chiral Pd enolates. Bottom: The structures of the different PP ligands.

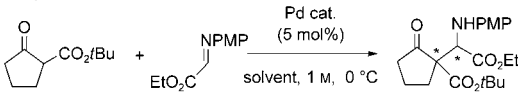
electrophiles was not examined. The development of such a reaction with broad generality with regard to imines would be extremely useful. Herein, we report a highly enantioselective Mannich-type reaction of β-ketoesters with various imines, including not only imino esters but also other imines derived from simple aldehydes [Eq. (1); PG = protecting group]. In these reactions, the sterically hindered vicinal tertiary and quaternary carbon centers were constructed in one step.[9]



(1)

Initially, the reaction of β-ketoester **3a** with the *N*-*p*-methoxyphenyl-protected imino ester **4a** was chosen as a model reaction (Table 1). Using 5 mol% of **1a**, various solvents were examined, and it was found that the solvent considerably affected the reaction efficiency. The Mannich reactions in CH_3CN, EtOH, and acetone gave poor enantioselectivities (Table 1, entries 1–3). Gratifyingly, however, the enantioselectivity was greatly improved when other solvents were used (Table 1, entries 4–7). Although a relatively prolonged reaction time (72 hours) was required, the reaction in *N*,*N*-dimethylformamide (DMF) gave an excellent diastereoselectivity (96:4). With respect to the reaction rate, THF was the best solvent (6 hours), and **7aa** was isolated in 77% yield with 98% *ee* (major). In contrast, the reaction of **3a** with **4a** using Pd complex **2a**, in which no protic acid was produced during the generation of Pd enolate **A**,[7a] resulted in only 23% yield of isolated product after 48 hours, and negligible asymmetric induction was observed for both diastereomers (Table 1, entry 8). These results are in accord with our initial hypothesis, which strongly indicate that cooperative activation of imines by the protic acid is essential for this reaction.

Table 1: Optimization of the reaction conditions.



Entry	Catalyst	Solvent	*t* [h]	Yield [%]	d.r.[a] (major:minor)	*ee*(major)/ *ee*(minor)[b]
1	**1a**	CH_3CN	11	73	94:6	3/9
2	**1a**	EtOH	12	76	96:4	15/53
3	**1a**	acetone	95	75	96:4	17/53
4	**1a**	CH_2Cl_2	24	72	80:20	86/91
5	**1a**	toluene	20	69	75:25	98/96
6	**1a**	DMF	72	74	96:4	97/87
7	**1a**	THF	6	77	83:17	98/97
8[c]	**2a**	THF	48	23	87:13	2/10
9	**1b**	THF	4	96	83:17	97/91
10	**1c**	THF	4	89	81:19	99/98
11	**1d**	THF	49	63	98:2	93/50

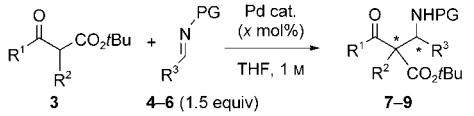
[a] d.r. = Diastereomeric ratio; determined by ^{1}H NMR spectroscopic analysis of the crude products. [b] *ee* = Enantiomeric excess. [c] The Pd complex **2a** (2.5 mol%) was used. PMP = *p*-Methoxyphenyl.

Next, we examined other bidentate chiral phosphane ligands using THF as the solvent (Table 1, entries 9–11). When tol-binap and segphos were used the chemical yields improved to 96 and 89%, respectively, maintaining the good diastereo- and excellent enantioselectivities (Table 1, entries 9, 10). On the other hand, the reaction using dm-segphos as a ligand was significantly slower, probably because of steric repulsion, although excellent diastereoselectivity was observed (Table 1, entry 11).

