Pure Appl. Chem., Vol. 78, No. 2, pp. 477–494, 2006.
doi:10.1351/pac200678020477

Acid–base catalysis using chiral palladium complexes*

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Abstract: Chiral Pd aqua and μ-hydroxo complexes were found to act as mild Brønsted acids and bases, and chiral Pd enolates were generated from these complexes even under acidic conditions. Highly enantioselective Michael addition, Mannich-type reaction, fluorination, and conjugate addition of amines have been developed based on the acid–base character of these Pd complexes.

Keywords: Brønsted acid; fluorination; Mannich reaction; Michael addition; palladium enolate; Brønsted base.

INTRODUCTION

Chiral Pd complexes are excellent catalysts for a variety of enantioselective reactions, such as cross-coupling, Heck reaction, and allylation [1]. These reactions involve unit processes, such as oxidative addition, reductive elimination, insertion, β-hydride elimination, and transmetallation, which are typical of transition-metal complexes. In these reactions, change of oxidation state between Pd(0) and Pd(II) plays a key role. Normally, these reactions are carried out under a nitrogen or an argon atmosphere, because Pd(0) complexes are rather unstable to oxidation. Chiral Lewis acids are also powerful catalysts for various enantioselective reactions [2], but classical Lewis acids such as B, Al, and Ti complexes often require anhydrous conditions and a nonpolar solvent due to their susceptibility to water and highly coordinating solvents. Recently, cationic chiral transition-metal complexes have attracted increasing attention as air- and water-stable Lewis acids. Many highly enantioselective reactions are catalyzed by chiral transition-metal complexes [2,3]. In these reactions, an electrophile activated by a chiral Lewis acid reacts with a mild nucleophile, such as silyl enol ether.

In the mid-1990s, we found that the chiral Pd aqua complexes **1** and μ-hydroxo complexes **2** (Fig. 1) were excellent catalysts for enantioselective aldol [4] and Mannich-type reactions [5] using silyl enol ethers (Scheme 1). The overall transformation seemed similar to simple Lewis acid catalysis, but mechanistic study clearly indicated that the reactions proceed in a different way. Namely, chiral Pd enolate was efficiently generated by transmetallation from the silyl enol ether, and this Pd enolate reacted with aldehyde or imine to afford the highly optically active product (Scheme 2). Since no Pd enolate formation was observed from the corresponding anhydrous complexes, nucleophilic attack of the hydroxyl group of the monomeric Pd hydroxo complex **3**, which can be generated either by deprotonation of the aqua complex **1** or by simple dissociation of the binuclear complex **2**, on the silicon atom would

Pure Appl. Chem.* **78, 197–523. An issue of reviews and research papers based on lectures presented at the 13th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS-13), Geneva, Switzerland, 17–21 July 2005.
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be the key to this transmetallation. Based on this background, we became interested in the hydroxyl group of the Pd complex as a Brønsted base. Although the Brønsted basicity of the Pd–OH group has not been thoroughly evaluated in synthetic organic chemistry, we expected that this group would react with carbonyl compounds to give chiral enolates directly if the Lewis acidity of the cationic Pd atom and Brønsted basicity of the hydroxyl group could cooperatively activate the carbonyl compound. Such enolates are expected to react with various electrophiles under mild and nonbasic conditions; thus, reactions that are difficult under conventional basic conditions should become feasible.

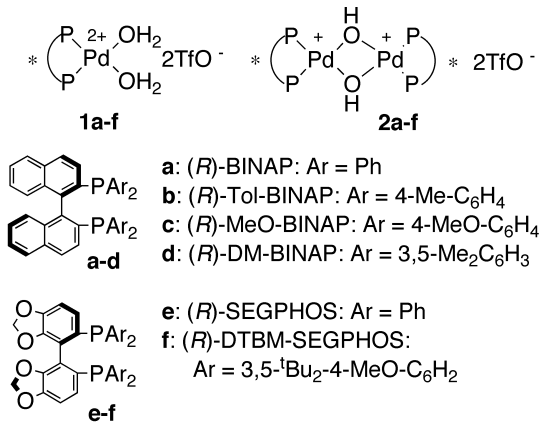
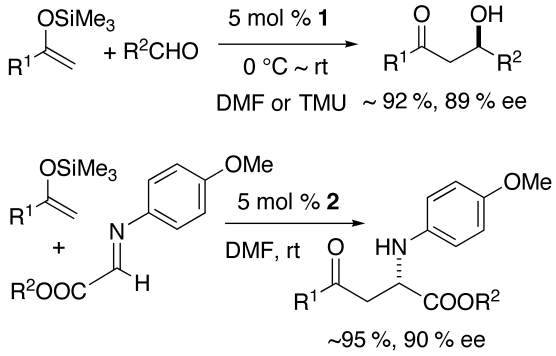
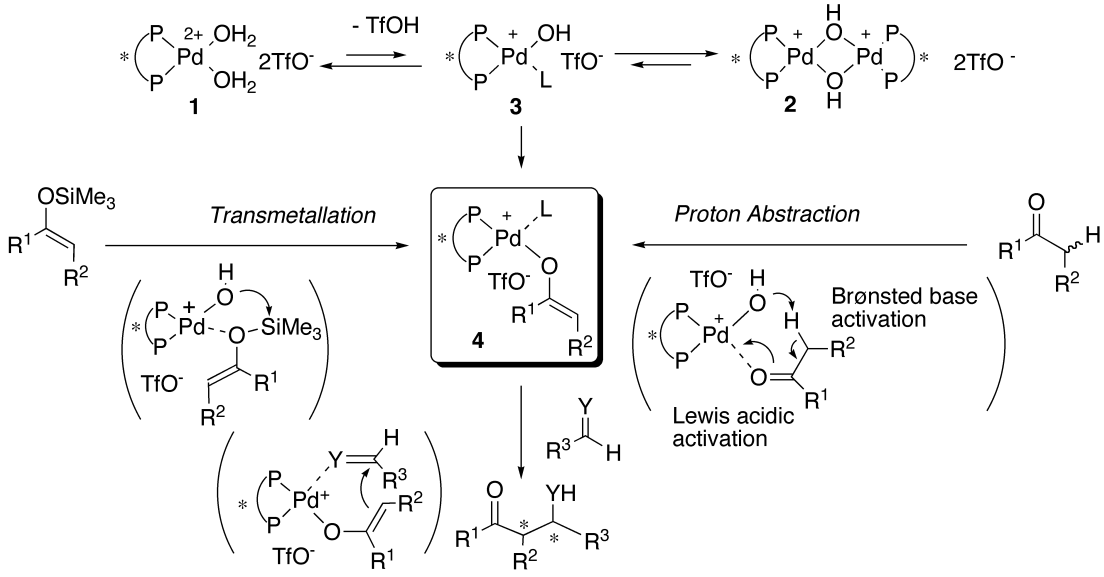


