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Synthesis of optically active heterocyclic compounds using Pd-catalyzed asymmetric reactions as a key step*

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Abstract: Highly enantioselective Pd(II)-catalyzed Michael addition, Mannich-type reaction, aldol reaction, fluorination, conjugate addition of amine, and conjugate reduction have been developed. Asymmetric synthesis of biologically interesting heterocyclic compounds, calycotomine, BMS-204352, torcetrapib, and warfarin, was achieved by using these Pd-catalyzed asymmetric reactions as a key step.

Keywords: torcetrapib; warfarin; BMS-204352; asymmetric synthesis; palladium catalyst.

INTRODUCTION

In 1995, we reported the first example of Pd-catalyzed asymmetric aldol reaction of a silyl enol ether via a chiral Pd enolate. Subsequently, two series of stable crystalline Pd complexes having a chiral bidentate phosphine ligand, Pd aqua complexes **1** and μ-hydroxo complexes **2** (Scheme 1), were found to be excellent catalysts for enantioselective aldol [1] and Mannich-type reactions [2] using silyl enol ethers. In these reactions, the chiral Pd enolate was efficiently generated by transmetallation from the silyl enol ether and reacted with aldehydes or imines to afford highly optically active products. Next, the chiral Pd enolates of 1,3-dicarbonyl compounds were found to be generated readily by proton abstraction using these complexes. 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**, would act as a mild Brønsted base catalyst. The chiral Pd enolates reacted with various electrophiles under acidic conditions. Highly enantioselective Michael addition [3], Mannich-type reaction [4], aldol reaction [5], and fluorination [6] have been achieved (Scheme 1) [7]. These Pd complexes were also found to be effective for enantioselective conjugate addition. The advantages of these catalytic systems include compatibility with various functional groups, and tolerance of air and moisture, and they are useful for the enantioselective synthesis of highly functionalized compounds including nitrogen-containing compounds. In this paper, we focus on the enantioselective syntheses of heterocyclic compounds using these reactions as key steps.

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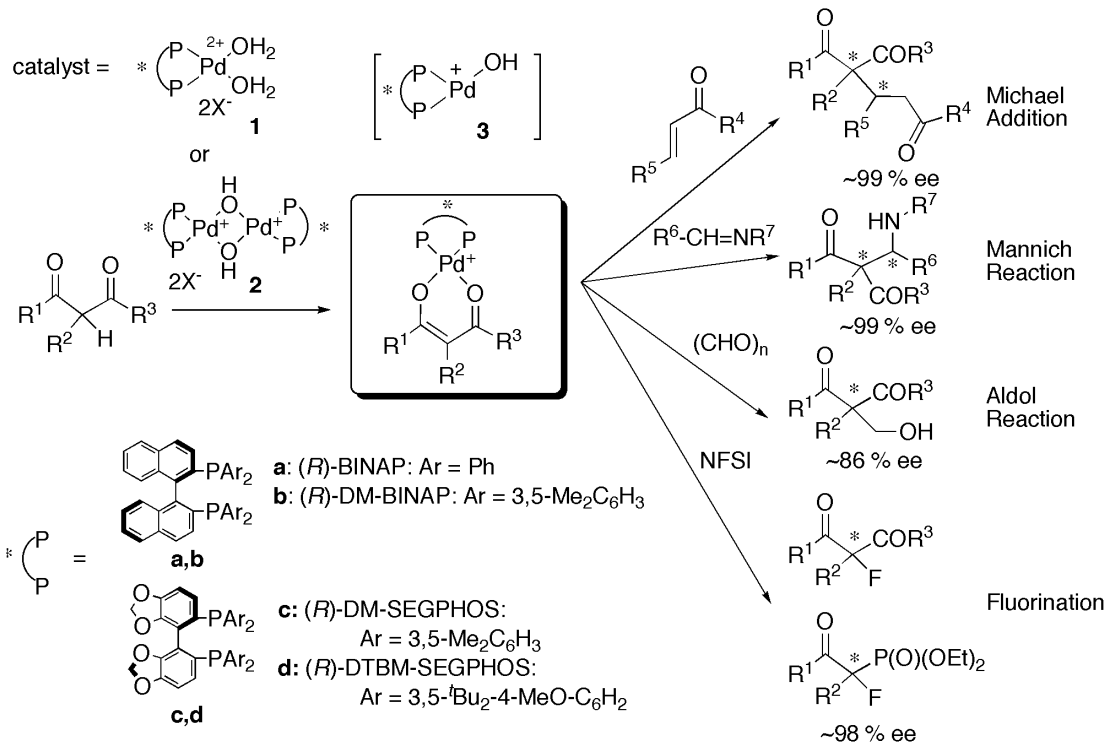
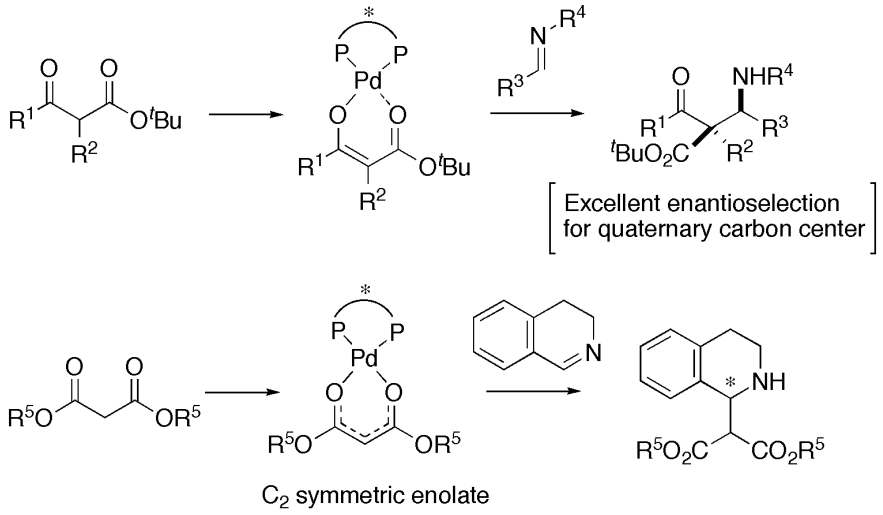


