

Award Accounts

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Development of Catalytic Enantioselective Reactions via Palladium Enolates as Key Intermediates

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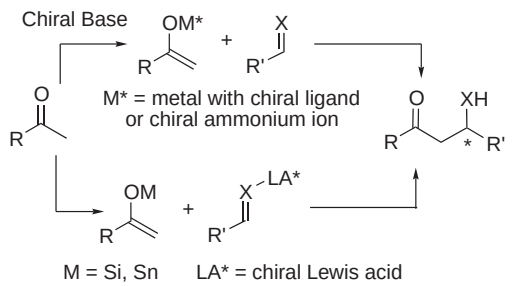
This article describes the catalytic reactions that involve the generation of chiral palladium enolates and their reaction with various electrophiles. Two methods to generate the chiral enolates were developed using the two types of novel chiral palladium complexes: Pd aqua complexes and binuclear Pd μ-hydroxo complexes. In these processes, aqua or hydroxo ligand on palladium metal plays an important role as a nucleophile to promote the transmetallation or as a Brønsted base to abstract an acidic α-proton of the carbonyl group. Using the chiral Pd enolates as key intermediates, a highly enantioselective, catalytic aldol reaction, a Mannich-type reaction, a Michael reaction, and a fluorination reaction were developed.

Nucleophilic reactions of metal enolates are fundamental reactions in synthetic organic chemistry. Among them, especially, aldol reaction, Mannich reaction, and Michael reaction are the most basic carbon–carbon bond-forming reactions not only in chemical synthesis but also in biosynthesis. While biosynthetic processes catalyzed by enzymes usually give enantiopure products, it is still a challenging task to develop highly enantioselective artificial catalysts for such important reactions. Classical representatives of metal enolates are highly nucleophilic alkali metal and alkaline earth metal enolates.[1] Generally, they are very sensitive to air and moisture, and the reactions must be carried out in anhydrous conditions under an inert gas. In addition, the reactivity of these enolates is so high that a low temperature such as -78 °C is required to avoid undesired side reactions. Other metal enolates including those of the early transition metals, for example B, Al, Ti, and Zr, have also been investigated, and many successful diastereoselective reactions and enantioselective reactions using a stoichiometric amount of chiral sources were reported even in the early 1990's. In contrast, late transition metal enolates had been less well studied.[1]

For the development of catalytic enantioselective reactions of the enolates, two major strategies are possible (Scheme 1). One is the catalytic generation of chiral enolates with chiral bases, and the other is the reaction of a less reactive enolate such as Si or Sn enolate with an electrophile activated by a chiral Lewis acid. Until the early 1990's, many synthetic chemists focused on the latter type of reactions, although some successful examples of the former type of reactions have been reported.[2] We were interested in the third possibility, that is, catalytic generation of chiral late transition metal enolates, because the late transition metal enolates might show distinct reactivity from the strongly basic ordinary metal enolates. Among various transition metals, we have been focusing on palladium.



Scheme 1. Two types of approaches to enantioselective reactions: chiral base vs chiral Lewis acid.

There have been many reports on the preparation and structure determination of various types of Pd enolate complexes, such as *O*-bound, *C*-bound, and oxo-π-allylic types (Scheme 2).[3] Synthetically useful reactions in which palladium enolate would be involved as a key intermediate were also reported.[4] Pioneering works were reported by Saegusa and Ito et al. in the late 1970's.[5] They reported that Pd enolates were formed by the treatment of silyl enol ethers with Pd(II) complexes; the subsequent β-hydrogen elimination afforded the enones. They also showed examples of the C–C bond-forming reactions. The intramolecular insertion of the Pd enolates to olefins and the subsequent β-hydrogen elimination gave the cyclic products (Scheme 3). These reactions have been widely

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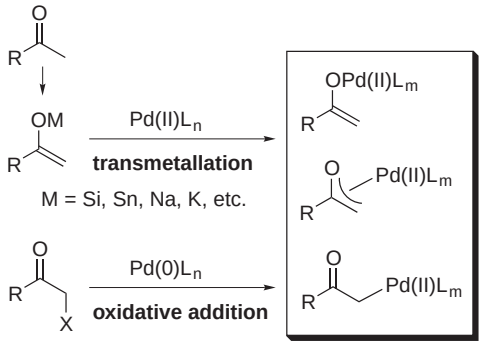
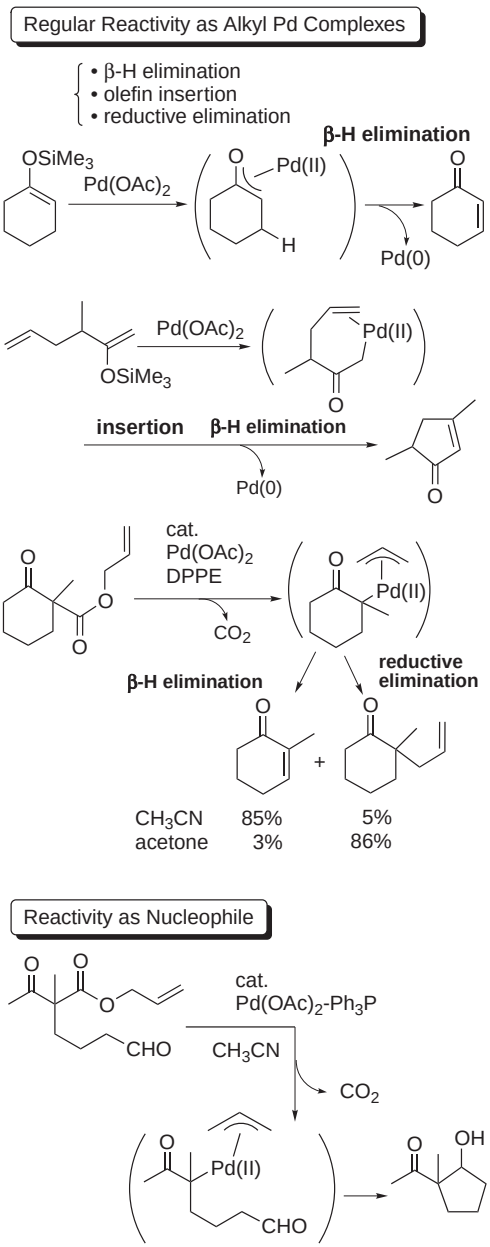


Scheme 2. Formation of three types of palladium enolates.



Scheme 3. Representative reactions of palladium enolates.

used by synthetic organic chemists. Efficient generation of π-allylpalladium enolates from allyl β-ketoesters via decarboxylation and their reductive elimination to afford allyl ketones were also reported.[6,7] Interestingly, the reaction pathways were different depending on the reaction conditions. As shown in Scheme 3, the enone was obtained as a major product of the reaction in CH_3CN, whereas allylation took place in acetone.[6c] The Pd-catalyzed α-arylation of the carbonyl compounds[8] and several other synthetically useful reactions of the Pd enolates have also been reported.[9] However, the nucleophilic reactions of palladium enolates had rarely been investigated. When we started this project in 1994, we were able to find only some examples reported by Tsuji et al.,[10] namely, intramolecular aldol and Michael-type reactions. Since the Pd enolate has a π-allyl ligand in their system, intermolecular aldol reaction gave lower yield due to the competitive allylation. But their results encouraged us to investigate the reactivity of chiral palladium enolates as nucleophiles.

We have succeeded in developing various highly enantioselective reactions in which palladium enolates play key roles. In this account, we describe the aldol reaction,[11] Mannich-type reaction,[12] Michael reaction,[13] and electrophilic fluorination reaction.[14]

1. Catalytic Enantioselective Aldol Reaction[11]

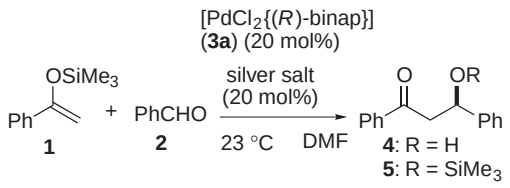
Since aldehyde is known to be a highly reactive electrophile, we decided to investigate the aldol reaction first. In addition to the Tsuji's work using Pd(0),[10] several pioneering studies on the aldol reaction via transition metal enolates had been reported.[15] Catalytic aldol reactions of achiral Rh(I) enolates were reported in the late 1980's by Matsuda et al. and Bergman and Heathcock et al. Furthermore, Ito and Hayashi et al. reported a beautiful work on the Au(I)-catalyzed enantioselective addition of isocyanides to aldehydes.[2a,16] Although ammonium enolates, not Au enolates, were proposed in the enantioselective reaction, these early works suggested possible development of the asymmetric aldol reaction using the transition metal enolates. To our knowledge, however, there had been no report of a catalytic asymmetric aldol reaction that proceeds via the putative transition metal enolate.[17] Therefore, we started a project for finding a new reaction system in which the chiral and nucleophilic palladium enolate is catalytically generated in situ.

