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Unique features of chiral palladium enolates derived from β-ketoamide: structure and catalytic asymmetric Michael and fluorination reactions

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ABSTRACT

We have previously reported enantioselective reactions of 1,3-diketones and β-ketoesters with various electrophiles catalyzed by chiral Pd complex, in which chiral Pd enolates play a key role. Here, we present a detailed examination of Pd-catalyzed enantioselective Michael addition and fluorination reactions of β-ketoamides. β-Ketoamide showed higher reactivity than 1,3-diketone and β-ketoester, though its α-proton is likely to be least acidic. Pd enolate formation of β-ketoamide was much faster than that of β-ketoester. The crystal structures of (*R*)-BINAP-Pd-diketone and ketoamide complexes were found to be quite distinct. Pd-diketone complex has bidentate square-planar geometry as have been predicted before, whereas Pd-ketoamide complex was greatly distorted, probably due to steric constraints of the amide bond.

1. Introduction

Catalytic enantioselective construction of fully substituted chiral carbon centers is important for the synthesis of bioactive molecules, but is a challenging task. Therefore, many approaches have been investigated.[1] We have been working on development of such reactions using chiral palladium enolate chemistry. We have developed Pd aqua complex **1** and Pd μ-hydroxo complex **2** (Fig. 1), which are thought to generate monomeric Pd hydroxo complex **3** either by dissociation of H_2O and TfOH from **1** or by simple dissociation to the monomer from **2** (Scheme 1).[2]

Complex **3** can act as both a Lewis acid and a Brønsted base, and chiral Pd enolates **4** are formed by reaction with 1,3-dicarbonyl compounds, such as 1,3-diketone or β-ketoester (Scheme 1).[3] Chiral Pd enolates **4** can react with various electrophiles such as enones, imines, formaldehyde, acetals, and *N*-fluorobenzenesulfonimide (NFSI) to produce highly enantio-enriched compounds having a chiral quaternary or fluorine-substituted carbon center (Scheme 1).[3]

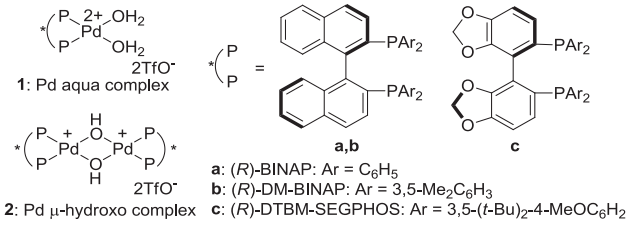

Fig. 1. Chiral palladium complexes.

In the case of β-ketoester, the bulkiness of the ester group is critical, and a *tert*-butyl group generally afforded a product with excellent ee. (*R*)-Products were obtained irrespective of the nature of the electrophiles when (*R*)-BINAP complex was used as a catalyst. We previously proposed that excellent enantioselectivity is a consequence of face selection of the putative square-planar BINAP-Pd bidentate enolate complex (Fig. 2).[3] In the case of (*R*)-BINAP-Pd enolate complex, the *si*-face is shielded by both the ligand phenyl group and the *tert*-butyl group of the substrate. We confirmed Pd enolate formation by NMR and ESI-MS, but the three-

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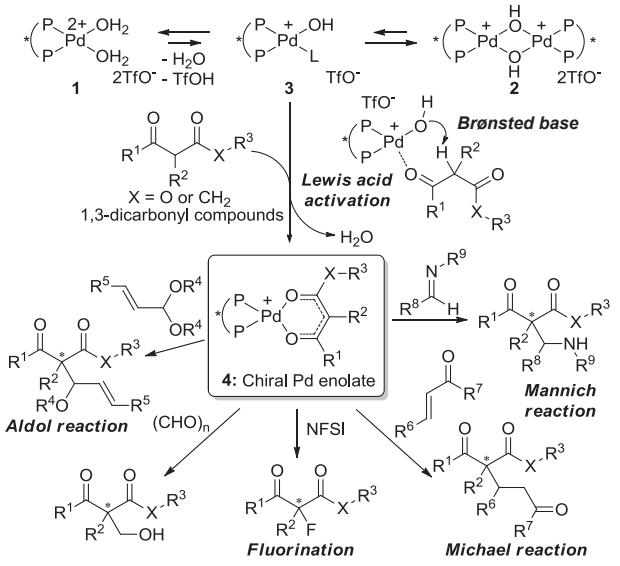


Scheme 1. Pd enolate formation and reaction with various electrophiles.

