Review

Acid-Base Catalysis of Chiral Pd Complexes: Development of Novel Catalytic Asymmetric Reactions and Their Application to Synthesis of Drug Candidates

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Using the unique character of the chiral Pd complexes 1 and 2, highly efficient catalytic asymmetric reactions have been developed. In contrast to conventional Pd(0)-catalyzed reactions, these complexes function as an acid-base catalyst. Thus active methine and methylene compounds were activated to form chiral palladium enolates, which underwent enantioselective carbon–carbon bond-forming reactions such as Michael reaction and Mannich-type reaction with up to 99% ee. Interestingly, these palladium enolates acted cooperatively with a strong protic acid, formed concomitantly during the formation of the enolates to activate electrophiles, thereby promoting the C–C bond-forming reaction. This palladium enolate chemistry was also applicable to electrophilic enantioselective fluorination reactions, and various carbonyl compounds including β-ketoesters, β-ketophosphonates, *tert*-butoxycarbonyl lactone/lactams, cyanoesters, and oxindole derivatives could be fluorinated in a highly enantioselective manner (up to 99% ee). Using this method, the catalytic enantioselective synthesis of BMS-204352, a promising anti-stroke agent, was achieved. In addition, the direct enantioselective conjugate addition of aromatic and aliphatic amines to α,β-unsaturated carbonyl compound was successfully demonstrated. In this reaction, combined use of the Pd complex 2 having basic character and the amine salt was the key to success, allowing controlled generation of the nucleophilic free amine. This aza-Michael reaction was successfully applied to asymmetric synthesis of the CETP inhibitor torcetrapib.

Key words Michael reaction; Mannich-type reaction; fluorination; aza-Michael reaction; acid-base catalysis; asymmetric reaction

Introduction

Synthetic organic chemistry has witnessed remarkable progress with the development of novel transition metal-mediated reactions. In particular, reactions catalyzed by Pd(0) complexes, such as the Heck reaction, allylic alkylation, and cross-coupling reactions, represent an extremely important class of organic transformations and have brought a paradigm shift in synthetic methodology.[2,3)] A main feature of palladium is its redox potential, and the reaction set of oxidative addition/reductive elimination is the key to success. In contrast, we have been focusing on the use of cationic palladium complexes. Because the cationic Pd(II) complex bearing a bidentate phosphine ligand can provide two configurationally defined coordination sites, it is expected that substrates coordinated to chiral Pd complexes would undergo reactions in an enantioselective manner. In addition to playing a role as π-acids, exemplified in Wacker-type reactions, Pd(II) can act as a chiral Lewis acid to activate carbonyl groups (Chart 1, **A**).[3)] If hydroxy compounds coordinate to Pd(II) through the oxygen atom, the acidity of the hydroxyl group should be enhanced, and this complex could function as a Brønsted acid (**B**). Being treated with a base, it will give a Pd-OR complex (**C**), which should work as a base. Because some of the above-mentioned species would be in equilibrium with each other, it is likely that cationic palladium complexes may show several kinds of reactivity at the same time, which might lead to novel reactions.

During the course of the investigation undertaken by our group, it was found that the chiral Pd complexes **1** and **2** promote catalytic enantioselective aldol reaction[4)] and Mannich-type reaction (Fig. 1, Chart 2).[5)] In these reactions, the Pd complex reacts with silyl enol ethers **4** to give the chiral palladium enolate I as a reactive intermediate. In the formation of the enolate, a hydroxo ligand on palladium acts as a nucleophile to promote cleavage of the oxygen-silicon bond of silyl enolates.

Although a role of the hydroxo ligand in transmetallation has been suggested in several reactions, the possibility of a

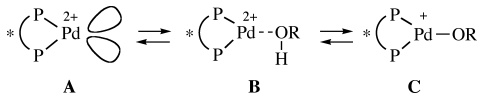

Chart 1

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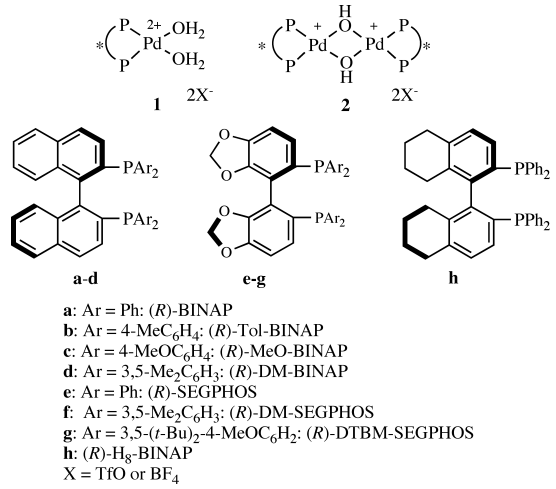


Fig. 1. Chiral Palladium Complexes

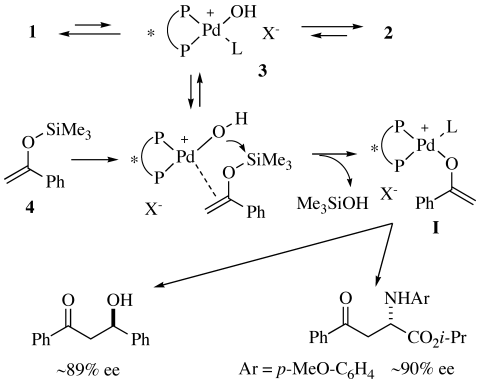


Chart 2. Formation of Chiral Palladium Enolate *via* Transmetallation

ligand acting as a Brønsted base has rarely been examined.[6,7] If the Pd hydroxo complex **3**, which is generated in an equilibrium reaction, shows Brønsted basicity, it should react with acidic substrates to give unique reactive intermediates.

Indeed, achiral palladium hydroxo complexes were reported to act as a Brønsted base, and the reaction with active methylene compounds gave the corresponding palladium enolates.[8—10] However, these studies focused on structural analysis, and use of the synthesized enolates in organic synthesis has been limited.[11,12] Thus we planned to examine the generation of chiral palladium enolates II from carbonyl compounds bearing an electron-withdrawing group, based on

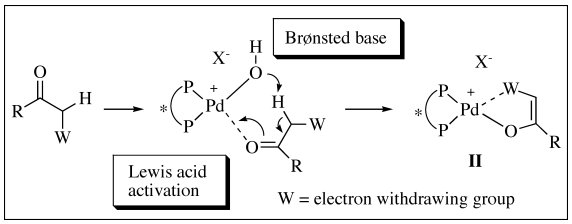


Chart 3. Direct Formation of Chiral Palladium Enolate from Acidic Carbon Pronucleophiles

the following assumptions: 1) The acidic proton of such compounds should be abstracted even by the weakly basic PdOH; 2) the bidentate nature of the substrate should facilitate formation of the structurally well-organized enolate, which would be favorable for asymmetric reactions (Chart 3). We expected that such enolates would undergo nucleophilic reactions with various electrophiles,[13] and in contrast to the conventional alkali metal and alkaline earth metal enolates, the palladium enolate should show mild reactivity, because the Pd–O bond is less polarized than the alkali metal-oxygen bond due to the relatively large electronegativity of palladium (Pauling's value: Pd, 2.2; Li, 1.0).[14] Interestingly, this enolate formation is considered to occur under non-basic conditions. As mentioned above, we expect that the palladium complexes could function as acid and base at the same time; these states are usually incompatible. If they could activate substrates independently, reactions that are difficult under conventional basic conditions could become feasible.

Additionally, we envisaged that this novel concept of acid-base catalysis of the Pd(II) complexes would be applicable to reactions with substrates other than carbonyl compounds, and unique reactions should be developed.

Taking advantage of the cationic Pd complexes **1** and **2**, we succeeded in developing highly enantioselective catalytic reactions. Through our investigation, we have revealed the unique reactivity of palladium enolates under non-basic conditions, derived from various active methylene/methine compounds. Furthermore, reactivity control of highly nucleophilic free amines was achieved using acid-base reaction of the Pd complexes **2** with amine salts. In this article, we describe catalytic asymmetric Michael reaction, Mannich-type reaction, electrophilic fluorination reaction, and aza-Michael reaction.

Yoshitaka Hamashima was born in Kagoshima in 1974. He received his B.S. (1997), M.S. (1999), and Ph.D. (2003) degrees from The University of Tokyo under the direction of Professor M. Shibasaki. In 2001, he joined Professor M. Sodeoka's group as Assistant Professor of Tohoku University and was promoted to Lecturer in 2005. He is now a researcher at RIKEN (The Institute of Physical and Chemical Research). He received Meiji Seika Award in Synthetic Organic Chemistry, Japan (2003), Thieme Journal Award (2006), and The PSJ Award for Young Scientists (2006). His current research interests include synthetic organic chemistry, organometallic chemistry, and asymmetric catalysis.