After examining several possibilities, we first found that the desired aldol product **4** was obtained by the treatment of the silyl enol ether **1** and the aldehyde **2** with the mixture of [$PdCl_2${(*R*)-binap}] (**3a**, 20 mol%) and $AgClO_4$ (20 mol%) in DMF for 43 h (Table 1). Although the chemical yield was low (27%), the optical purity of the product was found to be 63% ee. Encouraged by this result, we performed further examinations of reaction conditions. Since we had an experience that the counter anion of the cationic Pd species affected the chemical and optical yields of the products in the asymmetric Heck reaction,[18] we tested a variety of silver salts (Table 1).[19] We noticed that the reaction using silver-exchanged zeolite (Ag 20–25%, Aldrich) afforded better chemical and optical yields. Thus, we next examined the effect of molecular sieves 4A. Combined use of molecular sieves 4A with silver trifluoromethanesulfonate (AgOTf) greatly improved the chemical yield. But, when the catalyst was reduced to 5 mol%, the yield decreased. Finally we were pleased to find that the silyl ether **5** (69% ee) was obtained in 60% yield in addition to **4** (26%,

70% ee) (combined yield: 86%) when the cationic palladium catalyst (5 mol%) was prepared from **3a** and AgOTf in the presence of molecular sieves 4A in DMF and used after filtration (Table 2, entry 1). Since this drastic effect of molecular sieves suggested that hydrolysis of the silyl enol ether **1** should be a reason for the low chemical yield in the first reaction procedure, we next set up the same reaction using rigorously dried reagents and DMF. Unexpectedly, however, the reaction was very slow under such anhydrous conditions, and only 19% yield of **5** was produced even after 115 h. Addition of a small amount of water (1.8 v/v% in DMF, 2 equiv to **2**) accelerated the reaction to give 96% combined yield of the aldol products (**5**: 87%, 71% ee; **4**: 9%, 73% ee) after 13 h, indicating that *water is essential for the reaction*. These reaction conditions were applied to various substrates. For example, the silyl enol ether derived from cyclohexanone having β-hydrogen reacted with **2** to give the desired aldol products (syn: 43%, 72% ee; anti: 15%, 18% ee) after 109 h. Interestingly, no formation of cyclohexenone was observed.

Furthermore, increasing the Pd–Ag ratio from 1:1 to 1:2 dramatically enhanced the reaction rate (Table 2, entries 4 and 5). Thus, a catalyst prepared from 5 mol% of [$PdCl_2${(*R*)-tol-binap}] (**3b**) and 5 mol% of AgOTf required 19 h for the completion of the reaction. In contrast, when the amount of AgOTf was increased to 10 mol%, the reaction was completed within only 2.5 h, and the aldol products with the same optical purity (71% ee) were obtained in 94% combined yield. At the beginning, we speculated that a Pd monochloro complex would be an active catalyst; however, these experimental facts strongly indicated that the active catalyst would be a dicationic complex. Therefore, we next tried isolation of the dicationic complex. Consequently, the (*R*)-BINAP palladium diaqua complex **6a** (X = TfO or BF_4) was obtained in good yield as a stable crystal by recrystallization after the treatment of **3a** with 2 equiv of AgOTf or $AgBF_4$ in wet ace-

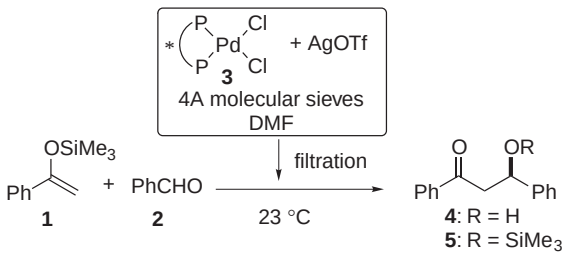
Table 1. Effects of Silver Salts on the Pd-Catalyzed Enantioselective Aldol Reaction



Silver salt	Time/h	Yield (**4**/**5**)/%	ee of **4**/**5**/%
$AgClO_4$	43	27 (27/0)	63/—
$AgNO_3$	11	12 (0/12)	—/73
AgOAc	15	47 (31/16)	63/64
AgOTf	15	46 (22/24)	69/68
$AgBF_4$	11	42 (35/7)	65/68
$AgPF_6$	11	44 (33/11)	67/69
$AgOCOCF_3$	13	42 (42/0)	70/—
Ag_2O	15	54 (47/7)	60/61
Ag_2CO_3	15	30 (15/15)	10/18
Ag_3PO_4	11	47 (0/47)	—/63
Ag-zeolite[a)]	60	66 (66/0)	74/—
AgOTf[b)]	38	87 (72/15)	69/70
AgOTf[c)]	12	42 (33/9)	61/61

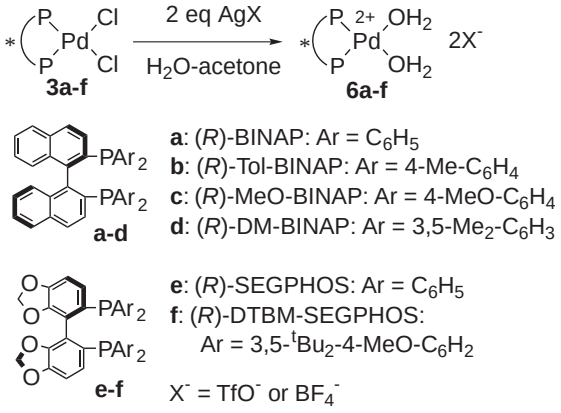
a) Silver-exchanged zeolite, powder, Ag 20–25% (Aldrich). b) Molecular sieves 4A was added. c) 5 mol% of Pd complex and AgOTf were used. Molecular sieves 4A was added.

Table 2. Catalytic Asymmetric Aldol Reaction Using the Pd(II) Catalyst

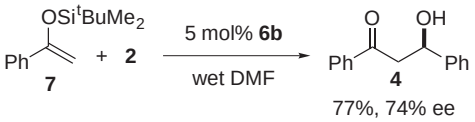


Entry	Pd complex	AgOTf	DMF	Time	Total yield	Product
1	[$PdCl_2${(*R*)-binap}]	undried	dist.[b)]	13 h	86%	**4** (26%) 70% ee
	(**3a**) (5 mol%)	(5 mol%)				**5** (60%) 69% ee
2	[$PdCl_2${(*R*)-binap}]	**dried**[a)]	**freshly dist.**[c)]	**115 h**	19%	**5** (19%) 68% ee
	(**3a**) (5 mol%)	(5 mol%)				
3	[$PdCl_2${(*R*)-binap}]	dried[a)]	freshly dist.[c)]	13 h	**96%**	**4** (9%) 73% ee
	(**3a**) (5 mol%)	(5 mol%)	**+ H_2O**[d)]			**5** (87%) 71% ee
4	[$PdCl_2${(*R*)-tol-binap}]	dried[a)]	freshly dist.[c)]	19 h	90%	**4** (22%) 70% ee
	(**3b**) (5 mol%)	(5 mol%)	+ H_2O[d)]			**5** (68%) 71% ee
5	[$PdCl_2${(*R*)-tol-binap}]	dried[a)]	freshly dist.[c)]	**2.5 h**	**94%**	**4** (22%) 71% ee
	(**3b**) (5 mol%)	**(10 mol%)**	+ H_2O[d)]			**5** (72%) 71% ee
6	[Pd{(*R*)-tol-binap}$(H_2O)_2$]$(BF_4)_2$	—	freshly dist.	**1.5 h**	**98%**	**4** (15%) 72% ee
	(**6b**) (5 mol%)					**5** (83%) 72% ee
7	[Pd{(*R*)-tol-binap}$(H_2O)_2$]$(BF_4)_2$	—	freshly dist.	42 h	84%[e)]	**4** (84%) 74% ee
	(**6b**) (**1 mol%**)					

a) Dried at 60 °C under vac. b) Distilled from CaH_2 and stored for several months. c) Freshly distilled from CaH_2. d) Water (1.8 v/v%) was added. e) The product was isolated after acidic workup.



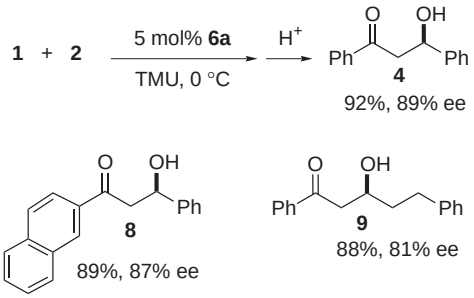
Scheme 4. Preparation of Pd aqua complexes.



Scheme 5. Reaction of *t*-butyldimethylsilyl enolate.

