Mechanism of Palladium Complex-Catalyzed Enantioselective Mannich-Type Reaction: Characterization of A Novel Binuclear Palladium Enolate Complex

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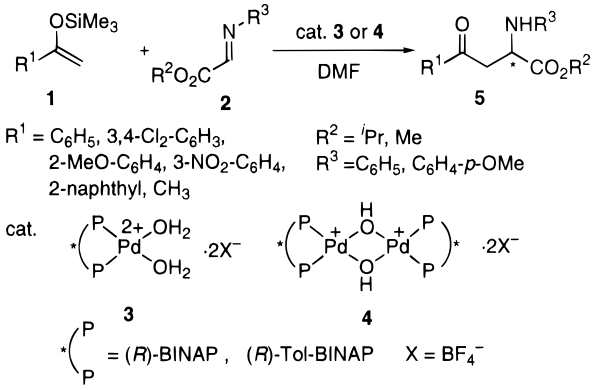
Abstract: Studies on the enantioselective addition of enol silyl ethers to imines catalyzed by optically active palladium diaquo complexes **3** or binuclear palladium μ-hydroxo complex **4** are described, with particular focus on the mechanistic aspects. Asymmetric induction in the reaction using $[Pd((R)\text{-binap})(H_2O)_2]^{2+}(BF_4^-)_2$ (**3a**) was quite sensitive to the reaction conditions, suggesting unfavorable effects of HBF_4 generated from **3a** in situ. Novel optically active binuclear μ-hydroxo complexes $[\{Pd((R)\text{-binap})(\mu\text{-OH})\}_2]^{2+}(BF_4^-)_2$ (**4a**), $[\{Pd((R)\text{-tol-binap})(\mu\text{-OH})\}_2]^{2+}(BF_4^-)_2$ (**4b**), $[\{Pd((R)\text{-binap})(\mu\text{-OH})\}_2]^{2+}(TfO^-)_2$ (**4c**), and $[\{Pd((R)\text{-tol-binap})(\mu\text{-OH})\}_2]^{2+}(TfO^-)_2$ (**4d**) were prepared and were found to be better catalysts for the asymmetric Mannich-type reaction. Benzoylalanine derivatives **5** were obtained in excellent chemical and optical yields (up to 90% ee). Mechanistic studies using ^1H NMR and electrospray ionization mass spectrometry indicated that a unique binuclear palladium-sandwiched enolate **12** was involved in the reaction of enol silyl ether **1** with imine **2** catalyzed by **4**.

Introduction

Carbon−carbon bond-forming reactions that involve the addition of resonance-stabilized nucleophiles, such as enols and enolates, to iminium salts and imines, the so-called Mannich-type reactions, comprise one of the most important classes of reactions in organic synthesis.[1] A number of methods for the diastereoselective reaction of imines with enolates of carboxylic acid derivatives or silyl ketene acetals have been reported, but examples of enantioselective variants of this type of reaction are quite limited.[2] Recently, we reported the first example of a Pd(II)-catalyzed enantioselective addition of enol silyl ethers to imines.[3] Reaction of various enol silyl ethers **1** with iminoacetic acid derivatives **2** using Pd(II) complex **3** or **4** as a catalyst proceeded smoothly to give optically active acylalanine derivatives **5** in good chemical and optical yields (Scheme 1).

The optically active **5** made available by this novel reaction has various potential applications. Substituted or unsubstituted benzoylalanines obtained by simple deprotection of **5** are known to be potent inhibitors of kynurenine 3-hydroxylase and kynureninase, potential drugs for the treatment of neurodegenerative disorders that function by controlling the toxic quinolinic acid concentration in the brain.[4] Since the carbonyl group in **5** would allow various modifications—such as reduction, alkylation, alkenylation, ketal formation, halogenation, etc.—the acylalanine derivatives **5** are also expected to be important synthetic intermediates for a wide variety of nonnatural amino acids. *N*-Arylated amino acid derivatives themselves would be quite attractive building blocks for the combinatorial synthesis, because *N*-arylation of the amide is expected to cause large conformational changes in peptide-type molecules. Despite the recent development of *N*-arylation methods,[5] however, arylation of the amino groups in optically active functionalized amino acids without racemization is still a problematic and difficult

Scheme 1



(1) For reviews, see: (a) Kleinman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 2, pp 893−951. (b) Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447−1465. (c) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044−1070 and references therein.

(2) For reactions using a stoichiometric amount of chiral source, see: (a) Corey, E. J.; Decicco, C. P.; Newbold, R. C. *Tetrahedron Lett.* **1991**, *32*, 5287−5290. (b) Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520−10524. (c) Kambara, T.; Hussein, A.; Fujieda, H.; Iida, A.; Tomioka, K. *Teterahedron Lett.* **1998**, *39*, 9055−9058. For reactions using a catalytic amount of chiral source, see: (d) Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060−2061. (e) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153−7154. (f) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431−432. (g) Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 307−310.

(3) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474−2475.

(4) (a) Giordani, A.; Corti, L.; Cini, M.; Brometti, R.; Marconi, M.; Veneroni, O.; Speciale, C.; Varasi, M. *Recent Advances in Tryptophan Research*; Plenum Press: New York, 1996; pp 531−534. (b) Giordani, A.; Pevarello, P.; Cini, M.; Bormetti, R.; Greco, F.; Toma, S.; Speciale, C.; Varaqsi, M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2907−2912 and references therein.

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process. Thus, the optically active *N*-aryl-amino acid derivatives made available by this novel Mannich-type reaction would offer a good source of diversity for use in a combinatorial library.

After our preliminary report,[3] Lectka et al. reported a reaction of **1** with **2** (R^2 = Et, R^3 = tosyl) using a chiral dicationic palladium complex, $[Pd((R)\text{-binap})(CH_3CN)_2]^{2+}(ClO_4^-)_2$, as a Lewis acid catalyst.[6] Although their results seem similar to ours, the mechanism of our reaction is quite distinct from the well-known Lewis acid-catalyzed one. In this paper we describe the full details of our studies on the Pd(II) complex-catalyzed enantioselective addition of enol silyl ethers to iminoacetic acid derivatives, with a particular focus on the reaction mechanism.

Results and Discussion

Pd Aquo Complex-Catalyzed Reaction. That the ketone−imine addition is relatively more difficult to promote than the ester/thioester−imine addition may be due to the relatively higher reactivity of ketones, which may cause undesired side reactions. Thus, our strategy involved the use of a less nucleophilic transition metal enolate in place of the highly nucleophilic metal enolate and/or strong Lewis acid catalyst. Because we had already reported the catalytic asymmetric addition of enol silyl ethers to aldehydes with the chiral palladium(II) diaquo complexes, $[Pd((R)\text{-binap})(H_2O)_2]^{2+}(BF_4^-)_2$ (**3a**) or $[Pd((R)\text{-tol-binap})(H_2O)_2]^{2+}(BF_4^-)_2$ (**3b**),[7] we suspected that this chiral palladium catalyst system might be useful for reactions with imines.

First, based on the best reaction conditions for the aldol reaction, we tested the reaction of enol silyl ether **1a** with the imine **2** in DMF at 0 °C in the presence of the Pd diaquo complex **3a** (10 mol %); however, only a negligible asymmetric induction was observed. After extensive experimentation, we found that **5a** could be obtained in 67% ee and 85% yield using the following rather complicated procedure. A solution of Pd diaquo complex **3a** (10 mol %) and **1a** (1.5 equiv) in DMF was stirred at 25 °C for 1 h, after which time the solution was warmed to 60 °C, and a solution of imine **2a** was added over 4 h using a syringe pump. During the addition of **2a**, additional **1a** (three times 0.5 equiv at 1-h intervals) was supplied to the reaction mixture. The whole mixture was stirred at the same temperature for an additional 2 h. As shown in Figure 1, the enantiomeric excess of the product (**5a**) decreased from 67% to 3% ee as the reaction temperature was lowered from 60 to 25 °C. This temperature-dependent decrease of enantioselectivity was also observed with methyl ester **2b**.

The imine concentration should be kept low during the reaction. When imine **2b** was added in one portion, the enantioselectivity of **5b** was drastically decreased. Preincubation of **1a** with the Pd diaquo complex **3a** was also critical for the high asymmetric induction. As the preincubation time was reduced, the enantiomeric excess decreased significantly (see Supporting Information). Reactions in less polar solvents, such as dichloromethane and benzotrifluoride, were slower than that in DMF, and the ee's of the products were much lower (results for **5c**: in CH_2Cl_2, 35 °C, 9 h, 24%, 47% ee; in $C_6H_5CF_3$, 60 °C, 7 h, 36%, 38% ee; in DMF, 60 °C, 7 h, 70%, 62% ee). The unusual temperature dependence and the sensitivity of the reaction conditions strongly suggest the existence of an undesired competitive reaction pathway that affords the racemic product.