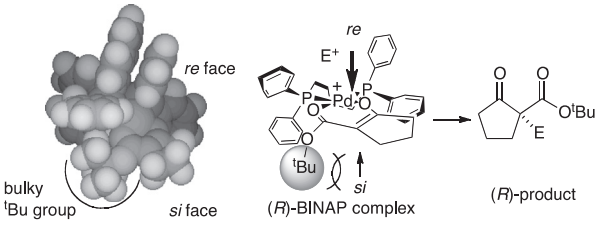


Fig. 2. Structural model of Pd enolate complex and proposed mechanistic basis of enantioselection.

dimensional (3D) structure of BINAP-Pd enolate complex was not established. Recently Pregosin and Albinati reported that the BINAP-Pd enolate complex of 3-methyl-pentan-2,4-dione has a square-planar structure with bidentate coordination of enolate as expected.[4]

Nitrogen-containing molecules are very important class of molecules in medicinal chemistry. Therefore, catalytic enantioselective reactions of β-ketoamide are attractive, because the products are expected to be potent intermediates for bioactive molecules.[5] In contrast to the many reports on β-ketoester, however, few reactions of β-ketoamide have been described. Togni reported catalytic enatioselective fluorination of tertiary ketoamide by using chiral TADDOL-titanium complex.[6] Mezzetti examined Michael addition to methyl vinyl ketone (MVK) and fluorination reaction of β-ketoamides by using their chiral Ru-PNNP complex.[7] Recently, Rodriguez and Constantieux reported catalytic enantioselective Michael reaction of secondary β-ketoamide with enones by using organocatalyst.[8] Liu and Feng reported highly enantioselective Michael reaction of secondary β-ketoamide with nitroolefins and alkynones catalyzed by their *N,N′*-dioxide-Co complex.[9] However, each reaction has a rather restricted substrate scope, and there are only a few examples of highly enantioselective and efficient reactions.

In addition to 1,3-diketones and β-ketoesters, we have applied our Pd enolate chemistry to enantioselective fluorination of α-*tert*-butoxycarbonyl-substituted lactones and lactams.[3n] Reactions of lactones (diester-type substrates) proceeded well, whereas reactions of lactams (ester-amide type substrates) were found to be very slow and required the addition of 2,6-lutidine to facilitate the reaction. These facts suggested that the pK_a value of the α-proton is critical for the formation of Pd enolate, and/or the existence of acidic amide NH may affect the reaction. Therefore, we planned to examine the Pd-catalyzed asymmetric reactions of β-ketoamides, which are less acidic than β-ketoesters.

Here, we present the results of a systematic study on Pd enolate formation of 1,3-diketone, β-ketoester, and β-ketoamide, as well as X-ray structural analysis of BINAP-Pd enolate complexes of 1,3-diketone and β-ketoamide. We also report catalytic enantioselective Michael and fluorination reactions of secondary and tertiary β-ketoamides.

2. Results and discussion

Previously we reported clean formation of Pd enolate simply by mixing 1,3-diketone **5a** with 0.5 equiv of (*R*)-Tol-BINAP-Pd μ-hydroxo complex.[3a] Its structure was confirmed by ^{1}H NMR and ESI-MS. Formation of Pd enolate could be easily monitored by ^{31}P NMR. Therefore, to compare the potency for Pd enolate formation, we first examined the reactions of 1,3-diketone **5a**, β-ketoester **5b**, and β-ketoamide **5c** with 0.5 equiv of **2a**, and monitored Pd enolate formation by ^{31}P NMR (Fig. 3a). In the case of 1,3-diketone **5a**, the peak of **2a** (29.6 ppm) disappeared and a new sharp peak at 31.6 ppm was observed at 15 min after mixing **5a** and **2a**, indicating that enolate formation is very fast and the electron is delocalized over the two carbonyl groups. In contrast, reaction of β-ketoester **5b** was very slow, and the peak of **2a** remained even after 10 h. In the case of **5b**, signals of two phosphine atoms appeared at different chemical shifts (27.6 and 35.2 ppm), indicating different nature

