Contribution

Development of Novel Catalytic Asymmetric Reactions using Cationic Group-10 Metal Complexes: With a Special Focus on Reactions in which Palladium Enolate Plays a Key Role

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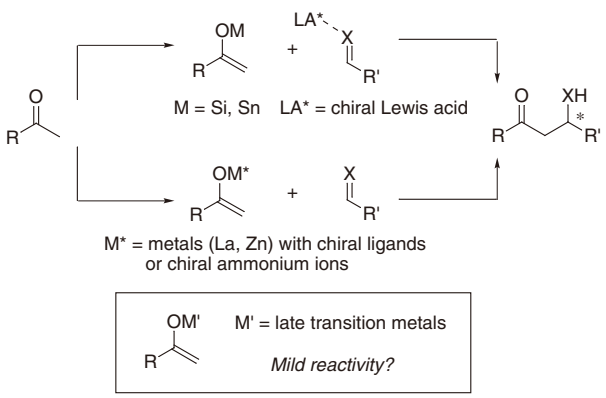
1. Introduction

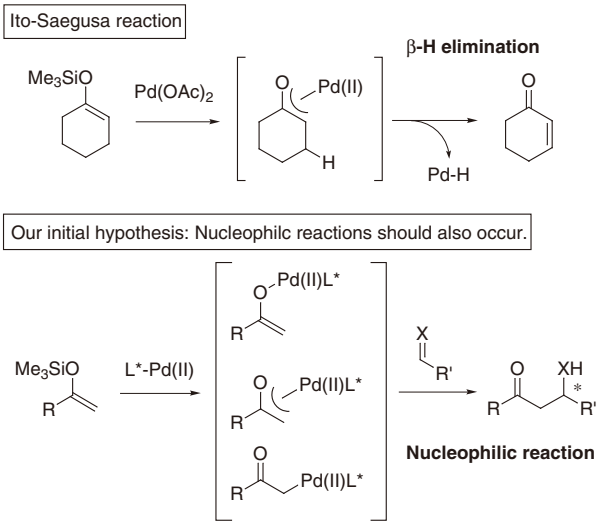
Metal enolates of carbonyl compounds are highly versatile nucleophilic reagents that can be used in reactions with various electrophilic agents. They are regarded as essential synthetic intermediates in organic chemistry.[1] Conventionally, two main approaches have been directed to develop asymmetric catalysis employing enolates as nucleophilic agents. One way is to prepare Si or Sn enolates prior to the reaction followed by activation of the electrophilic agent with a chiral Lewis acid catalyst (B, Al, Ti, Cu, etc.) to promote the reaction. Another approach utilizes chiral base catalysts to produce chiral enolates (La, Zn, Ca, R_4N^+) directly from ketones. The latter approach features high atom efficiency, and as with organocatalysis, dramatic advances have been made in this area in recent years.[2]

We have pursued another path, focusing on the use of late transition metal enolates, especially palladium. The electronegativity of late transition metals being significantly greater than that of the alkali metals in conventional enolates; the extent of enolate polarization in the former case is expected to be smaller. Therefore, late transition metal enolates should display moderate reactivity and hence might not require the low temperatures and anhydrous conditions required for reactions involving enolates of typical metals (Li, Mg, B, Al, etc.) and early transition metals (Ti, Zr, etc.). As a consequence, the use of these unconventional Pd-enolates triggered our research interest.



Scheme 1. Representative approaches to achieve enantioselective reactions with enolates.

In the Ito-Saegusa reaction, the enone is synthesized by β-hydride elimination from the Pd enolate generated from silyl enolate.[3] It is known that the Pd enolate species can also induce coupling and insertion reactions to multiple bonds, similar to the alkyl palladium species. The focus of our interest therefore became the reactivity of the Pd enolate generated as a chemical intermediate. By proper tuning of the ligands and reaction conditions, we believed that the enolates should exhibit sufficient nucleophilicity to promote the aldol reaction with aldehydes under mild reaction conditions. At the time, little was known regarding the reactivity of Pd enolates as nucleophiles, the only information available being a report by Tsuji's group on the intramolecular aldol and Michael reactions of Pd enolates generated from allyl β-ketoester by decarboxylation.[4] We were greatly encouraged by this pioneering study and launched our research endeavors on Pd enolates with an objective of developing novel asymmetric reactions.



Scheme 2. Our original hypothesis.

In this review, we will describe the characteristic reactivity of several cationic transition metal complexes developed during the course of our research and introduce the various types of asymmetric reactions. Studies from other research groups reporting excellent results in this area, both before and after

the issue of our own reports, are beyond this article. We would however refer our readers to the respective articles for additional useful information on these studies.

2. Preparation Methods of Chiral Complexes

The optically active, cationic group-10 metal complexes used in the present work are illustrated in Figure 1 (**1-6**). As shown in Scheme 3, the Pd-aqua complex **1** can be efficiently synthesized by an anion-exchange reaction between the Pd chloride complex having BINAP derivatives as ligands and a silver salt in the presence of water. Furthermore, the Pd μ-hydroxo complex **2** can be synthesized by treating the acidic aqua complex with an equivalent of a base. The resulting complex is a stable solid ranging in color from yellow to orange depending on the coordinating ligand and can be handled in air without any special precautions.

Nickel and platinum complexes can also be synthesized by following an almost identical procedure, and the complexes obtained in such cases are also solid, with a blackish-purple color for nickel (Ni) and pale yellow for platinum (Pt). Complexes **3-6** on the other hand were prepared under anhydrous conditions and stored in an inert atmosphere.

3. Synthesis of Palladium Enolate via Transmetalation and Asymmetric Catalysis

After considering the various conditions based on the aforementioned hypothesis, we found that the asymmetric aldol reaction indeed progressed smoothly between silyl enolate **8** and aldehyde **9** when Pd-aqua complex **1** was used.[7] The characteristic feature of this reaction is that it proceeds smoothly in polar solvents such as DMF and tetramethylurea (TMU), however the reaction was extremely slow under anhydrous conditions. These observations are in sharp contrast to the common Lewis acid–catalyzed asymmetric Mukaiyama aldol reaction.[2] A detailed investigation of the above reaction mechanism revealed that water (or PdOH produced from **1**) acted as a nucleophile on the silyl group, as shown in Scheme 4, and chiral Pd enolates (**I**) were generated as the key chemical intermediates through transmetallation. While the final product is identical to the Lewis acid–catalyzed Mukaiyama aldol reaction, the reaction mechanism is entirely different. Furthermore, no enone synthesis occurred, even in

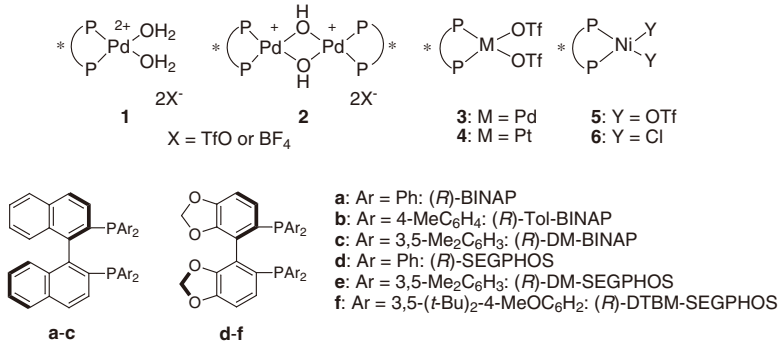
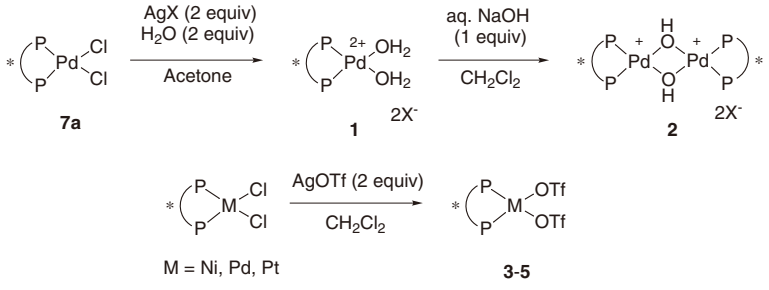
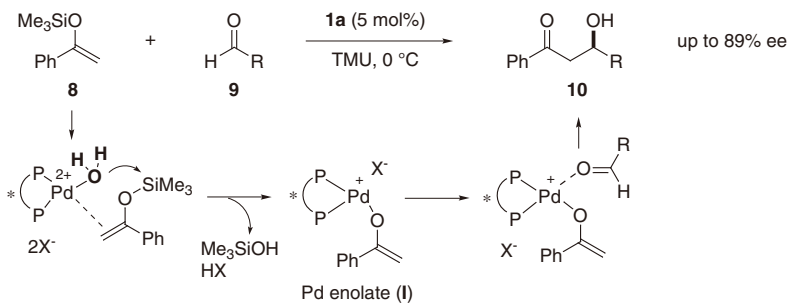


Figure 1. Chiral group 10 metal complexes used in our work.