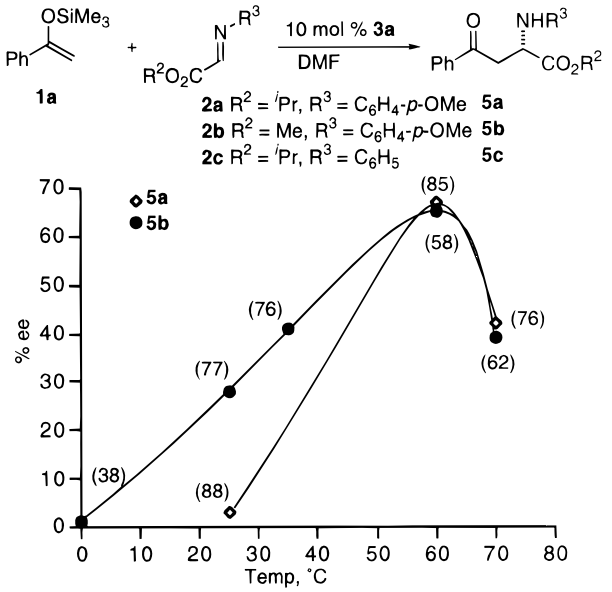


Figure 1. Temperature effect on the enantioselectivity in the palladium-catalyzed Mannich-type reaction. Yields are shown in parentheses.

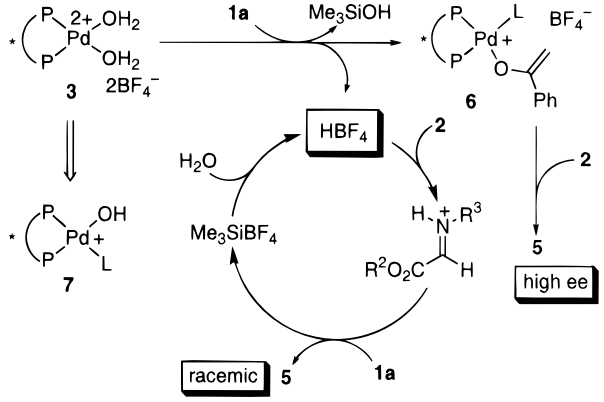


Figure 2.

Our preliminary mechanistic studies on the aldol reaction[7] suggested the formation of Pd enolate **6** from enol silyl ether **1a** and Pd aquo complex **3**. If the reaction to produce highly optically active **5** proceeds via the palladium enolate **6**, one plausible route to racemic **5** would be a proton-catalyzed one (Figure 2). Upon generation of the palladium enolate from **1a** and the diaquo complex **3**, an equivalent amount of tetrafluoroboric acid should be generated, and this strong protonic acid could catalyze the unselective addition of **1a** to **2**. Indeed, HBF_4 (5 mol %) prepared from $AgBF_4$ and trimethylsilyl chloride in DMF (containing a trace amount of water) did catalyze the reaction of **1a** with **2a** to give **5a** in 76% yield after 3 h at 25 °C. To neutralize the HBF_4 generated in situ, various bases were tested as an additive to the **3a**-catalyzed reaction (Table 1). As expected, various amine bases and also calcium carbonate were found to be effective to improve the asymmetric induction, and the ee of the product increased to around 80% (entries 1−6). In the presence of $CaCO_3$, however, reaction at 25 °C afforded

(5) A limited number of examples of *N*-arylation of optically active α-amino acids and intramolecular arylation of α -amino acid ester have been reported. See: (a) Ma, D.; Yao, H. *Tetrahedron: Asymmetry* **1996**, *7*, 3075−3078. (b) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451−8458. (c) Ma, D.; Zhang, Y.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459−12467. For a review on the *N*-arylation, see: (d) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2047−2067 and references therein.

(6) (a) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548−4549. (b) Ferraris, D.; Young, B.; Cox, C.; Drury, W. J. III; Dudding, T.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 6090−6091.

(7) (a) Sodeoka, M.; Ohrai, K.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 2648−2649. (b) Sodeoka, M.; Tokunoh, R.; Miyazaki, F.; Hagiwara, E.; Shibasaki, M. *Synlett* **1997**, 463−466. (c) Sodeoka, M.; Shibasaki, M. *Pure Appl. Chem.* **1998**, *70*, 411−414.

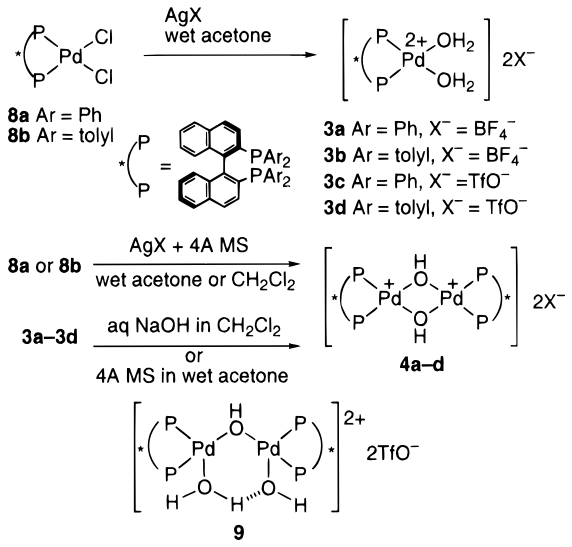
Table 1. Effect of Base in Enantioselective Mannich-Type Reaction Catalyzed by Aqua Pd Complex **3a**[a]

1a + **2a** $\xrightarrow[\text{DMF}]{\text{10 mol \% 3a}}$ **5a**

entry	additive (equiv)	temp (°C)	time (h)	yield (%)	ee (%)
1	–	60	10	85	67
2	NEt_3 (0.13)	60	12	28	78
3	iPr_2NEt (0.5)	60	5	57	67
4	pyridine (0.48)	60	5	85	80
5	2,6-lutidine (0.5)	60	6	81	75
6	$CaCO_3$ (1.0)	60	15	84	79
7[b]	$CaCO_3$ (1.0)	25	10	86	40
8	K_2CO_3 (1.1)	60	12	–	–

[a] After preincubation of **3a** with **1a** at 25 °C for 40 min and then addition of base, **2a** was added by syringe pump over 4 h at 60 °C. [b] To the mixture of **3a**, **1a**, and $CaCO_3$ was added **2a** in one portion.

Scheme 2



the product with lower ee (entry 7). Addition of more soluble inorganic bases, such as potassium carbonate and sodium bicarbonate, accelerated decomposition of the imine, and no product was obtained (entry 8).

Preparation of Binuclear μ-Hydroxo Pd Complex. To overcome these unfavorable protonic acid effects, we next attempted to prepare a mono-hydroxo complex **7**, which is expected to give a palladium enolate without undesired formation of HBF_4. It has been reported that simple treatment of a palladium dichloride complex of 1,2-bis(diphenylphosphino)-propane (DPPP) or 1,1′-bis(diphenylphosphino)ferrocene (DPPF) with silver salt in wet solvent affords a corresponding binuclear μ-hydroxo complex that is a dimeric form of the mono-hydroxo complex.[8] However, it has also been demonstrated that simple treatment of $PdCl_2$((*R*)-binap) (**8a**) and $PdCl_2$((*R*)-tol-binap) (**8b**) with silver tetrafluoroborate in wet acetone gave the aquo complexes **3a** and **3b** in excellent yield.[7b] Steric bulkiness of optically active ligands may prevent automatic formation of the binuclear complex under these conditions (Scheme 2). We therefore tried to remove 1 equiv of HBF_4 from the diaquo complex. After examination of a variety of possibilities, we determined that either of the binuclear μ-hydroxo complexes, [{Pd((*R*)-binap)(μ-OH)}$_2$]$^{2+}$(BF_4^-)$_2$ (**4a**), [{Pd((*R*)-tol-binap)-(μ-OH)}$_2$]$^{2+}$(BF_4^-)$_2$ (**4b**), [{Pd((*R*)-binap)(μ-OH)}$_2$]$^{2+}$(TfO^-)$_2$ (**4c**), or [{Pd((*R*)-tol-binap)(μ-OH)}$_2$]$^{2+}$(TfO^-)$_2$ (**4d**), could be made by the treatment of the diaquo complex **3a**, **3b**, **3c**, or **3d**, respectively, with 4-Å molecular sieves in wet acetone. Furthermore, it was found that these μ-hydroxo complexes could be obtained directly from the dichloride complexes **8a** or **8b** by the treatment of silver salts in the presence of 4-Å molecular sieves in wet acetone[9] or CH_2Cl_2, but that a large amount of molecular sieves was required for the complete transformation to the μ-hydroxo complex. Finally, simple treatment of a solution of the aquo complexes **3a**−**d** in CH_2Cl_2 with aqueous NaOH solution was found to give these μ-hydroxo complexes **4a**−**d** in excellent yield.

The ^{1}H NMR spectrum of **4d** in $CDCl_3$, which contained a singlet at −3.03 ppm, as is often the case for a μ-hydroxo group, was clearly distinct from that of **3d**.[10] Interestingly, treatment of **3d** with an insufficient amount of 4-Å molecular sieves resulted in production of the binuclear momo-μ-hydroxo species **9**. Chemical shifts of the tolyl methyl groups of Tol-BINAP would thus seem to be a good marker of the ligand environment. The monomeric complex [Pd((*R*)-tol-binap)(H_2O)$_2$]$^{2+}$(TfO^-)$_2$ (**3d**) showed two singlets at each of 2.05 and 2.42 ppm. One of the singlets at 2.42 ppm moves to a higher field in the spectrum of the binuclear complex [{Pd((*R*)-tol-binap)(μ-OH)}$_2$]$^{2+}$(TfO^-)$_2$ (**4d**) (1.96, 2.11 ppm), probably because of the anisotropic effect of the tolyl group of another ligand. In addition to these aquo and μ-hydroxo complexes, mononuclear $PdCl_2$((*R*)-tol-binap) complex **8b** and binuclear μ-chloro complex prepared by treatment of **8b** with 1 equiv of silver triflate in CH_2Cl_2 also show a similar pattern of chemical shifts (2.00, 2.38 and 2.02, 2.06 ppm, respectively, in $CDCl_3$).[11] In contrast to these highly symmetric complexes, the binuclear mono-μ-hydroxo complex **9** shows four singlets at each of 1.82, 2.06, 2.14, and 2.24 ppm, suggesting less symmetrical structure.