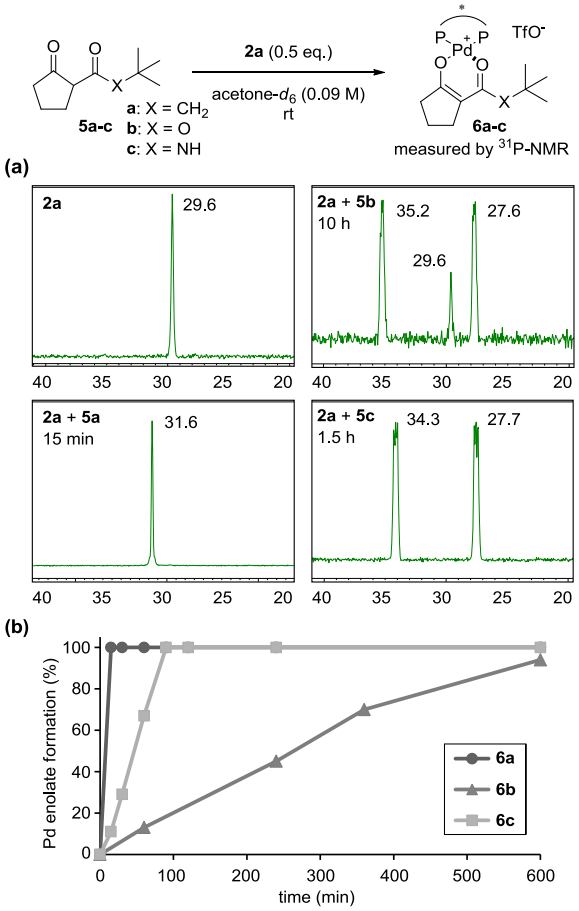


Fig. 3. Pd enolate formation of **5a**–**c**. (a) ^{31}P NMR spectra of the mixture of **2a** and **5a**–**c** in acetone-d_6. (b) Time course of the Pd enolate formation determined by ^{31}P NMR.

of the two carbonyl groups of the β-ketoester. Surprisingly, enolate formation of β-ketoamide **5c** was found to be much faster than that of β-ketoester **5b**. The reaction was completed after 1.5 h, and again, two distinct signals were observed (27.7 and 34.3 ppm). The time courses of formation of enolate **6a**–**c** are summarized in Fig. 3b. The rate of enolate formation of β-ketoamide **5c** is much faster than would be expected from the pK_a values of these compounds (reported pK_a values of acetylacetone, ethyl acetoacetate, and *N*,*N*-dimethylacetoacetamide are 13.3, 14.2, and 18.2, respectively).[10]

Fig. 4 compares the ^{13}C NMR chemical shifts of the 1,3-dicarbonyl compounds **5a**–**c** and their Pd enolates **6a**–**c**. In the case of **5a**, the signals of the carbonyl groups were shifted from 213.2 and 204.3 ppm to 185.4 and 193.0 ppm, indicating highly delocalized nature. In contrast, the chemical shifts of the ester and amide carbonyl groups of **5b** and **5c** showed little change after enolate formation, while those of the ketone carbonyl groups changed from 212.6 and 217.2 to 189.7 and 182.1 ppm, respectively.[3o] These results suggest that Pd enolates of β-ketoester and β-ketoamide have basically similar structure.

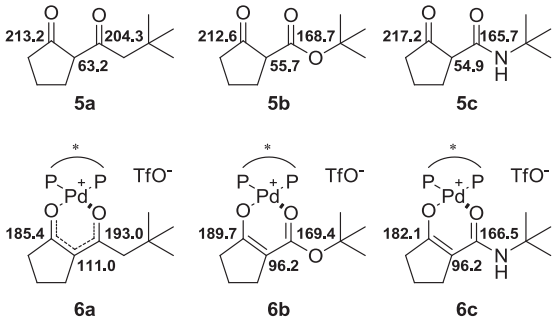
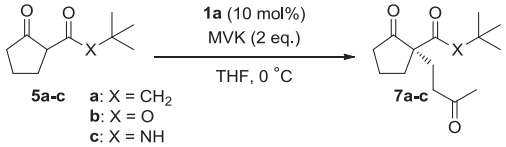


Fig. 4. ^{13}C NMR analysis of Pd enolate. Characteristic chemical shifts of 1,3-dicarbonyl compounds **5a**–**c** and their Pd enolates **6a**–**c** in CD_2Cl_2.