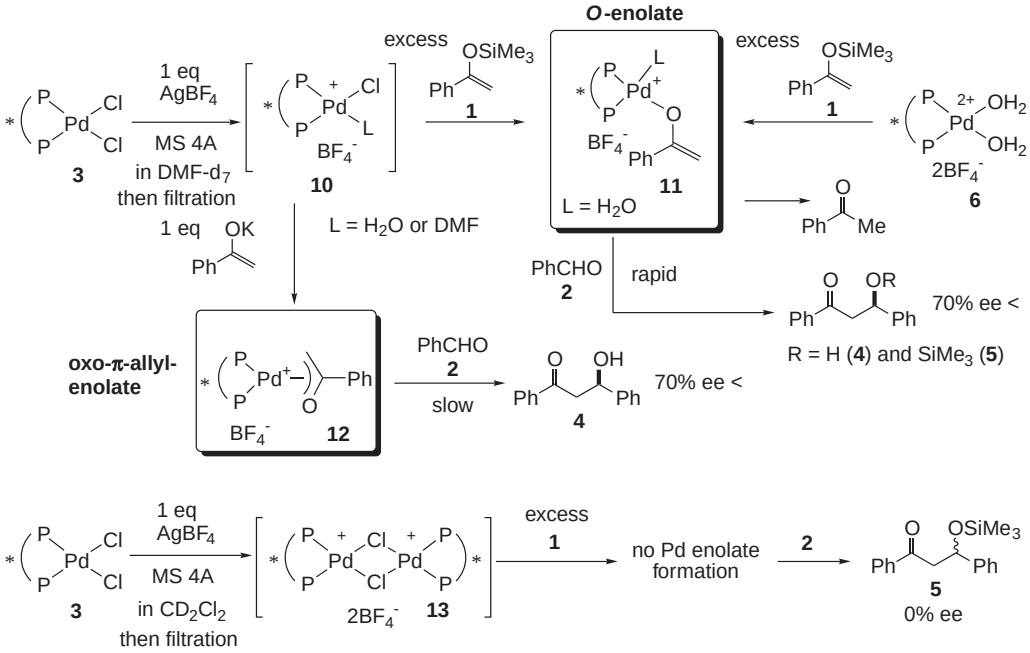
tone, and subsequent filtration (Scheme 4). In addition to **6a**, **6b–6f** having various chiral ligands were prepared according to similar procedures. As expected, these chiral Pd diaqua complexes catalyzed the aldol reaction efficiently even in freshly distilled DMF without addition of extra water (Table 2, entries 6 and 7). For example, the reaction of **1** and **2** using **6b** ($X = BF_4$, 5 mol%) completed in only 1.5 h to give the desired aldol products (**4**: 15%, 72% ee; **5**: 83%, 72% ee). When the amount of the catalyst was reduced to 1 mol%, the reaction still reached completion after 42 h, and **4** was obtained in good chemical (84%) and optical yield (74%) after acidic workup. It is noteworthy that these aqua complexes can also activate *t*-butyldimethylsilyl enol ethers, which are less susceptible to hydrolysis (Scheme 5). Although the reaction in dry DMF was very slow, addition of water was again effective to enhance the reaction. The reaction of **7** with **2** catalyzed by **6b** ($X = BF_4$, 5 mol%) in DMF containing a large amount of water proceeded smoothly to give **4** (17 h, 77%, 74% ee), whereas the reaction in dry DMF afforded only 17% yield of **4** (73% ee) after 17 h. Further investigation revealed that tetramethylurea (TMU) was a better solvent. The highest enantioselectivity (89% ee) was obtained by performing the reaction in TMU at 0 °C using **6a** ($X = BF_4$) as a catalyst (Scheme 6). Other aldol products such as **8** and **9** were also obtained in more than 80% optical yield under these conditions.

As described above, this reaction favored polar solvents such as DMF and TMU rather than the less polar solvents like CH_2Cl_2 which are commonly used in Lewis acid catalysis. Furthermore, water was essential to facilitate the reaction, whereas the ordinary B- or Ti-based Lewis acids were known to prefer anhydrous conditions. These results suggested the operation of a completely different reaction mechanism. But the possibility of a simple Lewis acid mechanism could not be ruled out, because the overall transformation using silyl enol ethers is the same as the common Lewis acid-catalyzed process, and the cationic transition metal complex could act as a

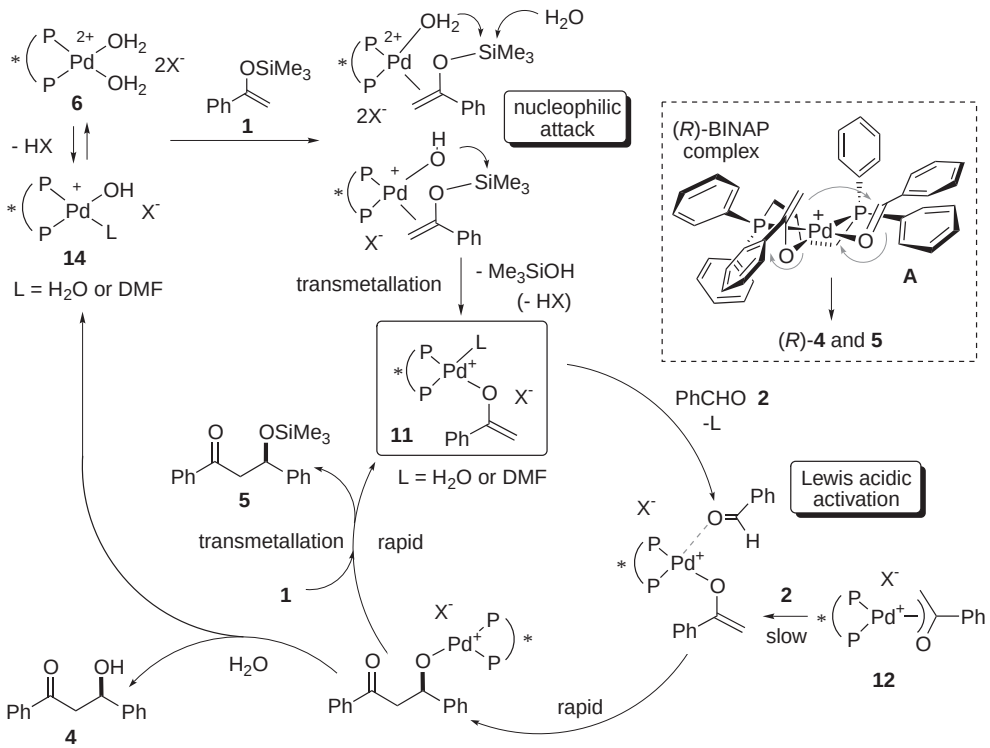


Scheme 6. Reactions using Pd aqua complexes.

Lewis acid. Therefore, in order to examine our hypothesis that a chiral Pd enolate would be formed transiently in the catalytic cycle, we carried out NMR experiments (Scheme 7). When **3a** (or **3b**) was treated with 1 equiv of $AgBF_4$ (or AgOTf) in the presence of molecular sieves 4A in wet DMF-d_7, the monomeric Pd complex, which was most likely to be the monochloro complex **10a** (or **10b**) ($L = H_2O$ or DMF), was formed. Upon addition of excess silyl enol ether **1** to this Pd complex, formation of *O*-bound Pd enolate **11a** (or **11b**) was observed. Careful NMR analysis suggested that the ligand L on the Pd-enolate complex **11** is a water molecule. The same Pd enolate **11a** (or **11b**) was generated from the aqua complex **6a** (or **6b**). In the absence of aldehyde, **11a** (or **11b**) was quickly decomposed to acetophenone. In these experiments the amount of water contained was very important. Too much water caused quick decomposition of **11**, but no Pd enolate was formed when rigorously dried DMF was used, indicating that water is important for the generation of the Pd enolate rather than for its reaction with aldehyde. After formation of the Pd enolate under the optimized conditions, **2** (1 equiv to Pd) was added to the mixture. Rapid consumption of the Pd enolate **11a** (or **11b**) and formation of **4** and **5** were observed, and then the remaining **1** reacted slowly. As these products had similar optical purities to those of the products from the catalytic reaction, we were convinced that the Pd *O*-enolate **11** is a key intermediate in this asymmetric aldol reaction. In these experiments, however, some silyl enol ether **1** remained in the reaction mixture, and it was difficult to exclude the possibility of the direct reaction of **1** with the aldehyde activated by the cationic Pd complex. This concern was, however, ruled out by the other experiments using a potassium enolate. Formation of the oxo-π-allyic Pd enolate **12a** was observed in the reaction of the cationic Pd complex **10a** with a potassium enolate of acetophenone (1 equiv) in DMF-d_7. This oxo-π-allyic Pd enolate **12a** slowly reacted with the aldehyde **2** to give **4** having the same absolute stereochemistry and a similar optical purity, as observed in the catalytic reactions. Because neither potassium enolate nor silyl enol ether existed in the reaction mixture, it was confirmed that the Pd enolate **12a** acted as a nucleophile to afford the optically active **4**. Furthermore, **3a** (or **3b**) was similarly treated with $AgBF_4$ (1 equiv) in the presence of molecular sieves 4A in CD_2Cl_2 or $CDCl_3$. The NMR spectrum of the resulting Pd complex prepared from **3b** suggested that the monochloro complex would exist as the binuclear μ-Cl Pd complex **13b** in such less coordinating solvent. No Pd enolate formation was observed upon addition of **1** to this complex, and **1** remained. Addition of **2** to this mixture caused the for-



Scheme 7. NMR experiments on Pd enolate formation.



Scheme 8. Proposed mechanism of Pd-catalyzed enantioselective aldol reaction.

mation of the aldol product **5**, but it was racemic.