This system was applicable to other nucleophiles (Table 2). Like **3a**, six-membered cyclic and acyclic β-ketoesters **3b** and **3c** underwent the Mannich reaction to afford **7ba** and **7ca**, respectively, in good yield with high enantioselectivity, except for the minor diastereomer of **7ca** (Table 2, entries 1, 2). Moreover, as the Pd–aqua complexes are tolerant to water we envisaged that a three-component reaction would be possible, in which a stoichiometric amount of water molecules is formed during the in situ imine formation (Scheme 2). Indeed, in the presence of 2.5 mol% of **1a**, the mixture of ethyl glyoxylate, an amine component, and **3a** in THF gave rise to the corresponding Mannich adduct in good yield. Notably, in the case of 3-chloroaniline, the diastereoselectivity was found to be 95:5, and excellent enantioselectivity was observed (major: 98% *ee*; minor: 88% *ee*). Thus, an operationally convenient and highly enantioselective Mannich reaction has become feasible. In addition, our results indicate that various aromatic amines other than anisidine are potentially available for this reaction.

If imines derived from simple aldehydes could be successfully employed, the synthetic utility of this reaction would be substantially enhanced. Therefore, we examined the reaction with *N*-*tert*-butyloxycarbonyl-protected imines **5** (Table 2, entries 3–8).[10,4f] The reaction of **3a** with **5a** was carried out in THF using 2.5 mol% of **1a** (Table 2, entry 3). The mixture was stirred for 5 hours with ice-cooling, and the corresponding product **8aa** was obtained in 93% yield with excellent enantioselectivity of more than 97% *ee* (d.r.

Table 2: Scope and limitations of the reaction.



3a: R^1-R^2 = $(CH_2)_3$
3b: R^1-R^2 = $(CH_2)_4$
3c: R^1 = R^2 = CH_3

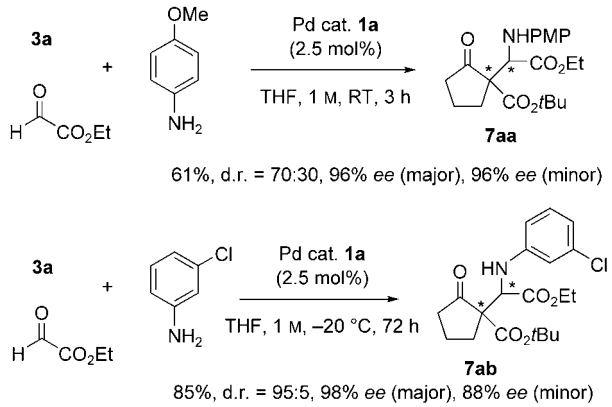
4a: PG = PMP, R^3 = EtO_2C

5a: PG = Boc, R^3 = Ph
5b: PG = Boc, R^3 = 4-MeC_6H_4
5c: PG = Boc, R^3 = 2-furyl

6a: PG = Ts, R^3 = 4-ClC_6H_4
6b: PG = Ts, R^3 = CH=CHPh

Entry	Catalyst (*x*)	β-Ketoester	Imine	Product	*T* [°C]	*t* [h]	Yield [%]	d.r.[a]	*ee*[b]
1	**1c** (5)	**3b**	**4a**	**7ba**	RT	35	63	77:23	99/91
2[c]	**1a** (5)	**3c**	**4a**	**7ca**	RT	42	70	74:26	86/55
3	**1a** (2.5)	**3a**	**5a**	**8aa**	0	5	93	88:12	99/97
4[d]	**1c** (2.5)	**3c**	**5a**	**8ca**	RT	4	84	86:14	98/95
5	**1a** (2.5)	**3a**	**5b**	**8ab**	0	2	72	50:50	99/95
6[d]	**1a** (2.5)	**3c**	**5b**	**8cb**	RT	5	61	69:31	95/94
7	**1a** (2.5)	**3a**	**5c**	**8ac**	0	2	75	>95:5	86/–[e]
8[d]	**1a** (2.5)	**3c**	**5c**	**8cc**	RT	3	71	82:18	96/99
9	**1c** (5)	**3a**	**6a**	**9aa**	RT	9	99	85:15	97/–[e]
10[f]	**1c** (1)	**3a**	**6b**	**9ab**	−20	24	88	90:10	99/99