Scheme 1 Pd(II)-catalyzed asymmetric reactions developed in our laboratory.

ENANTIOSELECTIVE SYNTHESIS OF TETRAHYDROISOQUINOLINE DERIVATIVES BY MANNICH-TYPE REACTION

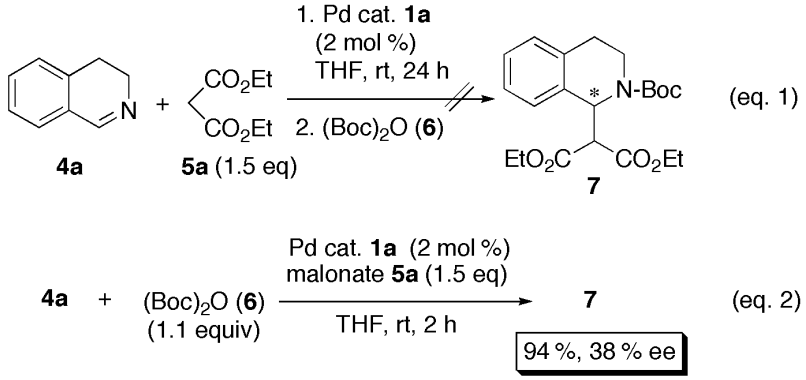
Tetrahydroisoquinolines (THIQs) bearing a stereogenic carbon center at the C1 position represent a fundamental structural motif found in many biologically active compounds [8]. Therefore, asymmetric synthesis of such molecules is of particular interest [9], and catalytic asymmetric addition reactions of enolate equivalents to dihydroisoquinolines (DHIQs) is an attractive approach to the functionalized THIQs [10]. We planned an asymmetric synthesis of the THIQs by utilizing the Pd-catalyzed Mannich-type reaction of the DHIQs with malonates (Scheme 2) [11]. This approach seemed to be more challenging than the reaction of acyclic imines with β-ketoesters [4] in the following respects: (1) malonates are less acidic than β-ketoesters, and the Pd enolate formation might be more difficult; (2) the Pd enolates generated from malonates are C2 symmetric; (3) face selection of cyclic imines seems to be more difficult than that of *trans*-acyclic imines.



Scheme 2 Addition reaction of malonates to cyclic imines.

Enantioselective addition of malonates to DHIQs

Initially, the reaction of DHIQ **4a** with diethyl malonate **5a** was carried out in the presence of 2 mol % of **1a** (Scheme 3), but no product formation was observed when $(Boc)_2O$ (**6**) was added to the reaction mixture after 24 h (eq. 1). We speculated that the starting imine coordinated to the Pd complex, deactivating the catalyst. However, a slight modification of the reaction procedure was found to be highly effective (eq. 2). Thus, when **4a** was treated with **6** prior to the addition of **5a** and **1a**, the desired Mannich-type product **7** was obtained in 94 % yield with 38 % ee after only 2 h.

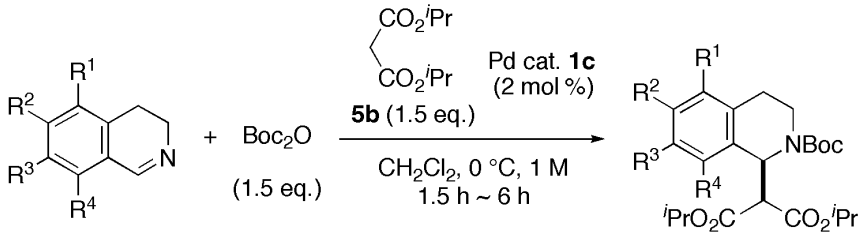


Scheme 3 Initial experiments.