Electrospray ionization mass spectrometry (ESI-MS) analysis clearly supports the above-determined structure of the mononuclear complex **3d** and the binuclear complexes **4d** and **9**.[12] A large peak at *m*/*z* 933 corresponding to the [Pd((*R*)-tol-binap)-(TfO)]$^+$ fragment was observed in the spectrum of the mononuclear complex **3d**. In contrast, a small peak at *m*/*z* 1752 corresponding to a monocationic fragment [{Pd((*R*)-tol-binap)-(μ-OH)}$_2$(TfO)]$^+$, and a large peak at *m*/*z* 802 corresponding to a dicationic fragment [{Pd((*R*)-tol-binap)(μ-OH)}$_2$]$^{2+}$, were observed in the spectrum of the binuclear complex **4d** (Figure 5c). The spectrum of the complex **9** shows peaks corresponding to [{Pd((*R*)-tol-binap)}$_2$(μ-OH)(OH)(H_2O)(TfO)]$^+$ (*m*/*z* 1772), [Pd((*R*)-tol-binap)(OH)(H_2O)]$^+$ (*m*/*z* 821), and [{Pd((*R*)-tol-binap)}$_2$(μ-OH)(OH)(H_2O)]$^{2+}$ (*m*/*z* 811). These data strongly indicate that ESI-MS is a powerful tool for analyzing these cationic palladium complexes.

(8) (a) Pisano, C.; Consiglio, G.; Sironi, A.; Moret, M. J. *J. Chem. Soc., Chem. Commun.* **1991**, 421−423. (b) Longato, B.; Pilloni, G.; Valle, G. Corain, B. *Inorg. Chem.* **1988**, *27*, 956−958. (c) Bushnell, G. W.; Dixon, K. R.; Hunter, R. G.; McFarland, J. J. *Can. J. Chem.* **1972**, *50*, 3694−3699.

(9) Prolonged reaction in acetone with a large amount of 4-Å molecular sieves caused byproduction of acetone dimer.

(10) Similar binuclear μ-hydroxo Pd complexes of dppp and dppf have been reported to show the OH signal at −2.3 and −2.32 ppm, respectively, in the ^{1}H NMR.[8a,b]

(11) Chemical shifts of the methyl groups of the monochloride complex in DMF-d_7 were 2.07 and 2.45 ppm, suggesting dissociation of the binuclear μ-chloro complex to the corresponding mononuclear complex similar to **10** in the coordinating solvent.

(12) For a review on ESI-MS of metal complexes, see: (a) Colton, R.; D'Agostino, A.; Traeger, J. C. *Mass Spectrom. Rev.* **1995**, *36*, 1718−1719. For examples of the use of ESI-MS to observe organometallic reaction intermediates, see: (b) Aliprantis, A. O.; Canary, J. W. *J. Am. Chem. Soc* **1994**, *116*, 6985−6986. (c) Feichtinger, D.; Plattner, D. A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1718−1719. (d) Feichtinger, D.; Plattner, D. A.; Chen, P. *J. Am. Chem. Soc.* **1998**, *120*, 7125−7126 and references therein.

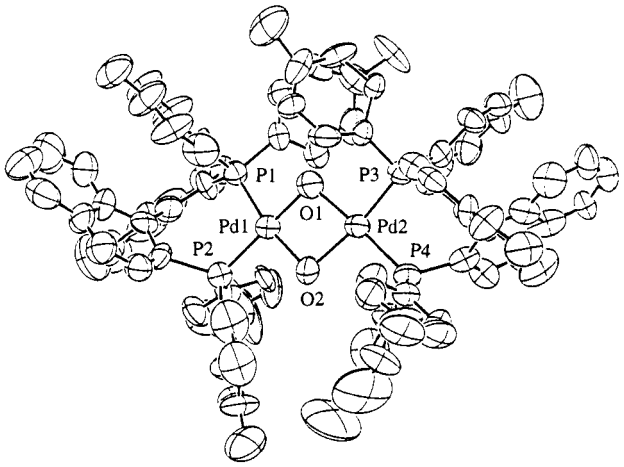


Figure 3. ORTEP diagram of the μ-hydroxy palladium complex of (*R*)-Tol-BINAP (**4d**). The TfO^- anions and hydrogens are omitted for clarity.

Table 2. Enantioselective Mannich-Type Reaction of **2a** Catalyzed by Binuclear μ-OH Pd Complex **4**[a]

$$\mathbf{1a} + \mathbf{2a} \xrightarrow[\text{solvent}]{\text{catalyst}} \mathbf{5a}$$

entry	catalyst (mol %)	solvent	time[b] A	time[b] B	time[b] C	yield (%)	ee (%)
1	**4b** (3)	DMF	30 min	4 h[c]	2 h[c]	73	76
2	**4b** (3)	DMF	15 min	4 h[c]	1 h[c]	82	80
3	**4b** (3)	DMF	60 min	2 min	24 h	80	81
4	**4a** (3)	DMF	45 min	2 min	24 h	87	83
5	**4b** (3)	CH_2Cl_2	60 min	4 h	119 h	45	53
6	**4b** (3)	DMI	45 min	4 h	3 h	75	81
7	**4b** (3)	TMU	40 min	5 min	21.5 h	59	82
8	**4b** (3)	THF	40 min	4 h	112 h	60	67
9	**4b** (3)	NMP	40 min	5 min	15 h	79	83
10	**4b** (5)	DMF	40 min	5 min	18.5 h	95	90
11	**4d** (5)	DMF	40 min	5 min	18 h	80	89

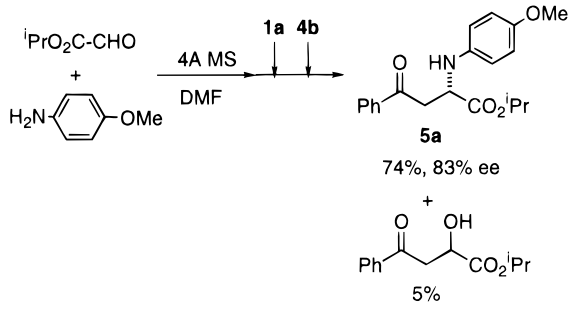
[a] Reaction was carried out at 25 °C. [b] A, preincubation time; B, time for addition of imine **2a**; C, additional reaction time. [c] Reaction was carried out at 60 °C.

Finally, the binuclear μ-hydroxo structure of **4d** was confirmed by X-ray crystallography. As shown in Figure 3, the crystal structure is slightly distorted from the complete symmetric structure to avoid steric interaction of the tolyl groups.

***μ*-Hydroxo Complex-Catalyzed Reactions.** Using the novel chiral complex **4b** (3 mol %) as a catalyst, we first tested the reaction using the procedure described above (Table 2, entry 1). As expected, **5a** was obtained in 73% yield and 76% ee without addition of any base. It was also found that the preincubation, slow addition, and warming to 60 °C were no longer necessary (entries 2 and 3). Catalysts **4a** and **4b** did not show much difference in reactivity and selectivity for these substrates (entries 3 and 4). The solvent effects were also reexamined, and amide or urea solvents were found to be suitable (entries 5−9). Finally, 95% chemical yield and 90% ee were achieved by the reaction of **1a** with **2a** at 25 °C using 5 mol % of the catalyst **4b** (entry 10). Since decomposition of **1a** was slow under these conditions, repeated addition of **1a** during the reaction was no longer necessary to complete the reaction. Similar results were also obtained using the triflate complex **4d** (entry 11). Optically pure **5a** was obtained by the simple recrystallization of the products with more than 80% ee.

Next, we tried a one-pot, three-component coupling reaction (Scheme 3). The imine **2a** was prepared in situ from the isopropyl glyoxylate and anisidine in DMF in the presence of 4-Å molecular sieves, and then enol silyl ether **1a** (1.5 equiv) and the catalyst **4b** (5 mol %) were added to this mixture. The desired product **5a** was obtained in 74% chemical yield and 83% ee, and only a small amount (5%) of the aldol product was obtained under these conditions. Since the catalyst **4** can also catalyze the aldol reaction,[13] and anisidine may cause deactivation of the catalyst, a clean formation of imine using molecular sieves was critical for achieving high chemical and optical yields.

Scheme 3



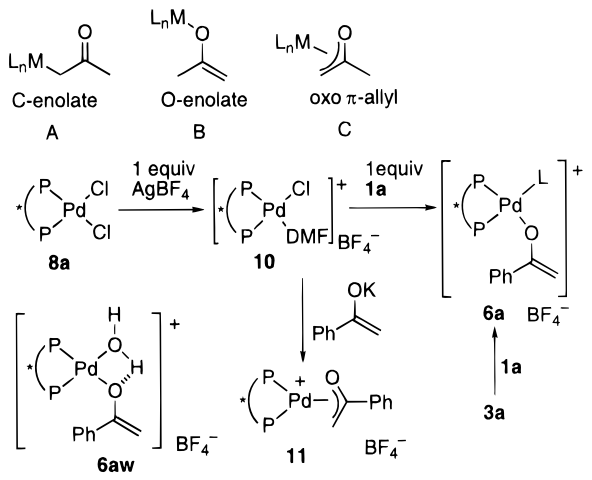
Reaction Mechanism. Enolate complexes of transition metals have received considerable attention in recent years. Several transition metal complexes with either carbon-bound (A), oxygen-bound (B), or oxo π-allylic-type (C) enolate ligands have been structurally characterized (Scheme 4).[14] In addition to our studies on asymmetric aldol[7] and Mannich-type[3] reactions, it has been proposed that palladium enolate was involved in several synthetically useful reactions.[15] The number of well-characterized palladium enolate complexes is, however, rather limited.[16] We have reported *O*-bound palladium enolate formation by the reaction of **1a** with the palladium complex **10**

(13) Fujii, A.; Sodeoka, M., unpublished results. Reaction of **1a** with benzaldehyde catalyzed by **4d** (1 mol %) in wet DMF at 23 °C for 7 h gave the aldol product in 71% yield and 72% ee.