Based on these experimental results, we propose the reaction mechanism as shown in Scheme 8. The key complex would be the Pd aqua complex **6** rather than the monochloro monocationic Pd complex **10**, even in the case of the original in situ procedure. The critical role of water in the transmetallation step is an interesting point of this reaction. We speculate that the Si–O bond of the silyl enol ether coordinated to the cationic Pd center would be cleaved by the nucleophilic attack on the silicon atom by water, affording the Pd enolate. It is also likely that the Pd-hydroxo complex **14** was formed from the aqua complex by losing a proton, and so the nucleophilic attack of the hydroxy group onto the silicon atom might trigger the transmetallation. Recently similar critical effects of water in the Pd- or Rh-catalyzed reactions of arylboronic acids and arylsilanes were also reported, and participation of water or

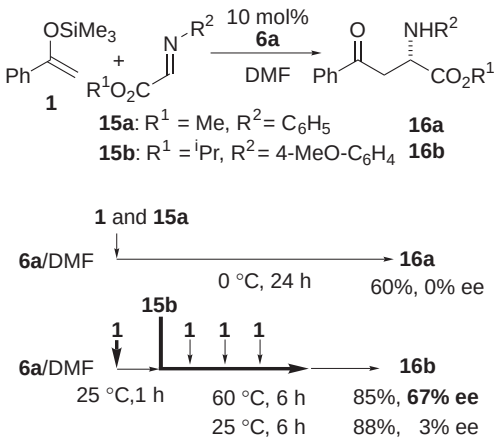
a hydroxy group was proposed.[20] In the next step, the ligand (L) of the Pd enolate **11** would be replaced by the aldehyde, and C–C bond formation would be promoted by the Lewis acidic activation of the aldehyde through coordination to the cationic Pd center. Since the reaction of **12** with **2** was much slower, **12** would not be involved in the catalytic cycle. The product **4** or **5** is produced either by hydrolysis of the resulting Pd alkoxide or by transmetallation with **1**. The Pd-hydroxo complex **14** or the Pd enolate **11** would be regenerated to complete the catalytic cycles. The absolute stereochemistry of the product is in accord with the proposed highly ordered transition state **A**.

Thus, we succeeded in demonstrating a new reactivity of a Pd enolate and, to our knowledge, this is the first example of a catalytic enantioselective aldol reaction using a chiral transition metal enolate derived from ketones. Attempts to use ketene silyl acetals instead of silyl enol ethers as the substrates were unsuccessful using our Pd catalyst system. But in 1998 Fujimura reported a successful asymmetric aldol reaction of ketene silyl acetals in which a chiral Pt enolate was involved instead of the Pd enolate.[21] Recently other examples of highly enantioselective aldol reactions, in which a transition metal enolate intermediate is proposed as an active species, have been reported.[22] Furthermore, Nakai et al. demonstrated the catalytic enantioselective protonation of silyl enol ethers in 1997.[23] Protonation of the chiral Pd enolate generated by using our procedure afforded optically active ketones (up to 80% ee).

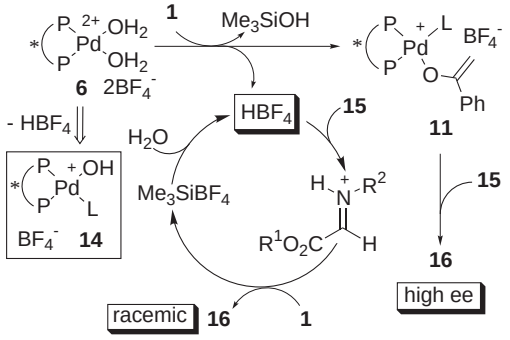
2. Catalytic Enantioselective Mannich-type Reaction: Development of A Novel Binuclear Pd μ-Hydroxo Complex[12]

With the availability of an efficient method for the generation of a chiral Pd enolate, we next turned our attention to the reaction with imines, the so-called Mannich-type reactions.[24] Despite the high degree of potential utility of Mannich products, namely, β-amino carbonyl compounds, we could not find an example of catalytic enantioselective Mannich-type reactions when we began our investigation in 1996. In 1997, the first two successful examples were reported, and these reactions utilized lithium enolates of esters or silyl ketene thioacetals as a nucleophile.[25] A number of methods for the diastereoselective reactions of imines with enolates of carboxylic acid derivatives or silyl ketene acetals have been reported. However, the addition of metal enolates of ketone or enol silyl ethers to imines appears to be even more difficult. The difficulty of the ketone–imine addition compared to the ester/thioester–imine addition may be due to the relatively high reactivity of ketones, and the reaction using highly nucleophilic metal enolates or strong Lewis acid catalysts may cause undesired side reactions. In contrast, reactivity of the Pd enolate seemed to be mild, and palladium was expected to have a high affinity for nitrogen. Thus we envisaged that the reaction of the chiral Pd enolate with imines should work. We focused on the reaction of iminoacetic acid derivative **15**, because the products were expected to be good synthetic intermediates for various useful α-amino acid derivatives including benzoylalanine and homophenylalanine derivatives.

Initially, we simply applied the reaction conditions for the aldol reaction to the reaction of **1** with **15a** (10 mol% **6a** (X = BF_4) in DMF at 0 °C). The desired product **16a** was obtained in 60% yield, but no asymmetric induction was observed. After persistent examinations we finally found a reaction procedure affording **16b** of 67% ee in 85% yield. Namely, a solution of Pd diaqua complex **6a** (10 mol%) and **1** (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 **15b** was added over 4 h using a syringe pump. During the addition of **15b**, additional **1** (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. These rather complicated reaction sequences (pre-incubation of **1** with **6**, slow addition of **15**, and additional supply of **1**) were critical for high asymmetric induction. The reaction temperature was also critical, and the enantiomeric excess of the product (**16b**) decreased from 67% ee to 3% ee when the reaction temperature was lowered to 25 °C from 60 °C (Scheme 9). Such unusual temperature dependence and such sensitivity of the reaction conditions strongly suggested the existence of an undesired competitive reaction pathway that would afford the racemic product. Like the aldol reaction described above, the chiral Pd O-enolate **11** would be an intermediate producing the highly optically active **16**. One plausible competitive catalyst giving racemic **16** seemed to be tetrafluoroboric acid, which was concomitantly generated with the palladium enolate from **1** and the diaqua complex **6** (Scheme 10). Recently, a protic acid has been reported to be a good catalyst for the reaction of silyl enol ether with imine in aqueous media,[26] but at



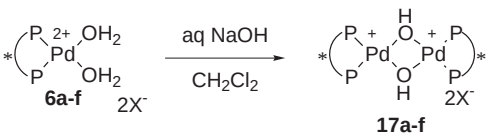
Scheme 9. Catalytic enantioselective Mannich-type reaction using the aqua complex **6a**.



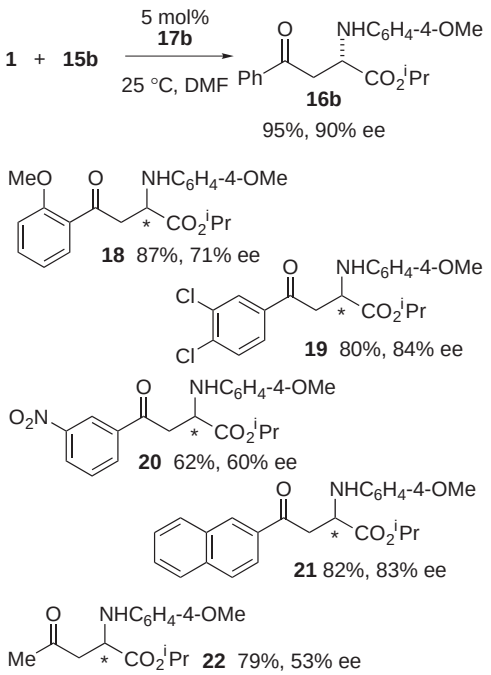
Scheme 10. Possible reaction pathways.

that time we were not sure whether the protic acid can promote the Mannich reaction of the silyl enol ether so efficiently even in wet DMF rather than hydrolysis of **1**. Therefore we tested this hypothesis. Indeed, HBF_4 (5 mol%) prepared from $AgBF_4$ and trimethylsilyl chloride in DMF (containing water) did catalyze the reaction of **1** with **15b** to give **16b** in 76% yield after only 3 h at 25 °C. Furthermore this hypothesis was further confirmed by the beneficial effect of various bases on the asymmetric induction. Mechanistic considerations suggested that a chiral Pd mono-hydroxo complex such as **14** could catalyze the reaction without forming the undesired protic acid (Scheme 10).