Yoshitaka Hamashima

1. Catalytic Enantioselective Michael Reaction: Direct Generation of Chiral Palladium Enolates from 1,3-Dicarbonyl Compounds[15,16]

The conjugate addition of acidic carbon nucleophiles to electron-deficient olefins, the so-called Michael reaction, is one of the most important carbon–carbon bond-forming reactions. This reaction is atom-economical and environmentally benign, because complete assembly of a Michael donor and an acceptor is possible. Due to the high synthetic utility of the Michael reactions, great efforts have been made for the development of efficient catalytic enantioselective Michael reactions.[17,18] The most frequently examined Michael donors are readily enolizable compounds such as β-ketoesters and malonates, and construction of chiral tertiary carbon centers at the acceptor side has been well investigated. In contrast, as for the synthesis of chiral quaternary carbon centers,[19,20] which are created at the donor side, the number of general methods has been quite limited, and expanding the scope of available substrates was difficult until recently. Therefore the development of an efficient method applicable to various 1,3-dicarbonyl compounds would be extremely useful. In particular, there had been no reports on the use of a 1,3-diketone as a nucleophile, which is unstable under basic conditions.[21] Inspired by reported examples using transition metal complexes,[22] we assumed that mild activation of 1,3-dicarbonyl compounds by the Pd complexes **1** and **2** would be effective for the development of a Michael reaction with broad substrate generality. As a first step to examine our hypothesis, we chose the 1,3-diketone **5a** as a model compound.

At first, we attempted the reaction of **5a** with the Pd μ-hydroxo complex **2b**. To our delight, the Pd μ-hydroxo complex acted as a base, and clean formation of the palladium enolate III was observed by ^{1}H-NMR when **5a** was treated with 0.5 eq of **2b** (X=TfO) in THF-d_8 for 2 h (Chart 4). Formation of the Pd enolate III was further confirmed by electron spray ionization (ESI) mass spectroscopy. To examine the reactivity of III, 2 eq of methyl vinyl ketone **6a** were added to this mixture. Unfortunately, however, the reaction did not proceed even at room temperature, probably because of the high stability of the square-planar palladium diketonato complex or because the bidentate coordination of **5a** might prevent the Lewis acidic activation of the enone by the cationic Pd center. Interestingly, however, addition of 1 eq of trifluoromethanesulfonic acid (TfOH) was found to promote the reaction. The Michael product **7a** was obtained in 96% isolated yield (5 h, 0 °C) and the enantioselectivity was determined as 97% ee. After completion of the reaction, formation of the Pd aqua complex **1b** was observed in the ^{1}H-NMR. We then performed similar experiments using **1b**.[23] Upon mixing **1b** and **5a** in THF-d_8 at room temperature, characteristic peaks of the same Pd enolate were detected, although the reaction did not complete, and **5a**, **1b**, and III existed as an equilibrium mixture. After addition of **6a** (2 eq) to the mixture, **5a** was smoothly converted to **7a** in 5 h, and results comparable to those above (99, 97% ee) were obtained (Chart 4). Additionally, the reaction with *tert*-butyl 2-oxo-cyclopentanecarboxylate **8a** gave similar results under the same reaction conditions (89, 99% ee). 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. Although the electrophilicity of III was not

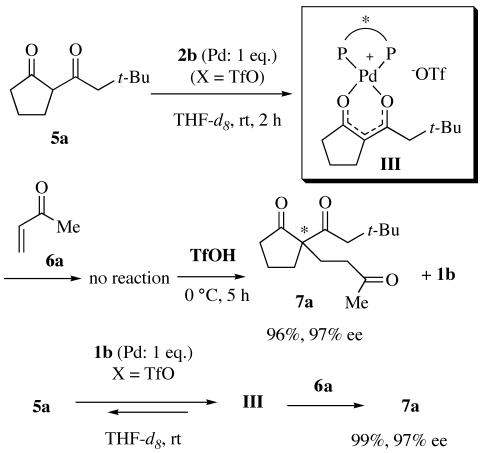


Chart 4. NMR Experiments on Formation of Pd Enolate

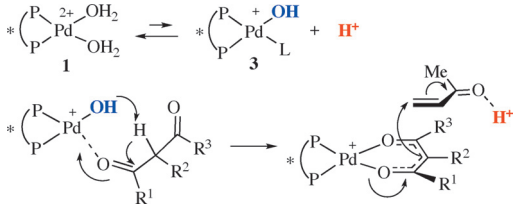


Chart 5. Dual Activation by Brønsted Base and Brønsted Acid

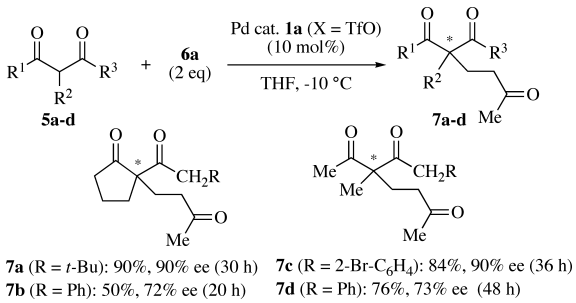


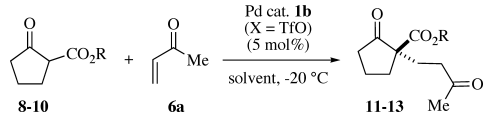
Chart 6. Catalytic Enantioselective Michael Reaction of 1,3-Diketones

sufficient for reaction with the enone, TfOH preferentially activated **6a** instead of protonating the enolate (Chart 5). 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.

Next, we attempted the same reaction using a catalytic amount of the Pd aqua complex **1** (Chart 6). In the presence of 10 mol% of **1a**, reaction of the 1,3-diketones **5a**—**d** proceeded smoothly. Although the enantioselectivity varied according to the steric size of the substrates, the Michael adducts **7** were obtained with up to 90% ee. In contrast to the ordinary basic conditions under which no desired product was obtained due to instability of the 1,3-diketones and the produced triketones, this reaction system gave the desired triketones in good yield,[20] indicating the utility of these mild reaction conditions.

To define the scope of this reaction, we next examined β-ketoesters **8**—**10** as nucleophile (Table 1). Gratifyingly, the reaction of **8a** proceeded smoothly in various solvents (entries 1—8), and notably, the reaction proceeded even in alco-

Table 1. Optimization of Reaction Conditions



Entry	Ester: R	Solvent	Conc. (M)	Time (h)	Product	Yield (%)	Ee (%)
1	**8a**: *t*-Bu	Acetone	1	12	**11a**	92	90
2	**8a**	THF	1	84	**11a**	87	94
3	**8a**	THF	4	24	**11a**	92	92
4	**8a**	—	—	15	**11a**	Quant.	88
5	**8a**	MeOH	1	72	**11a**	77	88
6	**8a**	EtOH	1	72	**11a**	72	91
7[a,b]	**8a**	H_2O	4	24	**11a**	92	86
8	**8a**	CH_2Cl_2	1	36	**11a**	96	89
9	**9**: Et	CH_2Cl_2	1	24	**12**	90	38
10	**10**: Me	CH_2Cl_2	1	24	**13**	83	25

a) Pd complex **1a** (5 mol%) was used. *b*) 4 °C.

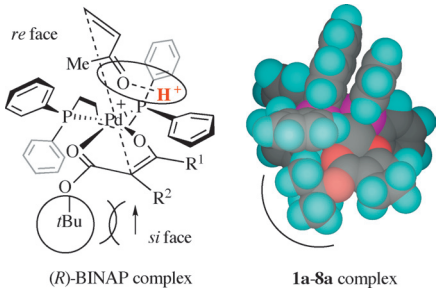
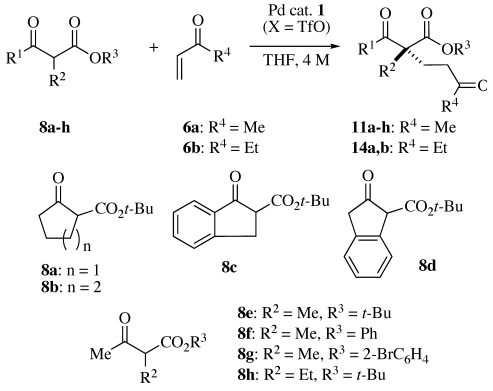


Fig. 2. Working Model of Chiral Pd Enolate

holic solvents and water, which might be attributed to the stability of the Pd complexes.[24] On the other hand, steric demand of the ester moiety was important for high asymmetric induction, and the ee was improved as the ester moiety became bulkier (entries 8—10). In contrast to the *t*-Bu ester **8a**, the ees of the products were low in the case of **9** and **10**. These experimental results, coupled with the observed absolute configuration of the product, can be explained by postulating involvement of the configurationally stable, square-planar palladium enolate shown in Fig. 2.[25] The bulky ester would avoid steric interaction with the aryl group located at one side of the enolate face. Thus the *si* face of the palladium enolate is blocked prefentially, and the incoming enone reacts with the palladium enolate at the *re* face in a highly enantioselective manner.