Scheme 3. Preparation of chiral metal complexes.



Scheme 4. Catalytic asymmetric aldol reaction via chiral Pd enolates.

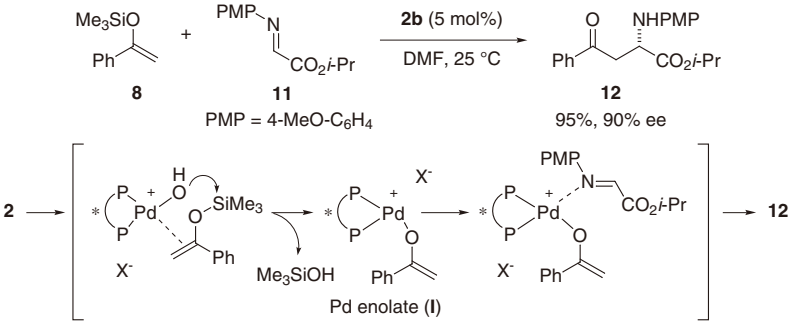
a substrate possessing β-hydrogen, and the aldol adducts were obtained in fair yields. This has been attributed to the fact that Pd enolates having bidentate chiral ligands such as BINAP tend to exist mainly as *O*-enolates. Additionally, it should be noted that an aldol reaction of Pd enolates was preferred over protonation, even though water and a protic acid (HX) generated via transmetallation were present in the reaction system. This unique feature has not been observed in other metal enolates exhibiting strongly basic properties and suggests the further potential of chiral Pd enolates.

Given the above findings, we began our research targeting the development of a noble unexplored catalytic asymmetric Mannich-type reaction by using our chiral Pd enolate chemistry.[8] While the reaction with imine **11** in the presence of aqua complex **1** proceeded smoothly, the product was almost racemic. Based on control experiments, we found that the protic acid generated from complex **1** activates the imine, thereby accelerating a racemic uncatalyzed reaction. Thus, we focused on developing such a catalyst that would generate the Pd enolates without producing protic acid. The Pd-μ-hydroxo complex **2** was found to be a catalyst of choice. As shown in Scheme 5, the mononuclear Pd-OH complex formed by the dissociation of **2** promotes transmetallation to form the chiral Pd enolates. As a result, we succeeded in developing the asymmetric Mannich-type reaction to obtain target product with high enantioselectivity.[6,9]

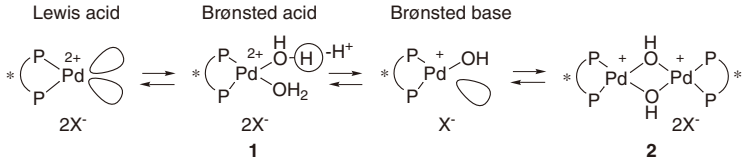
4. Cationic Pd Complexes as Acid-Base Catalysts

At the active site of carbonate dehydratase, zinc ions are known to change the acidity of water through coordination and to produce a hydroxide ion. Various phenomena observed during the process of our research suggested that the synthesized cationic Pd complexes would follow the relationship represented in Scheme 6. The cationic Pd complex not only functions as a Lewis acid but as a Brønsted acid as well due to the increased acidity of the coordinated water. Subsequent deprotonation would generate a Pd-OH mononuclear complex and its dimer μ-hydroxo complex. We believe these act not only as a nucleophile promoting the aforementioned transmetallation, but also, though weak, as Brønsted bases. Moreover since all of the complexes are considered to exist in equilibrium, we anticipated that complexes **1** and **2** would function as acid-base catalysts.

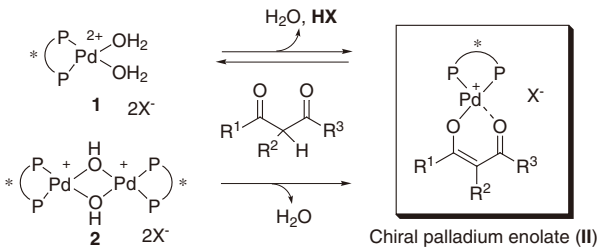
Following the above hypothesis, we found that the complexes **1** and **2** do indeed act as acid-base catalysts. When these are reacted with 1,3-dicarbonyl compounds such as β-diketone or β-ketoester, chiral Pd enolates (**II**) are produced directly upon deprotonation, as shown in Scheme 7. Although highly acidic compounds had been used in this case, we were intrigued by the fact that these enolate syntheses occurred under non-basic conditions and that a strong protic acid was generated simultaneously. This metal enolate under acidic condition indicates a novel reactivity distinct from enolates under conventional basic conditions.[5b]



Scheme 5. Catalytic asymmetric Mannich-type reaction via chiral Pd enolates.



Scheme 6. Chiral Pd complexes as acid-base catalysts.



Scheme 7. Formation of chiral Pd enolates of 1,3-dicarbonyl compounds.

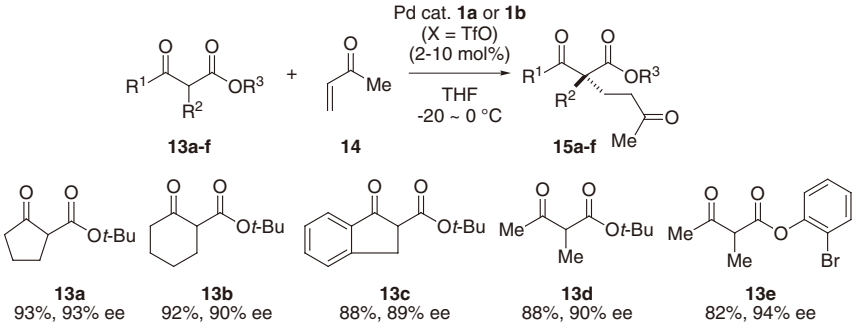
5. Catalytic Asymmetric Michael Addition

Pd enolates (**II**) have been shown to react with various electrophilic reagents. First, we studied the Michael addition with enones. While reactions in which chirality is induced on the enone side have been extensively investigated, the number of those in which chiral center is created on the side of the nucleophile with broad generality is still limited.[10] Our reaction catalyzed by the aqua complex **1** is one example among them. Reactions of various β-ketoesters and methyl vinyl ketone proceeded smoothly to give the Michael adducts having a chiral quaternary center in a highly enantioselective manner (Scheme 8).[11]