Fig. 1 Chiral Pd complexes developed in our laboratory.



Scheme 1 Aldol and Mannich-type reactions catalyzed by chiral Pd complexes.



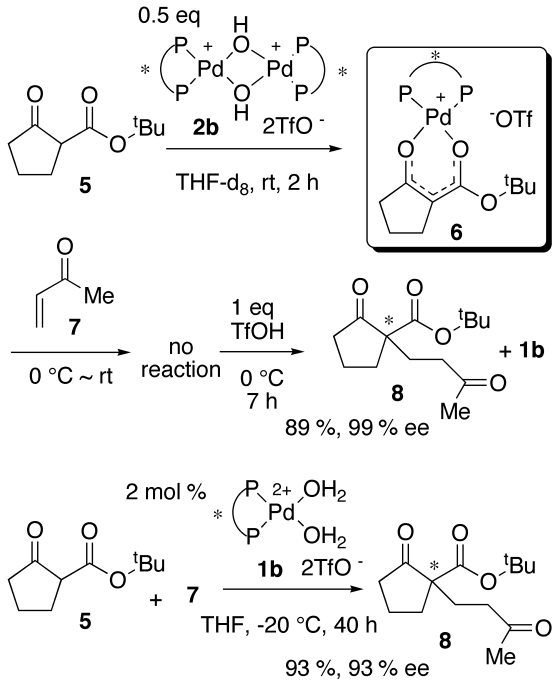
Scheme 2 Pd enolate as a key intermediate for the enantioselective reactions.

CATALYTIC ENANTIOSELECTIVE MICHAEL REACTION

A catalytic asymmetric Michael reaction of active methylene compounds is a powerful and reliable method for the synthesis of chiral tertiary carbon centers [6]. However, the number of efficient general methods for the construction of quaternary carbon centers is limited [7], and development of an efficient catalyst, which is applicable to various types of 1,3-dicarbonyl compounds and Michael acceptors, would be extremely useful. Therefore, as a first step to examine the above-mentioned hypothesis, we chose the Michael reaction as a model reaction.

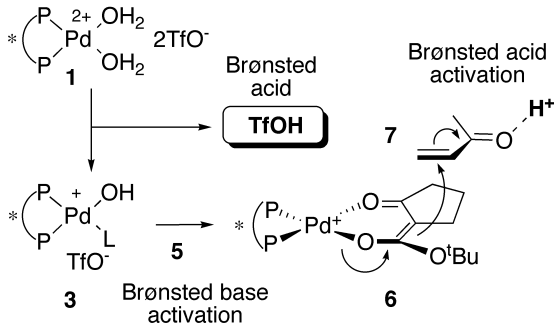
Michael reaction of β-keto esters

To establish whether the Pd hydroxo complex **2** can act as a Brønsted base, we first carried out ^{1}H NMR experiments. Clean formation of the Pd enolate **6** was observed when the β-keto ester **5** was treated with 0.5 equiv of the μ-hydroxo complex **2b** in THF-d_8 for 2 h (Scheme 3). Next, 2 equiv of methyl vinyl ketone **7** was added to this mixture, to examine the reactivity of **6**. Unfortunately, the reaction did not proceed, probably because of high stability of the square-planar Pd enolate complex. Interestingly, however, the addition of 1 equiv of TfOH was found to promote the reaction. The Michael product **8** was obtained in 89 % isolated yield (7 h, 0 °C) and the enantioselectivity was determined to be 99 % ee. After completion of the reaction, formation of the aqua complex **1b** was detected by means of the ^{1}H NMR. This result suggests that the aqua complex **1b** acts as a catalyst. Next, we tried the reaction using 2 mol % of **1b**, and we were pleased to find that the reaction of **5** with **7** proceeded smoothly to give **8** in 93 % yield with high enantioselectivity (93 % ee) [8]. Reaction of **5** also proceeded smoothly in various solvents, such as ethanol, acetone, and dichloromethane, to give **8** in excellent chemical and optical yields. It is noteworthy that comparable results were obtained even in water.



Scheme 3 NMR experiments on formation of the Pd enolate of β-keto ester and catalyic enantioselective Michael addition.