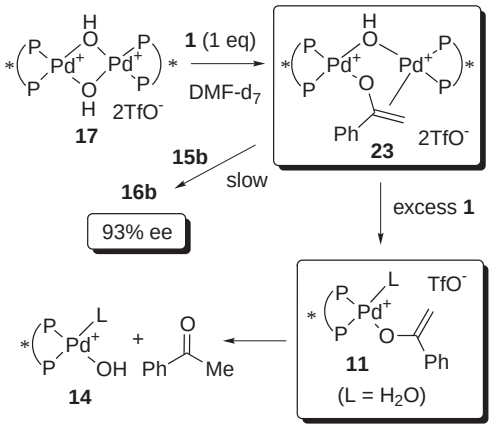
After examining several methods, we obtained the binuclear Pd μ-hydroxo complexes **17** having various ligands (**17a**–**17f**), which are dimeric form of the mono-hydroxo complexes **14**, as stable crystals. These complexes were easily prepared in good yield by treating the corresponding aqua complexes **6** dissolved in CH_2Cl_2 with 1 equivalent of aqueous NaOH (Scheme 11). The structure of the complex **17b** (X = TfO) was further confirmed by the X-ray crystallography.[12b] As expected, Mannich reaction proceeded smoothly in the presence of 5 mol% of the Pd complex **17b** (X = BF_4) to give the desired product **16b** in 95% yield, and the enantioselectivity was determined to be as high as 90% (Scheme 12). With this novel catalyst **17**, tedious operations such as slow addition of **15**, multiple supply of **1**, and warming at 60 °C were no longer necessary. Reactions with various silyl enol ethers were



Scheme 11. Preparation of Pd μ-OH complexes.



Scheme 12. Enantioselective Mannich-type reaction using **17**.

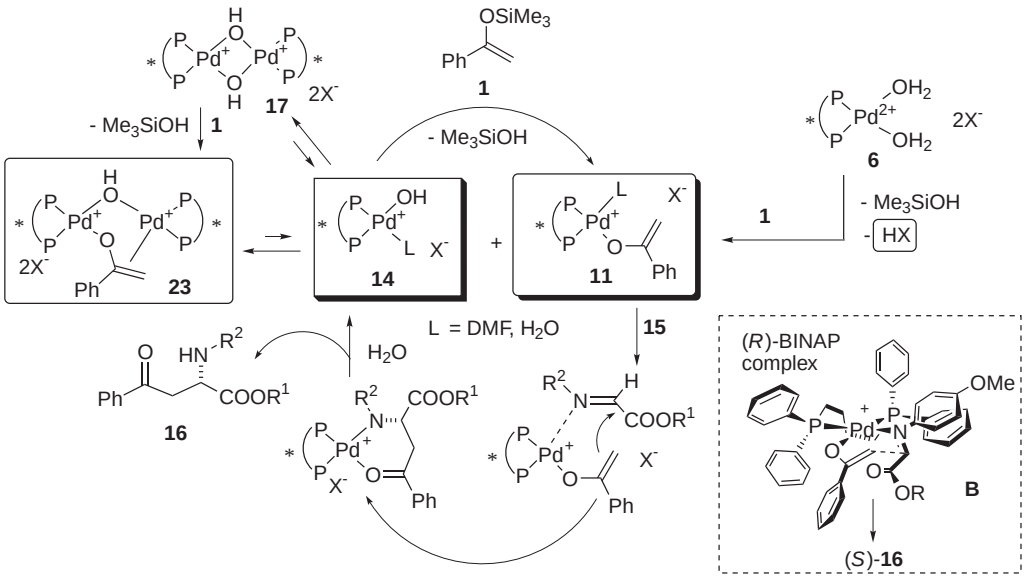


Scheme 13. Formation of novel binuclear Pd sandwiched enolate.

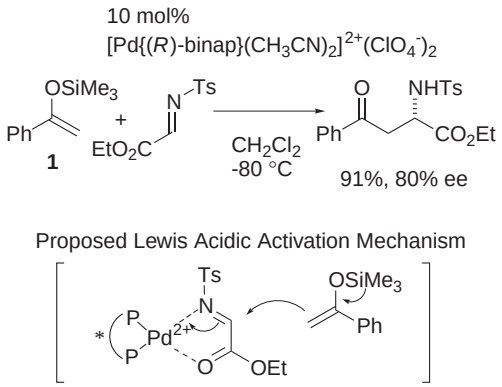
also examined, and benzoylalanine derivatives **18**–**21** were obtained in good chemical and optical yields (Scheme 12). Reaction of the silyl enol ether of acetone also proceeded smoothly to give the optically active **22**, although the ee was modest.

We further performed mechanistic studies using the μ-hydroxo complex **17a** and **17b**. Treatment of **17** with 1 equivalent of **1** gave a novel complex **23**, in which the enolate was sandwiched between the two Pd atoms. Structures of the enolate **23a** and **23b** were identified by ^{1}H NMR and ESI mass spectroscopy (Scheme 13). This complex **23a** seemed to be relatively stable, and no significant decomposition to acetophenone was observed at least several hours after consumption of **1**. When the imine **15b** was added to this solution, **23a** slowly reacted with **15b** to give the optically active **16b** (93% ee). On the other hand, when excess **1** was added to this solution, this complex **23a** disappeared and formation of the mononuclear Pd enolate **11a** was observed in ^{1}H NMR. Further hydrolysis of **11a** to acetophenone was also observed. ESI–MS measurements of this solution indicated formation of the mononuclear Pd hydroxo complex **14a** as well as **11a**. These experimental facts support the reaction mechanism shown in Scheme 14. Dissociation of the binuclear Pd μ-hydroxo complex **17** would generate the monomeric Pd hydroxo complex **14**, and this hydroxo complex reacted with **1** to give the Pd O-enolate **11** via transmetallation (see also Scheme 8). In the presence of **14**, **11** seemed to associate with **14** to form the stable sandwiched enolate **23**. Alternatively, **23** might form directly from **17**, and equilibrium would exist between **23**, **14**, and **11**. Further addition of excess **1** promoted the formation of **11** from **14**. Like aldol reaction, coordination of imine nitrogen to the chiral Pd enolate and subsequent C–C bond formation through a 6-membered transition state **B** is presumably the key to the high enantioselectivity. Thus, basically, the same catalytic cycle would be operative for the μ-hydroxo complex **17** as in the case of aqua complex **6**, but the undesired protic acid-catalyzed reaction affording the racemic product was completely suppressed by using **17**.

Just after our first report on these results in 1998, Lectka et al. reported a very similar reaction of *N*-tosyl-protected iminoesters using an anhydrous complex, $[Pd\{(R)\text{-binap}\}(CH_3CN)_2]^{2+}(ClO_4^-)_2$ (Scheme 15). Thus, we also examined the reactions of this *N*-tosyl-protected iminoester using our catalyst **6** or **17**, but no asymmetric induction was observed. This



Scheme 14. Proposed mechanism of the catalytic enantioselective Mannich-type reaction.



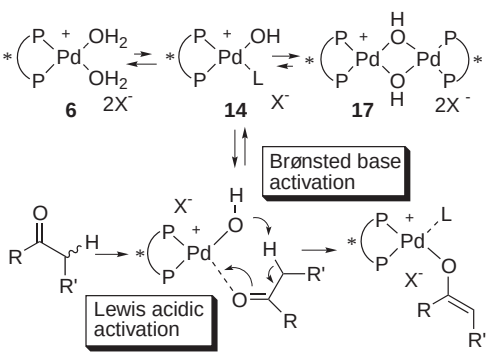
Scheme 15. $[Pd\{(R)\text{-binap}\}(CH_3CN)_2]^{2+}(ClO_4^-)_2$-catalyzed enantioselective Mannich-type reaction reported by Lectka et al.

iminoester reacted with **1** in DMF at room temperature even in the absence of any catalyst to give the racemic product. Reaction using the aqua complex **6** instead of the anhydrous complex in CH_2Cl_2 at -78 °C also afforded the racemic product, suggesting that the coordinated water can be a potential proton source causing nonselective reaction of the highly activated substrate. Lectka et al. reported that their Pd complex acted as a Lewis acid to activate *N*-tosyl-protected iminoesters in CH_2Cl_2.[27] 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. Furthermore, recently remarkable progress has been made in the field of the catalytic enantioselective Mannich-type reaction. Not only some reactions using the pre-formed enolate but also some successful examples of direct catalytic enantioselective Mannich-type reactions have been reported.[24]

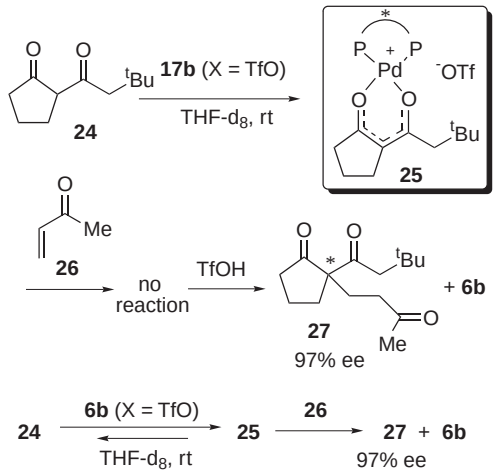
Thus we have succeeded to develop two highly enantioselective C–C bond-forming reactions, aldol reaction, and Mannich-type reaction, and proved the potency of the chiral palladium enolate as a nucleophile. Unlike the ordinary metal enolates such as alkali metal enolates, the mild and unique reactivity of this intermediate made it possible to accomplish the reaction even in the presence of water under very mild conditions (in most cases, at room temperature). Since the reaction mechanism of these reactions is completely distinctive from the generally documented Lewis acid–based reactions, preconversion of the carbonyl compound to the silyl enol ether may not be required if the chiral palladium enolate could be generated directly from the carbonyl compound.