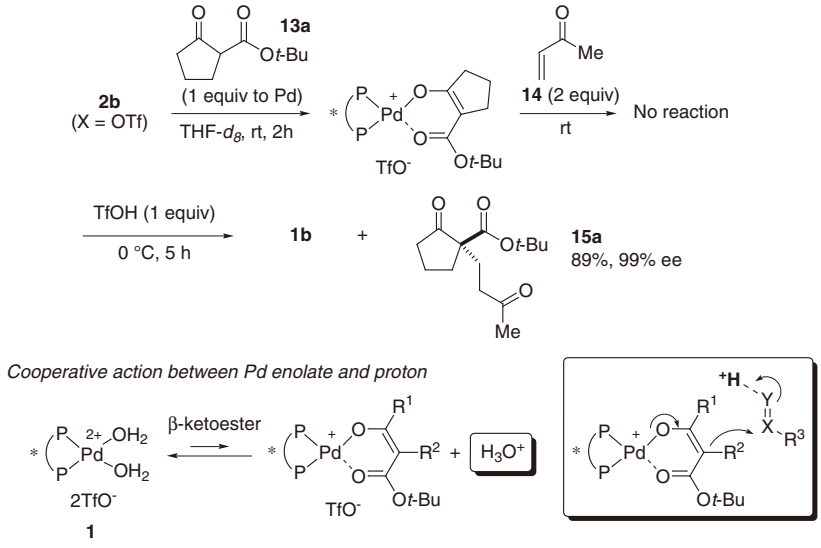
Mechanistic studies of this Michael reaction revealed the unique feature of the Pd enolate (Scheme 9). The reactivity of the Pd enolate prepared from β-ketoester **13a** and the complex **2** was not sufficient, and reaction with 2 equivalents of methyl vinyl ketone at room temperature did not proceed at all. However, when 1 equivalent of trifluoromethanesulfonic acid (TfOH) was added, the reaction occurred smoothly, giving the desired Michael adduct **15a** in 89% yield with 99% ee. In this reaction, the formation of the aqua complex **1b** was confirmed by NMR experiments. These results, together with those of Scheme 8, imply that while the nucleophilicity of the bidentate Pd enolates generated from the complex **2** is insufficient to react with enones, the reaction can occur thanks to the activation of enone by protic acid generated simultaneously from the aqua complex. In other words, a unique cooperative action of Pd enolates and a protic acid is operative in our reaction.

Because of the low reactivity of β-substituted enones, reported examples of catalytic asymmetric Michael addition with β-ketoesters with such enones are limited. However, in our cooperative activation system, β-substituted enones having methyl or phenyl groups as β-substituents could be used without problem. As shown in Scheme 10, for example, the reaction proceeded smoothly using 5 mol% of the aqua complex **1a**, affording a Michael adduct **17** with vicinal chiral quaternary and tertiary carbon centers with an extremely high enantioselectivity of 99% and satisfactory diastereoselectivity.

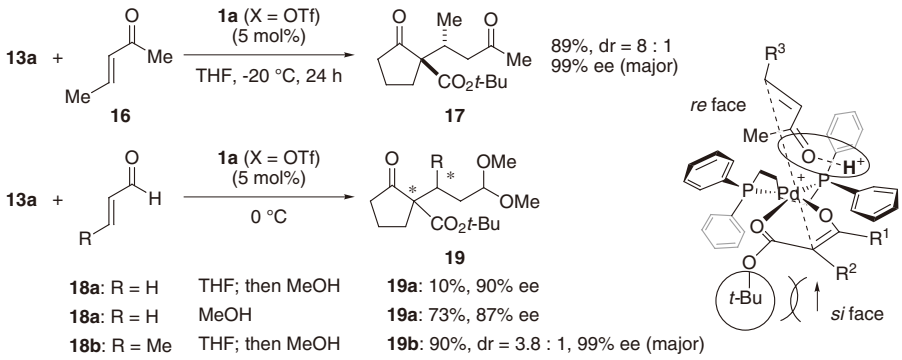
Furthermore, by taking advantage of the fact that the Pd catalyst is functional even in alcohols, we could carry out the reaction with the extremely unstable acrolein **18a** in high yield. When the reaction is performed in THF, large amounts of byproducts were formed, and the yield of the corresponding acetal was only 10%. However, in methanol, the yield of the acetal **19a** was significantly improved with similar enantioselectivity. In the case of crotonaldehyde, the reaction proceeded even in THF without difficulty. Following treatment with methanol, acetal **19b** was obtained in good yield with high enantioselectivity.[12] To achieve high asymmetric induction, it was important to use bulky ester groups of the substarte. This can be explained by postulating the Pd enolate with square planar geometry as depicted in Scheme 10. The electrophile is considerd to react with the Pd enolate at the less sterically hindered *re* face. This face selectivity of the enolate is also applicable to the following reactions.



Scheme 8. Catalytic asymmetric Michael reaction of β-ketoesters.



Scheme 9. Enantioselective Michael reaction of β-ketoesters.



Scheme 10. Michael reactions using other acceptors.

6. Catalytic Asymmetric Mannich-type Reaction with β-Ketoesters

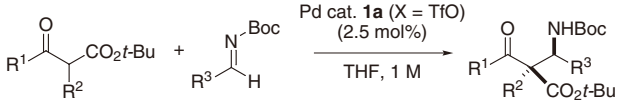
As described in Scheme 5, we found that protonation can significantly enhance the reactivity of imines. Therefore, encouraged by the cooperative action presented in Scheme 9, we also investigated a Mannich-type reaction employing imine, which exhibits high affinity to protic acid, as the electrophilic agent. We found that the aqua complex **1** was effective in promoting Mannich-type reactions with various imines and β-ketoesters.[13] In this article, results in the case of *N*-Boc imine are disucussed in Table 1. Due to the imine activation by protic acid, the reaction is dramatically accelerated compared to the case of Michael addition. In many cases, the reactions were completed within several hours. β-Aminocarbonyl compounds having vicinal tertiary and quaternary chiral centers were obtained efficiently.[14] Numerous reports have described the use of aldehydes and ketones as a nucleophile in the Mannich-type reactions. However, after our publication, a series of reports have appeared on reactions of readily enolizable β-ketoesters and malonic esters, since such reactions are promising as a useful method for synthesizing highly functionalized β-aminocarbonyl compounds.[15]

7. Catalytic Asymmetric Aldol-Type Reaction with Acetal

An aldol-type reaction with an acetal, which does not react under basic conditions, was developed, taking advantage of the enolate generation under acidic conditions. One well-known aldol-type reaction involving a highly acidic compound is nitro-aldol reaction. However, no examples exist for asymmetric reactions with an aldehyde and a 1,3-dicarbonyl compound, probably due to low nucleophilicity of the starting materials and the tendency of the final products to undergo reverse reactions.[16] We assumed that if an acetal could be used in place of an aldehyde, protonation would generate highly reactive oxonium ions, which would react efficiently with the Pd enolates. Furthermore, since the hydroxyl group of the product is protected, we anticipated that the reverse reaction would be suppressed (Scheme 11).

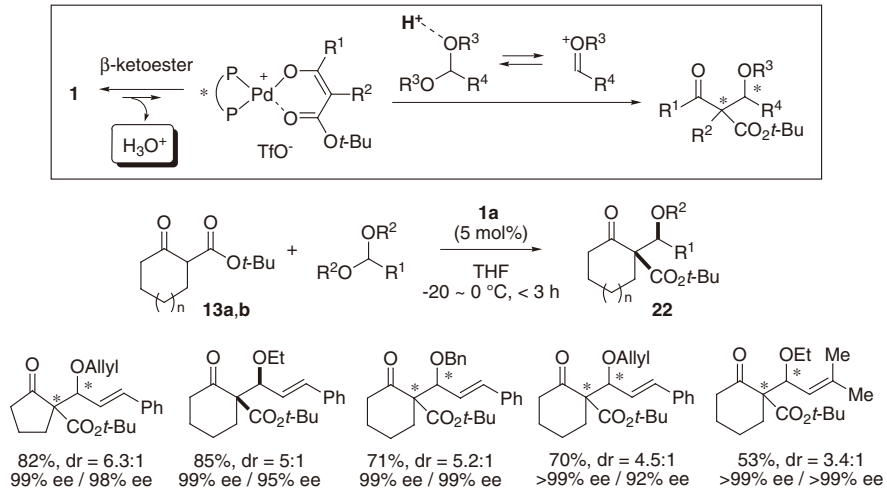
As predicted, the reaction between the cyclic β-ketoester and acetal proceeded smoothly in the presence of 5 mol% Pd catalyst **1a** and was complete within three hours (Scheme 11).[17] While simple aliphatic acetals were not usable, various acetals derived from aldehydes conjugated with unsaturated bonds participated in this reaction quite efficiently to give the aldol product **22** with high diastereoselectivity and almost perfect enantioselectivity. However, reactions of less acidic acyclic β-ketoesters were slow, and the Pd complex was reduced by the

Table 1. Catalytic Enantioselective Mannich-type Reactions of β-Ketoesters.