(14) For a review, see: (a) Mekelburger, H. B.; Wilcox, C. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 2, pp 99−131 and references therein. For recent selected examples of middle and late transition metal enolate complexes, see the following references. W and Mo: (b) Burkhardt, E. R.; Doney, J. J.; Slough, G. A.; Stack, J. M.; Heathcock, C. H.; Bergman, R. G. *Pure Appl. Chem.* **1988**, *60*, 1−6. (c) Faller, J. W.; Ma, Y. *Organometallics* **1993**, *12*, 1927−1930. Re: (d) Stack, J. G.; Simpson, R. D.; Hollander, F. J.; Bergman, R. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1990**, *112*, 2716−2729. Ru: (e) Rasley, B. T.; Rapta, M.; Kulawiec, R. J. *Organometallics* **1996**, *15*, 2852−2854. (f) Hartwig, J. F.; Bergman, R. G.; Andersen, R. A. *Organometallics* **1991**, *10*, 3326−3344. Rh and Ir: (g) Milstein, D. *J. Am. Chem. Soc.* **1982**, *104*, 5227−5228. (h) Aoyama, Y.; Yoshida, T.; Ogoshi, H. *Tetrahedron Lett.* **1985**, *26*, 6107−6108. (i) Slough, G. A.; Bergman, R. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1989**, *111*, 938−949. (j) Milstein, D.; Calabrese, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 3773−3774. Pt: (k) Cairns, M. A.; Dixon, K. R.; Smith, M. A. R. *J. Organomet. Chem.* **1977**, *135*, C33−C34. (l) Arnold, D. P.; Bennett, M. A. *J. Organomet. Chem.* **1980**, *199*, 119−135. (m) Almeida, J. F.; Pidcock, A. *J. Organomet. Chem.* **1981**, *209*, 415−423. (n) Fujimura, O. *J. Am. Chem. Soc.* **1998**, *120*, 10032−10039. Cu: (o) Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837−838 and references therein.

(15) (a) Ito, Y.; Hirano, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011−1013. (b) Ito, Y.; Aoyama, H.; Hirano, T.; Mochizuki, A.; Saegusa, T. *J. Am. Chem. Soc.* **1979**, *101*, 494−496. (c) Tsuji, J.; Mandai, T. *Acc. Chem. Res.* **1987**, *20*, 140−145. (d) Nokami, J.; Mandai, T.; Watanabe, H.; Ohyama, H.; Tsuji, J. *J. Am. Chem. Soc.* **1989**, *111*, 4126−4127. (e) Nokami, J.; Watanabe, H.; Mandai, T.; Kawada, M.; Tsuji, J. *Tetrahedron Lett.* **1989**, *30*, 4829−4832. (f) Masuyama, Y.; Sakai, T.; Kato, T.; Kurusu, Y. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2265−2272. (g) Kuwajima, I.; Urabe, H. *J. Am. Chem. Soc.* **1982**, *104*, 6831−6833. (h) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108−11109. (i) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382−12383. (j) Åhman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918−1919. (k) Sugiura, M.; Nakai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2366−2368 and references therein.

Scheme 4



prepared from **8a** and 1 equiv of silver tetrafluoroborate (Scheme 4).[7b] This palladium *O*-enolate **6a** was characterized in the ^{1}H NMR spectrum in DMF-d_7 as having three singlets at 4.41, 4.68, and 9.54 ppm. There were several possibilities for the ligand L of the complex. The possibility of the chloride anion has already been ruled out[7b] on the basis of the observation of the same three singlets after reaction of the aqua complex **3a** with **1a**. Since the hydroxy proton of the transition metal−OH complex usually appears at a very high field, as mentioned above,[10,17] it is not likely that the signal at 9.54 ppm represents Pd−OH. Silanol complex (L = Me_3SiOH) is also an unlikely candidate, because exactly the same three singlets were observed when the same NMR experiment was carried out using the corresponding diphenylmethylsilyl enol ether and **10**.[18] Thus, we assumed that the ligand L in the observed species was water (**6aw**), and that only one of the two protons of the water ligand which was stabilized by intramolecular hydrogen bonding to the enolate oxygen was observed as a singlet, while the other might rapidly exchange with water molecules in the solvent. Since this hydrogen-bonding proton is expected to have a character intermediate between those of the coordinating water and enol, the chemical shift at an unusually low field would be reasonable.

To determine whether the reaction using the μ-hydroxo complex proceeds via the same *O*-bound palladium enolate, we next undertook NMR experiments using **4c**. To a solution of the μ-hydroxo complex **4c** (0.01 mmol) in DMF-d_7 was added 0.01 mmol of the enol silyl ether **1a** (methylene singlets at 4.51 and 5.11 ppm) at room temperature. No rapid formation of the three singlets corresponding to **6cw** was observed. Instead, as the singlet at −1.70 ppm of the μ-OH proton of **4c** slowly decreased (Figure 4b), three new signals, a doublet of doublets

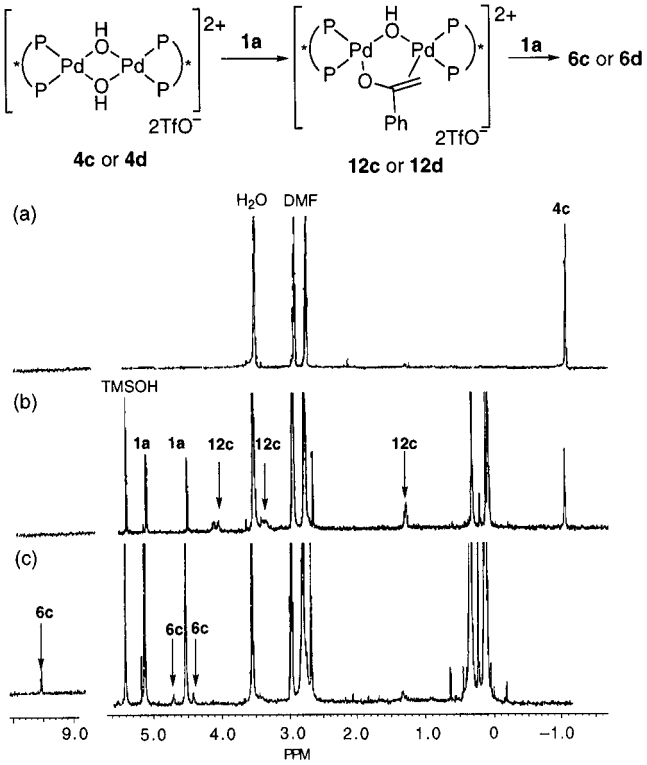


Figure 4. ^{1}H NMR spectra: (a) μ-hydroxy palladium complex **4c**; (b) reaction mixture at 40 min after the addition of **1a** (1 equiv to **4c**) to **4c** in DMF-d_7; (c) reaction mixture at 40 min after the addition of excess **1a** to the mixture in (b).

at 4.05 ppm, a multiplet at 3.35 ppm, and one broad singlet at 1.26 ppm, appeared (Figure 4b), indicating formation of a novel complex. Unlike **6cw** generated from **3c** in DMF-d_7, this novel complex was found to be fairly stable for several hours at room temperature. Furthermore, upon addition of excess **1a** (3 equiv to **4c**) to this mixture, signals of **6cw** were observed (Figure 4c), suggesting that this complex can be converted to **6cw**.

To obtain additional information about the structure of this novel complex, D_2O was added to the mixture. Two signals at 4.05 and 3.35 ppm survived, but rapid disappearance of the broad singlet at 1.26 ppm was also observed, suggesting that this third peak should be assigned to the exchangeable proton. The signals at 4.05 and 3.35 ppm, indicating apparent coupling with the phosphorus atoms of the ligand, suggest the π-coordination of enolate to the palladium. Since chemical shifts of protons of the oxo-π-allyl complex **11** prepared by the reaction of cationic complex **10** with the potassium enolate of acetophenone[7a] were completely different (dd at 3.98 ppm and m at 2.25−2.44 ppm), this novel complex would have η^2-coordination to the Pd atom. Finally, the structure of this complex was taken to be a unique binuclear palladium-sandwiched enolate **12c** on the basis of the results of ESI-MS analysis (Figure 5b). In addition to the signals derived from the original μ-hydroxo complex **4c** (*m*/*z* 746 for $[\{Pd((R)\text{-binap})(\mu\text{-OH})\}_2]^{2+}$, 1643 for $[\{Pd((R)\text{-binap})(\mu\text{-OH})\}_2(TfO)]^+$), three signals corresponding to the cationic fragments $[\{Pd((R)\text{-binap})\}_2(\mu\text{-O}-C(C_6H_5)=CH_2)(\mu\text{-OH})]^{2+}$ (*m*/*z* 797), $[Pd((R)\text{-binap})(O-C(C_6H_5)=CH_2)]^+$ (*m*/*z* 849), and $[\{Pd((R)\text{-binap})\}_2(\mu\text{-O}-C(C_6H_5)=CH_2)(\mu\text{-OH})(TfO)]^+$ (*m*/*z* 1744) were observed. There was good agreement between the experimental and calculated isotopic distributions of each ion. In this complex **12c**, the unstable mononuclear *O*-bound palladium enolate would be stabilized by the intramolecular η^2-coordination to the second palladium atom. Floriani et al. reported a symmetrical

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(17) For a review of hydroxo complexes of transition metals, see: (a) Bryndza, H. E.; Tam, W. *Chem. Rev.* **1988**, *88*, 1163−1188 and references therein. For hydroxo palladium complexes, see: (b) Yoshida, T.; Okano, T. Otsuka, S. *J. Chem. Soc., Dalton Trans.* **1976**, 993−999. (c) Grushin, V. V.; Alper, H. *Organometallics* **1993**, *12*, 1890−1901. (d) Grushin, V. V.; Alper, H. *Organometallics* **1996**, *15*, 5242−5245 and references therein.