3. Catalytic Enantioselective Michael Reaction: Direct Generation of Chiral Palladium Enolates from 1,3-Dicarbonyl Compounds[13]

As discussed before (Schemes 8 and 14), the monomeric Pd hydroxo complex plays a key role during the transmetallation process. We became interested in the hydroxy group of the Pd complex as a Brønsted base. Although Brønsted basicity of the Pd–OH group has not been thoroughly evaluated in synthetic organic chemistry, we expected that it would react with carbonyl compounds to give chiral enolates directly if the Lewis acidity of the cationic Pd atom and Brønsted basicity of the hydroxy group could activate the carbonyl compound cooperatively (Scheme 16). Such enolates are expected to react with



Scheme 16. Possible direct Pd enolate formation.

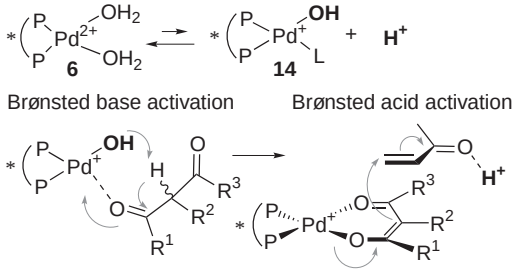


Scheme 17. NMR experiments on formation of the Pd enolate of 1,3-diketone.

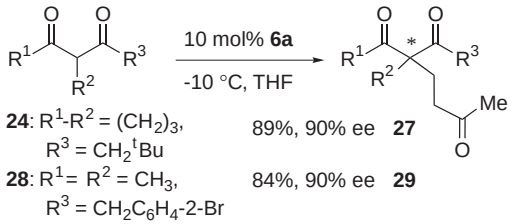
various electrophiles under mild and non-basic conditions; thus, reactions that are difficult under conventional basic conditions should become feasible.[28]

A catalytic asymmetric Michael reaction of active methylene compounds is a powerful and reliable method for the synthesis of chiral tertiary carbon centers.[29] However, the number of efficient general methods for the construction of quaternary carbon centers is limited.[30] Therefore, the development of an efficient catalyst which is applicable to various types of 1,3-dicarbonyl compounds would be extremely useful. In particular, there had been no report of the use of a *1,3-diketone* as a nucleophile. Therefore, as a first step to examine our hypothesis, we chose the 1,3-diketone **24** as a model compound.

Clean formation of the palladium enolate **25** was observed by ^{1}H NMR when **24** was treated with 0.5 equivalent of the μ-hydroxo complex **17b** (X = TfO, Pd:**24** = 1:1) in THF-d_8 for 2 h (Scheme 17).[31] Structure of the Pd enolate **25** was further confirmed by ESI mass spectroscopy. To this mixture was added 2 equivalents of methyl vinyl ketone **26** to examine the reactivity of **25**. Unfortunately, however, the reaction did not proceed, probably because of high stability of the square–planar palladium diketonato complex. The bidentate coordination of **24** might prevent the Lewis acidic activation of the enone by the cationic Pd center, which was operative in the above aldol and Mannich-type reactions. Interestingly, however, the addition of 1 equivalent of TfOH was found to promote the reaction. The Michael product **27** was obtained in 96% isolated yield (5 h, 0 °C) and the enantioselectivity was determined to be 97%. After completion of the reaction, formation of the aqua complex **6b** was observed in the ^{1}H NMR. We then performed similar experiments using the palladium aqua complex **6b**. Upon mixing **6b** and **24** in THF-d_8 at room temperature, characteristic peaks of the same Pd enolate were detected, although the reaction did not complete, and **24**, **6**, and **25** existed as an equilibrium mixture. After the addition of **26** (2 equiv) to the mixture, **25** (and the remaining **24**) was converted smoothly to **27** in 5 h; the results comparable to those above (99%, 97% ee) were obtained (Scheme 17). These results support our hypothesis that the hydroxo ligand on Pd can abstract an acidic α-proton of the substrate to form the palladium enolate complex **25**. Although the electrophilicity of **26** was not sufficient for reaction with **25**, TfOH favorably activated the enone **26** instead of protonating **25** (Scheme 18). It is interesting that the strong protic acid and inherently basic palladium enolate seem to act cooperatively to promote the carbon–carbon bond-forming reaction.



Scheme 18. Dual activation by Brønsted base and Brønsted acid.

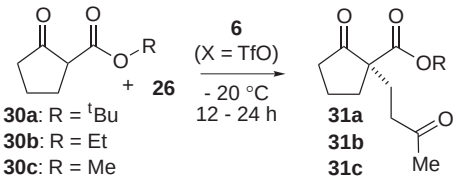


Scheme 19. Catalytic enantioselective Michael addition of 1,3-diketones.

Next, we attempted the same reaction using a catalytic amount of Pd aqua complexes. In the presence of 10 mol% of **6a**, the reaction of the 1,3-diketones, **24** and **28**, proceeded smoothly to give the corresponding Michael adducts **27** and **29** with high enantioselectivity (90% ee, respectively) (Scheme 19). In contrast to the ordinary basic conditions under which no desired product was obtained due to its instability, this reaction system gave the desired triketones in high yield. These examples indicate the benefit of these mild reaction conditions. Further studies to define the scope of this reaction system revealed that β-ketoesters were also good substrates (Table 3). Reaction of **30a** proceeded smoothly in various solvents to give **31a** in excellent chemical and optical yields (~94% ee). It is noteworthy that even the reaction in water gave results comparable to those obtained in THF.[32] The bulkiness of the ester group was found to be important for the asymmetric induction. As the ester group became smaller (**30a** > **30b** > **30c**), the ee of the product decreased. These experimental facts and the observed absolute stereochemistry of the products are explained by postulating the working model shown in Scheme 20. Since the *si* face of the Pd enolate is blocked by both the phenyl group of the ligand and the bulky *t*-butyl group of the substrate, the enone could approach the square planer Pd enolate complex preferentially from the *re* face.

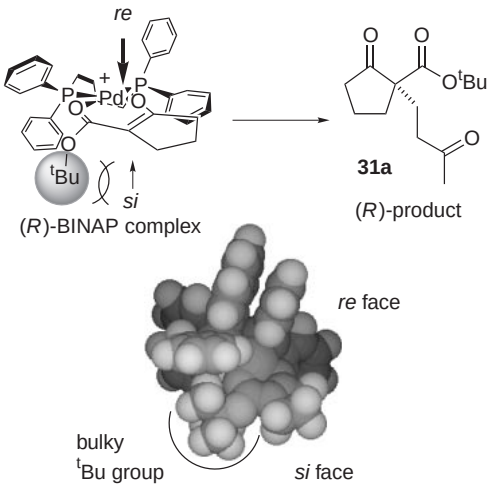
Under the optimized conditions, reactions of the various substrates including a 5- or 6-membered ring substrate, an indanone derivative, and acyclic substrates with methyl vinyl ketone **26** or ethyl vinyl ketone **32** afforded highly optically active products **33**–**39** (up to 94% ee) (Scheme 21). Further-

Table 3. Optimization of the Reaction Conditions



Substrate	Catalyst	Solvent	Yield, ee
30a	**6a** (5 mol%)	THF	84%, 88% ee
30a	**6a** (5 mol%)	H_2O[a)]	92%, 86% ee
30a	**6b** (**2 mol%**)	**THF**	**93%, 93% ee**
30a	**6b** (5 mol%)	THF	87%, 94% ee
30a	**6b** (5 mol%)	acetone	92%, 90% ee
30a	**6b** (5 mol%)	CH_2Cl_2	90%, 85% ee
30b	**6b** (5 mol%)	CH_2Cl_2	90%, 38% ee
30c	**6b** (5 mol%)	CH_2Cl_2	83%, 25% ee

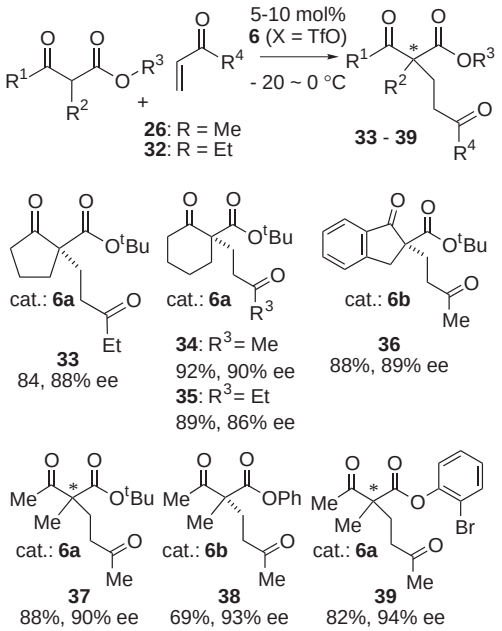
a) Reaction temp. = 4 °C, 24 h.