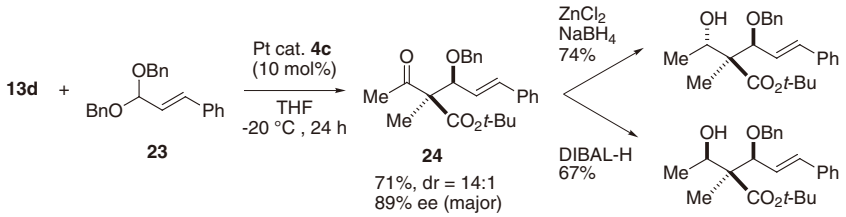


entry	ketoester	imine (R^3)	temp.	time (h)	yield (%)	dr	ee[a]
1	**13a**	**20a** (C_6H_5)	0 °C	5	93	88:12	99/97
2	**13a**	**20b** (*p*-MeC_6H_4)	0 °C	2	93	90:10	95/99
3	**13a**	**20c** (*o*-MeC_6H_4)	0 °C	5	74	93:7	94/-[b]
4	**13a**	**20e** (*o*-ClC_6H_4)	0 °C	1	52	95:5	93/-[b]
5	**13a**	**20f** (2-furyl)	0 °C	2	75	>95:5	86/-[b]
6[c]	**13d**	**20a** (C_6H_5)	rt	4	84	86:14	98/95
7	**13d**	**20b** (*p*-MeC_6H_4)	rt	4	86	90:10	97/85
8	**13d**	**20c** (*o*-MeC_6H_4)	rt	9	87	96:4	98/-[b]
9	**13d**	**20e** (*o*-ClC_6H_4)	rt	2	80	91:9	98/-[b]
10	**13d**	**20f** (2-furyl)	rt	3	71	82:18	96/99

[a] Major/Minor. [b] Not determined. [c] **1d** was used.



Scheme 11. Catalytic asymmetric aldol-type reaction with acetals.



Scheme 12. Catalytic asymmetric aldol-type reaction with acetals using Pt complex.

alcohol derived from the acetal, thereby the target compounds were not obtained in satisfactory yield.

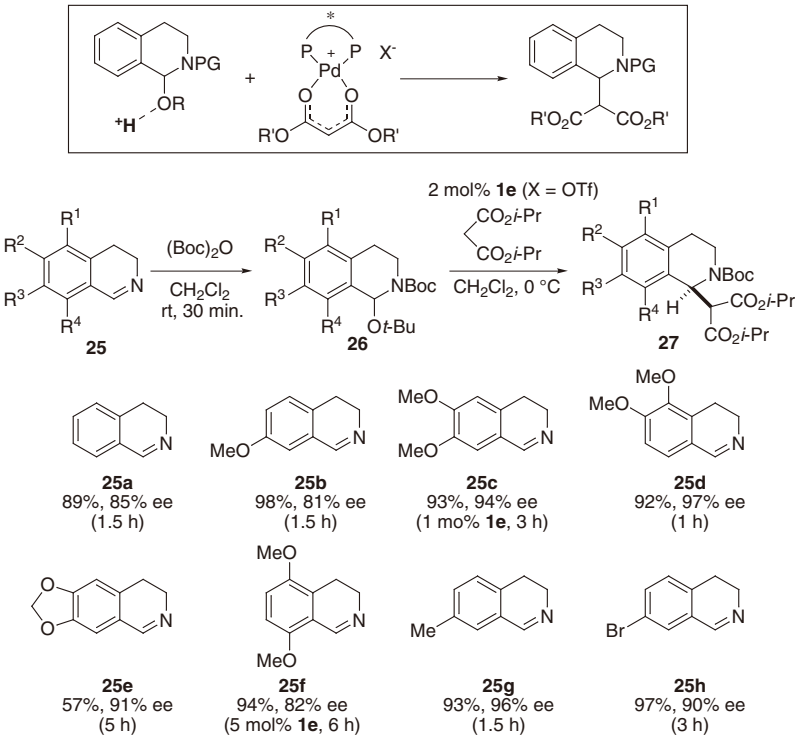
To overcome this problem, we investigated the use of an analogous Pt complex **4a** expecting that it would be more stable than the Pd complex. As expected, the reaction progressed smoothly, although the diastereomeric ratio was approximately 1:1. Ultimately, we achieved significant improvement in the diastereoselectivity by using another Pt complex **4c**, and the target compound **24** was formed in high yield with excellent stereoselectivity (Scheme 12). The compound **24** was converted to two diastereomers having three consecutive chiral centers with appropriate selection of reduction conditions, indicating the synthetic utility of the reaction.

8. Reaction with *N*,*O*-Acetal

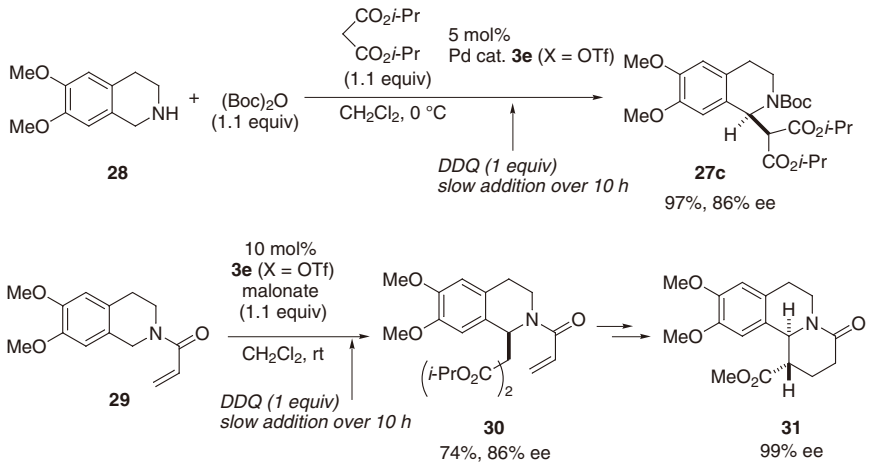
Like acetals, *N*,*O*-acetal could be also used in reactions with active methylene compounds. Since alkyl groups are attached to nitrogen atoms in cyclic imines, cyclic imines basically exhibit low reactivity, making it extremely difficult to use them in a catalytic Mannich-type reaction. However, the use of *N*,*O*-acetal in place of the cyclic imines should result in the smooth generation of reactive iminium ions through protonation (Scheme 13). Related reactions previously reported required a low temperature (-78 °C) to attenuate the reactivity of the highly reactive iminium ions. In our reaction scheme, cooperative activation allows the formation of the Pd enolate being associated with the generation of iminium ions, thus suppressing spontaneous racemic reactions. Thus, high asymmetric induction was achieved under mild reaction temperatures (0 °C ~ room temperature). In the present system, it was possible to use malonic ester as a nucleophile, and optically active tetrahydroisoquinolines, which is a fundamental structures of a multitude of bioactive compounds, were produced in a highly enantioselective manner.[18]

The *N*,*O*-acetal **26** can be readily prepared by reacting dihydroisoquinoline **25** with $(Boc)_2O$ in methylene chloride for 30 minutes. Most reactions were completed within three hours, and the target compound **27** was obtained in high yield (Scheme 13). Substrates with not only electron–donating methoxy and methyl groups but also electron–withdrawing bromo group were used without difficulty. Notably, Pd enolates under acidic condition were also extremely effective in this Mannich-type reaction. When μ-hydroxo complex **2e** that does not donate protons was used instead of aqua complex **1e**, the reaction failed to proceed even after a prolonged reaction time of 48 hours at room temperature.

We anticipated that the asymmetric Mannich-type reaction would proceed similarly if the iminium ions can be generated by the oxidation of tetrahydroisoquinolines instead of α-elimination of *N*,*O*-acetals. To our delight, the oxidative Mannich-type reaction did indeed proceed smoothly, when an oxidizing agent like DDQ in CH_2Cl_2 was added slowly (Scheme 14).[19] The present reaction must be performed at room temperature to promote DDQ oxidation, thereby the water derived from the catalyst induced side reactions at room temperature. But the use of anhydrous complex **3e** prevented such undesired reactions. After the reaction of tetrahydroisoquinolines **28** with $(Boc)_2O$, the oxidative Mannich reaction was carried out according to Scheme 14, and the target compound **27c** was directly formed almost quantitatively with 86% ee. For an efficient oxidative Mannich-type reaction, an electron donating substituent on the aromatic ring was necessary. However, we believe that this oxidative method is advantageous in that an asymmetric Mannich-type reaction is achieved without tedious preparation of dihydroisoquinolines.