(18) Fujii, A.; Sodeoka, M., unpublished results.

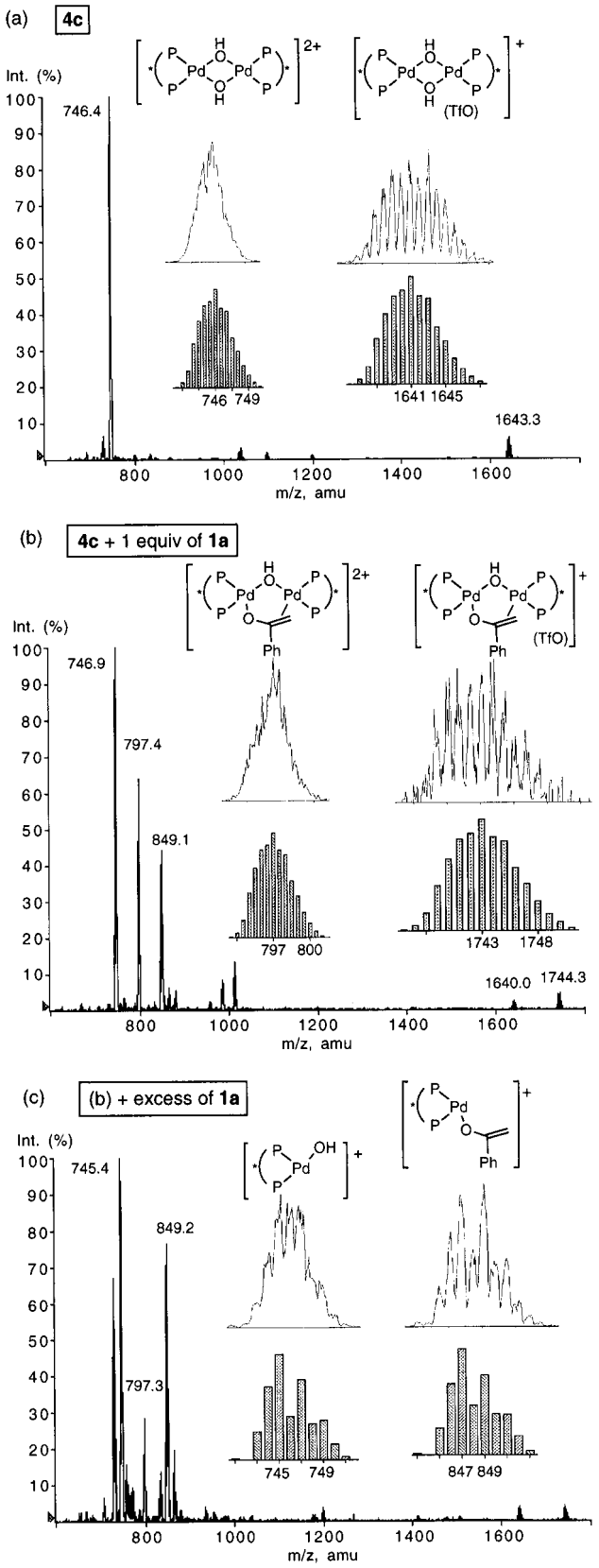


Figure 5. ESI mass spectra with observed (upper) and calculated (lower) isotope distribution for the peaks: (a) μ-hydroxo palladium complex **4c**; (b) reaction mixture at 40 min after the addition of **1a** (1 equiv to **4c**) to **4c** in DMF-d_7; (c) reaction mixture at 40 min after the addition of excess **1a** to the mixture in (b).

binuclear palladium complex in which two enolate anions bridge two $(Ph_3P)_2Pd$ fragments through the carbon and oxygen atoms.[16f] But the methylene protons of this complex appeared at much higher field (2.67 and 2.97 ppm) than those of **12c**, indicating that their binding mode was distinct from that of **12c**. Upon addition of excess **1a**, the intensity of the signal at *m*/*z* 849, which corresponded to the mononuclear enolate, was significantly increased in ESI-MS (Figure 5c).[19] These observations suggest that **6** generated from **12** under catalytic conditions would be an active intermediate for the reaction with imine. The same type of binuclear complex formation (**12d**) was observed in the experiments using the Tol-BINAP complex **4d**. Three similar signals (at 3.94, 3.33, and 0.92 ppm) were observed in ^{1}H NMR, and a similar fragmentation pattern (*m*/*z* 853, 903, and 1855) was observed in ESI-MS.

Finally, **12c** was found to react with imine **2a**. The imine **2a** (0.004 mmol) was added to the solution of **12c** prepared from **1a** (0.01 mmol) and **4c** (0.01 mmol) in DMF-d_7 after confirmation of complete consumption of the enol silyl ether **1a** (after 5 h) by the ^{1}H NMR. The complex **12c** was slowly reacted with **2a** to give the optically active product **5a** (93% ee) in 79% yield. This fact clearly indicated that the highly optically active product was formed from this novel complex **12c**, and not from the reaction of the enol silyl ether **1a** with imine simply activated by the palladium complex.

We next tried to isolate a mononuclear palladium enolate complex stabilized by intramolecular coordination. To accomplish this, the μ-hydroxo complex **4c** was mixed with the enol silyl ether of 2-acetyl pyridine **13** (1 equiv to Pd, methylene singlets at 4.59 and 5.67 ppm) in DMF-d_7. In this case, slow formation of two signals, ddd at 3.25 ppm (^2J(H−H) = 8.7 Hz, ^3J(P−H, trans) = 13.2 Hz, ^3J(P−H, cis) = 1.5 Hz) and ddd at 2.31 ppm (^2J(H−H) = 8.7 Hz, ^3J(P−H, trans) = 8.7 Hz, ^3J(P−H, cis) = 4.7 Hz), was observed, and this result was consistent with the formation of *C*-bound enolate **14c** (Figure 6a). The chemical shifts and the coupling pattern were similar to those observed in known Pd and Pt carbon-bound enolates,[16,20] but not to those in *O*-bound enolates. The same reaction was also carried out using the Tol-BINAP complex, and a clean conversion of the two singlets of the tolyl methyl group in **4d** to four singlets at 2.47, 2.32, 2.09, and 2.04 ppm indicated an almost quantitative formation of **14d** and supported the unsymmetrical monomeric structure. As shown in Figure 6b, ESI-MS analysis also supported the monomeric enolate structure **14**. It is likely that the mononuclear palladium enolate of acetophenone exists in rapid equilibrium between the *C*-bound and *O*-bound forms. And only the water-coordinated form **6w**, stabilized by intramolecular hydrogen bonding, was observed as sharp singlets in ^{1}H NMR. In the case of the enolate of 2-acetylpyridine, the *C*-bound form would be stabilized by the strong intramolecular coordination of the nitrogen to palladium. However, no reaction of these *C*-bound palladium enolates in DMF-d_7 with the imine **2a** or benzaldehyde was observed up to 50 °C. This low reactivity strongly suggests that reaction of the palladium enolate with imine (or aldehyde) requires a vacant coordination site on the palladium atom.

Possible reaction pathways using the μ-hydroxo complex are summarized in Scheme 5. First, the sandwiched enolate **12** would be formed from **4** by the reaction with **1a**, probably via the partially dissociated form **15**. Then, dissociation of **12** would afford the mononuclear palladium *O*-enolate complex **6** and the

(19) As shown in Figure 8c, the signal around *m*/*z* 745 showed a different pattern from that in Figure 8a, which was good agreement with the calculated isotope distribution for the monocationic fragment, [Pd((*R*)-binap)(OH)]$^+$. This fact indicated that the mononuclear complex **7** was formed in the reaction mixture.

(20) (a) Tsutui, M.; Ori, M.; Francis, J. *J. Am. Chem. Soc.* **1972**, *94*, 1414−1415. (b) Hillis, J.; Tsutui, M. *J. Am. Chem. Soc.* **1973**, *95*, 7907−7908.