Under optimized reaction conditions, reactions of other cyclic and acyclic substrates **8a**—**h** with methyl vinyl ketone **6a** or ethyl vinyl ketone **6b** afforded the products in a highly enantioselective manner (up to 94% ee) (Table 2). In addition to the *t*-Bu ester, aryl esters also gave excellent enantioselectivities. As shown in entry 6, the bromoarene was intact and **11g** was isolated in 82% yield with 94% ee, indicating that a Pd(0) species was not involved. Notably, the amount of catalyst could be reduced to as little as 2 mol% without any deterioration of the reaction efficiency (93, 93% ee) (entry 9). There are a few reports in which more than 90% ee was achieved for one specific β-ketoester, namely 1-oxo-2-indane carboxylate. In contrast, our catalysts exhibited high asymmetric induction for various substrates.

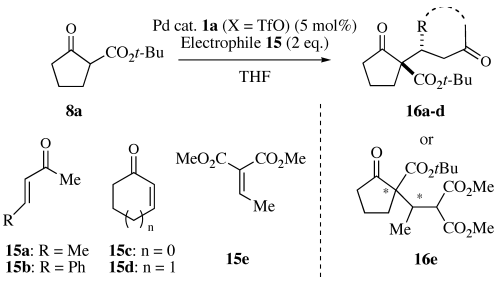
Table 2. Enantioselective Michael Reaction of Various β-Ketoesters



Entry	8	6	1 (mol%)	Temp. (°C)	Time (h)	Product	Yield (%)	Ee (%)	Conf.
1	**8a**	**6a**	**1b** (5)	−20	24	**11a**	92	92	*R*
2	**8b**	**6a**	**1a** (5)	0	72	**11b**	92	90	*R*
3[a]	**8c**	**6a**	**1b** (10)	−20	48	**11c**	88	89	*S*
4	**8d**	**6a**	**1b** (10)	0	66	**11d**	58	71	—
5	**8e**	**6a**	**1a** (10)	0	72	**11e**	88	90	—
6	**8f**	**6a**	**1b** (10)	0	72	**11f**	69	93	*R*
7	**8g**	**6a**	**1a** (10)	0	36	**11g**	82	94	—
8	**8h**	**6a**	**1a** (10)	rt	1 w	**11h**	41	65	—
9	**8a**	**6a**	**1a** (2)	−20	40	**11a**	93	93	*R*
10	**8a**	**6b**	**1a** (5)	−20	20	**14a**	84	88	—
11	**8b**	**6b**	**1a** (5)	0	72	**14b**	89	86	—

a) 1 M **8c**.

Table 3. Reactions with Other Michael Acceptors



Entry	Electrophile	Temp. (°C)	Time (h)	Yield (%)	Dr[a]	Ee[a] (%)
1	**15a**	−20	24	89	8/1	99/—[b]
2	**15b**	0	36	83	3.6/1	97/—[b]
3	**15c**	rt	12	85	1.2/1	93/86
4	**15d**	rt	12	98	1.6/1	96/97
5	**15e**	0—rt	72	79	2.9/1	96/—[b]

a) Major/minor. *b*) Not determined.

Encouraged by these results, we turned our attention to diastereoselective reactions. In spite of remarkable progress in asymmetric synthesis, it is still difficult to construct sterically hindered vicinal tertiary and quaternary carbon centers in an enantioselective manner. To our delight, the reaction with less reactive β-substituted enones proceeded smoothly (Table 3). The reactions of **8a** with acyclic *trans*-enones such as 3-penten-2-one **15a** and benzalacetone **15b** afforded the Michael adducts **16a**—**b** in good yield with good to high diastereoselectivity. To our surprise, the ees of the major products were 99 and 97%, respectively. Unfortunately, the reac-

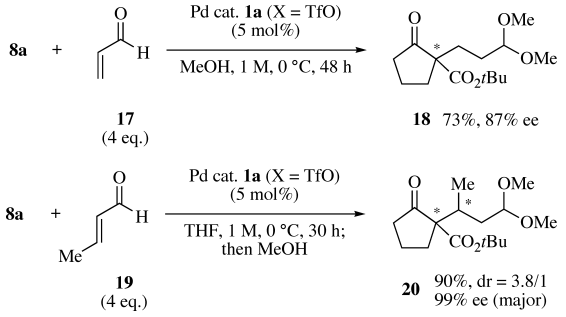


Chart 7. Asymmetric Michael Reactions with α,β-Unsaturated Aldehydes

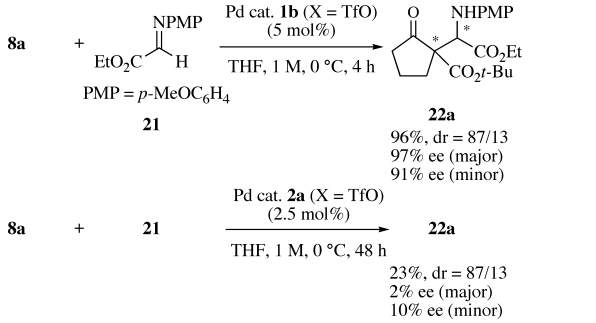


Chart 8. Catalytic Enantioselective Mannich Reaction of **8a** with Imino Ester **21**

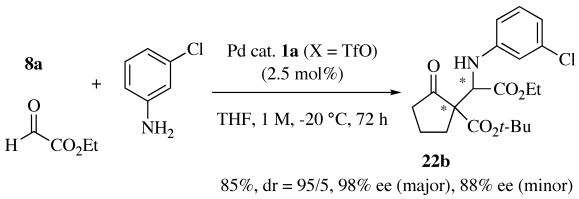


Chart 9. Three-Component Coupling Reaction

tion with cyclic enones (**15c**, **d**) and dimethyl ethylydenmalonate (**15e**) gave poor diastereoselectivity, but excellent enantioselectivity was always observed, which may be associated with excellent face selection of the putative palladium enolates. In these reactions, catalytic asymmetric construction of highly crowded vicinal tertiary and quaternary carbon centers was achieved in a single step. Even after our first report, only a few examples of distereo- and enantioselective Michael reaction of acidic carbon nucleophiles have been reported.[26,27]

Further studies to investigate the scope of the reaction revealed that α,β-unsaturated aldehydes could be used in our reaction (Chart 7).[28] In the case of acrolein **17**, simple application of the optimized condition gave a complex mixture, and the corresponding dimethyl acetal **18** was isolated in only 10% yield, but 90% ee, after treatment with methanol. However, when the reaction was carried out in methanol, chemical yield was greatly improved because *in situ* protection of the aldehydes suppressed undesired reactions. The reaction with crotonaldehyde **19** proceeded even in THF, and the desired acetal **20** was isolated with modest diastereoselectivity and excellent enantioselectivity (dr=3.8 : 1, 99% ee).

As described above, our catalytic system showed very high asymmetric induction for a variety of substrates. In addition, the mechanism of this reaction is unique. The palladium aqua complexes allow successive supply of a Brønsted base and a Brønsted acid. The former activates the carbonyl compounds to give the chiral palladium enolates and the latter cooperatively activates the enones (Chart 5). This is distinct from conventional acid- or base-catalyzed reactions. The wide scope of our Michael reaction can be explained by the involvement of the well-organized squareplaner Pd enolate intermediate. This intermediate was expected to react with other electrophiles with high affinity to a proton.