After examination of the reaction conditions, we finally found that the reaction of **4a** with diisopropyl malonate **5b** in CH_2Cl_2 at 0 °C afforded the desired product **8a** in 89 % yield with 85 % ee (Table 1). Various C1-substituted THIQs were accessible in a highly enantioselective manner (up to 97 % ee) [11]. It is noteworthy that our reaction system was compatible with the oxygen functionality. In particular, the 5,6- and 6,7-diMeO-substituted imines **4d** and **4e** underwent the reaction without difficulty irrespective of the possible bidentate coordination of the dimethoxy moiety to the catalyst (>90 % yield, 94 and 97 % ee, respectively). In addition to the MeO groups, the Me- and Br-substituted

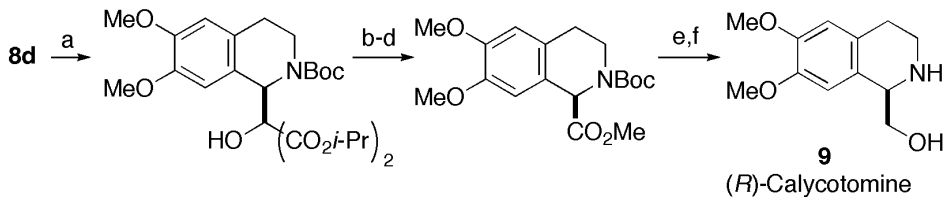
imines **4g** and **4h** were smoothly converted to **8g** and **8h** in excellent yield with 96 and 90 % ee, respectively. The reaction product **8d** was converted to (*R*)-calycotomine (**9**) (Scheme 4).

Table 1 Catalytic asymmetric addition of malonate to various DHIQs.



4 **8**

entry	$R^1/R^2/R^3/R^4$	**1c** (mol%)	product	time (h)	yield (%)	ee (%)
1	H/H/H/H (**4a**)	2	**8a**	1.5	89	85
2	H/H/MeO/H (**4b**)	2	**8b**	1.5	98	81
3	H/R^2-R^3 = OCH_2O/H (**4c**)	2	**8c**	5	57	91
4	H/MeO/MeO/H (**4d**)	1	**8d**	3	93	94 (*S*)
5	MeO/MeO/H/H (**4e**)	2	**8e**	1	92	97
6	MeO/H/H/MeO (**4f**)	5	**8f**	6	94	82
7	H/H/Me/H (**4g**)	2	**8g**	1.5	93	96
8	H/H/Br/H (**4h**)	2	**8h**	3	97	90
9	**4e**	0.5	**8e**	7	71	95

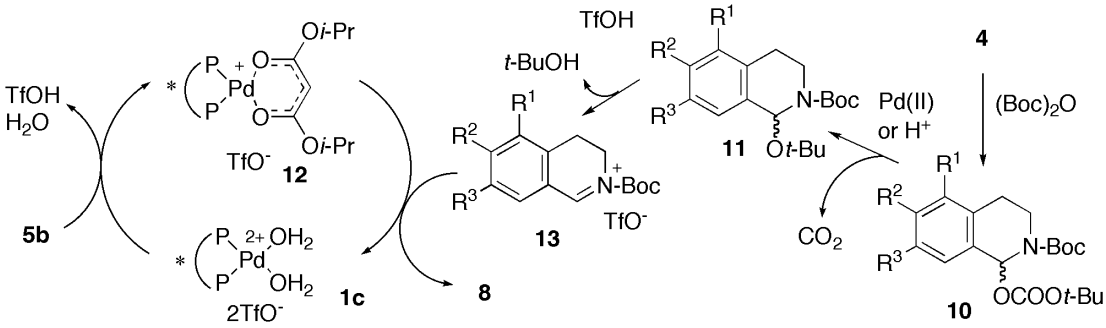


Reagents and conditions: (a) NaHMDS, DMDO, 96 %. (b) $LiAlH_4$. (c) $NaIO_4$, $KMnO_4$ (cat.). (d) $TMSCHN_2$, 50 % for 3 steps. (e) $LiALH_4$. (f) AcCl, MeOH, 90 % for 2 steps.

Scheme 4 Asymmetric synthesis of (*R*)-calycotomin.

Reaction mechanism

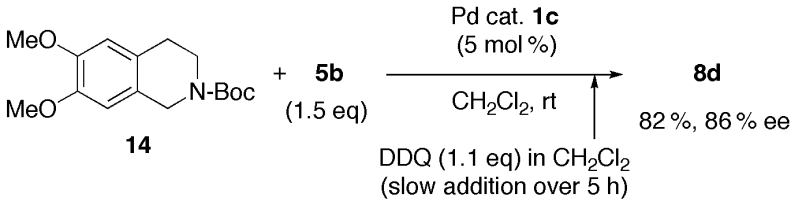
On the basis of mechanistic studies, we proposed the catalytic cycle outlined in Scheme 5. First, the cyclic imine **4** reacts with $(Boc)_2O$ to give the *N*,*O*-acetal **11** through the carbonate **10**. We speculated that a strong protic acid, generated during the formation of the Pd enolate **12**, would facilitate formation of the acyl iminium intermediate **13**, which would react with **12** to complete the catalytic cycle. In spite of the formation of the highly reactive species, high asymmetric induction was observed under mild conditions, presumably due to cooperative action of the chiral Pd enolate and the proton.