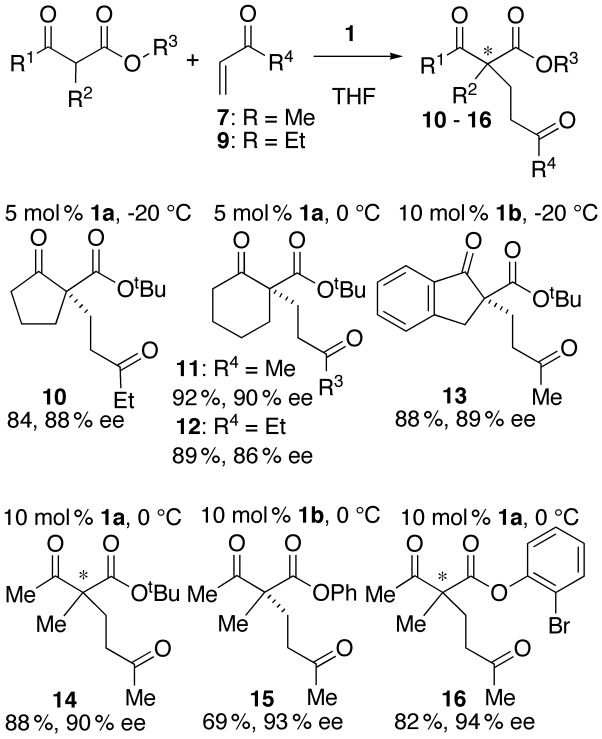
These results support our hypothesis that the hydroxo ligand on Pd can abstract an acidic α-proton of the substrate to form the stable Pd enolate complex **6**. Although the electrophilicity of **7** was not sufficient for reaction with **6**, TfOH favorably activated the enone **7** instead of protonating **6** (Scheme 4). It is interesting that the strong protic acid and inherently basic Pd enolate seem to act cooperatively to promote the C–C bond-forming reaction.



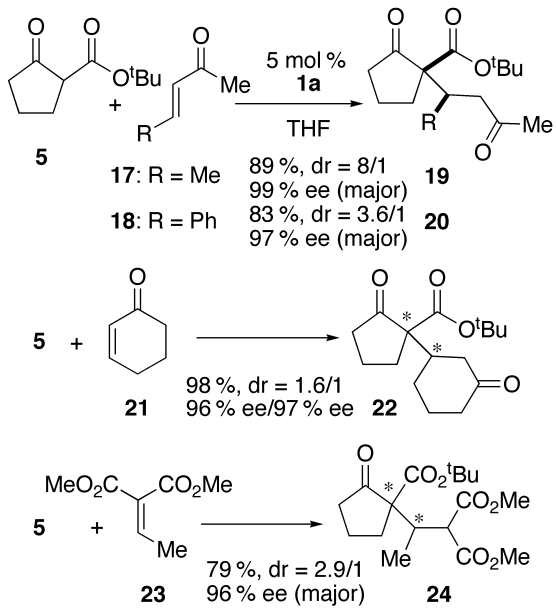
Scheme 4 Cooperative activation of nucleophile and electrophile by Brønsted base and acid.

Under the optimized conditions, the reactions of various substrates including a five- or six-membered ring substrate, an indanone derivative, and acyclic substrates with methyl vinyl ketone **7** or ethyl vinyl ketone afforded highly optically active products **10~16** (up to 94 % ee) (Scheme 5). For the high asymmetric induction, a bulky ester group, such as a *t*-butyl or an aryl group, was required. Furthermore, the reaction with less-reactive β-substituted enones proceeded smoothly (Scheme 6). The

reactions of **5** with 3-penten-2-one **17** and benzylideneacetone **18** afforded the Michael adducts **19** and **20** in good yields with moderate to good diastereoselectivities, and the ee's of the major products were found to be 99 and 97 %, respectively. In the case of the cyclic enone **21**, diastereoselectivity was low, but the enantioselectivity of both diastereomers was excellent (96~97 % ee). In addition, dimethyl ethylidenemalonate **23** reacted smoothly to give the corresponding adduct **24** with 96 % ee (79 %, dr = 2.9/1). In these reactions, catalytic asymmetric construction of highly crowded vicinal tertiary and quaternary carbon centers was achieved in a single step [8].



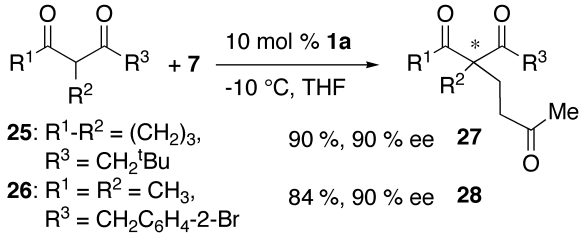
Scheme 5 Catalyic enantioselective Michael addition of various β-keto esters.



Scheme 6 Catalyic diastereo- and enantioselective Michael reactions.

Michael reaction of 1,3-diketones

Compared with β-keto esters, 1,3-diketones have rarely been used as Michael donors, probably due to the instability of the 1,3-diketones and their Michael adducts under basic conditions [9]. In fact, no Michael adduct between the 1,3-diketone **26** and **7** was obtained under common basic conditions (triethylamine, DBU, *t*-BuOK, or tetrabutylammonium hydroxide). In contrast, our reaction conditions were found to be effective for such compounds (Scheme 7). In the presence of 10 mol % of **1a**, the reactions of **25** and **26** with **7** proceeded well to give the desired triketones **27** and **28** with high enantioselectivity (90 % ee) in high chemical yields [8].