2. Catalytic Asymmetric Mannich-Type Reaction of β-Ketoesters with Various Imines[29,30]

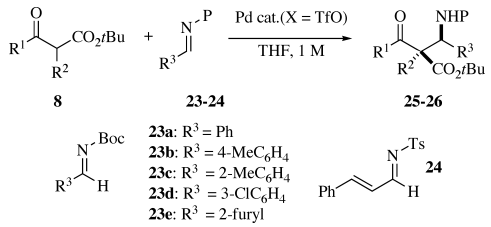
The Mannich-type reaction represents a fundamental carbon–carbon bond-forming reaction, being applicable to the synthesis of many natural and man-made compounds. Therefore development of efficient methods for catalytic enantioselective Mannich-type reaction is of great interest.[31,32] Much effort has been made to develop the reaction using simple carbonyl compounds such as aldehydes and ketones.[33] However, reaction of readily enolizable β-ketoesters has rarely been investigated.[34] Quite recently, several researchers have developed a highly enantioselective Mannich-type reaction of such pronucleophiles with acyl imines using cinchona alkaloids as catalysts.[35—38] As a powerful tool for the synthesis of highly functionalized β-amino carbonyl compounds, the development of efficient asymmetric addition reactions of β-ketoesters with broad generality as regards imines is now attracting considerable attention.

Provided that the reactivity of the imines is greatly enhanced by protonation, the unique reactivity of the palladium enolate found in the Michael reaction would be applicable to the Mannich-type reaction. Even though protic acids have been used as catalysts to promote Mannich reactions,[39,40] we expected that cooperative action of the chiral palladium enolate with the acid to activate the imines would be effective for the selective transformation.

At the outset, we examined the reaction of **8a** with *N*-*p*-methoxyphenyl (PMP)-protected imino ester **21** in THF using 5 mol% of **1b** (Chart 8). Probably because the imine was effectively activated by protonation, the reaction proceeded much faster than in the case of the Michael reactions. The reaction reached completion after 4 h, and the desired Mannich adduct **22a** was isolated in 96% yield with 97% ee (major). Furthermore, since the Pd complex **1** is tolerant to water molecules, a three-component reaction was possible (Chart 9). In contrast, the reaction using the Pd complex **2a**, where no protic acid was produced during the formation of the enolate, resulted in only 23% isolated yield after 48 h, and negligible asymmetric induction was observed for both diastereomers (Chart 8). These results are in accord with our initial hypothesis, strongly indicating that cooperative activation of imines by the protic acid is essential for this reaction.

Encouraged by this success, we next investigated the use of *N*-*tert*-butoxycarbonyl (Boc)-protected imines. Since these imines can be prepared from simple aldehydes, it might be possible to enhance the synthetic utility of our Mannich reaction. Under the optimized reaction conditions, **8a** reacted with **23a** under ice-bath cooling, and the corresponding

Table 4. Catalytic Enantioselective Mannich-Type Reactions of β-Ketoesters



Entry	Cat. (mol%)	8	Imine	Product	Temp. (°C)	Time (h)	Yield (%)	Dr[a]	Ee[b]
1	**1a** (2.5)	**8a**	**23a**	**25aa**	0	5	93	88/12	99/97
2	**1a** (2.5)	**8a**	**23b**	**25ab**	0	2	93	90/10	95/99
3	**1a** (2.5)	**8a**	**23c**	**25ac**	0	5	75	93/7	94/—[c]
4	**1a** (2.5)	**8a**	**23e**	**25ae**	0	2	75	>95/5	86/—[c]
5[d]	**1e** (2.5)	**8e**	**23a**	**25ea**	rt	4	84	86/14	98/95
6[d]	**1a** (2.5)	**8e**	**23c**	**25ec**	rt	9	86	96/4	98/—[c]
7[d]	**1a** (2.5)	**8e**	**23d**	**25ed**	rt	2	91	82/18	96/95
8[e]	**1a** (1)	**8a**	**24**	**26**	−20	24	88	90/10	99/99

a) Major/minor. *b*) Major/minor. *c*) Not determined. *d*) Imine (3 eq) was used. *e*) 0.25 M.

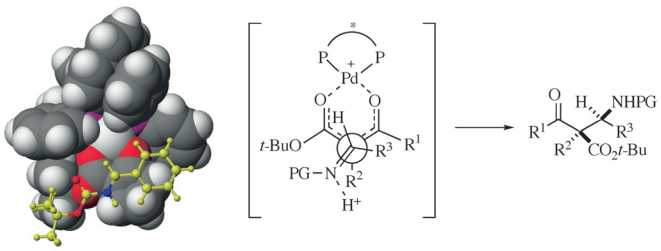


Fig. 3. Plausible Transition State Model

Mannich adduct **25aa** was isolated after 5 h in 93% yield with 99% ee (major) (Table 4, entry 1). We next examined the substrate scope of this reaction. Other *N*-Boc-protected imines with various substitution patterns were converted to the desired products within several hours in most cases, and high diastereoselectivities and excellent enantioselectivities were observed (up to 96/4, up to 99% ee). In particular, in spite of steric repulsion, our reaction was tolerant to *ortho*-substituted imines (entries 3, 6). As for the generality regarding the nucleophiles, the acyclic β-ketoester **8e** was also a good substrate. As shown in entries 5—7, reaction proceeded without problem, furnishing the desired Mannich adducts in a highly enantioselective manner (up to 98% ee). Moreover, *N*-toluenesulfonyl (Ts)-protected imines were available. As shown in entry 8, the imine **24** derived from cinnamaldehyde was converted to the corresponding product **26** at −20 °C, and excellent stereoselectivity (dr=90/10, 99% ee) was observed.

The excellent enantioselectivity observed in the Mannich reaction is deduced to come from face-selection of the chiral Pd enolate. Because the Pd complex **1** was superior to Pd complex **2**,[14] the protonated form of imines might be involved in the transition state. On the other hand, face-selection of the imines was responsible for the relative stereochemistry. We speculate that C–C bond-formation occurs with the appropriate geometry as described in Fig. 3 to cause the minimum steric interaction. This model is in accord with the relative stereochemistry of **25aa**, which was unequivocally determined by X-ray analysis.[30]

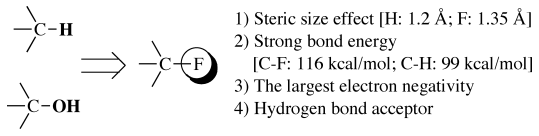


Chart 10. Properties of the Fluorine Atom and Carbon-Fluorine Bonds

Thus we developed a highly selective Mannich reaction of β-ketoesters with various imines regardless of their electronic and steric properties. In these reactions, construction of highly crowded vicinal quaternary and tertiary carbon centers was achieved in one step. The unique reaction mechanism, which is operative in this reaction, would be a guide to develop novel reactions. Further studies within this context are underway in our group.

3. Catalytic Enantioselective Fluorination Using Pd Enolate Chemistry[41,42]

3.1. Fluorination Reaction of β-Ketoesters[43,44] Acquisition of novel properties distinct from those of the parent compound by replacing an atom in a bioactive compound with other atoms is a very important aspect of medicinal chemistry. Incorporation of a fluorine atom, which rarely occurs in natural products, into bioactive compounds sometimes leads to significant improvement of their biological activity profiles, probably due to the unique properties of the fluorine atom and/or the carbon-fluorine bond as summarized in Chart 10.[45]

For this reason, substitution of a hydrogen or hydroxyl group in the parent compounds with a fluorine atom is now a common strategy in the course of development of new drug candidates. Most such investigations have focused on replacement of the hydrogen on an aromatic ring with a fluorine atom. In contrast, the effect of substitution at sp^3 carbons has been less well studied. Although chiral compounds that do not have a fluorine atom at a stereogenic carbon center can be prepared based on well-established asymmetric reactions starting from organofluorine compounds,[46] the use of

optically active compounds bearing a fluorine atom at a chiral carbon center is restricted by the limited availability of effective synthetic methods. Thus an efficient method for direct enantioselective construction of fluorinated stereogenic carbon centers is extremely important.[47,48] When we became interested in this work, there had been only two reported examples, where pioneering but limited success was achieved in respect to both substrate-generality and enantioselectivity.[49,50]

Electrophilic fluorination reactions of carbonyl compounds, in principle, are accompanied by concomitant generation of a stoichiometric amount of an acidic co-product (Chart 11). Therefore the use of strongly basic catalysts to abstract an acidic proton of substrate may be limited, because decomposition or neutralization of the catalysts might occur by the reaction with the acidic co-product. We considered that our palladium enolates under acidic or neutral conditions could be a promising alternative to carry out enantioselective electrophilic fluorination catalytically. Therefore we decided to embark on the project to develop efficient fluorination reactions to overcome these unsolved problems.