Scheme 5 Proposed reaction mechanism.

Dehydrogenative Mannich-type reaction of THIQ with malonates

The mechanistic studies led us to envisage that it would be useful if the reactive iminium intermediate could be formed in situ from THIQs. Inspired by the work of Li et al. [9f], we examined the dehydrogenative Mannich-type reaction with malonate (Scheme 6). Slow addition of DDQ allowed in situ generation of the reactive intermediate, such as **13**, from the *N*-Boc-protected THIQ **14**. As we expected, the coupling product **8d** was obtained at a synthetically useful level (82 and 86 % ee) [11]. Since preparation of the starting THIQ **14** is easier, this one-pot procedure represents a convenient variation of the reaction with DHIQs.



Scheme 6 Dehydrogenative Mannich-type reaction.

ENANTIOSELECTIVE FLUORINATION OF HETEROCYCLIC COMPOUNDS

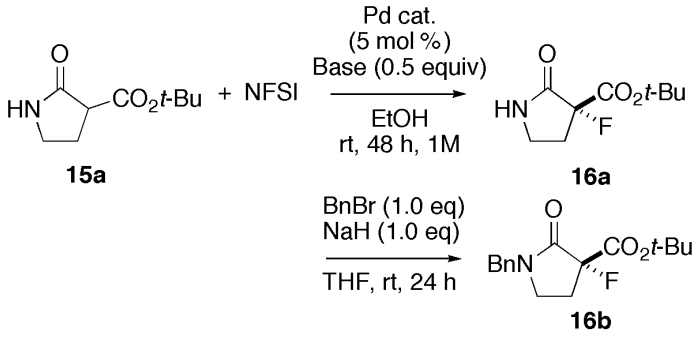
Introduction of fluorine atoms into bioactive compounds is a common approach to improve the biological activity profile [12]. Therefore, catalytic enantioselective fluorination has attracted growing interest [13,14]. We recently reported Pd-catalyzed fluorination reactions of β-ketoesters and β-ketophosphonates [6a–d]. To examine the scope and limitations of this reaction, we also examined fluorination reactions of less acidic substrates. Here, fluorination of two types of heterocyclic compounds, lactam [15], and oxindole derivatives [16] are described.

Enantioselective fluorination of lactam substrates

Fluorination of the lactam substrate **15a** with *N*-fluorobenzenesulfonimide (NFSI) was examined, and the ee of the product **16a** was determined after conversion to the N-benzylated product **16b**. With the Pd aqua complex **1b**, which was the best for β-ketoesters, high enantioselectivity (~90 % ee) was generally observed. But the reaction was slow and the chemical yield did not exceed 50 % after even 48 h (Table 2, entry 1). Notably, the bulky complex **1d** was completely inactive for this less acidic lactam substrate (entry 2). To promote the reaction, we next examined the effect of adding organic bases. When triethylamine (0.5 equiv) was added, the chemical yield was slightly improved (entry 3). Bases that can

coordinate to the catalyst inhibited the reaction (entries 5-8), but 2,6-lutidine significantly improved the chemical yield without any loss of enantioselectivity (80 % yield, 91 % ee, entry 9). However, the much bulkier 2,6-(t-Bu)$_2$-pyridine was found less effective (entry 10). It should be noted that even **1d** and **2d** promoted the reactions with the aid of 2,6-lutidine, and the desired product **16a** was obtained in modest yield (58 %) with almost complete enantioselectivity (99 % ee, entries 11 and 12). The high selectivity observed in this reaction strongly indicates that additional base alone is insufficient for the activation of the substrate, and the combined use of the Pd complex with 2,6-lutidine is essential for efficient generation of the Pd enolate. The absolute stereochemistry was determined to be *R* by X-ray analysis, [17] which is in accordance with our previous results (Fig. 1).

Table 2 Optimization of the fluorination reaction of lactam substrate.



entry	Pd cat.	Base	yield (%)	ee of **16b** (%)
1	**1b**	-	43	90
2	**1d**	-	trace (96 h)	-
3	**1b**	Et_3N	59	90
4	**1b**	morpholine	49	88
5	**1b**	pyridine	trace	-
6	**1b**	quinoline	NR	-
7	**1b**	isoquinoline	NR	-
8	**1b**	DMAP	trace	-
9	**1b**	2,6-lutidine	80	91
10	**1b**	2,6-(t-Bu)$_2$-pyridine	65	91
11	**1d**	2,6-lutidine	50	99
12	**2d**	2,6-lutidine	58	>99

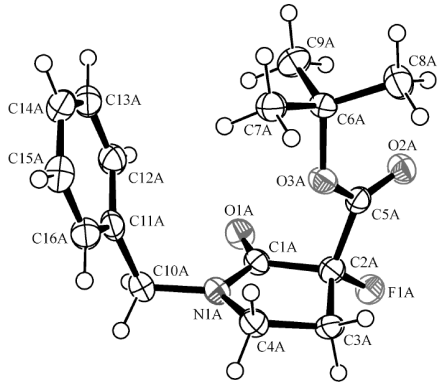
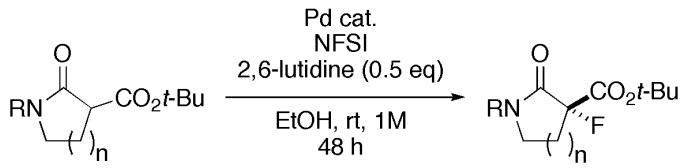


Fig. 1 X-ray structure of **16b**.