As in the case of 1,3-diketone-derived enolate **6a**, no reaction proceeded when MVK was added to a solution of **6a**, and TfOH was essential to promote the Michael addition. Therefore, we compared the reactivity of β-ketoamide with β-ketoester and 1,3-diketone using the aqua complex **1a** as a catalyst (Table 1), in order to examine the potential of β-ketoamide as a substrate for enantioselective Michael reaction. Previously we reported Michael reactions of 1,3-diketone **5a** and β-ketoester **5b** with MVK catalyzed by Pd complex **1a**. This reaction proceeded at high concentration (4 M),[3a] but slowed down under more diluted conditions, as shown in Table 1 (entries 1–4). In contrast, surprisingly, the reaction of β-ketoamide **5c** was much faster than that of **5a** or **5b**. Reaction of β-ketoamide **5c** with MVK was completed within 2 h, affording Michael adduct **7c** in high yield and high enantioselectivity (entry 5, 98%, 80% ee). Moreover, even at 0.1 M, β-ketoamide **5c** gave the product with 86% ee in 87% yield (entry 6). Although the enantioselectivity is slightly lower than that observed in the reaction of β-ketoester, β-ketoamide was found to be a good substrate for our Pd-catalyzed enantioselective Michael reaction and showed the highest reactivity among related 1,3-dicarbonyl compounds. It is noteworthy that the reactivity of the 1,3-diketone was very low, despite very fast formation of the Pd enolate. The highly delocalized structure of Pd enolate **6a** may contribute to its stability and low reactivity. In contrast, enolate formation of β-ketoester **5b** was very slow, but its reaction was much faster than that of **5a**. These results suggest that the rate-determining step may be different for each substrate. The β-ketoamide-derived enolate **6c** appears to have good balance of facile formation and high reactivity.

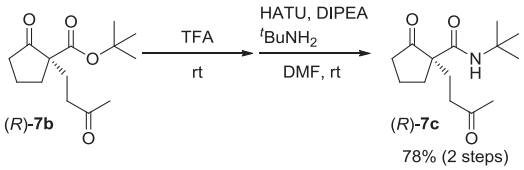
Table 1
Michael reaction between 1,3-dicarbonyl compound and methyl vinyl ketone



Entry	5	Concentration (M)	Time (h)	Yield (%)	ee (%)	Recovery of SM (%)
1	**5a**	1	2	11	ND	54
2	**5a**	0.1	6	9	ND	62
3	**5b**	1	2	82	99	—
4	**5b**	0.1	6	28	98	40
5	**5c**	1	2	98	80	—
6	**5c**	0.1	6	87	86	—

ND:not determined.

We also determined the absolute stereochemistry of the Michael adduct **7c** derived from β-ketoamide **5c**. As previously reported,[3a,f] Michael reaction of β-ketoester **5b** gave (*R*)-adduct **7b**. Since Michael adduct **7c** has never been reported, we examined conversion of (*R*)-**7b** to (*R*)-**7c**. As shown in Scheme 2, (*R*)-**7b** was first converted to the carboxylic acid by treatment with trifluoroacetic acid (TFA), and the following coupling reaction with *tert*-butyl amine afforded (*R*)-**7c** (Scheme 2). By means of HPLC comparison of (*R*)-**7c** with **7c** obtained from the reaction of **5c** using (*R*)-BINAP-Pd complex **1a**, the absolute stereochemistry was determined as (*R*). This result indicates that the enantioselectivity of β-ketoamide is similar to that of β-ketoester.



Scheme 2. Conversion of (*R*)-**7b** to (*R*)-**7c**: determination of the absolute configuration of β-ketoamide **7c**.

In order to confirm the structure of the complex and to investigate the origin of the high enantioselectivity, we next tried to isolate the Pd enolate complexes. After examination of various conditions, we finally succeeded in obtaining crystals of **6a** and **6c**, whose mass values and isotope distribution matched calculated ones (see Supplementary data). The crystal structures of these complexes were solved by X-ray analysis.

The crystal structure of 1,3-diketone-derived Pd enolate **6a** is shown in Fig. 5a. Two ligand P atoms, P(1) and P(2), and two enolate O atoms, O(1) and O(2) are aligned in almost the same plane (the P–Pd–O angles are 176.75 and 175.82°) to form a typical square-planar complex. The distances between Pd and the two P atoms (2.252 and 2.254 Å) are similar, as are those between Pd and the two O atoms (2.034 and 2.049 Å); the bond distances of C(2)–C(3) and C(3)–C(4) (1.407 and 1.393 Å, respectively) are also very similar, indicating the highly delocalized nature of the enolate. As we previously predicted, the *tert*-butyl group is located at the *si*-face side of the enolate plane to avoid steric repulsion with the ligand phenyl group (the torsional angle of O(1)–C(2)–C(1)-^{t}Bu is 77.10°), and blocks a part of the *si*-face. This crystal structure well explains the excellent enantioselectivities observed for **5a** and **5b**. Fig. 5b shows the crystal structure of β-ketoamide-derived Pd enolate **6c**, which also has a square-planar structure with bidentate coordination of the β-ketoamide, but it is greatly distorted. As predicted from the ^{13}C NMR, the C(1)–O(1) bond distance (1.263 Å) is slightly longer than that of a regular amide carbonyl group (1.231 Å),[11] whereas the C(3)–O(2) distance of the ketone (1.286 Å)