First, we tested several electrophilic fluorination reagents and found that *N*-fluorobenzenesulfonimide (NFSI) **27** was most effective. As we expected, the reaction of **8a** with NFSI catalyzed by **1a** proceeded smoothly and the desired product **28a** was isolated in 72% yield with 79% ee (Table 5, entry 1). The observed enantioselectivity was attributed to the bidentate Pd enolate as in the case of the reactions described above (Chart 12). Due to the small size of the fluorine atom, face discrimination of the enolate was insufficient when (*R*)-BINAP was used as ligand. To improve the enantioselectivity, we examined a series of chiral bisphosphine ligands (entries 2—7).[51] The substituents at the meta positions of the aryl group on phosphine were found important, allowing better face selection of the enolates (Chart 12). Among the ligands examined, the (*R*)-DM-BINAP and (*R*)-DTBM-SEGPHOS complexes (**1d**, **g**) gave improved enantioselectivities of 88 and 90%, respectively. In contrast to the Michael reaction and the Mannich-type reaction, where the use of **1** was essential, the Pd μ-hydroxo complex **2g** was also a good catalyst, and the best selectivity (92% ee) was observed (entry 8). This difference in reactivity may be attributed to the electrophilicity of NFSI being higher than that of enones. Further optimization of the reaction conditions revealed that the reaction proceeded more rapidly in polar solvents (entries 9—12). Interestingly, an alcoholic solvent such as EtOH and *i*-PrOH was the best of those tested, and the reaction time was dramatically reduced from 48 to 18 h without any loss of enantioselectivity. ^{1}H-NMR study revealed that stoichiometric reaction of **8a** with **2b** was completed within 10 min in CD_3OD, while the same reaction in THF-d_8 took 2 h for completion. Thus we speculated that alcoholic solvents played a key role in the rapid formation of the chiral palladium enolates, and thereby significantly accelerating the fluorination reactions.

As summarized in Table 6, this reaction was applicable to a wide range of β-ketoesters including cyclic and acyclic substrates. More than 90% ee was observed for most substrates examined in this study, indicating the high substrate-

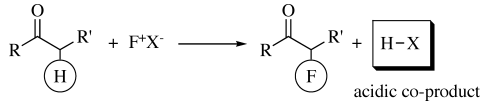
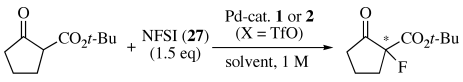


Chart 11

Table 5. Optimization of Reaction Conditions



8a **28a**

Entry	Catalyst (mol%)	Solvent	Temp. (°C)	Time (h)	Yield (%)	Ee (%)
1	**1a** (5)	THF	−20	12	72	79
2	**1b** (5)	THF	−20	12	87	83
3	**1c** (5)	THF	−20	7.5	92	80
4	**1d** (5)	THF	−20	39	99	88
5	**1e** (5)	THF	−20	39	82	71
6	**1g** (5)	THF	0	72	89	90
7	**1h** (5)	THF	−20	7.5	92	82
8	**2g** (2.5)	THF	10	48	83	92
9	**2g** (2.5)	Acetone	10	48	93	92
10	**2g** (2.5)	EtOH	20	18	73	92
11	**2g** (2.5)	*i*-PrOH	20	18	90	92
12	**2g** (2.5)	*t*-BuOH	20	18	68	93

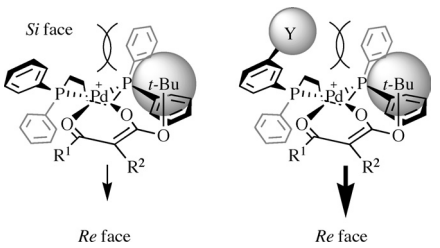
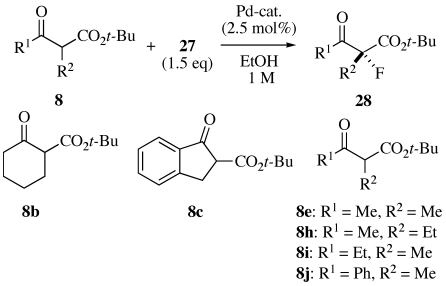


Chart 12

Table 6. Catalytic Enantioselective Fluorination Reactions of β-Ketoesters



Entry	**8**	Catalyst (X)	Temp. (°C)	Time (h)	Yield (%)	Ee (%)
1	**8b**	**2d** (BF_4)	−10	20	91	94
2	**8c**	**2d** (TfO)	−20	36	85	83[a]
3	**8e**	**2f** (TfO)	20	72	49[b]	91
4	**8h**	**2d** (TfO)	20	42	88	87
5	**8i**	**2d** (TfO)	20	72	47	69
6	**8j**	**2d** (BF_4)	20	40	92	91
7[c]	**8b**	**2d** (BF_4)	0	20	82	91
8[d]	**8j**	**1d** (TfO)	20	48	96	91[a]

a) The absolute configuration was determined to be *R* after conversion to the known compound. *b*) Lower yield due to the volatility of **27e**. *c*) 1 mol% of **2d**. *d*) 1 g scale.

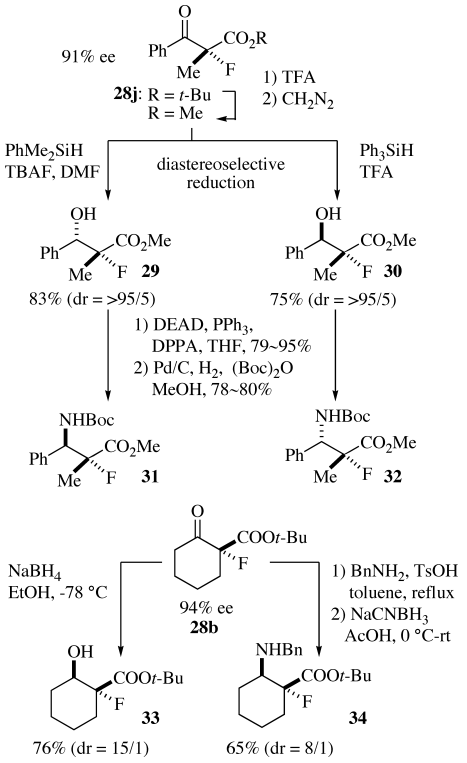


Chart 13. Stereoselective Conversion

generality of our reaction. Even when the amount of catalyst was reduced to 1 mol%, the reaction proceeded without significant loss of efficiency (entry 7). It is also noteworthy that this reaction could easily be scaled up using reagent-grade non-distilled EtOH as solvent (entry 8). Furthermore, reaction in water proceeded without problem [2.5 mol% **2d** (X=TfO), room temperature, 75 h, **28j**: 76, 89% ee]. It is environmentally advantageous that this reaction proceeds well in alcoholic solvents and even in water.

The obtained optically active α-substituted α-fluoro-β-ketoesters are potentially useful as nonenolizable β-ketoesters, and a related structure was manipulated to enhance the antibiotic activity of ketolides such as telithromycin.[52] In addition, since ketone is a versatile functionality, transformation of the products was readily performed. Thus optically active β-hydroxyl or β-amino acid derivatives **29**—**34** were synthesized by way of stereoselective reductions developed by Hiyama and coworkers (Chart 13).[53] These compounds are fluorinated derivatives of fundamental units found in various natural and man-made compounds and are expected to have many applications in medicinal chemistry.

Although the mechanism of the present fluorination reaction has not been completely clarified, ^{1}H-NMR studies suggest that the chiral palladium enolates should be key intermediates. As shown in Chart 14, the Pd μ-hydroxo complexes act as a base to form the chiral enolates III. Reaction of III with NFSI gives the intermediate IV. The following anion exchange reaction of $(PhSO_2)N^-$ with water molecules would complete the catalytic cycle. Alternatively, considering the acidity of benzenesulfonimide and water, direct formation of III from IV is also plausible. A similar catalytic cycle can be drawn when using the aqua complexes **1**.