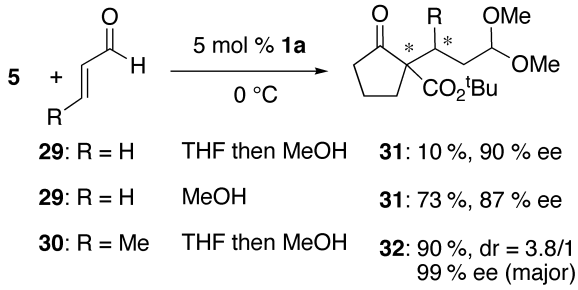


Scheme 7 Catalyic enantioselective Michael addition of 1,3-diketones.

Michael reaction with α,β-unsaturated aldehydes

α,β-Unsaturated aldehydes are also difficult substrates for Michael reaction under basic conditions, because of their instability [10]. Therefore, we next planned to examine the use of acrolein **29** (Scheme 8). Reaction of **5** with **29** in THF gave a complex mixture; however, reaction in MeOH at 0 °C afforded the desired Michael adduct as dimethyl acetal **31** in 73 % yield with 87 % ee. Furthermore, when crotonaldehyde **30** was used as a substrate, the reaction proceeded without difficulty even in THF, and subse-

quent addition of MeOH afforded the dimethyl acetal **32** in 90 % yield. Although diastereoselectivity was moderate, the ee of the major product was as high as 99 % [8].



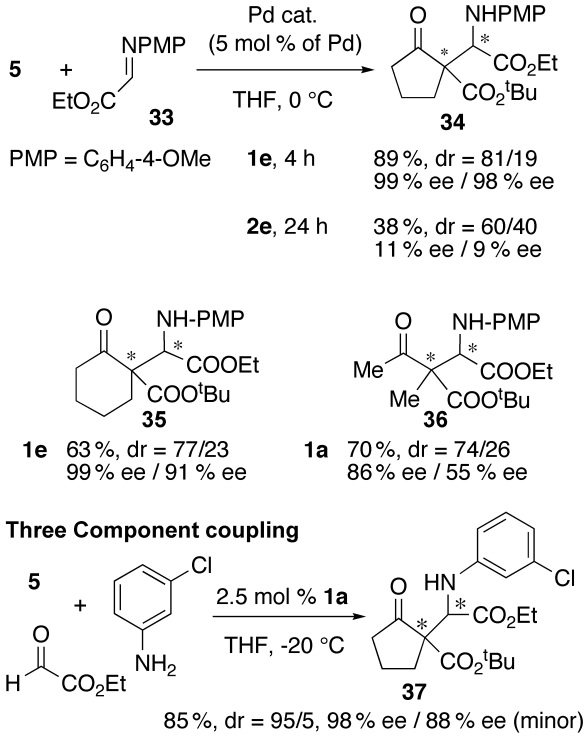
Scheme 8 Enantioselective Michael addition to α,β-unsaturated aldehydes.

CATALYTIC ENANTIOSELECTIVE MANNICH REACTION

The above-mentioned study on the Michael reaction indicated that activation of enones by protic acid smoothly promoted the reaction. Previously, we found that the reactivity of imines is greatly enhanced by protonation, which caused formation of racemic products in the Mannich-type reactions of silyl enol ether using the aqua complex **1** [5]. Thus, we anticipated that the above-mentioned Pd enolate chemistry would be applicable to the Mannich reaction. To our knowledge, there has been only one reported example of the use of β-keto esters in a catalytic asymmetric Mannich-type reaction [11,12].

Mannich reaction with imino acetate esters

Initially, the reaction of the β-keto ester **5** with the *N*-*p*-methoxyphenyl (PMP)-protected imino ester **33** was examined [13]. Using 5 mol % of **1e**, reaction in THF proceeded smoothly to afford **34** in 89 % yield. The diastereomer ratio was 81:19 and the ee's of both diastereomers were 98 %. In contrast, the reaction of **5** with **33** using the Pd complex **2e**, in which no protic acid was produced during the generation of the Pd enolate **6**, resulted in only 38 % isolated yield after 24 h, and very low asymmetric induction was observed for both diastereomers (Scheme 9). These results are in accord with our initial hypothesis, strongly supporting the idea that cooperative activation of imines by the protic acid is essential for this reaction.

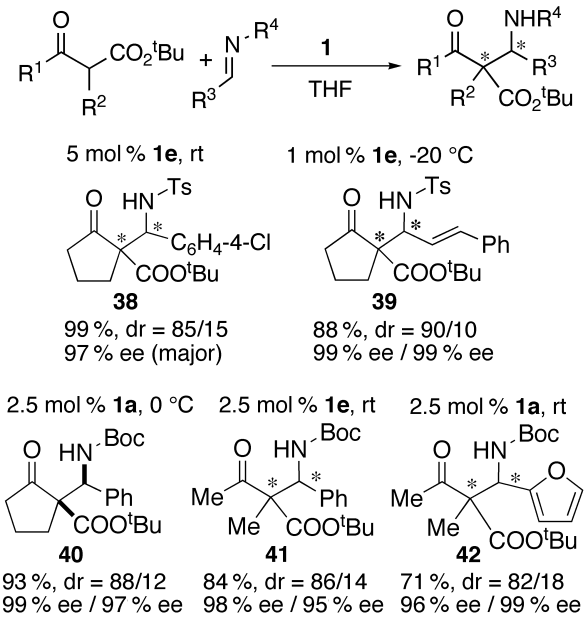


Scheme 9 Enantioselective Mannich reaction with imino esters.