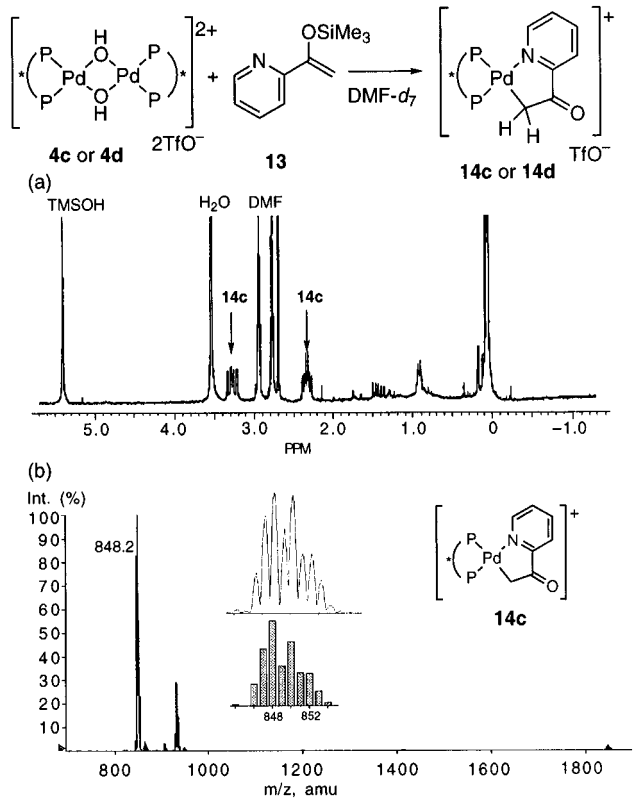
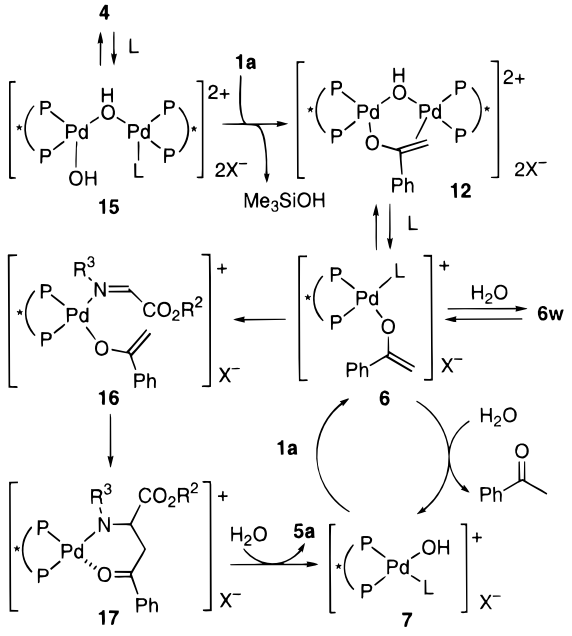


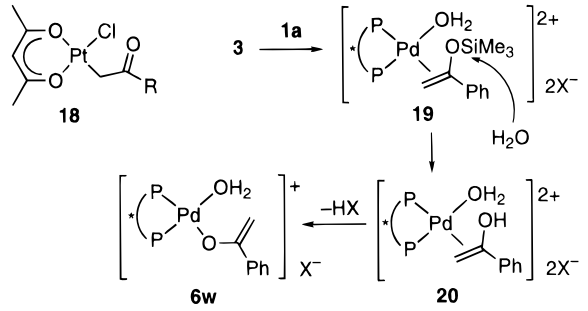
Figure 6. ^{1}H NMR spectra (a) and ESI mass spectra (b) of palladium C-enolate with observed (upper) and calculated (lower) isotope distributions for the peak.

Scheme 5



mononuclear hydroxo palladium complex **7**. In the presence of excess enol silyl ether **1a**, the hydroxo complex **7** would be further converted to the enolate complex **6**. Alternatively, a certain amount of enolate complex **6** might be decomposed by water to give acetophenone and **7**. Coordination of imine to the palladium (**16**) would then activate both enolate and imine, and C−C bond formation would occur through the highly ordered transition state to give **17**. Hydrolysis of **17** would give the highly optically active product **5a** and regenerate **7**. Palladium enolate formation from the aquo complex was faster

Scheme 6



than that from the μ-hydroxo complex **7**, although decomposition was also much faster. It is possible that palladium enolate **6** would be generated from **3** via a different mechanism. Tsutui et al. reported a stepwise preparation of a *C*-bound platinum enolate **18** via π-complex of the enol silyl ether followed by formation of the enol complex by acid hydrolysis.[20] It is likely that the palladium enolate **6** is formed from **3** via such a pathway (Scheme 6). In the case of palladium, however, the enol or the enolate complex would be very unstable in the presence of protonic acid and water.

Lectka et al. reported that reaction of **1a** with **2d** (R^2 = Et, R^3 = tosyl) in CH_2Cl_2 at −80 °C using a dicationic palladium complex, $[Pd((R)\text{-binap})(CH_3CN)_2]^{2+}(ClO_4^-)_2$ (**21**), gave **5d** (R^2 = Et, R^3 = tosyl) of 80% ee.[6] Because we wondered if their reaction also proceeded via a mechanism similar to that reported here, we tested the tosylimine substrate **2d** using our catalysts. Surprisingly, however, no asymmetric induction was observed for the substrate **2d** using the catalyst **3** or **4** in DMF or CH_2Cl_2 at any temperature. The highly activated imine **2d** reacted with **1a** in DMF at 23 °C even in the absence of any catalyst to give the racemic product in good yield. Rigorous anhydrous conditions and low temperature for the reaction using **21** in CH_2Cl_2 were required for the high asymmetric induction. Although the structures of the complexes **3** and **21** are quite similar, it is reasonable that the reaction using aquo complex **3** in CH_2Cl_2 at −78 °C afforded racemic **2d**, since the coordinated water can be a potential proton source, causing nonselective reaction of the highly activated substrate. Reaction of **1a** with **2a** using the dicationic complex, such as **21** in CH_2Cl_2 at −78 °C, gave **5a**, but only in low chemical and optical yields. Next, to determine the difference between the reaction mechanisms involved in polar (e.g., DMF) and nonpolar solvents, several ^{1}H NMR experiments were carried out. In contrast to the observations described above for DMF-d_7, no Pd enolate formation from **3** or **4** was observed in $CDCl_3$. Though no change in the spectrum of imine **2a** was observed upon mixing with **3** or **4** in DMF-d_7, some broadening of the peaks of **2a** was observed in $CDCl_3$ upon mixing with 1 equiv of the aquo complex **3d**, suggesting strong coordination of the imine to palladium in the nonpolar solvent. Based on these observations, we agree that the reaction using **21** in nonpolar solvent would proceed via a simple Lewis acid mechanism. It is quite interesting that these two similar Pd(II)-catalyzed reactions proceed via completely different reaction mechanisms according to the nature of the catalyst, solvent, and substrate.

Conclusion

We have found that highly optically active acylalanine derivatives (up to 90% ee) can be obtained by the enantioselective Mannich-type reaction of enol silyl ethers **1** with *N*-arylaminoacetic acid esters **2** catalyzed by chiral palladium(II) complexes. Preliminary studies using the known palladium (II)

diaquo complex **3** indicated undesirable effects of protonic acid generated in situ, but this problem was overcome by development of the novel chiral binuclear μ-hydroxo palladium(II) complex **4**. Mechanistic studies using NMR and ESI-MS indicate that this reaction proceeds via optically active palladium enolate. The unique binuclear palladium-sandwiched enolate **12** was observed in the reaction of the μ-hydroxo palladium complex **4** with the enol silyl ether **1a**. To the best of our knowledge, this is the first example of characterization of chiral binuclear *O*- and π-bound palladium enolate complexes possessing high reactivity as nucleophiles.

Experimental Section

General. All melting points were determined with a Yamato MP-21 microscale melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO FT/IR-5300 infrared spectrometer. NMR spectra were measured on a Brucker AC-200 spectrometer, operating at 200 MHz, for ^{1}H NMR. Chemical shifts were reported in the δ scale relative to tetramethylsilane (TMS). Optical rotation was measured on a Horiba SEPA-200 automatic digital polarimeter. Low-resolution mass spectra were taken with a Hitachi RMU-6MG spectrometer, and high-resolution mass spectra were obtained on a Hitachi M-80A spectrometer. In general, reactions were carried out in dry solvents under argon atmosphere, unless otherwise mentioned. *N*,*N*-Dimethylformamide (DMF) and dichloromethane were distilled from calcium hydride.

Preparation of Imines. Iminoacetic acid esters **2a**−**c** were prepared according to the reported procedure.[21] Namely, for **2a**, to a stirred solution of freshly distilled isopropyl glyoxylate[22] (568 mg, 4.9 mmol) in CH_2Cl_2 (10 mL) was added at 0 °C a solution of *p*-anisidine (570 mg, 4.6 mmol) in CH_2Cl_2 (10 mL). After 15 min, $MgSO_4$ (3.14 g) was added, and stirring was continued for 1 h. After completion of the reaction, $MgSO_4$ was filtered off with suction under an atmosphere of argon, and the solvent was removed in vacuo to give **2a** as a pale yellow oil in quantitative yield. The imine **2a** can be further purified by distillation (Kugelrohr distillation at 110−115 °C, 0.1 mmHg).

Isopropyl *N*-(4-Methoxyphenylimino)acetate (2a): IR (neat) 1740, 1590, 1290, 1165, 1107, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.38 (d, J = 6.3 Hz, 6H), 3.83 (s, 3H), 5.26 (sept, J = 6.3 Hz, 1H), 6.92 (d, J = 9.0 Hz, 2H), 7.35 (d, J = 9.0 Hz, 2H), 7.91 (s, 1H); MS(EI) *m*/*z* 221(M^+), 134 (bp); HRMS *m*/*z* calcd for $C_{12}H_{15}NO_3$ 221.1051, found 221.1057; GC analysis, SE-30 on uniport B, 30%, 1 m, He 50 mL/min, 100 °C, 2 min, then 100−240 °C (16 °C/min), retention time = 11.1 min.