3.2. Fluorination of β-Ketophoshponates and Related Compounds[44,54]

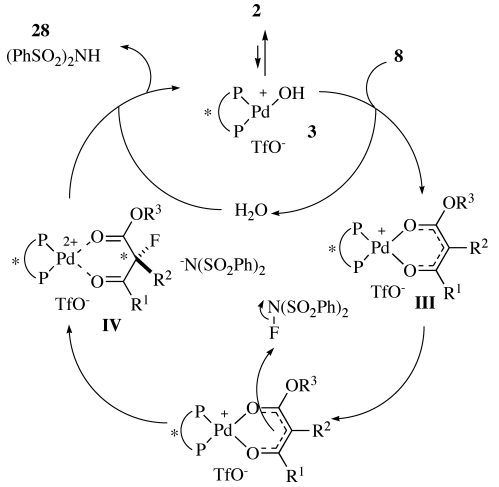
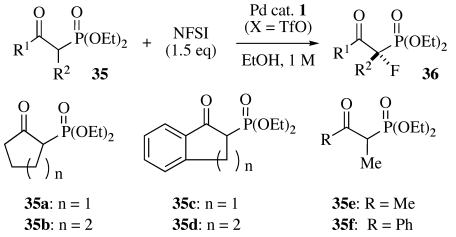


Chart 14. Proposed Catalytic Cycle

Table 7. Catalytic Enantioselective Fluorination of β-Ketophosphonates



Entry	35	Catalyst (mol%)	Temp. (°C)	Time (h)	Yield (%)	Ee (%)
1	**35a**	**1d** (1)	rt	12	82	95
2	**35b**	**1d** (5)	rt	8	93	96
3	**35c**	**1d** (5)	rt	3	84	95
4	**35d**	**1d** (5)	rt	3	97	94[a]
5	**35d**	**1d** (5)	0	24	90	97
6	**35d**	**1d** (1)	rt	7	83	95
7	**35e**	**1f** (10)	40	48	57	94[b]
8	**35f**	**1f** (10)	40	48	38	95

a) Absolute configuration determined by X-ray analysis. *b*) The ee was determined after conversion.

Next, we turned our attention to other active methine compounds. We expected that other bidentate carbonyl compounds could undergo catalytic asymmetric fluorination reactions as well. Among several candidates, we focused on β-ketophosphonates, because difluoro- and monofluorophosphonates have been utilized in drug design as mimics of phosphates.[55] Compared with non-fluorinated phosphonates and difluorophosphonates, α-monofluorophosphonates are expected to be a better surrogate of phosphates, because they show similar 2nd pK_a values (*ca.* 6.5) to those of biological phosphates (*ca.* 6.5).[55] Before we started our research, there had been no example of catalytic asymmetric fluorination of β-ketophosphonates.

As in the case of β-ketoesters, optimization of the reaction conditions revealed that the combination of **1d** and ethanol as solvent was the most appropriate for reactions of β-ketophosphonates. This catalytic system was effective for various substrates, which were fluorinated in a highly enantioselective manner (more than 94% ee) (Table 7). In striking contrast to

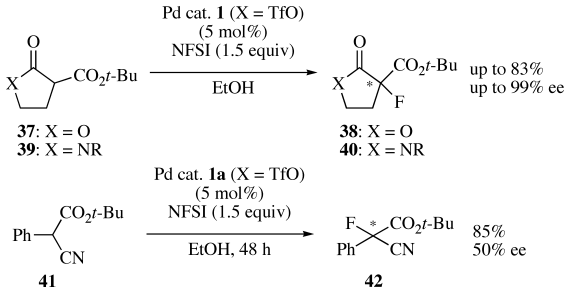


Chart 15. Enantioselective Fluorination of Related Compounds

cyclic substrates (entries 1—6), the reactions of acyclic substrates were slow (entries 7, 8), but excellent level of the ees was maintained. For these reactions, **1f** gave a slightly better selectivity than **1d**. The absolute configuration of the products was determined by X-ray analysis after the conversion, which can be understood by assuming participation of the palladium enolates similar to those of β-ketoesters.

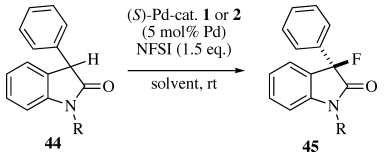
Recent study within this context has revealed that other active methine compounds activated by esters or amides also underwent the fluorination reaction (Chart 15). Compound **37** reacted with NFSI under standard conditions, affording the desired product **38** in good yield with 98% ee. On the other hand, addition of a base was necessary for efficient conversion of the lactam **39**. Thus the desired product **40**, which is a possible precursor of fluorinated cyclic amine derivatives, was obtained in good yield with 99% ee. Details of this study will be reported elsewhere soon.[56] Additionally, the reaction of cyanoacetate **41** was promoted by the Pd complex **1a**, albeit with modest enantioselectivity.

3.3. Catalytic Enantioselective Fluorination of Oxindole Derivatives[57] As described above, our palladium enolate chemistry was found an efficient tool for catalytic asymmetric fluorination reactions. In most cases, however, available substrates were restricted to 1,3-dicarbonyl compounds. As a part of our research progress, we succeeded in developing a highly efficient catalytic asymmetric fluorination reaction of oxindole derivatives for the first time.

BMS 204352 (MaxiPost™) **43** (see Chart 16) developed by Bristol-Myers Squibb is a promising agent for the treatment of stroke, and is now undergoing phase III clinical trial.[58] It was reported that replacement of a hydroxyl group at the 3-position of the oxindole ring by a fluorine atom played a key role in enhancing its pharmaceutical efficacy. Because the oxindole ring is widely found among natural products, its optically active fluorinated derivatives could have many applications in the field of medicinal chemistry.

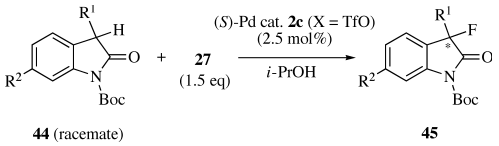
Initially, we examined the reaction of the 3-phenyl-substituted oxindole **44a** using (*S*)-DM-BINAP as a chiral ligand based on our previous results (Table 8). Unfortunately, however, the reaction with NFSI was sluggish, and the product **45a** was obtained with negligible asymmetric induction (entry 1). Expecting more effective formation of a configurationally stable palladium enolate, we protected the nitrogen moiety of **44a** with an electron-withdrawing group. Among the protecting groups tested, a *t*-butoxycarbonyl (Boc) group was best, and reaction of **44b** in THF afforded the desired product **45b** in 53% yield with 81% ee (entry 2). In accordance with our previous results,[43,44] polar solvents such as 2-propanol (IPA) and acetone gave better selectivity (entries 3, 4). However, due to the acidic nature of **1**, removal of the Boc group of **44b** was a significant side reaction, resulting in unsatisfactory chemical yield. This problem was overcome by using the less acidic Pd complex (*S*)-**2d**, and **45b** was isolated in 90% yield without any loss of enantioselectivity (88% ee) (entry 5).

Table 8. Optimization of Reaction Conditions



Entry	Pd-cat.	44	Solvent	Time (h)	Yield (%)	Ee (%)
1	**1d**	**44a** (R=H)	THF	60	20	5
2	**1d**	**44b** (R=Boc)	THF	12	53	81
3	**1d**	**44b**	IPA	3	66	88
4	**1d**	**44b**	Acetone	3	58	89
5	**2d**	**44b**	IPA	5	90	88

Table 9. Catalytic Enantioselective Fluorination of Various Oxindoles



Entry	44	R^1/R^2	Temp. (°C)	Time (h)	Yield (%)	Ee (%)
1	**44b**	Ph/H	0	18	96	90
2	**44c**	*p*-MeC_6H_4/H	rt	3	97	86
3	**44c**	*p*-MeC_6H_4/H	0	18	92	88
4	**44d**	*p*-FC_6H_4/H	rt	3	94	84
5[a]	**44e**	*o*-$MeOC_6H_4/CF_3$	rt	3	80	75
6	**44f**	Me/H	rt	5	86	95
7	**44f**	Me/H	0	18	85	96
8	**44g**	Et/H	rt	10	85	92
9	**44h**	$CH_2C(O)CH_3$/H	rt	2	85	86
10	**44i**	Bn/H	rt	4	72	80
11	**44j**	*i*-Bu/H	rt	2	85	75

a) Acetone was used as solvent.

Under the optimized reaction conditions, various oxindoles were fluorinated in a highly enantioselective manner. The results are summarized in Table 9. Regardless of the electronic nature of the substituents on the aromatic rings, other aryl-substituted oxindoles **44b**—**e** were also good substrates (entries 1—5). In addition, the reaction of alkyl-substituted substrates **44f**—**j** proceeded well in good yield with high to excellent enantioselectivities (75—96% ee) (entries 6—11). Notably, since our reaction conditions are mild, the compound **45h** was obtained in good yield, although it tended to undergo β-elimination of the fluorine atom.