This system was applicable to other nucleophiles, and six-membered cyclic and acyclic Mannich adducts such as **35** and **36** were obtained in good yield with high enantioselectivity. Moreover, a three-component reaction also proceeded without problem. Indeed, in the presence of 2.5 mol % of **1a**, the mixture of ethyl glyoxylate, *m*-chloroaniline, and **5** in THF gave rise to the corresponding Mannich adduct **37** in good yield. The diastereoselectivity was found to be 95/5, and excellent enantioselectivity was observed (major: 98 % ee, minor: 88 % ee).

Mannich reaction with imines derived from aryl and alkenyl aldehydes

Encouraged by this success, we next turned our attention to the use of other imines derived from aryl or alkenyl aldehydes. We examined the reaction with *N*-Ts- or *N*-Boc-protected imines in order to extend the synthetic utility of this reaction. The reactions in THF using the Pd aqua complexes **1** afforded various Mannich adducts **38~42** in good diastereo- and excellent enantioselectivities (Scheme 10) [13].



Scheme 10 Enantioselective Mannich reaction with various imines.

CATALYTIC ENANTIOSELECTIVE FLUORINATION

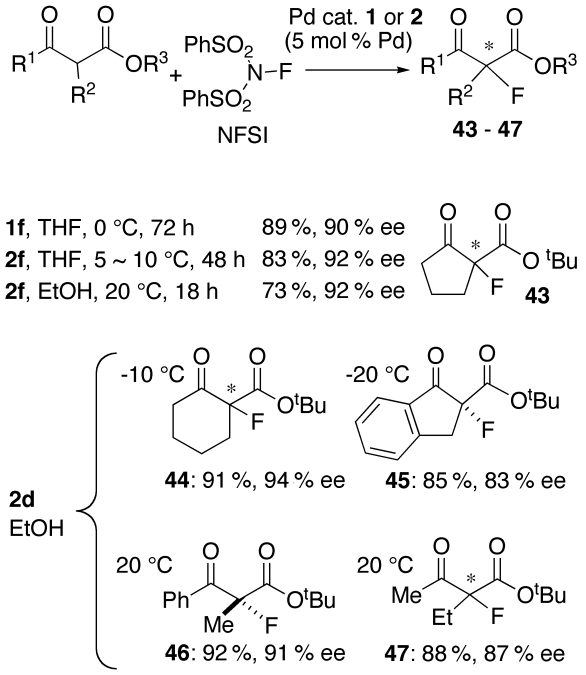
Fluoroorganic molecules have attracted much attention because they often show different characters from their parent compounds due to the unique properties of the carbon–fluorine bond. For this reason, an efficient method for direct enantioselective construction of fluorinated stereogenic carbon centers is extremely important [14]. So far, most approaches have relied on the use of a stoichiometric amount of chiral fluorinating reagent [15] or chiral starting material [14]. As for catalytic enantioselective reactions, only two examples using β-keto esters as substrates were known before our first report in 2002 [16,17]. Optically active α-substituted α-fluoro-β-keto esters are especially attractive because they are regarded as nonenolizable β-keto esters, and 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-keto esters [18].

Fluorination of β-keto esters

First, we tested several electrophilic fluorination reagents using the β-keto ester **5** and found that *N*-fluorobenzenesulfonimide (NFSI) was the most effective. The reaction of **5** with NFSI catalyzed by (*R*)-DTBM-SEGPHOS complexes **1f** proceeded smoothly, and the desired product was isolated in 89 % yield with 90 % ee (Scheme 11). In contrast to the Michael reaction, the use of the Pd μ-hydroxo complex **2f** 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 alcoholic solvents such as EtOH and ^{i}PrOH [18].

As summarized in Scheme 11, various substrates were smoothly fluorinated in a highly enantioselective manner using 2.5 mol % of the catalyst **2d**. 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 precautions to exclude moisture or air are necessary. Furthermore, fluorination in ionic liquid ([hmin][BF_4]) at room temperature also proceeded smoothly to give the product **46** in good yield with

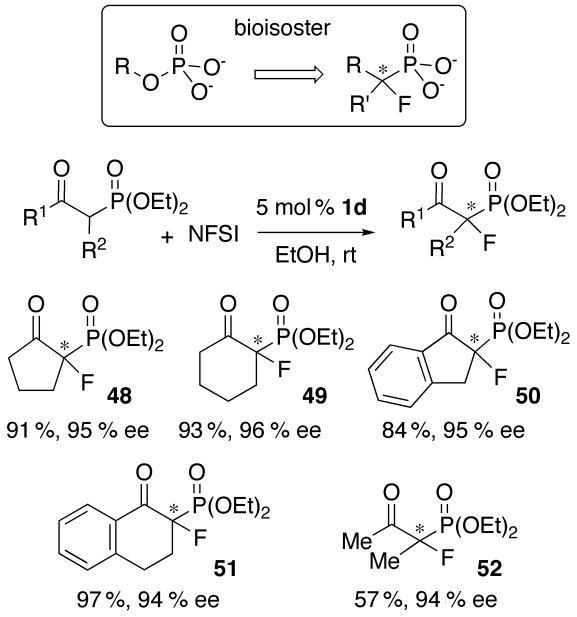
excellent enantioselectivity, comparable with that obtained in EtOH. Efficient recovery and reuse of the catalyst were achieved. After completion of the reaction, the product **46** and the co-product, benzenesulfonimide, were separated by simple extraction with ether. The Pd catalyst was retained in the ionic liquid phase. The catalyst could be recycled at least 9 times, maintaining excellent enantioselectivity (91 % ee) [19]. These optically active fluorinated β-keto esters were converted to β-hydroxy or β-amino acid derivatives, which are fundamental units in various natural and synthetic compounds.