The imines **2b** and **2c** were prepared in a similar manner from the corresponding glyoxylate ester and amine. Since imines **2b** and **2c** were unstable, these imines were used for the ketone−imine addition without further purification.

Methyl *N*-(4-Methoxyphenylimino)acetate (2b): ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 3H), 3.95 (s, 3H), 6.94 (d, J = 9.0 Hz, 2H), 7.37 (d, J = 9.0 Hz, 2H), 7.96 (s, 1H); MS(EI) *m*/*z* 193 (M^+), 134 (bp); GC analysis, same conditions as for **2a**, retention time = 10.4 min.

Isopropyl *N*-(4-Phenylimino)acetate (2c): ^{1}H NMR ($CDCl_3$) δ 1.40 (d, J = 6.3 Hz, 6H), 5.26 (sept, J = 6.3 Hz, 1H), 7.10−7.50 (m, 5H), 7.89 (s, 1H); MS(EI) *m*/*z* 191 (M^+), 104 (bp); GC analysis, same conditions as for **2a**, retention time = 9.0 min.

Preparation of Palladium Aqua Complexes. Preparation of **3a** and **3b** was already reported.[7b] Palladium complexes **3c** and **3d** were also prepared by a similar method.

[Pd((*R*)-tol-binap)(H_2O)$_2$]$^{2+}$(TfO$^-$)$_2$ (3d). To a solution of **8b** (110 mg, 0.128 mmol) in acetone (0.5% v/v H_2O) was added AgOTf (66 mg, 0.256 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 5 h. The precipitated AgCl was filtered off on Celite, and the filtrate was evaporated under reduced pressure. The product was recrystallized from CH_2Cl_2−ether to afford **3d** (96.0 mg, 71%): yellow powder; mp 135 °C dec; IR (KBr) 3250, 1280, 1030, 630 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.05 (s, 6H), 2.42 (s, 6H), 3.75 (br s, >4H, coordinated and free H_2O), 6.65 (br s, 2H), 6.71 (d, J = 8.6 Hz, 2H), 7.22 (dd, J = 7.5, 7.5 Hz, 2H), 7.38−7.70 (m, 22H); $[\alpha]^{20}_D$ +357.8 (*c* 0.25, $CHCl_3$).

[Pd((*R*)-binap)(H_2O)$_2$]$^{2+}$(TfO$^-$)$_2$ (3c): yellow powder; mp 125 °C dec; IR (KBr) 3200, 1290, 1170, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.46 (br s, >6H, coordinated and free H_2O), 6.69 (d, J = 8.7 Hz, 2H), 6.78−7.06 (m, 6H), 7.21 (dd, J = 7.5, 7.5 Hz, 2H), 7.45−7.87 (m, 22H); $[\alpha]^{20}_D$ +365.3 (*c* 0.38, $CHCl_3$).

Representative Procedure for the Reaction Using the Aquo Complexes. To a solution of **3a** (9.6 mg, 0.010 mmol) in DMF (1.0 mL, distilled from CaH_2) was added **1a** (31 μL, 0.15 mmol) at 25 °C under an atmosphere of argon. After being stirred at 25 °C for 1 h, the mixture was then warmed to 60 °C. To this mixture was added a solution of imine **2a** (22.0 mg, 0.10 mmol) in DMF (0.5 mL) by syringe pump over 4 h. During the addition of **2a**, **1a** (0.5 equiv) was added three times at 1-h intervals. The whole reaction mixture was stirred at 60 °C for an additional 2 h, diluted with ether, and filtered through a short silica gel column. The solution was poured into water and extracted with ether (2 × 5 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by preparative silica gel thin-layer chromatography (AcOEt/hexane = 1/4) to afford **5a** (26.7 mg, 85%). The ee of **5a** was determined to be 67% by HPLC analysis using Daicel Chiralcel OG (hexane:^{i}PrOH = 9:1). Similarly, the reactions were carried out at various temperatures (Figure 1), with various preincubation times (Supporting Information), or in the presence of bases (Table 1).

***N*-(4-Methoxyphenyl)benzoylalanine Isopropyl Ester (5a):** colorless needles; mp 113.0−113.5 °C (100% ee); IR (KBr) 3370, 2355, 2340, 1725, 1680, 1515, 1280, 1220, 1195, 1110, 820 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.14 (d, J = 6.3 Hz, 3H), 1.19 (d, J = 6.3 Hz, 3H), 3.50 (d, J = 5.4 Hz, 2H), 3.73 (s, 3H), 4.18 (br s, 1H), 4.50 (br t, J = 5.4 Hz, 1H), 5.03 (sept, J = 6.3 Hz, 1H), 6.68 (d, J = 9.1 Hz, 2H), 6.77 (d, J = 9.1 Hz, 2H), 7.41−7.61 (m, 3H), 7.94 (d, J = 7.0 Hz, 2H); MS (EI) *m*/*z* 341 (M^+); HRMS *m*/*z* calcd for $C_{20}H_{23}NO_4$ 341.1625, found 341.1613; $[\alpha]^{20}_D$ +30.4 (*c* 0.54, $CHCl_3$) (100% ee); HPLC analysis, Daicel Chiralcel OG, hexane:^{i}PrOH = 9:1, 0.5 mL/min, 42 min (major, *S*-enantiomer), 48 min (minor, *R*-enantiomer). The following conditions are recommended for a recent lot of Chiralcel OG, because the stationary phase of Chiralcel OG had recently been changed: hexane:EtOH:Et_2NH = 9:1:0.1, 0.7 mL/min, 34 min (major), 36 min (minor).

***N*-(4-Methoxyphenyl)benzoylalanine Methyl Ester (5b):** pale yellow solid (65% ee); IR (KBr) 3358, 2361, 1742, 1680, 1514, 1238, 1194, 822 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.55 (d, J = 5.3 Hz, 2H), 3.72 (s, 3H), 3.73 (s, 3H), 4.55 (br t, J = 5.3 Hz, 1H), 6.68 (d, J = 9.1 Hz, 2H), 6.78 (d, J = 9.1 Hz, 2H), 7.41−7.63 (m, 3H), 7.94 (d, J = 7.0 Hz, 2H); MS (EI) *m*/*z* 313 (M^+); HRMS *m*/*z* calcd for $C_{18}H_{19}NO_4$ 313.1312, found 313.1304; $[\alpha]^{20}_D$ +26.0 (*c* 0.52, $CHCl_3$) (65% ee); HPLC analysis, Daicel Chiralpak AD, hexane:^{i}PrOH = 9:1, 1.0 mL/min, 41 min (major), 45 min (minor).

***N*-(4-Phenyl)benzoylalanine Isopropyl Ester (5c):** colorless oil; IR (neat) 3387, 1732, 1684, 1603, 1508, 1215, 1107, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.15 (d, J = 6.3 Hz, 3H), 1.21 (d, J = 6.3 Hz, 3H), 3.55 (d, J = 5.3 Hz, 2H), 4.58 (br t, J = 5.3 Hz, 1H), 5.05 (sept, J = 6.3 Hz, 1H), 6.66−6.79 (m, 3H), 7.14−7.24 (m, 2H), 7.41−7.63 (m, 3H), 7.94 (d, J = 7.0 Hz, 2H); MS (EI) *m*/*z* 311 (M^+); HRMS *m*/*z* calcd for $C_{19}H_{21}NO_3$ 311.1520, found 311.1512; $[\alpha]^{20}_D$ +24.9 (*c* 0.76, $CHCl_3$) (64% ee); HPLC analysis, Daicel Chiralpak AD, hexane:^{i}PrOH = 9:1, 1.0 mL/min, 19 min (major), 21 min (minor).

Reaction Catalyzed by Tetrafluoroboric Acid. To a solution of chlorotrimethylsilane (63 μL, 0.50 mmol) in DMF (5 mL) was added $AgBF_4$ (97 mg, 0.5 mmol). The mixture was stirred at 25 °C for 2 h, and the supernatant solution was used as 0.1 M HBF_4 solution. To a solution of imine **2a** (22 mg, 0.1 mmol) in DMF (0.5 mL) were added **1a** (31 μL, 0.15 mmol) and 0.1 M HBF_4 solution (50 μL, 0.005 mmol). The mixture was stirred at 25 °C for 3 h, diluted with water, and extracted with Et_2O. The organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by preparative thin-layer chromatography (AcOEt/hexane = 1/4) to afford **5a** (25.9 mg, 76%).

Preparation of Complexes 4a−d. The μ-hydroxo complexes **4a**−**d** can be prepared either from **3a**−**d**, or **8a** and **8b**. The representative procedures are as follows.

(21) Tietze, L. F.; Bratz, M. *Synthesis* **1989**, 439−442.

(22) Kelly, T. R.; Schmid, T. E.; Haggerty, J. G. *Synthesis* **1972**, 544−545.