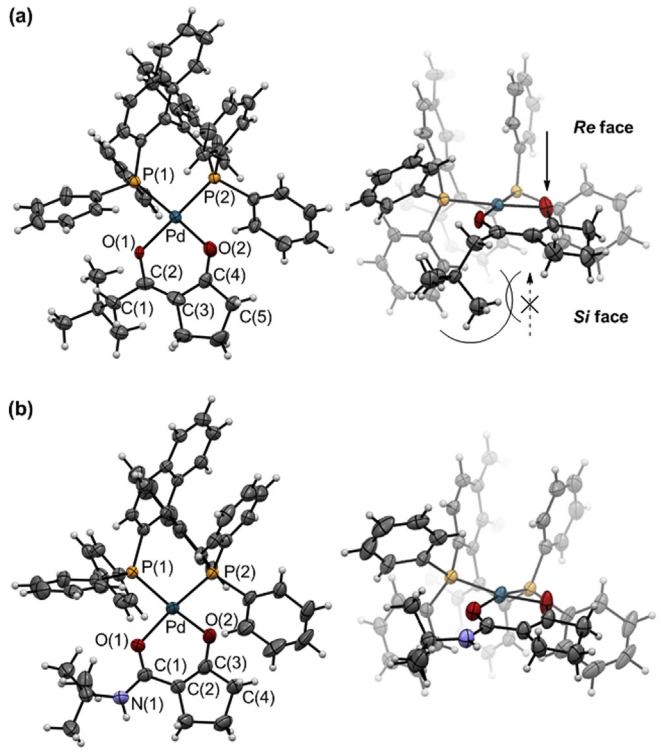
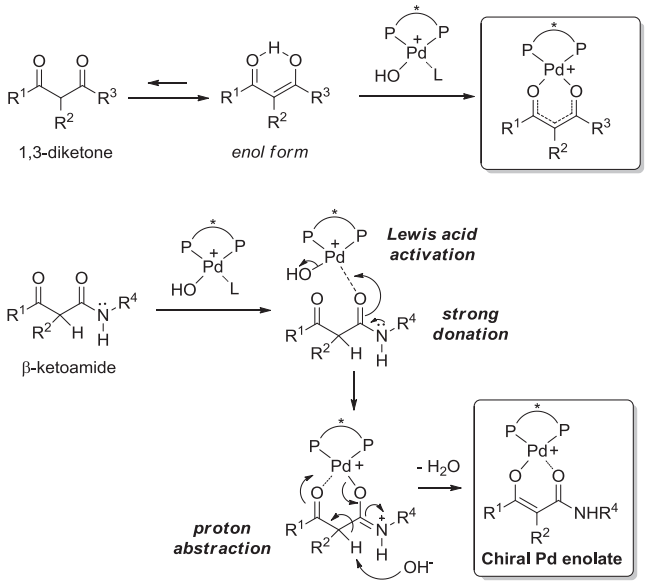


Fig. 5. X-ray crystal structures of Pd enolates **6a** (a) and **6c** (b) derived from 1,3-diketone **5a** and β-ketoamide **5c**, respectively. Selected distances (Å) and angles (deg) are as follows: (a) Pd–P(1) 2.252, Pd–P(2) 2.254, Pd–O(1) 2.049, Pd–O(2) 2.034, C(1)–C(2) 1.500, C(2)–O(1) 1.279, C(2)–C(3) 1.407, C(3)–C(4) 1.393, C(4)–O(2) 1.278, C(4)–C(5) 1.478, P(1)–Pd–P(2) 92.14, P(1)–Pd–O(1) 86.49, O(1)–Pd–O(2) 91.34, O(2)–Pd–P(2) 90.20, P(1)–Pd–O(2) 175.82, P(2)–Pd–O(1) 176.75, (b) Pd–P(1) 2.263, Pd–P(2) 2.246, Pd–O(1) 2.073, Pd–O(2) 2.032, N(1)–C(1) 1.344, C(1)–O(1) 1.263, C(1)–C(2) 1.459, C(2)–C(3) 1.356, C(3)–O(2) 1.286, C(3)–C(4) 1.507, P(1)–Pd–P(2) 91.83, P(1)–Pd–O(1) 90.73, O(1)–Pd–O(2) 92.49, O(2)–Pd–P(2) 86.70, P(1)–Pd–O(2) 171.29, P(2)–Pd–O(1) 167.91. CCDC-1060704 (**6a**) and CCDC-1060705 (**6c**) contain the supplementary crystallographic data.