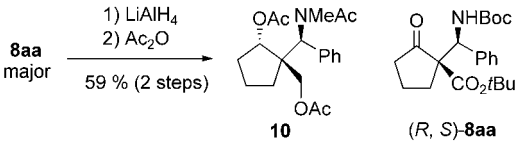
[a] d.r.(major:minor); determined by ^{1}H NMR spectroscopic analysis of the crude products. [b] *ee*(major)/*ee*(minor); determined by chiral high performance liquid chromatographic analysis. [c] Concentration = 4 M. [d] The imine (3 equiv) was used. [e] Not determined. [f] Concentration = 0.25 M. Boc = *tert*-butoxycarbonyl, Ts = *p*-toluenesulfonyl, RT = room temperature (23–25 °C).



Scheme 2. Three-component coupling reactions.

= 88:12). In addition to the cyclic substrate, the less reactive acyclic substrate **3c** also reacted completely with **5a** within 5 hours and afforded **8ca** in good diastereo- and excellent enantioselectivity (major: 98 % *ee*; Table 2, entry 4). Although the diastereoselectivity was decreased in the case of **5b**, high enantioselectivities of up to 99 % *ee* were still maintained for both **3a** and **3c** (Table 2, entries 5, 6). A furane-ring-substituted imine **5c**, which is unstable under acidic conditions, reacted smoothly with **3a** and **3c**, with good to excellent diastereoselectivity, and the corresponding Mannich adducts **8ac** and **8cc** were formed in a highly enantioselective manner (Table 2, entries 7, 8). Furthermore, *N*-*p*-toluenesulfonyl-protected imines[11] were also good substrates, and with **3a** as the substrate uniformly high enantioselectivities were produced (Table 2, entries 9, 10). The reaction of **6b** proceeded smoothly in the presence of as little as 1 mol % of the catalyst **1c**, and so the desired product was afforded in 88 % yield with almost perfect stereocontrol (99 % *ee*). To our knowledge, this is the first demonstration of an enantioselective Mannich-type reaction of β-ketoesters with various imines. Another feature of this reaction is that the reaction can be conducted without the exclusion of air and moisture.

As shown in Scheme 3, stereoselective reduction of the major diastereomer of **8aa** with $LiAlH_4$ followed by acetylation afforded compound **10**, which possesses three successive chiral centers. Since the opposite enantiomer of **10** has been synthesized by Karlsson et al. through the enantioselective 1,3-dipolar cycloaddition of nitrone,[12] the absolute configuration of **10** was determined by optical rotation studies.[13] Consequently, the absolute configuration of the quaternary carbon center in the major diastereomer of **8aa** was revealed to be *R*, and that of the tertiary carbon center was *S*. In addition, ^{1}H NMR spectroscopic analysis indicated that the same Pd enolate as described in Scheme 1 was formed in this Mannich-type reaction.[14] On the basis of these results, coupled with our previous studies on the catalytic enantioselective Michael reaction and fluorination reaction,[7] the excellent enantioselectivity was deduced to come from face-selection of the chiral Pd enolate (Figure 1). Thus, a bulky *t*Bu group was preferentially located at one of the faces of the Pd enolate to avoid steric repulsion with the equatorial phenyl group of binap. Therefore, the imines preferentially approached the enolate from the less-crowded *Re* face. Because Pd complex **1** was superior to the Pd complex **2** as a catalyst,[15] we speculate that protonated imines may be involved in the transition-state.[16] On the other hand, face-



Scheme 3. Conversion of **8aa** into **10**.