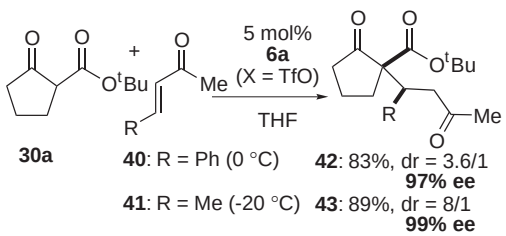
Scheme 20. Structural model of the chiral Pd enolate.

more, the reaction with less reactive β-substituted enones proceeded smoothly (Scheme 22). The reactions of **30a** with benzylideneacetone **40** and 3-penten-2-one **41** afforded the Michael adducts **42** and **43** in good yields with moderate to good diastereoselectivities. Surprisingly, the ees of the major products were found to be 97% and 99%, respectively. In these reactions, catalytic asymmetric construction of highly crowded vicinal tertiary and quaternary carbon centers was achieved in a single step.

As described above, our catalysts showed very high asymmetric induction for a variety of substrates. In addition, the mechanism of this reaction is unique. The palladium aqua complex allows successive supply of a Brønsted base and a Brønsted acid. The former activates the carbonyl compound to give the chiral palladium enolate and the latter cooperatively activates the enone (Scheme 18). This is quite distinct from conventional acid- or base-catalyzed reactions. The wide scope of this reaction would be explained by the participation of the highly organized squareplaner Pd intermediate. This type of intermediate was expected to react with other types of electrophiles.



Scheme 21. Catalytic enantioselective Michael addition of various β-ketoesters.



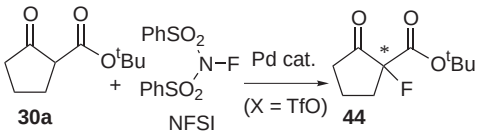
Scheme 22. Catalytic diastereo- and enantioselective Michael reactions.

4. Catalytic Enantioselective Fluorination of β-Ketoesters[14]

Fluoroorganic molecules have attracted much attention because they often show different characters from their parent compounds due to the unique properties of the carbon–fluorine bond. For this reason, an efficient method for direct enantioselective construction of fluorinated stereogenic carbon centers is extremely important.[33] So far, most approaches have relied on the use of a stoichiometric amount of chiral fluorinating reagent[34] or chiral starting material. As for catalytic enantioselective reactions, only two examples using β-ketoesters as substrates were known before our report in 2002.[35] Optically active α-substituted α-fluoro-β-ketoesters are especially attractive because they are regarded as non-enolizable β-ketoesters. In addition, since a ketone is easily converted to some other functional group, α-substituted α-fluoro-β-ketoesters would be versatile synthetic precursors of various α-fluorinated carboxylic acid derivatives. Therefore we next planned to apply the Pd enolate chemistry to the enantioselective fluorination of β-ketoesters.

First, we tested several electrophilic fluorination reagents using the ketoester **30a** and found that *N*-fluorobenzenesulfonimide (NFSI) was the most effective. The reaction of **30a** with

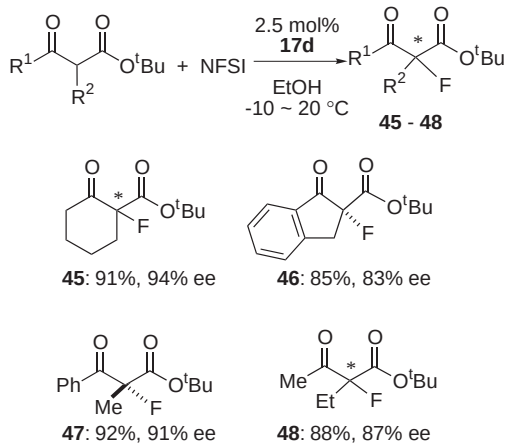
Table 4. Catalytic Enantioselective Fluorination of **30a**



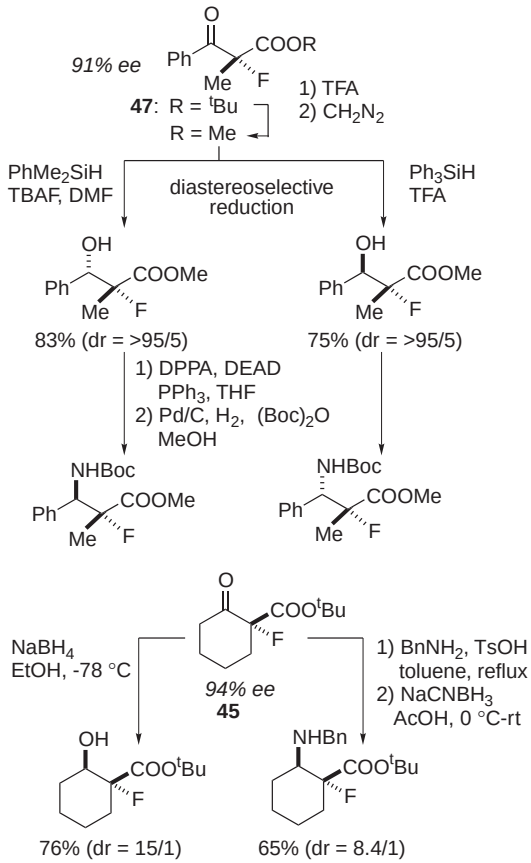
Catalyst /mol%	Solvent	Temp. /°C	Time /h	Yield, ee
6a (5)	THF	−20	12	72%, 79% ee
6b (5)	THF	−20	12	87%, 83% ee
6c (5)	THF	−20	7.5	92%, 80% ee
6d (5)	THF	−20	39	99%, 88% ee
6e (5)	THF	−20	39	82%, 71% ee
6f (5)	THF	0	72	89%, 90% ee
17f (2.5)	THF	10	48	83%, 92% ee
17f (2.5)	acetone	10	48	93%, 92% ee
17f (2.5)	**EtOH**	20	18	73%, 92% ee
17f (2.5)	**^{i}PrOH**	20	18	**90%, 92% ee**

NFSI catalyzed by **6a** proceeded smoothly and the desired product was isolated in 72% yield with 79% ee (Table 4). It should be noted that the palladium complex retained its catalytic activity until the completion of the reaction. In contrast, a stoichiometric amount of a conventional base would be required for the reaction with NFSI, because sulfonimide [$(PhSO_2)_2NH$] with high acidity was concomitantly formed during the reaction. Therefore, our reaction system was considered suitable for the development of catalytic electrophilic fluorination. To improve the enantioselectivity, we examined a series of chiral phosphine ligands. The substituents at the meta positions of the aryl group on phosphine were found to be important. Among the ligands examined, the (*R*)-DM-BINAP and (*R*)-DTBM-SEGPHOS complexes (**6d** and **6f**) gave improved enantioselectivities of 88% and 90%, respectively. In contrast to the Michael reaction, the use of the Pd μ-hydroxo complex **17f** also smoothly promoted the reaction, and the best selectivity (92% ee) was observed. This difference in reactivity may be attributed to the electrophilicity of NFSI being higher than that of the enone. Further optimization of the reaction conditions revealed that the reaction proceeded more rapidly in polar solvents. Interestingly, alcoholic solvents such as EtOH and ^{i}PrOH were the best of those tested, and the reaction time was dramatically reduced from 48 h to 18 h without any loss of enantioselectivity.

As summarized in Scheme 23, various substrates were smoothly fluorinated using 2.5 mol% of the catalyst **17d**. Other cyclic fluoro-compounds **45** and **46** were obtained in 94% ee and 83% ee, respectively. The reactions of acyclic substrates also afforded fluorinated products **47** and **48** with high enantioselectivities. Even when the amount of catalyst was reduced to 1 mol%, comparable results were obtained (**17d** (X = TfO), 0 °C, 20 h, **45**: 82% and 91% ee). It is also noteworthy that this reaction could be easily scaled up using reagent-grade non-distilled EtOH as a solvent. Furthermore, reaction in water proceeded without problem (2.5 mol% **17d** (X = TfO), room temperature, 75 h, **47**: 76% 89% ee). In these reactions, we found that **17d** and **17f** were effective catalysts, and that various substrates were selectively fluorinated by employing either of these two catalysts according to the nature of the β-ketoester.



Scheme 23. Enantioselective fluorination of various ketoesters.



Scheme 24. Stereoselective conversion of the optically active α-fluoro-β-ketoesters to the β-hydroxy or β-amino esters.