Scheme 13. Catalytic asymmetric Mannich-type reaction of malonate to dihydroisoquinolines.



Scheme 14. Oxidative Mannich-type reaction starting from tetrahydroisoquinolines.

In addition, this oxidative reaction was applicable to *N*-acryloyl-substituted **29**. Under the optimized conditinos, the target compound **30** was synthesized in 74% yield with 86% ee. The acryloyl group in **30** was used for further conversion. After the construction of a six-membered ring by an intramolecular Michael addition, we were able to synthesize tricyclic compound **31** as a single isomer, which can be a basic structure found in ipecac alkaloids.

9. Asymmetric Fluorination of Active Methine Compounds

In the field of medicinal chemistry, it is widely recognized that the substitution of hydrogen or the hydroxyl group of the parent compound with fluorine atom often improves pharmacological activity. Although the substitution of the hydrogen atom bonded to the sp^2 carbon with a fluorine atom is generally investigated, several drug candidates having a fluorine atom at a stereogenic carbon center have appeared in recent years. Consequently, development of efficient catalytic asymmetric fluorination is attracting considerable attention.[20] In the electrophilic fluorination of carbonyl compounds, acidic compounds derived from the α-protons are co-produced during the reaction. Thus it is in principle difficult to carry out the reaction catalytically using basic catalysts (Table 2). This is because the catalyst reacts with the acidic co-product leading to the decomposition of the basic catalysts. In contrast, the Pd enolate chemistry appears appropriate for realizing catalytic fluorination, since it can occur under non-basic conditions. When we began our research in this area, the reaction developed by Togni *et al*. using Ti-TADDOL as a catalyst was the only reported example, and the substrate was restricted to a specific β-ketoester.[21,22]

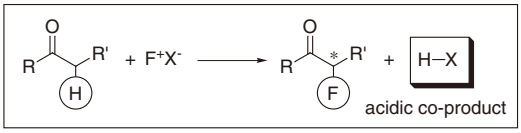
As shown in table 2, we found that Pd-μ-hydroxo

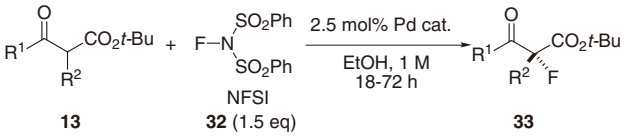
complex **2c** or **2f** with bulky bisphosphine ligands allows the smooth progress of the reaction between β-ketoester **13** and *N*-fluorobenzenesulfonimide (NFSI) **32**. The reaction proved to be highly general, and the fluorinated derivatives were obtained from various β-ketoesters with excellent enantioselectivity.[23] Unlike the aforementioned C-C bond forming reaction, this reaction proceeded smoothly even when μ-hydroxo complex **2** was used in place of aqua complex **1**. This is probably because the fluorinating reagent used in the reaction displays sufficient reactivity. Furthermore, the fluorination reaction proceeds smoothly in alcoholic solvents compared with usual organic solvents such as THF or methylene chloride. It is noteworthy that this reaction can be performed in air using ethanol an environmentally friendly solvent. We also found that the fluorination reaction could be carried out even in ionic liquids as solvents without affecting the stereoselectivity. Since the cationic Pd complex is not extracted with diethyl ether from [hmim][BF_4], the catalyst can be recycled as shown in Table 3.[24]

The synthesized fluorinated products were further converted into β-hydroxyesters **35** and **37** and β-amino esters **36** and **38** through a key stereoselective silane reduction of the ketone group, which constitute the basic structure of bioactive compounds (Scheme 15).

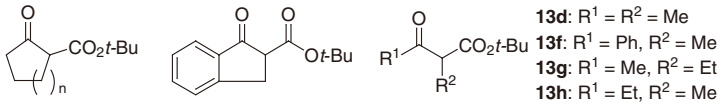
As our extension, we also investigated enantioselective

Table 2. Catalytic asymmetric fluorination reactions of β-ketoesters.





13 **32** (1.5 eq) **33**



13a: n = 1
13b: n = 2

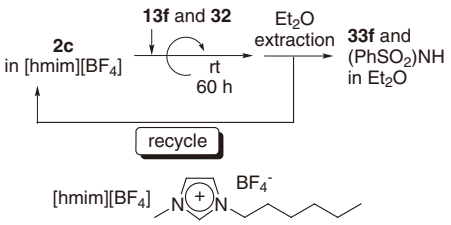
13c

13d: $R^1 = R^2$ = Me
13f: R^1 = Ph, R^2 = Me
13g: R^1 = Me, R^2 = Et
13h: R^1 = Et, R^2 = Me

entry	ketoester	product	catalyst (X)	temp. (°C)	yield (%)	ee (%)
1[a]	**13a**	**33a**	**2f** (TfO)	20	90	92
2	**13b**	**33b**	**2c** (BF_4)	-10	91	94
3	**13c**	**33c**	**2c** (TfO)	-20	85	83
4	**13d**	**33d**	**2f** (TfO)	20	49[c]	91
5	**13f**	**33f**	**2c** (BF_4)	20	92	91
6[b]	**13f**	**33f**	**1c** (TfO)	20	96	91
7	**13g**	**33g**	**2c** (TfO)	20	88	87
8	**13h**	**33h**	**2c** (TfO)	20	47	69

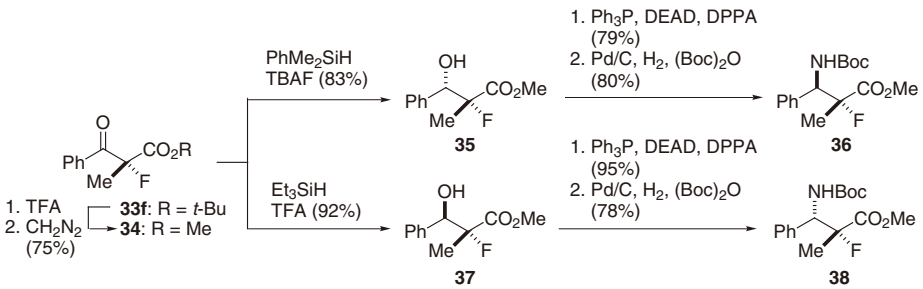
[a] *i*-PrOH was used.
[b] 1g scale. 5 mol% **1c**.
[c] Lower yield due to the volatility of **33d**.

Table 3. 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.



Scheme 15. Conversion of the fluorinated β-ketoester.

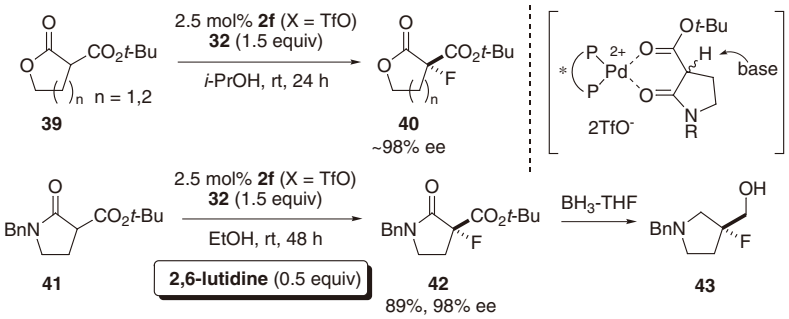
fluorination of *tert*-butoxycarbonyl lactone **39** and lactam **41** (Scheme 16).[25] In the case of lactam **41**, the acidity of the substrate was slightly reduced, hence the reaction failed to proceed with only the μ-hydroxo complex **2f**. However, the addition of 2,6-lutidine promoted the reaction smoothly to give fluorinated derivative **42** in high yield with 98% ee. The high optical yield observed suggests that the reaction would not be promoted with only a base, but occurred via the chiral Pd enolates as a result of the double activation of the Pd complex and the base. It is possible to synthesize the fluorinated cyclic amine **43** by borane reduction of **42**.