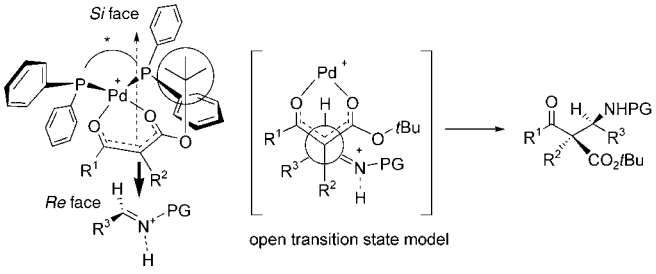


Figure 1. Proposed transition-state model.

selection of the imines was probably responsible for the relative stereochemistry. When such an iminium ion is involved, it has been proposed that the reaction proceeds through an open transition-state model.[17,18] Thus, we speculate that C–C bond-formation in our Mannich-type reaction occurs with the appropriate geometry as described in Figure 1 to minimize steric interactions.

In summary, we have developed a highly enantioselective catalytic Mannich-type reaction of β-ketoesters. The reaction was applicable to a variety of imines derived from glyoxylate, as well as simple aromatic and α,β-unsaturated aldehydes. This method affords stereochemically elaborated β-amino carbonyl compounds in up to 99% *ee*, thus indicating that such addition reactions of β-ketoesters to various imines would be useful to provide versatile intermediates for the synthesis of chiral nitrogen-containing compounds. In this reaction, the protic acid generated during the formation of the Pd enolate would play a role in activating the imine. Since protic acids are good catalysts for the nonenantioselective Mannich reaction, it is surprising that our Mannich reaction is highly enantioselective. We think that simultaneous activation of both reactants is the key to success, and this distinctive reaction mechanism could be an important guide to the design of novel reaction systems. Further studies to elucidate the mechanism and extend the scope of the reaction are under way.

Experimental Section

Representative procedure for the synthesis of **8aa**: β-Ketoester **3a** (20 μL, 108.6 μmol) and palladium complex **1a** (2.9 mg, 2.5 mol%) were added successively to a solution of **5a** (33.4 mg, 162.8 μmol) in THF (110 μL) at 0 °C. The reaction mixture was stirred for 5 hours at the same temperature. The reaction was monitored by TLC (hexane/ethyl acetate, 3:1) and after completion was quenched by addition of ethyl acetate (5 mL) and brine (3 mL). The aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with water and brine then dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. At this stage, the diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude products. Further purification was performed by medium pressure liquid chromatography on silica gel (hexane/ethyl acetate, 4:1; major: 35.0 mg, 82%; minor: 4.6 mg, 11%). The *ee* values of the diastereomers were determined by chiral high performance liquid chromatography analysis.

Received: October 5, 2004
Published online: January 31, 2005

Keywords: asymmetric catalysis · enolates · Mannich reaction · palladium · Schiff bases

[1] a) E. F. Kleinman in *Comprehensive Organic Synthesis*, *Vol. 2* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, chap. 4.1; b) M. Arend, B. Westermann, N. Risch, *Angew. Chem.* **1998**, *110*, 1096–1122; *Angew. Chem. Int. Ed.* **1998**, *37*, 1044–1070.

[2] For the synthesis of β-amino acids: a) *Enantioselective Synthesis of β-Amino Acids* (Ed.: E. Juaristi), Wiley, New York, **1997**; b) M. Liu, M. P. Sibi, *Tetrahedron* **2002**, *58*, 7991–8035; c) P. A. Magriotis, *Angew. Chem.* **2001**, *113*, 4507–4509; *Angew. Chem. Int. Ed.* **2001**, *40*, 4377–4379; d) J.-A. Ma, *Angew. Chem.* **2003**, *115*, 4426–4435; *Angew. Chem. Int. Ed.* **2003**, *42*, 4290–4299; e) N. Sewald, *Angew. Chem.* **2003**, *115*, 5972–5973; *Angew. Chem. Int. Ed.* **2003**, *42*, 5794–5795.

[3] a) E. Hagiwara, A. Fujii, M. Sodeoka, *J. Am. Chem. Soc.* **1998**, *120*, 2474–2475; b) A. Fujii, E. Hagiwara, M. Sodeoka, *J. Am. Chem. Soc.* **1999**, *121*, 5450–5458; c) A. Fujii, M. Sodeoka, *Tetrahedron Lett.* **1999**, *40*, 8011–8014.