is much longer than that of cyclopentanones (1.208 Å).[11] The result that the C(2)–C(3) bond (1.356 Å) is much shorter than the C(1)–C(2) bond (1.459 Å) clearly indicates a much less delocalized nature of the enolate. Furthermore, the distance between Pd and O(1) (2.073 Å) is much longer than that between Pd and O(2) (2.032 Å). Thus, it is likely that these two oxygen ligands have different trans effects. Indeed, the Pd–P distances are also different (2.246 and 2.263 Å), in accordance with the fact that the signals of the two P atoms were observed at different chemical shifts in ^{31}P NMR. Furthermore, the bond length between C(1) and N(1) (1.344 Å) is similar to that of a normal secondary amide bond (1.334 Å)[12] and the amide structure is almost planar (torsional angle of O(1)–C(1)–N(1)–^{t}Bu is 5.14°), indicating that the nitrogen lone pair is partially delocalized to the carbonyl group as in a regular amide. It is noteworthy that this complex is greatly distorted from the typical square-planar type structure (the P(2)–Pd–O(1) and P(1)–Pd–O(2) angles are 167.91 and 171.29°, respectively). Steric repulsion between the bulky *tert*-butyl group on the amide nitrogen and the ligand phenyl group may cause the distortion. The observed high enantioselectivity in the Michael reaction of this β-ketoamide **5c** could be explained differently from the cases of 1,3-diketone **5a** and β-ketoester **5b**. In this Pd complex **6c**, the *tert*-butyl group is located in the same plane as the enolate and cannot contribute to discrimination of the two faces. Instead, the *tert*-butyl group has van der Waals contact with a ligand phenyl group and this interaction could be the driving force to distort the enolate plane. As a result, ligand phenyl group located on the *si*-face side is closer to the α-carbon of the enolate than that located on the *re*-face. Thus, MVK would react from the *re*-face to give the *R*-enantiomer in a selective manner.

The kinetics and mechanisms of the reactions between metal ions and 1,3-diketone or β-ketoamide are reported to be different.[12] As for 1,3-diketone **5a**, its enol form was observed to be the major form by ^{1}H NMR, and enolate formation was very rapid. Therefore, we consider that Pd enolate would be produced by reaction between enol and Pd complex, in accordance with the literature[12] (Scheme 3). On the other hand, β-ketoester **5b** and β-ketoamide **5c** mainly exist as keto forms. Therefore, to cleave α-C–H bond, Pd complex **3** is expected to activate the substrate as a Lewis acid. Coordination of the carbonyl group to the cationic Pd center would increase both the acidity of the α-proton and the Brønsted basicity of the hydroxo ligand. Compared with the ester carbonyl group, the amide carbonyl group would have partial negative charge and be more nucleophilic due to strong electron donation from nitrogen,[12] leading to rapid coordination to Pd, rapid proton abstraction, and Pd enolate formation. In contrast to 1,3-diketone **5a**, β-ketoamide **5c** showed the highest reactivity to MVK. Under diluted conditions, reaction of β-ketoamide proceeded much faster than that of **5a** or **5b**. In addition, in the case of the (*R*)-BINAP-Pd enolate complex **6c**, the distorted square-planar structure might affect the reactivity.

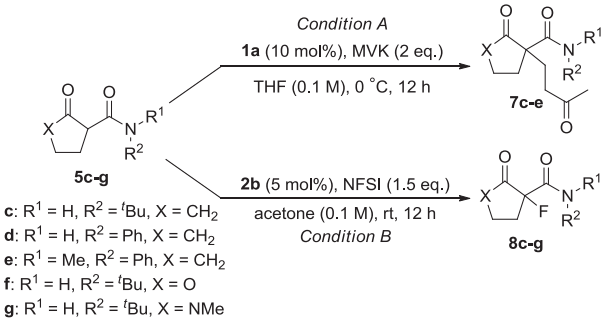


Scheme 3. Plausible pathways for Pd enolate formation from 1,3-diketone and β-ketoamide.