Scheme 11 Catalyic enantioselective fluorination of β-keto esters.

Fluorination of β-keto phosphonates

With the success of enantioselective fluorination of β-keto esters in hand, we next focused on the fluorination of β-keto phosphonates, because fluorophosphonates have been intensively investigated in drug design as mimics of phosphates [20]. As we expected, the reactions of various β-keto phosphonates proceeded to give **48~52** in a highly enantioselective manner (Scheme 12) [21].

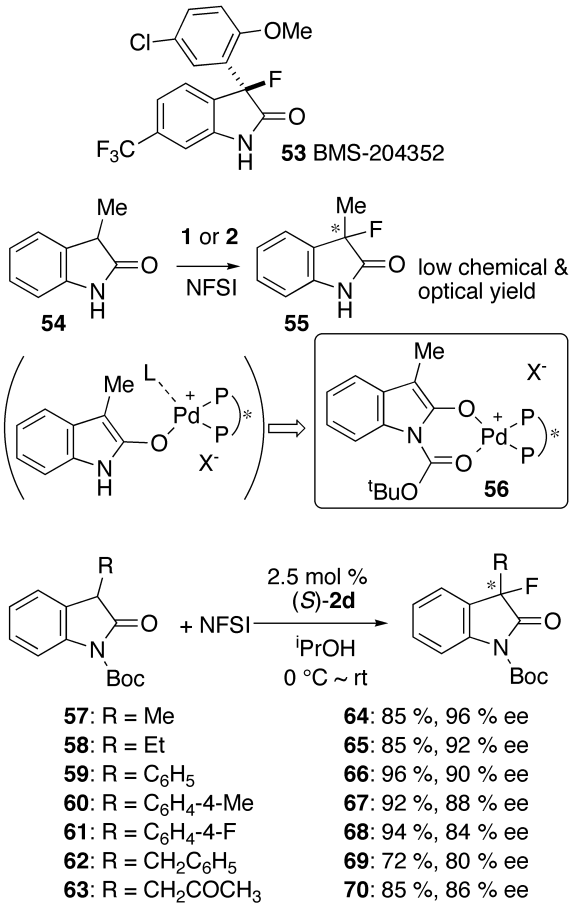


Scheme 12 Catalyic enantioselective fluorination of β-keto phosphonate.

Fluorination of oxindoles

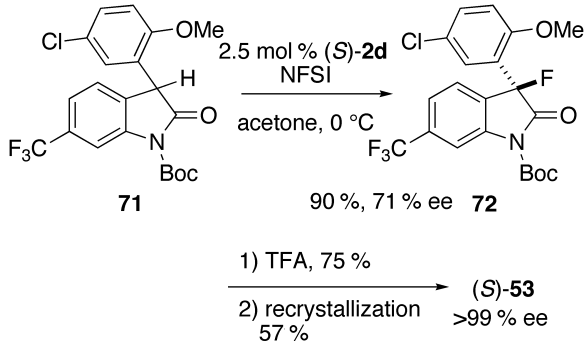
BMS 204352 (MaxiPost™) **53**, developed by Bristol-Myers Squibb, is a promising agent for the treatment of stroke, and is undergoing phase III clinical trial [22]. It was reported that replacement of a hydroxyl group at the 3-position of the oxindole ring with a fluorine atom played a key role in enhancing the 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. Thus, we next tried the catalytic enantioselective fluorination of oxindoles using chiral Pd complexes **1** and **2** [23].

Initially, we examined the reaction of the oxindole **54**; however, the reaction was sluggish, and low asymmetric induction was observed (Scheme 13). Thus, we planned to protect the nitrogen moiety of **54** with a *t*-butoxycarbonyl (Boc) group, expecting that the *N*-Boc-protected oxindoles **57** would be activated effectively to form a configurationally stable Pd enolate **56**. Gratifyingly, the reaction of **57** using 5 mol % of **2d** in 2-propanol (IPA) proceeded smoothly to give the desired product **64** with 96 % ee in 85 % yield. Various other 3-fluoro-3-alkyl- or aryl-substituted oxindole derivatives **65**~**70** were also obtained in a highly enantioselective manner.



Scheme 13 Catalyic enantioselective fluorination of oxindole derivatives.

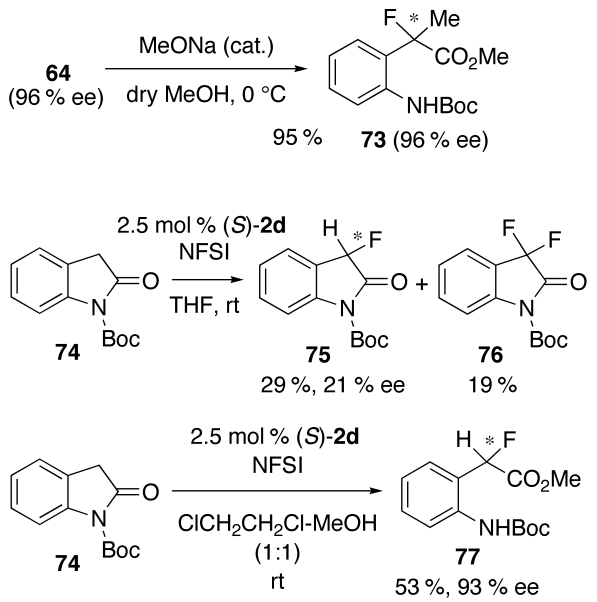
With these results in hand, we applied our reaction to the catalytic asymmetric synthesis of **53** (Scheme 14). Compound **71** was subjected to the fluorination reaction, and the desired product **72** was isolated in 90 % yield with 71 % ee. After treatment with TFA, recrystallization furnished optically pure (*S*)-**53** (>99 % ee).