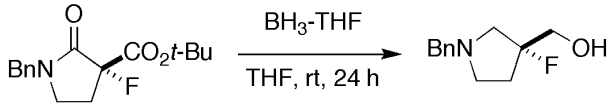
Reactions of N-benzylated and N-methylated lactam substrates **15b** and **15c** proceeded smoothly, and the desired products **16b** and **16c** were obtained in good yield (89 and 77 %, respectively) with excellent enantioselectivity (98 and 99 % ee, respectively) (Table 3) [15]. Protection of the amide group might suppress the competitive abstraction of the amide proton, favoring the generation of the desired Pd enolate. The N-acylated substrate **15d** was also fluorinated in a highly enantioselective manner (99 % ee). In the case of the six-membered substrate **15e**, no protection of the amide was necessary, and **16e** was obtained in 74 % yield with 94 % ee. Further, this fluorination reaction is potentially useful for the preparation of optically active fluorinated cyclic amines. For example, reduction of **16b** by BH_3 in tetrahydrofuran (THF) afforded the corresponding fluoroamine **17** in 60 % yield (Scheme 7).

Table 3 Reactions of other lactam substrates.



15 **16**

entry	substrate	catalyst (mol %)	product	yield (%)	ee (%)
1	R = Bn, n = 1 (**15b**)	**2d** (5)	**16b**	89	98
2	R = Me, n = 1 (**15c**)	**2d** (5)	**16c**	77	99
3	R = $COOCHPh_2$, n = 1 (**15d**)	**1b** (5)	**16d**	45	99
4	R = H, n = 2 (**15e**)	**2d** (5)	**16e**	74	94

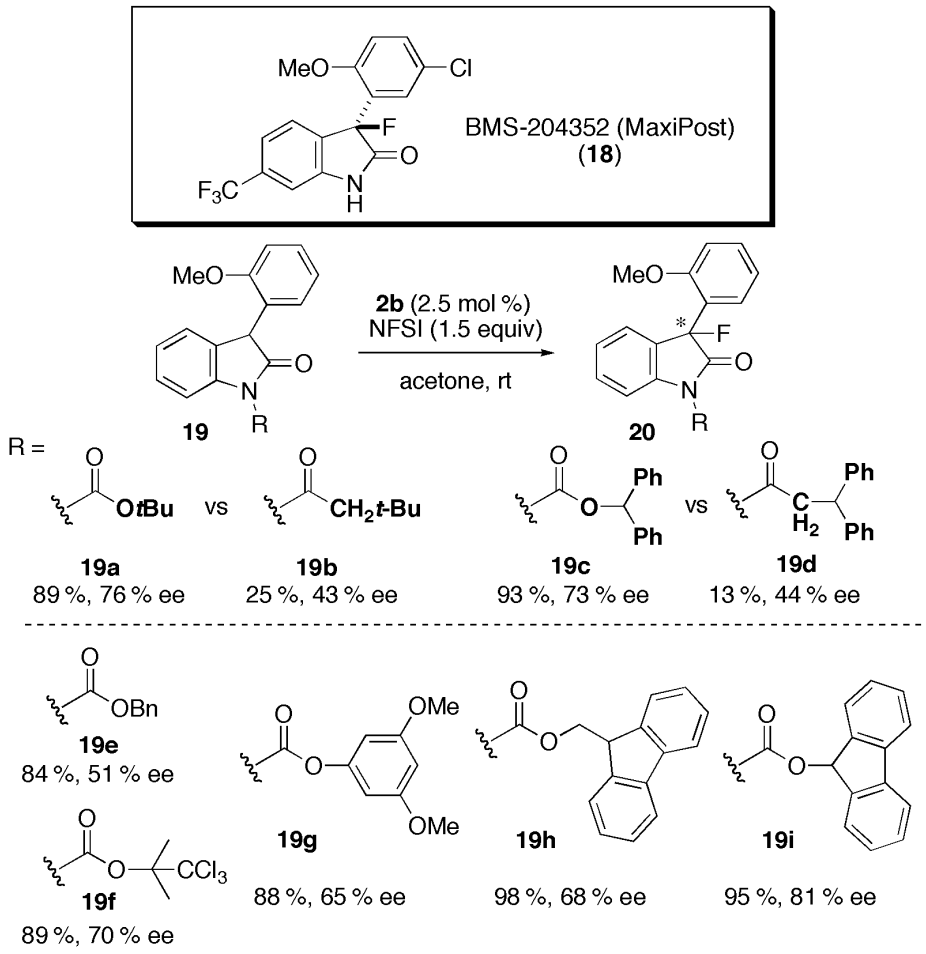


16b 60 % **17**

Scheme 7 Conversion to fluorinated cyclic amine.