With these results in hand, we applied our reaction to the catalytic asymmetric synthesis of **43** (Chart 16).[59,60] In spite of possible steric interaction caused by the methoxy group at the ortho position, the *N*-Boc-protected BMS compound **46** was fluorinated smoothly to give the product **47** in 90% yield

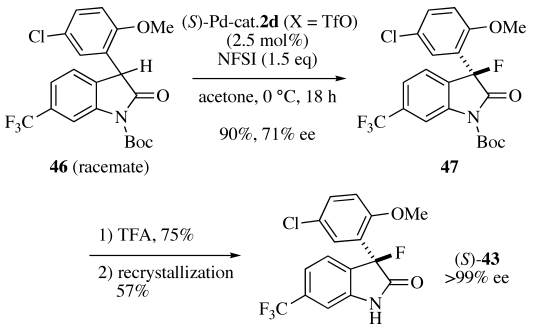


Chart 16. Catalytic Asymmetric Synthesis of (*S*)-BMS-204352

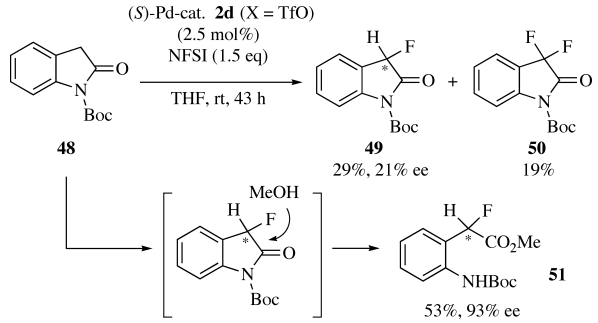


Chart 17. Catalytic Enantioselective Monofluorination of **48**

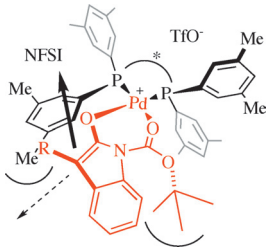


Fig. 4. Putative Pd Enolate

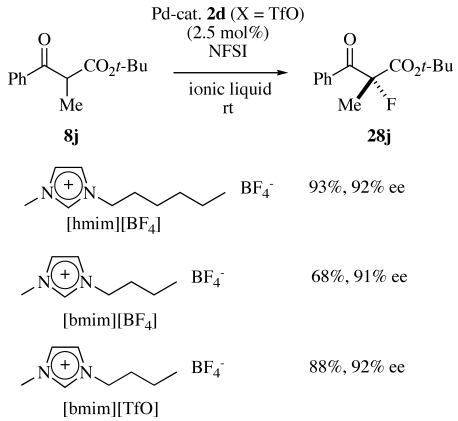


Chart 18. Catalytic Asymmetric Fluorination in Ionic Liquids

with 71% ee. Deprotection with TFA, followed by single recrytstallization, furnished optically pure **43** (>99% ee).

In addition to the absolute configuration of **43**, that of **44b** was unambiguously determined by X-ray structural analysis after conversion. Although we could not observe a key intermediate by spectroscopic analysis, we are convinced that the sense of enantioselection observed in this reaction is due to a putative chiral Pd enolate (Fig. 4).

In contrast to the fluorination to construct chiral quaternary carbon centers, the catalytic asymmetric synthesis of a tertiary stereogenic carbon center having a fluorine atom is still a formidable challenge. This observation prompted us to attempt enantioselective monofluorination of **48** (Chart 17).[57] Unfortunately, however, the reaction in THF afforded the product **49** in 29% yield with low enantioselectivity (21% ee), together with the difluorinated compound **50** (19% yield). It was likely that fluorination occurred enantioselectively, but considerable racemization decreased the ee value. We envisaged that solvolysis of **49** with MeOH before racemization might be possible, allowing for synthesis of **51** with high optical purity. As we hoped, when the reaction was carried out in the mixture of dichloroethane–MeOH (1 : 1), the monofluorinated ester **51** was obtained with an excellent enantioselectivity of 93%, albeit in 53% yield due to competitive solvolysis of **48**. Importantly, in our reaction asymmetric monofluorination of the ester was achieved, although indirectly, which has no precedent in the literature.

In the last few years, catalytic enantioselective fluorination has witnessed great progress, and the scope of available substrates for asymmetric fluorination is rapidly expanding.[61—64] However, continuing exploitation of novel catalysts, including metal complexes and organic catalysts, is necessary to meet the need for various chiral fluorinated compounds, many of which are expected to find applications in the fields of medicinal chemistry, chemical biology, and material sciences.

4. Immobilization and Reuse of the Pd Complexes Using Ionic Liquids[65]

While we could use environmentally friendly solvents, such as EtOH and water, recovery of the Pd complexes from the reaction mixtures was not easy. Therefore we decided to examine immobilization and reuse of the Pd complexes.[66] We envisaged that our catalysts might be immobilized in ionic liquid 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.[67]

Enantioselective fluorinations of the β-ketoester **8j** in several ionic liquids were examined (Chart 18). Gratifyingly, fluorination proceeded smoothly. After completion of the reaction, the desired product **28j** and co-product benzenesulfonimide were separated by simple extraction with ether. The ionic liquid [hmim] [BF_4] readily formed a bilayer with ether, and **28j** was isolated with comparable results to those obtained in EtOH. Judging from the yellow color of the ionic liquid, the Pd catalyst was retained in the ionic liquid phase.

Next, reuse of the catalyst immobilized in [hmim] [BF_4] was examined (Table 10). The catalyst was recycled no less than 10 times. A slight decrease of reaction rate was finally observed in the 10th reaction cycle. However, prolonged reaction time (84 h) allowed completion of the reaction in the 11th run. To our knowledge, this is the first time that catalytic asymmetric fluorination has been performed repeatedly in an ionic liquid. In addition, this method was also applicable to the catalytic asymmetric Michael reaction, and the catalyst in [bmim] [TfO] could be recycled 5 times. Our asym-

metric reactions in ionic liquids have been demonstrated practical from both an economical and an environmental point of view.

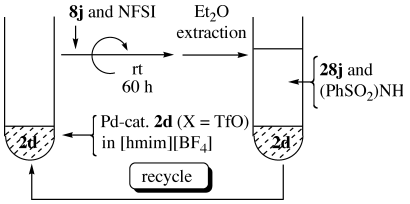
As described above, we developed highly enantioselective catalytic reactions, highlighting the versatility of the chiral palladium enolates. Finally, we would like to describe an interesting example where acid-base catalysis of the Pd complexes was the key to success, thereby the reactivity of the free amine was properly controlled to solve problems found in aza-Michael reaction catalyzed by Lewis acids.

5. Catalytic Asymmetric Conjugate Addition of Various Amines and Asymmetric Protonation[68)]

Catalytic asymmetric conjugate addition of nitrogen nucleophiles is a useful reaction because the products are recognized as key compounds for the synthesis of not only chiral natural and unnatural β-amino acids.[69)] Excellent enantioselectivity was achieved in several examples using hydroxylamine, azide, or carbamates as nitrogen source. In contrast, reaction with aromatic and aliphatic amines is still difficult, and only minor enantioselectivity was observed.[70)] Indeed, the reaction using the chiral Pd-aqua complex **1** as a Lewis acid to activate alkenoyl oxazolidinones gave negligible asymmetric induction (*ca.* 2% ee) in the case of amines such as anisidine and benzylamine. We speculated that this phenomenon was due to deactivation of Lewis acid catalysts by coordination of amines and spontaneous reaction of highly nucleophilic amines (Chart 19). Thus on the basis of our finding that the cationic Pd complexes **1** and **2** work well in the presence of a Brønsted acid, we envisaged that the use of a proton to block the lone pair of amines might be effective to suppress such unfavorable side reactions. For this purpose, it is necessary to generate appropriate amounts of nucleophilic free amine from the salt in the reaction mixture. Considering a role of the Pd complex as a base, we hypothesized that the reaction of **2** with the salt would generate a Lewis acidic Pd complex **1′** and adequately regulate generation of free amine, thus avoiding unfavorable side reactions.

We carried out the reaction of **52a** with **53a** in THF using 1 mol% of **2a** (Table 11, entry 1). The reaction proceeded smoothly to give the desired product **54aa** in 92% yield after 12 h. To our delight, the ee of **54aa** was as high as 98%, which is in striking contrast to the reaction using anisidine itself (2% ee). As summarized in Table 11, this method was applicable to other substrates. The reaction with simple aniline or electron-deficient CF_3-substituted aniline (**53b**, **c**) proceeded in a highly enantioselective manner (entries 2, 3). Other Michael acceptors bearing ethyl and benzyloxymethyl

Table 10. 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.