To examine the reaction scope using Pd enolate from β-ketoamide, we prepared cyclic substrates **5d–g** and carried out Michael and fluorination reactions. As shown in Table 2, Michael reaction of *N*-phenylketoamide **5d** catalyzed by Pd aqua complex **1a** in THF (condition A) smoothly proceeded to give the desired product **7d**, though the ee was not as good as in the case of **7c** (entries 1 and 2). The absolute configuration of compound **7d** was determined to be *R* by comparison of its optical rotation with the reported value.[8b] In addition, reaction of tertiary β-ketoamide **5e** proceeded at room temperature without difficulty (entries 3 and 4); this is the first enantioselective Michael reaction using tertiary β-ketoamide, to our knowledge. Unfortunately, the Michael reaction did not proceed for substrates **5f** and **5g**.

Reaction of **5c** with NFSI catalyzed by **2a** also proceeded smoothly to give the fluorinated product **8c** in 98% yield and 72% ee (entry 5). The enantioselectivity was increased to 88% ee by using (*R*)-DM-BINAP-Pd complex **2b** as a catalyst (entry 6). Moreover,

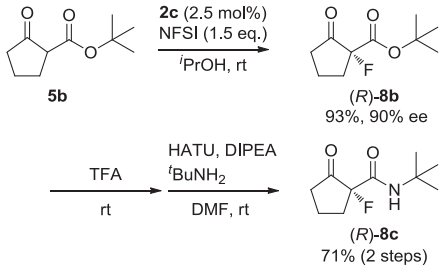
Table 2
Michael and fluorination reactions of cyclic β-ketoamide compounds



Entry	5	Condition	Product	Yield (%)	ee (%)	Recovery of SM (%)
1	**5c**	A	**7c**	98	88	—
2	**5d**	A	**7d**	98	69	—
3	**5e**	A	**7e**	21	62	71
4	**5e**	A[a]	**7e**	77	61	—
5	**5c**	B[b,c]	**8c**	98	72	—
6	**5c**	B[c]	**8c**	85	88	—
7	**5c**	B	**8c**	72	90	—
8	**5d**	B	**8d**	86	66	—
9	**5e**	B	**8e**	81	59	—
10	**5f**	B[d]	**8f**	96	79	—
11	**5g**	B[d]	**8g**	29	77	>70
12	**5g**	B[d,e]	**8g**	66	83	10

[a] Reaction temperature: rt.
[b] Catalyst: **2a**.
[c] Solvent: THF.
[d] Reaction time: 24 h.
[e] 2,6-Lutidine of 1 equiv was added.

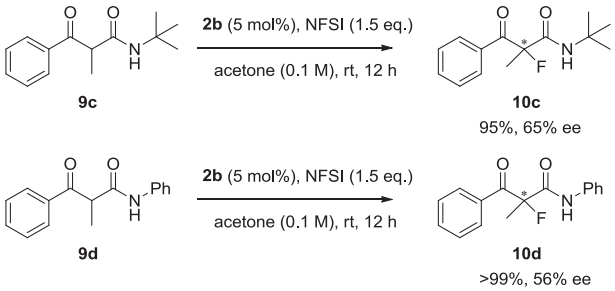
when acetone was used as a solvent instead of THF (condition B), fluorinated β-ketoamide **8c** was obtained with the highest enantioselectivity (entry 7, 72%, 90% ee). The absolute configuration of the fluorinated β-ketoamide **8c** was determined in the same manner as described for **7c**. The known fluorinated β-ketoester (*R*)-**8b**[3a,7a] was obtained by fluorination reaction using Pd catalyst **2c**, and converted to (*R*)-**8c** through the carboxylic acid (Scheme 4). HPLC analysis indicated the absolute stereochemistry of **8c** obtained by the reaction of **5c** to be (*R*). This enantioselectivity is also in agreement with the prediction based on the X-ray crystal structure. In the fluorination reaction using Pd μ-hydroxo complex **2b**, both secondary and tertiary ketoamides **5d** and **5e** showed high reactivity, and products **8d** and **8e** with modest ee were obtained in good yields (entries 8 and 9).



Scheme 4. Determination of the absolute configuration of β-ketoamide **8c**.

Moreover, in contrast to Michael reaction, amide-ester compound **5f** smoothly reacted with highly electrophilic NFSI, providing fluorinated product **8f** with good enantioselectivity in excellent yield (entry 10, 96%, 79% ee). However, fluorination reaction of diamide compound **5g** was much slower, and more than 70% of the starting material was recovered (entry 11). But, addition of 2,6-lutidine[3n] promoted the reaction to give the product **8g** with 83% ee in 66% yield (entry 12).

Fluorination reactions of the acyclic compounds **9c** and **9d** were also examined, and the products **10c** and **10d** were obtained in excellent yields with moderate enantioselectivities (Scheme 5).