Enantioselective fluorination of oxindoles and synthesis of MaxiPost™

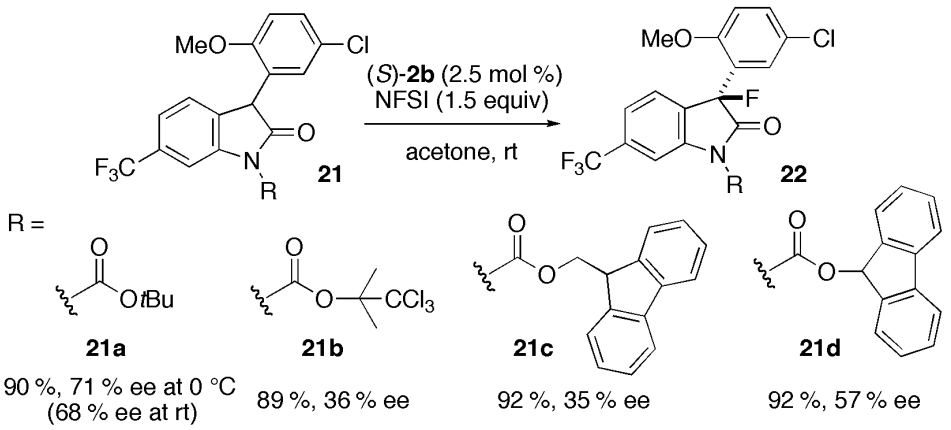
BMS 204352 (MaxiPost™) **18**, developed by Bristol-Myers Squibb, is a promising agent for the treatment of stroke, and is undergoing phase III clinical trial [18]. Because the oxindole ring is found widely in nature, we thought that asymmetric fluorination of oxindoles would be useful in medicinal chemistry. Initial studies revealed that the reaction of nitrogen-free 3-phenyloxindole was sluggish under the reaction conditions established for β-keto esters, so we next examined the reaction of N-protected oxindoles. To achieve an asymmetric synthesis of the target compound, we selected *ortho*-MeO-phenyl-substituted oxindole as a model substrate. As shown in Scheme 8, various electron-withdrawing groups were tested as a protecting group of the nitrogen atom. Among them, the reaction of *N*-Boc-protected **19a** proceeded smoothly to give **20a** in 89 % yield with 76 % ee. To improve the enantioselectivity, several bulkier protecting groups were tested, and a slightly better ee (81 % ee) was observed for the *N*-fluorenyloxycarbonyl-protected derivative **19i**. It is noteworthy that the *N*-acyl derivatives **19b** and **19d** gave much lower chemical and optical yields than the corresponding *N*-alkoxycarbonyl derivatives.



Scheme 8 Effect of acyl- and oxycarbonyl-type groups in asymmetric fluorination of oxindole.

With these results in hand, we applied our reaction to the catalytic asymmetric synthesis of **18** (Scheme 9). Compounds **21** were subjected to the fluorination reaction, and the desired products **22** were obtained in good chemical yield. The reaction of the *N*-Boc-protected derivative **21a** was found to be the most enantioselective, and **22a** was isolated in 90 % yield with 71 % ee. After deprotection of **22a** with trifluoroacetic acid (TFA), recrystallization furnished optically pure (*S*)-**18** (>99 % ee) [16].

Importantly, this reaction displayed broad generality as regards substituents at the 3-position. Various other 3-alkyl- or aryl-substituted oxindole derivatives were also fluorinated in a highly enantioselective manner (up to 96 % ee) [16].



Scheme 9 Application to asymmetric synthesis of **18**.

ENANTIOSELECTIVE SYNTHESIS OF TORCETRAPIB BY CONJUGATE ADDITION OF AMINE

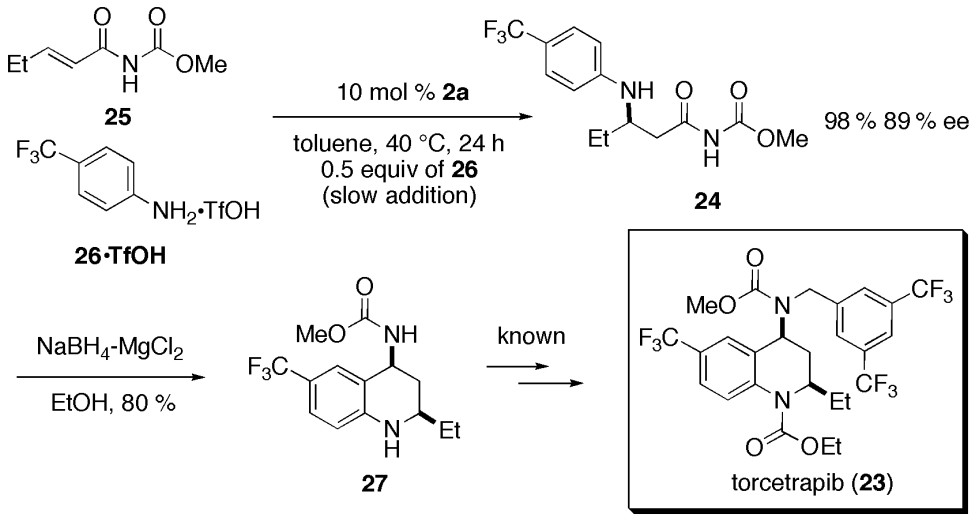
With the success in using a bidentate Pd enolate motif in several asymmetric reactions, we speculated that Pd complexes having two vacant coordination sites would act as bidentate chiral Lewis acids. We developed a highly enantioselective conjugate addition of aromatic amines to α,β-unsaturated imide-type compounds [19], and employed it in an asymmetric synthesis of torcetrapib [20].