Besides the 1,3-dicarbonyl compounds, the present fluorination reaction is also applicable to β-keto phosphonate **44**.[26,27] Monofluorinated phosphonates shows second p*K*a value similar to physiological phosphate esters. Therefore monofluorinated phosphonates are expected to be good mimetic compounds. As shown in Table 4, although the reactivity of the acyclic substrate was low, high asymmetric induction was observed. In the case of cyclic substrates, excellent yield and stereoselectivity were achieved without difficulty. The sense of enantioselection of this reaction was the same as that for β-ketoester, which can be explained by postulating the bidentate Pd enolates. For further application, we confirmed that treatment of **45** with TMSI allowed de-ethylation to give the corresponding phosphonic acid.

10. Fluorination of Oxindoles

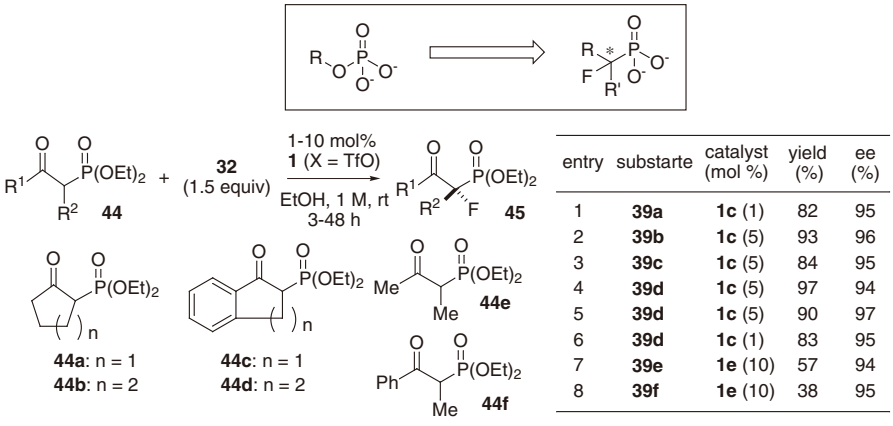
The BMS compound **46** shown in Scheme 17 is currently a promising candidate drug for stroke. It was reported that its pharmacological activity was improved by substituting the tertiary hydroxyl group of oxindole with fluorine atom.[28] Since oxindole is a basic structure found in various bioactive compounds, the development of an asymmetric fluorination reaction of oxindole should be useful in medicinal chemistry. Based on the above results, an attempt was made to fluorinate a simple oxindole. However, poor results were obtained in terms of both yield and enantioselectivity. Taking the bidentate-coordinated enolate structure motif , we attempted reaction of *N*-Boc-protected substrate **47**.

To our delight, when the reaction was carried out in *i*-PrOH using μ-hydroxo complex **2c** as a catalyst, the reaction

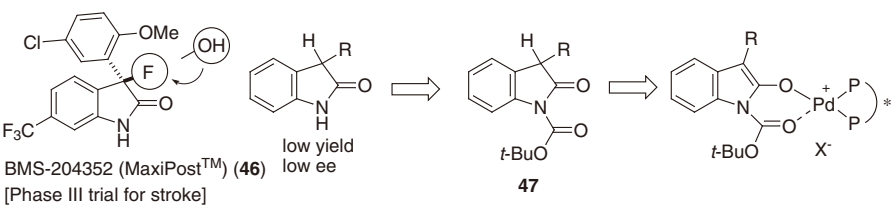


Scheme 16. Reactions of other related compounds.

Table 4. Fluorination reactions of β-ketophosphonates.



entry	substarte	catalyst (mol %)	yield (%)	ee (%)
1	**39a**	**1c** (1)	82	95
2	**39b**	**1c** (5)	93	96
3	**39c**	**1c** (5)	84	95
4	**39d**	**1c** (5)	97	94
5	**39d**	**1c** (5)	90	97
6	**39d**	**1c** (1)	83	95
7	**39e**	**1e** (10)	57	94
8	**39f**	**1e** (10)	38	95



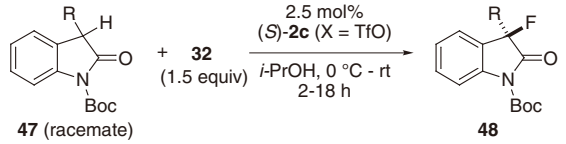
Scheme 17. Catalytic asymmetric fluorination reactions of oxindoles.

proceeded efficiently for a wide range of oxindoles including 3-alkyl- and aryl-substituted substrates (Table 5).[29] Unlike the aforementioned Pd enolates, the reactive center is outside the chelate ring. Nevertheless, high asymmetric induction was achieved, which can be attributed to the effective shielding of the *re* face of the enolate by the aryl group of the ligand.

Based on this observation, we next examined catalytic asymmetric synthesis of the BMS compound **46** (Scheme 18).[29] Due to the steric hindrance arising from the methoxy group at the ortho position, selectivity was reduced compared to **47a**. However, the fluorination reaction of **49** proceeded with good yield. Following removal of the Boc group from **50**, optically pure BMS compound was successfully obtained by recrystallization. Shibata and Toru *et al*. also reported similar asymmetric fluorination reaction of *N*-Boc oxindoles using a Ni catalyst.[30]

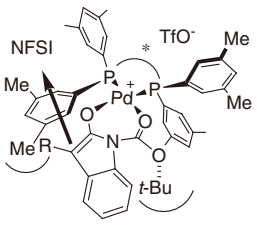
Taking advantage of the fact that cationic Pd complexes can function in alcoholic solvents, we have also succeeded in the monofluorination of 3-unsubstituted oxindole **51** (Scheme 19). Since the acidity of the monofluorinated compound **52** is expected to be higher than that of **51**, high asymmetric induction for **52** represents a major challenge. Indeed, the optical yield of **52** was only 21% ee, when the reaction was carried out in THF. Interestingly, however, excellent enantioselectivity was achieved in using a mixture of MeOH-CH_2Cl_2 as solvent. Thus the enantioselective fluorination reaction, followed by solvolysis with methanol before racemization occurred, giving methyl ester **54** with 93% ee, albeit in moderate yield.[29] Although the substrate for this reaction is restricted to oxindoles, this is the only reported example of catalytic synthesis of a chiral monofluorinated ester, to our knowledge.

Table 5. Catalytic asymmetric fluorination reactions of *N*-Boc oxindoles.

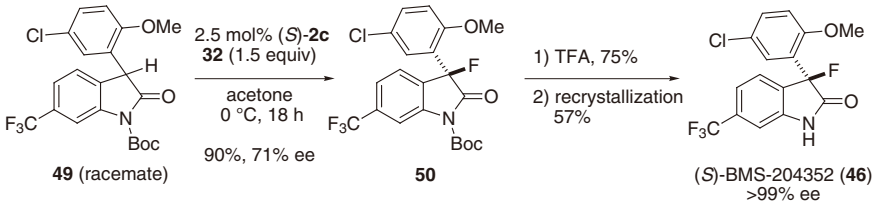


R	yield (%)	ee (%)
Ph (**47a**)	96	90
p-MeC_6H_4 (**47b**)	92	88
p-FC_6H_4 (**47c**)	94	84
Me (**47d**)	85	96

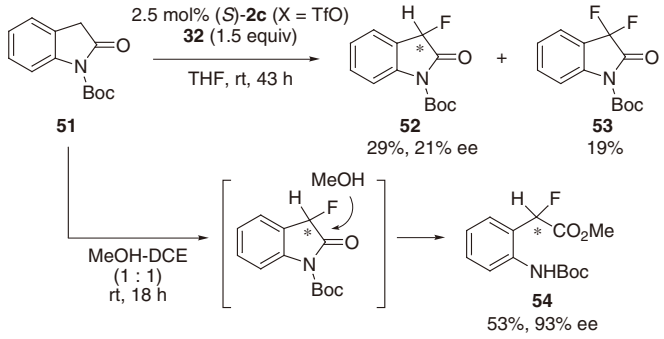
R	yield (%)	ee (%)
Et (**47e**)	85	92
$CH_2C(O)CH_3$ (**47f**)	85	86
Bn (**47g**)	72	80
i-Bu (**47h**)	85	75



Putative Pd enolate.



Scheme 18. Application to asymmetric synthesis of the BMS compound.