Scheme 14 Catalyic asymmetric synthesis of BMS 204352.

As shown in Scheme 15, the optically active α-fluoro-α-arylacetate **73** was readily obtained by treatment with MeONa in MeOH. In view of the versatility of the amine moiety for further functionalization, this procedure should be useful for the synthesis of various α-fluorophenylacetate derivatives.

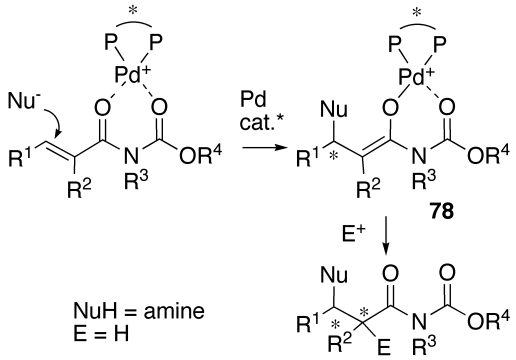
We next decided to try the more challenging enantioselective mono-fluorination of the unsubstituted *N*-Boc-oxindole [23]. Since the fluorinated product **75** would be more susceptible to enolization than **74**, racemization of the product was considered unavoidable. Indeed, an attempt at obtaining **74** using THF as a solvent was unsuccessful. The optical purity of the desired product was low, and a significant amount of undesired di-fluoro product **76** was produced. In the light of the above-mentioned ring-opening reaction of the product, we envisaged that solvolysis of **75** with alcohol before racemization would be possible. After examining several solvents, we found that the use of a halogenated solvent mixed with MeOH (1:1) afforded the monofluorinated product **77** with an excellent enantioselectivity of 93 % in reasonable yield. Although competitive solvolysis of **74** should be suppressed to increase the chemical yield, catalytic asymmetric monofluorination, which is considered to be difficult under basic conditions, was achieved at a synthetically useful level.



Scheme 15 Selective ring-opening reaction and catalyic enantioselective mono-fluorination of oxindole derivative.

CATALYTIC ENANTIOSELECTIVE CONJUGATE ADDITION OF AMINES

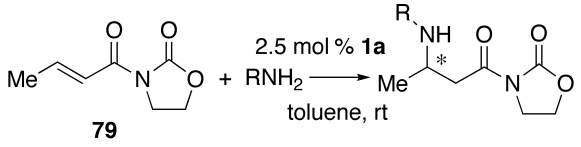
Success of the highly enantioselective fluorination of the oxindole derivatives indicates that approach of the electrophile to the bidentate Pd enolate **56**, which has no carbonyl group at the β-position, occurred in a highly controlled manner. This fact suggested that similar types of Pd enolate **78** should be generated by the conjugate addition of a nucleophile to an α,β-unsaturated imide-type compound activated with the cationic Pd complex, and the Pd enolate **78** could react with an electrophile in a highly enantioselective manner (Scheme 16) . This idea was very attractive because a variety of optically active molecules should be efficiently obtainable using this chemistry, if it works. As the first step to explore this challenging goal, we decided to examine enantioselective conjugate addition of amine to α,β-unsaturated carbonyl compounds because optically active β-amino acid derivatives are a versatile resource for the synthesis of biologically active compounds [24].



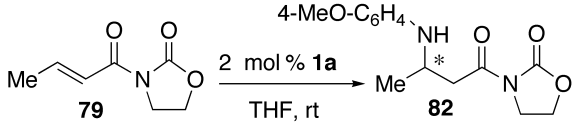
Scheme 16 Generation of Pd enolate by the addition of nucleophile.

Problem with the enantioselective conjugated addition catalyzed by Lewis acid

The reactions of **79** with several aromatic amines or benzylamine were first carried out using 2.5 mol % of Pd aqua complex **1a**. As shown in Scheme 17, high asymmetric induction was observed for the reactions with aniline or aromatic amine bearing an electron-withdrawing group, but, unfortunately, negligible asymmetric induction was observed for the reaction with highly nucleophilic anisidine or benzylamine. Indeed, these results were similar to the results reported previously by other researchers [25]. Based on this reaction, we anticipate that the cationic Pd aqua complex should act as a Lewis acid, and high asymmetric induction should be achieved if nucleophilic attack of the amine occurs on the α,β-unsaturated carbonyl compound coordinated with the cationic chiral Pd complex. However, obviously highly nucleophilic amines can react with **79** without activation by the cationic Pd complex to afford the racemic product. In addition, the basic character of amines often causes deactivation of Lewis acid catalysts by coordination to the metal center. To obtain highly optically active adducts of nucleophilic amines, this basic problem has to be solved.