[4] For recent examples of the catalytic enantioselective Mannich reactions using preformed metal enolates: a) H. Fujieda, M. Kanai, T. Kambara, A. Iida, K. Tomioka, *J. Am. Chem. Soc.* **1997**, *119*, 2060–2061; b) H. Ishitani, M. Ueno, S. Kobayashi, *J. Am. Chem. Soc.* **1997**, *119*, 7153–7154; c) S. Xue, S. Yu, Y. Deng, W. D. Wulff, *Angew. Chem.* **2001**, *113*, 2331–2334; *Angew. Chem. Int. Ed.* **2001**, *40*, 2271–2274; d) D. Ferraris, B. Young, C. Cox, T. Dudding, W. J. Drury III, L. Ryzhkov, A. E. Taggi, T. Lectka, *J. Am. Chem. Soc.* **2002**, *124*, 67–77; e) S. Kobayashi, T. Hamada, K. Manabe, *J. Am. Chem. Soc.* **2002**, *124*, 5640–5641; f) A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965; g) S. Kobayashi, R. Matsubara, Y. Nakamura, H. Kitagawa, M. Sugiura, *J. Am. Chem. Soc.* **2003**, *125*, 2507–2515; h) N. S. Josephsohn, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**, *126*, 3734–3735; i) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem.* **2004**, *116*, 1592–1594; *Angew. Chem. Int. Ed.* **2004**, *43*, 1566–1568; j) S. Kobayashi, M. Ueno, S. Saito, Y. Mizuki, H. Ishitani, Y. Yamashita, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5476–5481.

[5] S. Kobayashi, M. Ueno in *Comprehensive Asymmetric Catalysis*, Supplement 1 (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **2003**, chap. 29.5, p. 143.

[6] Recent examples of direct catalytic asymmetric Mannich reactions: a) S. Yamasaki, T. Iida, M. Shibasaki, *Tetrahedron* **1999**, *55*, 8857–8867; b) K. Juhl, N. Gathergood, K. A. Jørgensen, *Angew. Chem.* **2001**, *113*, 3083–3085; *Angew. Chem. Int. Ed.* **2001**, *40*, 2995–2997; c) B. List, P. Pojarliev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 827–833; d) A. Córdova, W. Notz, G. Zhong, J. M. Betancort, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1842–1843; e) W. Notz, F. Tanaka, S.-i. Watanabe, N. S. Chowdari, J. M. Turner, R. Thayumanavan, C. F. Barbas III, *J. Org. Chem.* **2003**, *68*, 9624–9634; f) T. Itoh, M. Yokoya, K. Miyauchi, K. Nagata, A. Ohsawa, *Org. Lett.* **2003**, *5*, 4301–4304; g) Y. Hayashi, W. Tsuboi, I. Ashimine, T. Urushima, M. Shoji, K. Sakai, *Angew. Chem.* **2003**, *115*, 3805–3808; *Angew. Chem. Int. Ed.* **2003**, *42*, 3677–3680; h) L. Bernardi, A. S. Gothelf, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2003**, *68*, 2583–2591; i) B. M. Trost, L. R. Terrell, *J. Am. Chem. Soc.* **2003**, *125*, 338–339; j) S. Matsunaga, T. Yoshida, H. Morimoto, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 8777–8785; k) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357; l) W. Zhuang, S. Saaby, K. A. Jørgensen, *Angew. Chem.* **2004**, *116*, 4576–4578; *Angew. Chem. Int. Ed.* **2004**, *43*, 4476–4478; m) A. J. A. Cobb, D. M. Shaw, S. V. Ley, *Synlett* **2004**, 558–560; n) A. Córdova, *Chem. Eur. J.* **2004**, *10*, 1987–1997; see also, o) A. Córdova, *Acc. Chem. Res.* **2004**, *37*, 102–112.