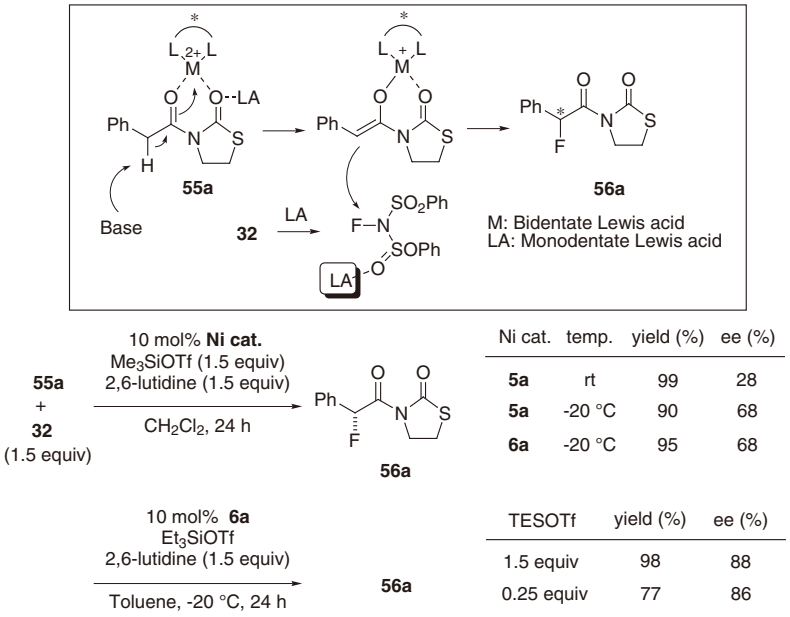
Scheme 19. Catalytic asymmetric monofluorination-solvolysis of oxindole.

11. Catalytic asymmetric fluorination of Aryl Acetic Acid Derivatives Using Trinary Activation System

Toward the development of a more general method of catalytic asymmetric α-monofluorination of carboxylic acid derivatives, we planned to investigate catalytic asymmetric monofluorination reaction of phenylacetic acid derivatives. Initially, we presumed that the double activation by organic base and Lewis acid as in Scheme 16 would be applicable. However, the reaction failed to proceed in any combinations of various reaction parameters including catalysts as well as bases. We envisaged that if both of the reactants (**55** and NFSI) were activated simultaneously, as was observed in the cooperative action between Pd enolates and protic acid, the reaction would proceed in spite of the low concentration of chiral metal enolate. Thus, as shown in Scheme 20, we examined the combination of bidentate Lewis acid catalysts and supplementary monodentate Lewis acids. Additionally, it was expected that the interaction of the secondary Lewis acid with the substrate would also be effective to promote the formation of the enolate.

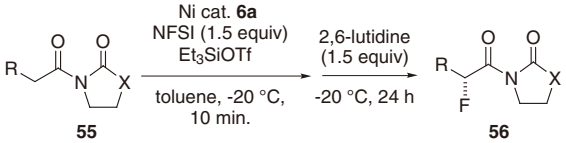
After various attempts, we found that the fluorination proceeded almost quantitatively, although with only 28% ee, when a Ni complex **5a** was used in combination with a silyl triflate as a secondary Lewis acid and 2,6-lutidine as a organic base (Scheme 20). It was essential to use the trinary system of nickel/silyl triflate/2,6-lutidine. Interestingly, when Pd complex **3a** was used in place of Ni complex **5a**, the reaction failed to proceed. Reduction of the temperature to -20 °C improved the enantioselectivity to 68%. It should be noted that almost identical results were obtained even when nickel chloride complex **6a** was used instead of the triflate complex **5a**. This suggests that the identical active species was generated in both cases. Finally, the best results were obtained by using toluene as solvent, and the target monofluorinated compound **56a** was obtained with 88% ee. We also discovered that the amount of silyl triflate could be reduced to 0.25 equivalent without significant deterioration of reaction efficiency.[31]

Under the optimal reaction conditions presented above, various aryl acetic acid derivatives underwent the fluorination reaction in high yield and with satisfactory enantioselectivities of up to 88%, as shown in Table 6.[31] While the reason remains unclear at the present, it was confirmed that racemization of **56** does not occur under similar reaction conditions. This may

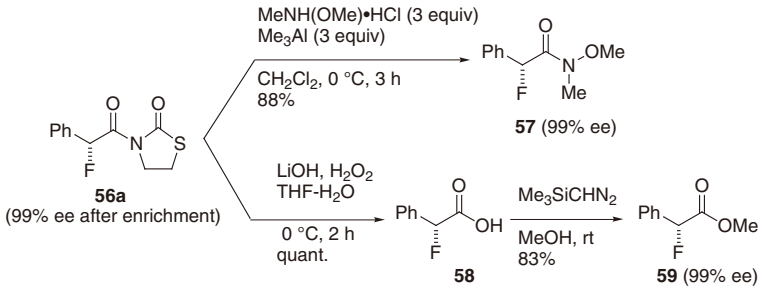


Scheme 20. A novel trinary system for asymmetric fluorination of **55a**.

Table 6. Catalytic asymmetric monofluorination of aryl acetic acid derivatives.



entry	substrate	X	R	catalyst (mol %)	yield (%)	ee (%)
1	**55a**	S	Ph	5	99	88
2	**55b**	S	*p*-FC_6H_4	5	90	83
3	**55c**	S	*p*-$MeOC_6H_4$	5	92	81
4	**55d**	S	*m*-$MeOC_6H_4$	10	95	82
5	**55e**	S	*o*-$MeOC_6H_4$	10	87	78
6	**55f**	S	2-naphthyl	10	99	83
7	**55g**	S	1-naphthyl	5	94	87
8	**55h**	O	Ph	5	95	87



Scheme 21. Conversion of the fluorinated product.

be the key to success to allow the present monofluorination to proceed in an enantioselective manner.

To confirm the utility of our fluorination reaction, further transformation of the synthesized products were carried out (Scheme 21).[31] Fortunately, we were able to obtain optically pure monofluorinated **56a** after single recrystallization. Substitution reaction of the auxiliary group in **56a** with *N*-methoxy-*N*-methylamine gave the Weireb amide **57** in high yield without marked decrease in optical yield. In addition, we performed hydrolysis under basic conditions, and the corresponding monofluorinated acid was obtained without racemization. In contrast, a previous report on diastereoselective fluorination of enolates having chiral oxazoridinone described that considerable racemization occurred during the removal of the chiral auxiliary.[32]

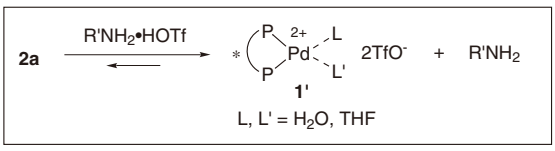
12. Asymmetric Conjugate Addition Reaction of Amine Using Acid-Base Effect of Pd Complexes

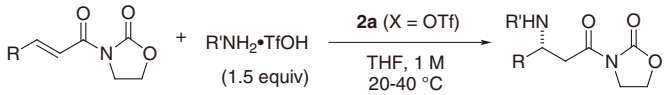
The conjugate addition reaction of nitrogen–containing nucleophiles to α,β-unsaturated carbonyl compounds is as important a reaction as the Mannich reaction for the efficient synthesis of β-aminocarbonyl compounds.[33] Several highly enantioselective catalytic reactions have been reported, in which the key to success is the use of less basic nitrogen nucleophiles. Amines with high basicity/nucleophilicity are still difficult to use for asymmetric catalysis due to problems involving the deactivation of the catalyst and uncatalyzed spontaneous reactions. We anticipated that the side-reaction caused by the excess amine could be overcome if we use amine salt instead of amine, because catalytically active Lewis acid catalyst **1'** and the equimolar amount of free amine would be formed by neutralization of Pd-μ-hydroxo complex and the amine salt (Table 7).[34]

As we hoped, even in reactions involving aromatic amines with high basicity/nucleophilicity such as anisidine, the target compound **62a** was produced in 92% yield with 98% ee using as little as 1 mol% of the catalyst, when the corresponding amine salt **61a** was used (Table 7).[34] In contrast, when anisidine itself was used, the ee was only 2%. Furthermore, as shown in entry 6, the catalyst amount could be reduced to 0.2 mol% without problem. Various nucleophiles could be used. Among them, it is noteworthy that benzylamine could be used in aza-Michael reaction in an enantioselective manner.