R = 4-CF_3-C_6H_4	**80**: 75 %, 83 % ee
R = C_6H_5	**81**: 65 %, 72 % ee
R = 4-MeO-C_6H_4	**82**: 82 %, 2 % ee
R = $C_6H_5CH_2$	**83**: 53 %, 0 % ee



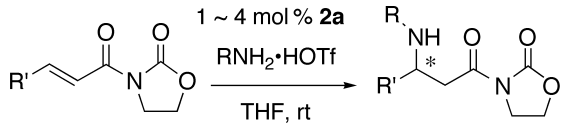
4-MeO-$C_6H_4NH_2$	35 %, 2 % ee
4-MeO-$C_6H_4NH_2$ + TfOH (1: 0.8)	99 %, 12 % ee
4-MeO-$C_6H_4NH_2$•HOTf (salt)	25 %, 88 % ee

Scheme 17 Catalyic enantioselective conjugate addition of amines catalyzed by **1a**.

Control of nucleophilicity of the amine by salt formation

On the basis of our finding that the cationic Pd complexes **1** and **2** work well under acidic conditions [6], we planned to use a protic acid to modulate the nucleophilicity of the amine by blocking its lone pair. Reaction of **79** with anisidine using 2 mol % of Pd aqua complex **1a** was sluggish, and the ee of the product **82** was only 2 %. Addition of triflic acid increased the chemical yield, but the improvement of the ee of the product was insufficient. Finally, the enantioselectivity was greatly improved to 88 % by using the isolated salt. In this case, however, the reaction proceeded slowly (25 % after 24 h), probably because the concentration of the free amine was too low (Scheme 17). These results suggest that strictly controlled release of the free amine would be necessary to achieve high chemical and optical yields simultaneously. To solve this difficult problem, we turned our attention to the Brønsted base character of the Pd complex **2**. By using a catalytic amount of the complex **2a** and the triflic acid salt, exactly equal amounts of the free amine and the catalytically active dicationic Pd complex are expected to be generated in the reaction mixture, thus avoiding unfavorable side reactions. As shown in Scheme 18, the reaction of **79** with anisidine was carried out in THF using 1 mol % of **2a**. Gratifyingly, the reaction proceeded smoothly, and the desired product was obtained in 92 % yield and 98 % ee [26].

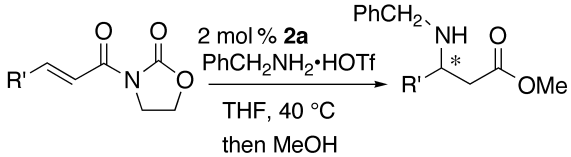
This method was also applicable to the synthesis of other optically active β-amino acid derivatives, as depicted in Scheme 18 [26]. The reaction with simple aniline derivatives gave the Michael adducts **80**~**87** with excellent enantioselectivity (Scheme 18). It is noteworthy that the reaction with benzylamine also proceeded without difficulty. Although the benzylamine adducts such as **83** were unstable, **88** and **89** were isolated in good chemical and optical yields after methanol treatment.



R = 4-MeO-C_6H_4, R' = Me — **82**: 92 %, 98 % ee
R = 4-CF_3-C_6H_4, R' = Me — **80**: 77 %, 97 % ee
R = C_6H_5, R' = Me — **81**: 90 %, 98 % ee

R = 4-MeO-C_6H_4, R' = Et — **84**: 80 %, 94 % ee
R = C_6H_5, R' = Et — **85**: 98 %, 95 % ee

R = 4-MeO-C_6H_4, R' = $PhCH_2OCH_2$ — **86**: 98 %, 97 % ee
R = C_6H_5, R' = $PhCH_2OCH_2$ — **87**: 76 %, 96 % ee

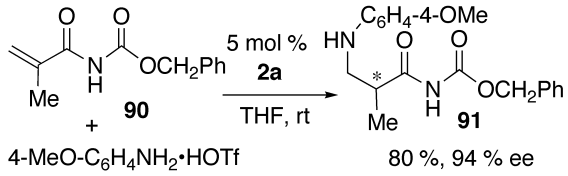


R' = Me — **88**: 75 %, 86 % ee
R' = $PhCH_2OCH_2$ — **89**: 74 %, 80 % ee

Scheme 18 Catalyic enantioselective conjugate addition of amines catalyzed by **2a**.

Conjugate addition-enantioselective protonation reaction

In the reactions described above, a new chiral center was generated at the β-position of the substrate. When compound **90** having a substituent at the α-position was used as the substrate for the conjugate addition reaction, highly enantioselective protonation was observed to give the product **91** (94 % ee) in 80 % yield [26] (Scheme 19).



Scheme 19 Catalyic enantioselective protonation in the conjugate addition of anisidine.

CONCLUSION

We have described highly efficient enantioselective reactions including Michael reaction, Mannich reaction, fluorination, and conjugate addition of amines, catalyzed by the two types of chiral Pd complexes **1** and **2**. In these reactions, the acid–base characters of the Pd aqua complexes **1** and the binuclear Pd μ-hydroxo complexes **2** are important, and the stable chiral Pd enolates play a key role. It is anticipated that this Pd enolate chemistry can be extended to various other electrophiles.

ACKNOWLEDGMENTS

We would like to express our appreciation to all our coworkers, whose names are cited in the references, for their contribution. The work was partly supported by the Precursory Research for Embryonic Science and Technology (PRESTO) project of Japan Science and Technology Agency (JST), as well as Grants-in-Aid from Japan Society for the Promotion of Science (JSPS), and the Ministry of Education, Culture, Sports, Science and Technology (MEXT). We also thank Takasago International Corporation for their generous support.

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