It is environmentally advantageous that this reaction proceeds well in alcoholic solvents and even in water. This reaction seems to be very robust, and no care to control moisture or air is necessary. These optically active fluorinated β-ketoesters were converted to β-hydroxy or β-amino acid derivatives, which are fundamental units in various natural or artificial compounds (Scheme 24).[36]

Our Pd enolate chemistry provides a new method for the synthesis of optically active fluorinated compounds, and the

availability of α-fluoro-β-hydroxy- or α-fluoro-β-amino acid derivatives for drug design should be valuable in medicinal studies. Currently, the scope of the substrates other than β-ketoesters has been successfully expanded to oxindole derivatives, and catalytic enantioselective synthesis of MaxiPost (BMS-204352), a drug candidate for strokes, has been achieved.[37]

With these successful results on the enantioselective Michael reaction and fluorination of the β-ketoesters in hand, we also investigated the enantioselective Mannich-type reaction of the β-ketoesters. Recently, we were pleased to find that the reactions of β-ketoesters with various imines proceeded smoothly, and the desired products having vicinal quaternary and tertiary chiral carbon centers were obtained in excellent enantioselectivity (up to 99% ee).[38]

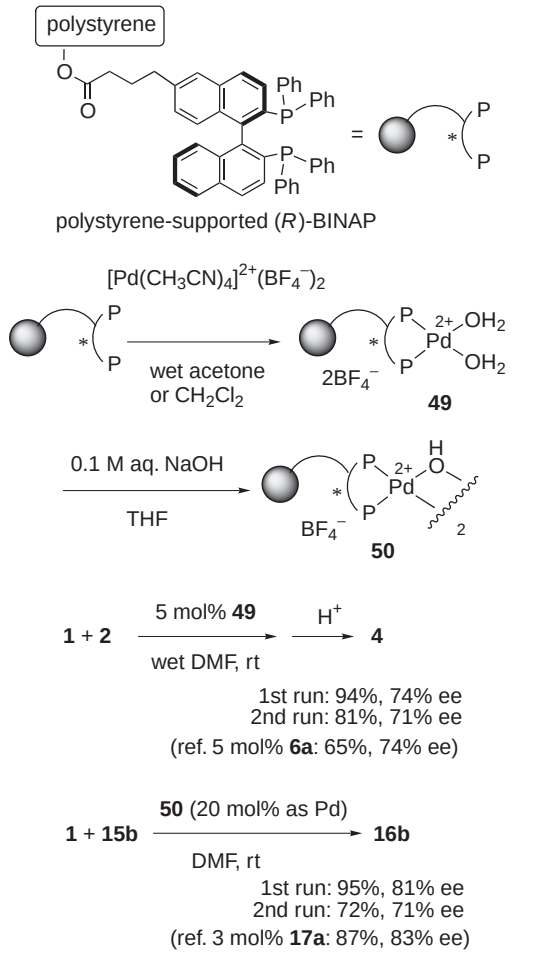
5. Immobilization and Reuse of the Pd Complexes[39,40]

While the use of environmentally friendly solvents, such as EtOH and water, is advantageous, recovery of the palladium complexes from the reaction mixtures is not easy. In the past decade, the recovery and reuse of catalysts has attracted an increased amount of interest to meet the need for environmentally friendly and cost-effective reaction processes.[41] Therefore, we decided to examine the recovery and reuse of the Pd catalyst.

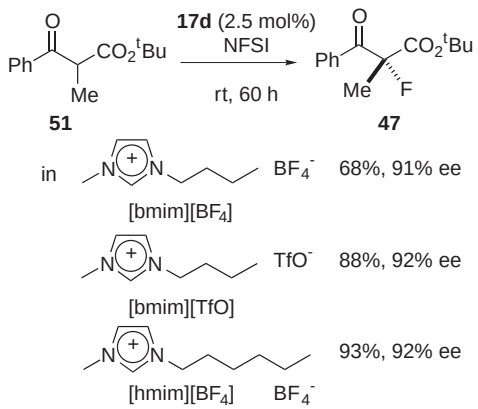
First, the polymer-supported aqua complex **49** and μ-hydroxo complex **50** were prepared using a commercially available polystyrene-supported BINAP (Scheme 25). These complexes catalyzed the asymmetric aldol reaction and Mannich-type reaction to give results similar to those obtained using **6a** and **17a**. The recovered **49** and **50** were usable for the second reactions after appropriate water or base treatment, but the results were not as good as the first run. To prepare better polymer-supported catalyst, one would require optimization of polymer and/or linker as well as of the chiral ligand structure itself. But synthesis of such modified ligands is not easy. Therefore we next examined different approaches.

Recently, organic salts which are liquid at ambient temperatures, the so-called "ionic liquids", have emerged as alternative solvents because they have essentially no vapor pressure, and provide good solubility for a wide range of organic, inorganic, and organometallic compounds.[42] We envisaged that the palladium complexes **6** and **17** might be immobilized in such ionic liquids due to their cationic property, and that a high level of enantioselectivity would be retained provided that the palladium enolate remains configurationally stable even in a polar ionic liquid.

Enantioselective fluorinations of the β-ketoester **51** in several ionic liquids, which have either triflate or tetrafluoroborate as a counter anion, were examined (Scheme 26). Gratifyingly, fluorination proceeded smoothly using these ionic liquids. After completion of the reaction, the desired product **47** and the co-product, benzenesulfonimide, were separated by simple extraction. Among the organic solvents tested, ether was found to be the best solvent in terms of extraction efficiency. The ionic liquid [hmim][BF_4] (hmim: 1-hexyl-3-methylimidazolium) readily formed a bilayer with ether. From the ether layer, **47** was isolated in good yield with excellent enantioselectivity comparable with those obtained in EtOH. The Pd catalyst



Scheme 25. Preparation of polymer-supported BINAP aqua and hydroxo complexes.

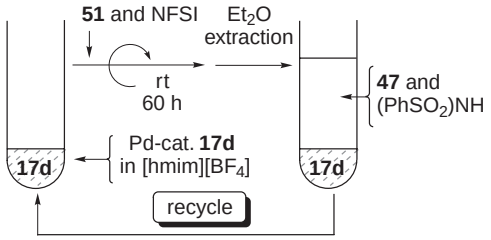


Scheme 26. Enantioselective fluorination in ionic liquids.

was retained in the ionic liquid phase.

Next, the reuse of the catalyst immobilized in [hmim][BF_4] was examined (Table 5). The catalyst was recycled no less than 10 times, maintaining excellent enantioselectivity (91% ee). A slight decrease of the reaction rate was finally observed in the 10th reaction cycle. However, a prolonged reaction time (84 h) allowed completion of the reaction, and the fluorinated

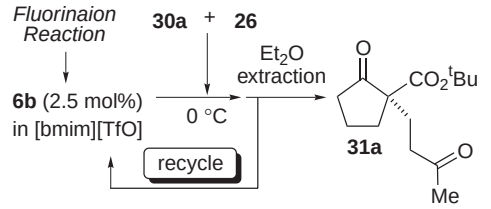
Table 5. Recovery and Reuse of Pd Catalyst in Ionic Liquid



Cycle	Yield /%	ee /%	Cycle	Yield /%	ee /%
1	93	92	6	91	91
2	80	91	7	91	91
3	81	91	8	86	91
4	91	91	9	86	91
5	81	91	10	67	91
			11[a)]	82	91

a) 84 h.

Table 6. Consecutive Michael Reaction Using **6b** Pretreated under the Fluorination Conditions



Cycle	Time/h	Yield/%	ee/%
1	8	98	83
2	8	98	84
3	8	92	83
4	8	91	84
5	15	94	84

product was isolated in 82% yield and 91% ee on the 11th run. To our knowledge, this is the first time that catalytic asymmetric fluorination has been performed repeatedly in an ionic liquid. Our asymmetric reactions in ionic liquids have been shown to be practical from both an economical and an environmental point of view.

Enantioselective Michael reactions in the ionic liquids also proceeded without problem. For example, **31a** was obtained in 97% yield and 88% ee by the reaction of **30a** with **26** catalyzed by **6b** (5 mol%) in [hmim][BF_4] at -20 °C for 15 h. Unfortunately, the reaction using the recovered Pd complex in the ionic liquid afforded less satisfactory results. Interestingly, however, we found that acceleration of the Michael reaction was observed by using the Pd complex in the ionic liquid which was recovered from the fluorination reaction. The Pd catalyst **6a** in [bmim][TfO] (bmim: 1-butyl-3-methylimidazolium) recovered from the fluorination reaction was recycled up to 5 times as shown in Table 6. We speculate that a small amount of acidic benzenesulfonimide, a co-product of the fluorination, remained in the ionic liquid, and activated the enone causing the acceleration of the reaction.

Conclusion

Since our first report in 1995, we have been investigating the chemistry of palladium enolates. Although various reactions using metal enolates as nucleophiles in the synthesis of organic molecules have been studied and employed ubiquitously, variants involving late transition metals such as Pd had not been well investigated. We found two methods for generating Pd enolates using novel chiral Pd complexes **6** and **17**. In the first part of this article, we described the formation of Pd enolates via transmetallation with silyl enol ether. Then, we demonstrated that Pd complexes **6** and **17** react with 1,3-dicarbonyl compounds to form chiral Pd enolates directly. Importantly, water or hydroxo ligands play a key role in the formation of Pd enolates. The Pd enolates generated under these conditions were found to have sufficient reactivity, and several highly efficient catalytic asymmetric reactions were successfully developed. Further expansions of this chemistry to various other carbonyl compounds as well as electrophiles are currently ongoing.

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