Preparation of [{Pd((*R*)-binap)(*μ*-OH)}$_2$]$^{2+}$(BF$_4^-$)$_2$ (4a) from 8a. To a solution of **8a** (100 mg, 0.125 mmol) in wet CH_2Cl_2 (10 mL) were added 4-Å molecular sieves (1.5 g) and $AgBF_4$ (48 mg, 0.25 mmol). The mixture was stirred at 25 °C for 30 h and filtered through a Celite pad. The filtrate was concentrated to give **4a** (86 mg, 79%): reddish orange prisms; mp 217 °C dec; IR ($CHCl_3$) 3580, 3050, 1430, 1310, 1050, 810, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ −2.90 (s, 2H), 6.55 (d, J = 8.4 Hz, 4H), 6.60−7.75 (m, 60H); [α]$^{20}_D$ +735.6 (*c* 0.32 $CHCl_3$).

Preparation of [{Pd((*R*)-tol-binap)(*μ*-OH)}$_2$]$^{2+}$(BF$_4^-$)$_2$ (4b) from 3b Using 4-Å Molecular Sieves. To a solution of **3b** (50 mg, 0.05 mmol) in acetone (5 mL) was added dried 4-Å molecular sieves (powder, 300 mg). The mixture was stirred at 25 °C for 3 h. After filtration through a Celite pad, the filtrate was concentrated to give **4b** (42 mg, 88%): reddish orange prisms; mp 247 °C dec; IR (KBr) 3480, 1260, 1030, 810, 510 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ −3.03 (s, 2H), 1.96 (s, 12H), 2.11 (s, 12H), 6.53 (d, J = 8.6 Hz, 4H), 6.60−7.75 (m, 52H); [α]$^{20}_D$ +590.3 (*c* 0.2, $CHCl_3$).

[{Pd((*R*)-tol-binap)(*μ*-OH)}$_2$]$^{2+}$(TfO$^-$)$_2$ (4c): reddish orange prisms; mp 195 °C dec; IR (KBr) 3500, 3060, 1430, 1260, 1030, 740, cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ −2.86 (s, 2H), 6.56 (d, J = 8.4 Hz, 4H), 6.80−7.67 (m, 60H); [α]$^{20}_D$ +683.6 (*c* 0.5 $CHCl_3$).

Preparation of [{Pd((*R*)-tol-binap)(*μ*-OH)}$_2$]$^{2+}$(TfO$^-$)$_2$ (4d) from 3d Using NaOH. To a solution of **3d** (235 mg, 0.21 mmol) in CH_2Cl_2 (3.0 mL) were added water (1.0 mL) and 0.1 N NaOH (2.1 mL). The mixture was stirred at 25 °C for 4 h. The organic phase was separated, washed with water, and dried over Na_2SO_4. The solvent was removed in vacuo to give **4d** (173 mg, 87%) as a red-orange solid. Recrystallization from CH_2Cl_2−Et_2O afforded yellow crystals: mp 228 °C dec; IR ($CHCl_3$) 3620, 2950, 1270, 1010, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ −3.00 (s, 2H), 1.96 (s, 12H), 2.11 (s, 12H), 6.53 (d, J = 8.6 Hz, 4H), 6.60−7.75 (m, 52H); [α]$^{20}_D$ +628.6 (*c* 0.3 $CHCl_3$).

Single-Crystal X-ray Analysis Data for 4d. The molecular structure for **4d** determined by single-crystal X-ray analysis is shown in Figure 3. A yellow prism crystal of $C_{98}H_{82}O_8P_4S_2F_6Pd_2$, having approximate dimensions of 0.40 × 0.20 × 0.12 mm, was mounted on a glass fiber. All measurements were made on a Rigaku RAXIS-II imaging plate area detector with graphite-monochromated Mo Kα radiation. A single crystal of **4d** was orthorhombic, having a space group $P2_12_12_1$, a = 14.577(6) Å, b = 16.488(5) Å, c = 41.32(2) Å, V = 9931(14) Å^3, Z = 4. The final R factor was 0.104 for 6892 measured reflections. Selected distances (Å) and angles (deg) are as follow: Pd(1)−P(1) 2.242(5), Pd(1)−P(2) 2.231(7), Pd(1)−O(1) 2.04(2), Pd(1)−O(2) 2.12(1), Pd(2)−P(3) 2.219(6), Pd(2)−P(4) 2.243(5), Pd(2)−O(1) 2.07(1), Pd(2)−O(2) 2.11(1), P(1)−Pd(1)−P(2) 93.1(2), P(1)−Pd(1)−O(2) 169.6(4), P(2)−Pd(1)−O(1) 174.1(6), O(1)−Pd(1)−O(2) 80.0(6), P(3)−Pd(2)−P(4) 93.0(2), P(3)−Pd(2)−O(2) 170.2(4), P(4)−Pd(2)−O(1) 172.1(6), O(1)−Pd(2)−O(2) 79.5(5). Details associated with data collection, data reduction, and structure solution and refinement are given in the Supporting Information.

Preparation of 9. To a solution of **3d** (35 mg, 0.031 mmol) in acetone was added 4-Å molecular sieves (40 mg). The mixture was stirred at 25 °C for 5 h. After filtration through a Celite pad, the filtrate was concentrated to give **9** (24.1 mg, 81%): orange powder; mp 191 °C dec; IR (KBr) 3480, 1260, 815, cm^{-1}; ^{1}H NMR (200 MHz) δ −3.07 (s, 1H), 1.82 (s, 6H), 2.06 (s, 6H), 2.14 (s, 6H), 2.24 (s, 6H), 6.56 (d, J = 8.6 Hz, 4H), 6.66 (d, J = 8.6 Hz, 4H), 7.01−7.75 (m, 48H); [α]$^{20}_D$ +731.3 (c 0.23 $CHCl_3$).

Mass Spectrometric Investigation of Isolated Palladium Complexes 3d, 4d, and 9 by Electrospray Ionization Mass Spectrometry (ESI-MS). For mass spectra of palladium complexes, a 10−20 μM solution of **3d**, **4d**, or **9** in THF was infused into a PE SCIEX API 300 mass spectrometer at 0.5 μL/min using a syringe pump. The ionspray needle was maintained at 2000−3000 V, and the orifice was at 20−60 V. The scan range was from *m*/*z* 200 to 3000. The mass spectra of **3d**, **4d**, and **9** were shown in Figure 5.

Representative Procedure for Table 2. To a solution of **4b** (8.9 mg, 0.005 mmol) in DMF (1.0 mL) was added **1a** (41 μL, 0.20 mmol) at 25 °C under an atmosphere of argon. After the mixture was stirred at 25 °C for 40 min, a solution of imine **2a** (22.0 mg, 0.10 mmol) in DMF (0.5 mL) was added. The whole reaction mixture was stirred at 25 °C for overnight, then diluted with ether and filtered through a short silica gel column. The solution was poured into water and extracted with ether (2 × 5 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by preparative silica gel thin-layer chromatography (AcOEt/hexane = 1/4) to afford **5a** (32.3 mg, 95%). The ee of **5a** was determined to be 90% by HPLC analysis using Daicel Chiralcel OG (hexane:^{i}PrOH = 9:1). This sample (28 mg) was recrystallized from ethyl acetate−hexane to give an optically pure sample (21 mg, 75% recovery).

One-Pot Reaction. To a solution of freshly distilled isopropyl glyoxylate (23 mg, 0.20 mmol) in DMF (2 mL) were added *p*-anisidine (26.0 mg, 0.20 mmol) and 4-Å molecular sieves (100 mg). After this mixture was stirred at 25 °C for 3 h, **1a** (60 μL, 0.30 mmol) and **4d** (19.0 mg, 10.0 μmol) were added. The whole reaction mixture was stirred at 25 °C for 40 h, diluted with ether, and filtered through a short silica gel column. The filtrate was poured into water and extracted with ether. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by preparative silica gel thin-layer chromatography (AcOEt/hexane = 1/4) to afford **5a** (51.0 mg, 74%). The ee of **5a** was determined to be 83% by HPLC analysis using Daicel Chiralcel OG.

NMR and ESI-MS Experiment for the Reaction of 4c and 1a. To an NMR tube containing a solution of palladium complex **4c** (18.0 mg, 0.01 mmol) in DMF-d_7 (0.6 mL) was added enol silyl ether **1a** (2.1 μL, 0.01 mmol) at 25 °C. After 40 min at 25 °C, ^{1}H NMR was measured (Figure 4b), and a 5-μL sample was withdrawn from the solution using a microsyringe, diluted with THF (5 mL), and analyzed by ESI-MS as described above (Figure 5b). To the reaction mixture were added 0.5 equiv (1.0 μL, 0.005 mmol) and 3.0 equiv (3.2 μL, 0.015 mmol) of **1a** after 40 min and 1.5 h. After 30 min at 25 °C, ^{1}H NMR (Figure 4c) and ESI-MS (Figure 5c) were measured according to the same manner as above.

NMR and ESI-MS Experiment for the Reaction of 4c and 13. To an NMR tube containing a solution of palladium complex **4c** (18.0 mg, 0.01 mmol) in DMF-d_7 (0.6 mL) was added enol silyl ether **14** (2.3 mg, 0.012 mmol). After 10 h, ^{1}H NMR was measured (Figure 6a), and a 5-μL sample was withdrawn from the solution using a microsyringe, diluted with wet acetone (5 mL), and analyzed by ESI-MS as described above (Figure 6b).

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Supporting Information Available: Effects of preincubation time on the asymmetric induction, ^{1}H NMR spectra of **2a**, **3c**, **3d**, **4a**, **4d**, and **9**, ESI-MS data of **3d**, **4d**, and **9**, X-ray structural information on **4d**, and ^{1}H NMR and ESI-MS data on the reactions of **4d** with **1a** and **13** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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