Catalytic enantioselective conjugate addition of amines

Optically active β-amino acid derivatives are a versatile resource for the synthesis of biologically active nitrogen-containing compounds [21]. It is known that the catalytic enantioselective conjugate addition of highly nucleophilic amine is extremely difficult, because the noncatalyzed process competes with the desired catalyzed process. We found that the catalytic enantioselective conjugate addition of amines to 3-[(*E*)-2-alkenoyl]oxazolidin-2-one proceeded well with the combined use of the μ-hydroxo complex **2a** having a Brønsted base character and amine salts, affording highly optically active products (up to 98 % ee) [19].

Catalytic enantioselective synthesis of torcetrapib

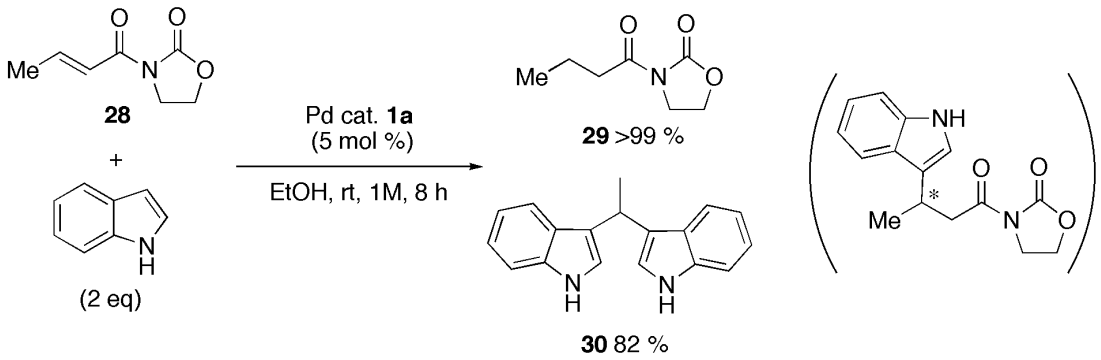
Torcetrapib (**23**) is a potent cholesteryl ester transfer protein (CETP) inhibitor [22], and the compound **24** was reported to be a key synthetic intermediate. We applied our enantioselective conjugate addition reaction to the synthesis of **23**. Under the established conditions, however, the reaction of methyl pentenoylcarbamate **25** with the salt of 4-trifluoromethylaniline **26** was slow. This might be attributed to low nucleophilicity of **26** and unfavorable steric interaction with the β-substituent of **25**. After examining various reaction conditions, we found that toluene was a better solvent, and slow addition of **26** (0.5 equiv over 12 h) was effective to achieve high chemical yield (Scheme 10). Thus, the Michael adduct **24** was produced in 98 % yield with 89 % ee [20]. This compound was converted to the tetrahydroquinoline derivative **27** by reductive cyclization. Hii et al. also recently reported similar results [23].



Scheme 10 Asymmetric synthesis of **23** using conjugate addition of amine catalyzed by **2a**.

ENANTIOSELECTIVE SYNTHESIS OF WARFARIN BY CONJUGATE REDUCTION

During the course of our examination of enantioselective conjugate addition of indole to **28**, we encountered very interesting results. When ethanol was used as the solvent, no conjugate addition occurred. Instead, unexpectedly, the reduced product **29** was formed in quantitative yield (Scheme 11). The structure of the by-product **30** strongly suggested that ethanol acted as an efficient hydride source. Based on this finding, we developed an enantioselective conjugate reduction of α,β-unsaturated ketones, and it was applied to the asymmetric synthesis of warfarin [24].

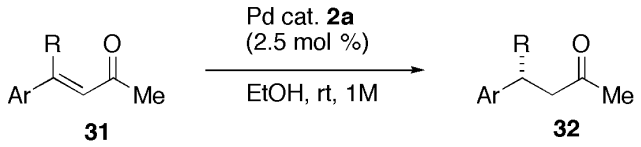


Scheme 11 Conjugate reduction catalyzed by **1a** in ethanol.