With respect to Michael acceptors, substrates with acyclic auxiliary groups were available without difficulty (Scheme 22). In the presence of catalyst **2a**, the reaction of **63** with trifluoromethyl-substituted aniline **61c** occurred smoothly, and the target compound **64** was produced with 89% ee. This compound is an important chemical intermediate that can be converted to cholesteryl ester transfer protein inhibitor according to known procedures.[35] Furthermore, it was possible

Table 7. Catalytic asymmetric conjugate addition of amines.





60 61 62

entry	R	R'	cat. (mol %)	time (h)	yield (%)	ee (%)
1	Me	*p*-$MeOC_6H_4$ (**a**)	1	12	92	98
2	Me	C_6H_5 (**b**)	1	36	83	96
3[a]	Me	*p*-$CF_3C_6H_4$ (**c**)	2	24	77	97
4	Et	*p*-$MeOC_6H_4$ (**a**)	2	24	80	94
5	$BnOCH_2$	*p*-$MeOC_6H_4$ (**a**)	2	6	98	97
6	Me	*p*-$MeOC_6H_4$ (**a**)	0.2	16	98	96
7[b]	Me	Bn (**d**)	2	60	75	86
8[b]	$BnOCH_2$	Bn (**d**)	2	60	74	80

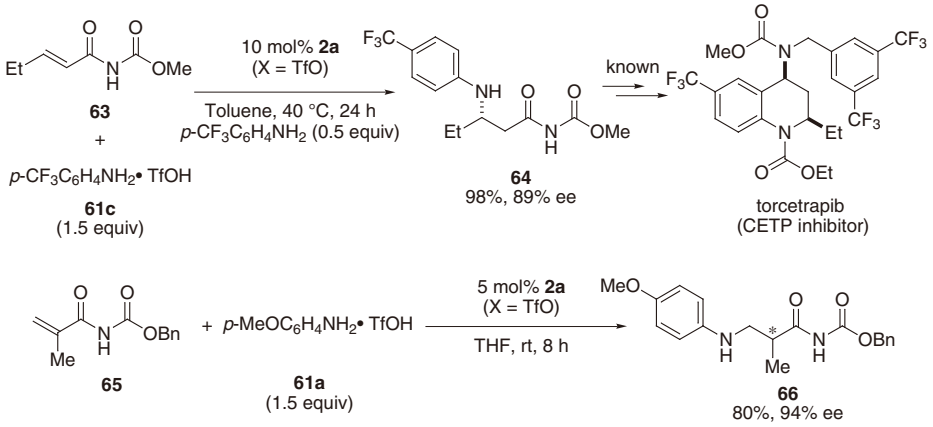
[a] THF/toluene = 1/2. [b] The product was isolated as the corrsponding methyl ester.

to use substrates having substituents at the α position such as **65**. In such cases, the protonation of the putative Pd enolate intermediates generated after conjugate addition of amine proceeded enantioselectively, and **66** having a chiral center at the α position was produced with as high as 94% ee.[34]

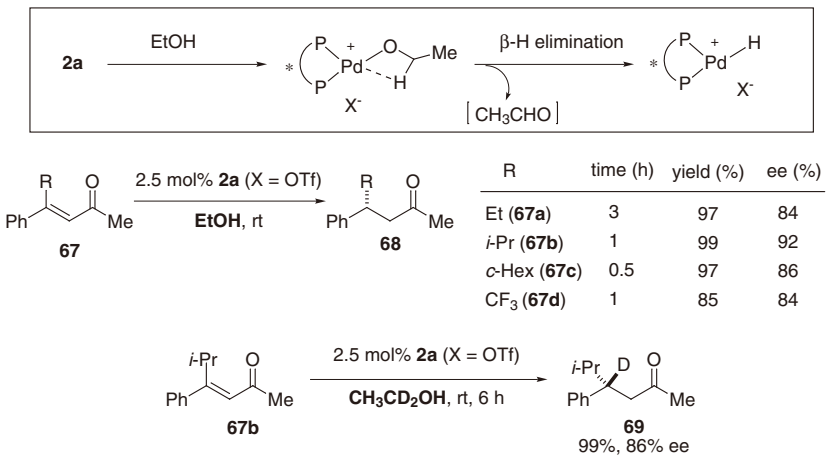
13. Conjugate Reduction using Pd Hydride Species

In the absence of bidentate ligands such as 1,3-dicarbonyl compounds, μ-hydroxo complex **2** acts as a base and reacts with alcohol. When ethanol is used as solvent, chiral Pd hydride species is expected to generate via the formation of a Pd ethoxide, followed by β-hydride elimination (Scheme 23).[36] In fact, this hydride species acted as a reducing agent, being applicable to conjugate reduction of enones.[37] When β,β-disubstituted enone **67** was reacted with catalyst **2a** in ethanol, the conjugate reduction proceeded smoothly to afford **68** with 92% ee. Since chemoselectivity of Pd hydride species was high, ketones and halogens on aromatic ring did not react at all. Furthermore, when partially deuterated ethanol (CH_3CD_2OH) was used as solvent, deuterated compound **69** was obtained selectively.

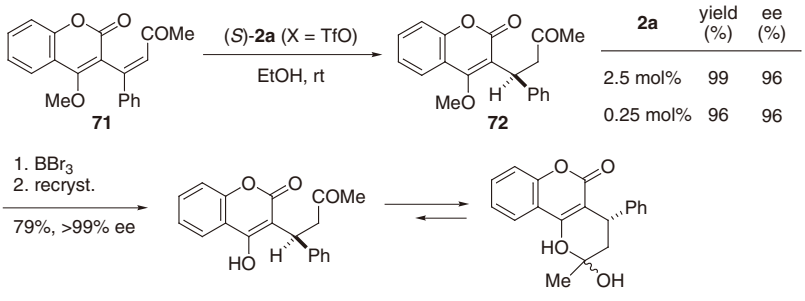
For catalytic asymmetric conjugate reduction reaction, copper and rhodium catalysts have been extensively studied.[38] However, such reactions require silanes as reducing agents such



Scheme 22. Catalytic asymmetric reactions using carbamate-type substrates.



Scheme 23. Catalytic asymmetric conjugate reduction of enones.



Scheme 24. Catalytic asymmetric synthesis of (*S*)-warfarin.

as polymethylhydrosiloxane (PMSH), which cause lots of waste material. In contrast, our reaction uses ethanol as both solvent and a hydride source. We expect that future improvement will lead to the development of a practical environmentally-friendly reaction.

Finally, as an application of our conjugate reduction, we will introduce the asymmetric synthesis of warfarin **70** clinically used as an anticoagulant (Scheme 24).[39] Even though there is difference in efficacy between each enantiomer of warfarin, it is still prescribed as racemate. When 4-methyl-dehydrowarfarin **71** was reacted with μ-hydroxo complex **2a** in ethanol at room temperature, the reduced compound **72** was obtained almost quantitatively with 96% ee. Even when the catalyst amount was reduced to 0.25 mol%, comparable results were obtained. After the removal of the methyl group, single recrystallization gave optically pure (*S*)-warfarin in good yield. [37]

14. Conclusion

Since initiating our research project in the mid-1990s with an interest in the mild reactivity of late transition metal enolates, we have developed various asymmetric catalytic reactions based on two methods for the formation of chiral metal enolates. During the course of our initial investigations on Pd enolates generated by transmetallation, we have succeeded in developing two cationic Pd complexes with distinct property, the aqua complex and the μ-hydroxo complex. We next focused on the acid/base character of these complexes, which led us to the discovery that the active methylene and methine compounds react readily with the Pd complexes to form the enolates. This direct enolate formation was found to be applicable to various asymmetric reactions. In addition, we demonstrated that some nickel and platinum complexes are good catalysts as well. Our studies also showed that acid-base catalysis were not restricted to enolate chemistry, but were also effective in conjugate addition of amines and conjugate reduction with ethanol as the hydride source.

Finally, we hope that the essence of our results will stimulate future research in the development of more beneficial organic reactions and catalytic reactions.

Acknowledgments

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