[7] a) Y. Hamashima, D. Hotta, M. Sodeoka, *J. Am. Chem. Soc.* **2002**, *124*, 11240–11241; b) Y. Hamashima, K. Yagi, H. Takano, L. Támas, M. Sodeoka, *J. Am. Chem. Soc.* **2002**, *124*, 14530–14531; c) Y. Hamashima, H. Takano, D. Hotta, M. Sodeoka, *Org. Lett.* **2003**, *5*, 3225–3228; d) Y. Hamashima, M. Sodeoka, *Chem. Rec.* **2004**, *4*, 231–242.

[8] M. Marigo, A. Kjærsgaard, K. Juhl, N. Gathergood, K. A. Jørgensen, *Chem. Eur. J.* **2003**, *9*, 2359–2367.

[9] A report on the asymmetric synthesis of α-tetrasubstituted β-amino acids appeared during the preparation of this manuscript: N. S. Chowdari, J. T. Suri, C. F. Barbas III, *Org. Lett.* **2004**, *6*, 2507–2510.

[10] A. M. Kanazawa, J.-N. Denis, A. E. Greene, *J. Org. Chem.* **1994**, *59*, 1238 – 1240.
[11] a) B. E. Love, P. S. Raje, T. C. Williams II, *Synlett* **1994**, 493 – 494; b) F. Chemla, V. Hebbe, J.-F. Normant, *Synthesis* **2000**, 75 – 77.
[12] S. Karlsson, H.-E. Högberg, *Eur. J. Org. Chem.* **2003**, 2782 – 2791.
[13] See Supporting Information.
[14] In accord with our previous results, mixture of **1b** and **3a** (1:1) in [d_8]THF at room temperature gave an equilibrium mixture of the Pd enolate and **3a**. Upon addition of 0.6 equivalents of **4a**, rapid formation of the Mannich adducut **7aa** was observed. At that time, approximately half of the remaining **3a** was found to exist as the Pd enolate [a *t*Bu group of the Pd enolate (0.71 ppm) relative to THF (3.58 ppm) as an internal standard was observed]. Details of these ^{1}H NMR spectroscopy experiments will be discussed elsewhere. For details of characterization of the Pd enolate, see: Ref. [7a] and Supporting Information therein.
[15] The reaction of **3a** with **5a** in the presence of **2a** was found to be less efficient than that in the case of **1a** under the same reaction conditions (0 °C, 5 hours) [**1a** (2.5 mol %): see Table 2, entry 3; **2a** (5 mol % to Pd): 58 %, d.r. = 89:11, 92 % *ee* (major), 86 % *ee* (minor)]. Similar diastereo- and enantioselectivities were obtained. However, the reaction rate was considerably slower in the case of **2a**, although the two-fold Pd complex was used. This clearly indicates that a proton plays a role in the acceleration of the reaction. Also, compare entries 7 and 8 in Table 1.
[16] A recent example of the in situ generation of iminium ions by protonation of enamines: C. Koradin, K. Polborn, P. Knochel, *Angew. Chem.* **2002**, *114*, 2651 – 2654; *Angew. Chem. Int. Ed.* **2002**, *41*, 2535 – 2538.
[17] An open transition-state was proposed as an important candidate. See, D. Enders, D. Ward, J. Adam, G. Raabe, *Angew. Chem.* **1996**, *108*, 1059 – 1062; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 981 – 984.
[18] The involvement of the protonated imines raises another possibility. Seebach et al. have proposed an electrostatic interaction of a Ti enolate with an iminium cation in their *anti*-selective Mannich reaction. However, in our case, such a transition-state would cause severe steric repulsion between the protecting group of the imine and the Pd catalyst. See, a) D. Seebach, C. Betschart, M. Schiess, *Helv. Chim. Acta* **1984**, *67*, 1593 – 1597; b) D. Seebach, M. Schiess, W. B. Schweizer, *Chimia* **1985**, *39*, 272 – 273.