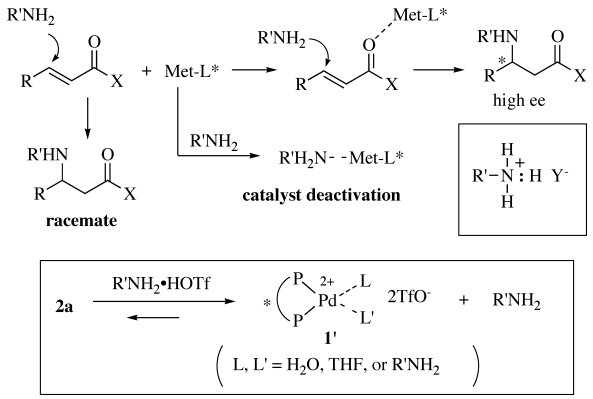
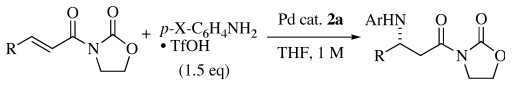


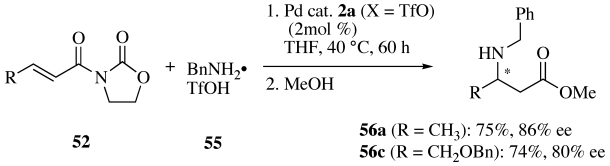
Chart 19. Our Idea to Suppress Undesired Pathways

Table 11. Catalytic Asymmetric Conjugate Addition of Amines



Entry	R	X	Cat. (mol%)	Temp. (°C)	Time (h)	Yield (%)	Ee (%)
1	Me (**52a**)	MeO (**53a**)	1	20	12	92	98
2[a)]	**52a**	H (**53b**)	1	20	36	83	96
3[b)]	**52a**	CF_3 (**53c**)	2	40	24	77	97
4	Et (**52b**)	**53a**	2	40	24	80	94
5	**52b**	**53b**	2	40	24	98	95
6[c)]	**52b**	**53c**	4	20	72	49	85
7	$BnOCH_2$ (**52c**)	**53a**	2	20	6	98	97
8	**52c**	**53b**	2	20	12	76	96
9[c)]	**52c**	**53c**	4	20	16	98	94
10	**52a**	**53a**	0.2	20	16	98	96

a) The absolute configuration was determined to be *S* after conversion of the product to the known carboxylic acid. *b*) THF/toluene=1/2. *c*) **53c** (1 eq. to Pd) was added.



52 55

Chart 20. Reaction with Benzylamine

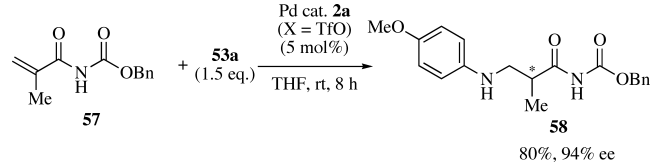


Chart 22. Catalytic Asymmetric Protonation in aza-Michael Reaction

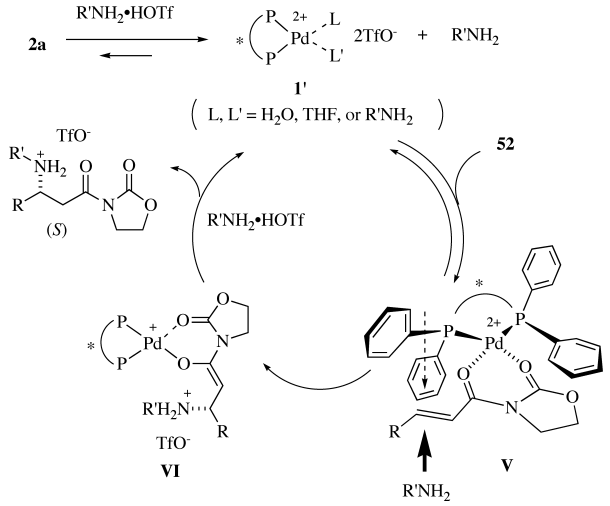


Chart 21. Proposed Catalytic Cycle

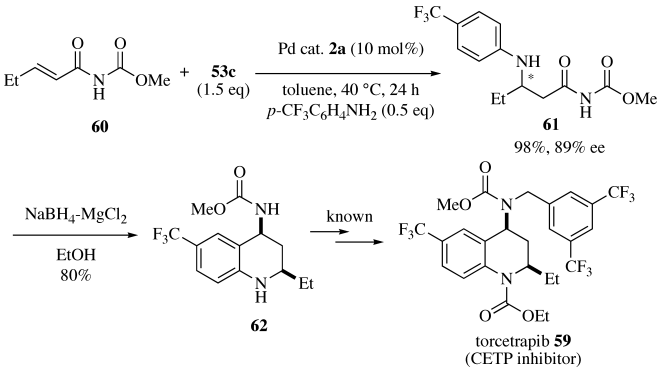


Chart 23. Formal Asymmetric Synthesis of Torcetrapib

groups were also good substrates, affording the corresponding amines in good yield with excellent enantioselectivity (entries 4—9). In entry 10, the catalyst amount was reduced to 0.2 mol%, and comparable results were obtained. Furthermore, primary and secondary alkyl amines could be employed in our reaction. For example, benzylamine reacted with **52a** in the presence of 2 mol% of the Pd complex **2a** in THF (40 °C, 60 h) (Chart 20). The desired adduct was isolated as a Me ester in good yield with high enantioselectivity. In these reactions, no double addition product was formed. Since the catalytic reaction with alkyl amines is still an unsolved problem,[70] the considerable potential of this reaction system is indicated by these examples.

On the basis of NMR experiments, we propose that the following catalytic cycle is operative (Chart 21). First, the reaction of **2a** with excess salt affords the monomeric Pd complex **1′**, which activates **52** in a bidentate fashion (V). Then, the concomitantly formed free amine attacks the double bond as shown in Chart 21. Subsequent protonation of the resulting Pd enolate (VI) followed by dissociation of the product as the salt completes the catalytic cycle. In this step, protonation of the product might prevent product inhibition. The observed absolute stereochemistry of the product was in accord with the working model.

In this catalytic cycle, it was expected that protonation of the intermediate VI should occur stereoselectively. To examine this hypothesis, we next examined enantioselective protonation in the conjugate addition of amines (Chart 22).[71] Thus the methacrylate derivative **57** was treated with **53a** in the presence of the Pd complex **2a** (5 mol%). The reaction was completed after 8 h, and the desired β-amino acid derivative **58** with a newly formed chirality at the α-position was isolated in 80% yield. As we expected, the ee of the product was 94%.[68] It is noteworthy that the small proton approached the transient Pd enolate with high enantioselectivity. Further studies revealed that various α-alkyl- and α-aryl-substituted acrylate derivatives underwent enantioselective protonation (up to 98% ee).[72]

Finally, to confirm the utility of our aza-Michael reaction, we examined the formal asymmetric synthesis of torcetrapib **59**, an important inhibitor of the cholesteryl ester transfer protein (CETP).[73] As shown in Chart 23, methyl pentenoylcarbamate **60** was subjected to reaction with **53c** under the optimized conditions, affording the adduct **61** in 98% yield with 89% ee. This compound was converted to the tetrahydroquinoline derivative **62** by reductive cyclization, which is a known intermediate.[74]

6. Conclusion

In this article, we describe our efforts to develop novel catalytic asymmetric reactions using cationic Pd complexes. In addition to the conventional roles of the Pd(0) and Pd(II) complexes, our research revealed that the complexes **1** and **2** can act as highly versatile acid-base catalysts applicable to various reactions. We demonstrated that the Pd complexes reacted with active methylene and methine compounds to form chiral palladium enolates directly. These enolates were generated under non-basic conditions, and their reactions could be performed without any particular precautions to air and moisture. In carbon–carbon bond-forming reactions, we found that the palladium enolates acted cooperatively with a strong protic acid, which is distinct from basic conditions. Such palladium enolates were also extremely useful for fluorination reactions of various substrates. Additionally, combined use of the Pd complex **2** and amine salts was highly effective for catalytic aza-Michael reaction. To confirm the synthetic utility of our reactions, we demonstrated not only conversion of the products to fundamental units but also the asymmetric synthesis of two drug candidates. We believe that the unique reactivity of the cationic Pd complexes would be a

guide for future studies, and that harmonization of our present work with the soft character of Pd will lead to the development of various novel transformations.

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