Enantioselective conjugate reduction using ethanol as a hydride source

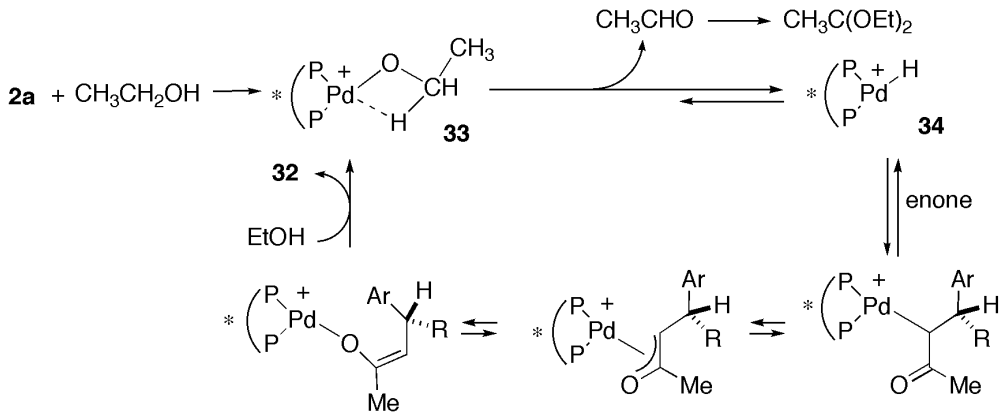
We investigated catalytic enantioselective conjugate reduction of α,β-unsaturated ketones in ethanol [24]. As summarized in Table 4, various enones **31** were smoothly reduced to give **32** in a highly enantioselective manner using 2.5 mol % of the catalyst **2a**. In this reaction, ethanol acts as both a reducing agent and a solvent, and it is environmentally and economically advantageous compared with other conjugate reductions using metal hydride or dihydropyridines as a reducing agent [25].

Table 4 Catalytic asymmetric conjugate reduction.



entry	Ar	R	product	time (h)	yield (%)	ee (%)
1	Ph	Me	**32a**	6 (12)	>99	74
2	Ph	Et	**32b**	3	97	84
3	Ph	^{i}Pr	**32c**	1	>99	92
4	Ph	^{c}Hex	**32d**	0.5	97	86
5	Ph	CF_3	**32e**	1	85	84
6	2-BrC_6H_4	Me	**32f**	6	>99	80

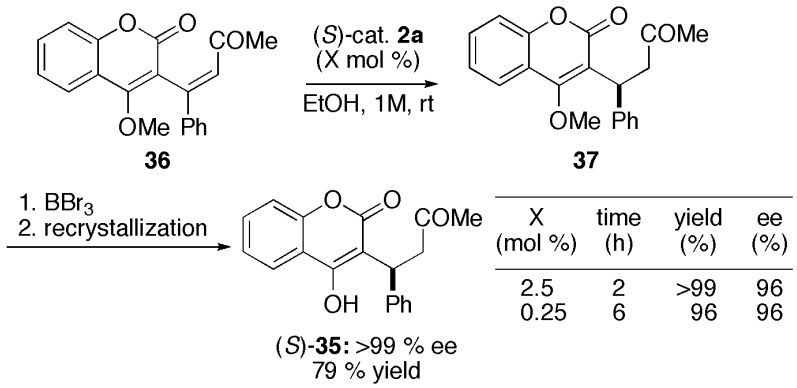
We proposed the reaction mechanism shown in Scheme 12, based on the results of experiments using deuterium-labeled ethanol. The chiral Pd-hydride complex **34** generated by β-hydride elimination of the Pd ethoxide complex **33** is considered to be a key intermediate [26].



Scheme 12 Proposed catalytic cycle.

Catalytic enantioselective synthesis of (*S*)-warfarin

We applied our novel conjugate reduction to the asymmetric synthesis of warfarin **35**, a well-known anti-coagulant (Scheme 13). Although the biological activity of the *S* enantiomer is about 5–8 times higher than that of the *R* enantiomer, warfarin has been clinically used as a racemate for a long time [27]. Reaction of dehydrowarfarin was unsuccessful because of facile intramolecular cyclization to give the corresponding mixed ketal. Therefore, we examined the conjugate reduction of 4-Me-dehydrowarfarin **36** (Scheme 13). Gratifyingly, the reaction proceeded smoothly in the presence of the (*S*)-Pd complex **2a** (2.5 mol %) to afford the reduced product **37** quantitatively. The ee of **37** was as high as 96 %. Furthermore, the amount of catalyst could be reduced to as little as 0.25 mol % without any loss of enantioselectivity. Demethylation with BBr_3, followed by a single recrystallization, gave optically pure (*S*)-warfarin **35** [24].



Scheme 13 Asymmetric synthesis of warfarin.

CONCLUSION

We have described highly efficient enantioselective syntheses of heterocyclic compounds using chiral Pd complexes. C1-Substituted THIQs were synthesized by catalytic enantioselective Mannich-type reaction. Fluorine-containing heterocycles such as the drug candidate MaxiPost were synthesized by asymmetric fluorination. A key intermediate for the synthesis of the biologically interesting CEPT inhibitor torcetrapib was obtained by the catalytic asymmetric conjugate addition reaction of amine. The active (*S*)-form of the clinically important anti-coagulant warfarin was successfully synthesized by using the Pd-catalyzed conjugate reduction with ethanol as a hydride source.

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