Scheme 5. Fluorination reaction of acyclic β-ketoamides.

3. Conclusions

In this study, we examined enantioselective Michael and fluorination reactions of β-ketoamides catalyzed by Pd complex. The Michael reaction of β-ketoamide was found to be much faster than that of 1,3-diketone or β-ketoester. The rate of Pd enolate formation of β-ketoamide was faster than that of β-ketoester, suggesting an important role of coordination of the amide carbonyl group to cationic Pd for enolate formation. The crystal structures of (*R*)-BINAP-Pd enolate complexes **6a** and **6c** derived from 1,3-diketone and β-ketoamide were solved, and explain the origin of the observed high enantioselectivity. Our Pd enolate chemistry is applicable to both secondary and tertiary β-ketoamides, indicating that reactions via β-ketoamide-derived Pd enolate have a broad scope. Enantioselectivity varied depending on substrate and ligand structures. The crystal structures of the Pd enolates obtained in this study should be useful information for selecting appropriate chiral ligand and substrate combinations.

4. Experimental section

4.1. General

All asymmetric reactions were performed without precautions to exclude air and moisture. Catalysts were prepared according to the reported procedure.[2b,3a] NMR spectra were measured on a JEOL JNM-ECS-400 or JNM-AL 300 spectrometer. For ^{1}H NMR and ^{13}C NMR, chemical shifts were reported relative to the solvent (internal standard). For ^{19}F NMR, chemical shifts were reported in the scale relative to $CFCl_3$ as an external standard. ^{31}P NMR chemical shifts are reported relative to triphenylphosphine as an external standard. ESI-MS was taken on a Bruker micrOTOF-QII-RSL. Optical rotation was measured with a JASCO P-2200 polarimeter. Column chromatography was performed with silica gel 60N (40–50 μm) purchased from Kanto Chemical Co., Inc. The enantiomeric excesses were determined by HPLC. HPLC was performed on JASCO HPLC systems consisting of the following components: pump, PU-2080 Plus; detector, CD-2095 Plus set at 254 or 280 nm; column, DAICEL CHIRALPACK AD-H and AS-H; mobile phase, hexane/2-propanol (IPA). Dehydrated solvents were purchased from Kanto Chemical Co., Inc.

4.2. Procedure for measuring kinetics of Pd enolate formation

A dry NMR tube was charged with compound **5** (10 mg, 0.055 mmol), Pd μ-hydroxo complex **2a** ((*R*)-BINAP, 49 mg,

0.027 mmol), and acetone-d_6 (0.6 mL). The sample was quickly loaded into the NMR machine, and the ^{31}P NMR spectrum was measured. Formation of Pd enolate complex was followed in terms of the signal integration ratio between Pd μ-hydroxo complex and Pd enolate.

4.3. Isolation of Pd enolate complex 6

*4.3.1. Pd enolate complex **6a**.* To a solution of compound **5a** (30 mg, 0.17 mmol) in CH_2Cl_2 (1.7 mL) was added catalyst **2a** (150 mg, 0.083 mmol) at ambient temperature. The resultant solution was stirred at ambient temperature for 1 h. To obtain the Pd enolate complex as a solid, hexane was added to the solution. The Pd enolate complex was precipitated as a yellow powder. The powder was collected by filtration, and washed with hexane. The desired Pd enolate complex **6a** was obtained in 82% yield (143.5 mg), and was recrystallized from CH_2Cl_2/*n*-hexane.

^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.69–7.37 (m, 22H), 7.21–7.16 (m, 2H), 7.01–6.98 (m, 2H), 6.85–6.73 (m, 4H), 6.73–6.69 (m, 2H), 2.65–2.56 (m, 2H), 2.16 (d, *J*=11.8 Hz, 1H), 2.03–1.95 (m, 1H), 1.88–1.80 (m, 1H), 1.75–1.68 (m, 2H), 1.19 (d, *J*=11.8 Hz, 1H), 0.48 (s, 9H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 193.0, 185.4, 139.8–119.9 (m, 44C), 110.9, 50.4, 38.8, 32.5, 30.7, 29.9 (3C), 21.4; ^{31}P NMR (160 MHz, CD_2Cl_2): δ 31.7; HRMS (ESI) calcd for $C_{55}H_{49}O_2P_2Pd$ $[M]^+$ 909.2256, found 909.2175.

*4.3.2. Pd enolate complex **6c**.* To a solution of compound **5c** (20 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) was added catalyst **2a** (100 mg, 0.056 mmol) at ambient temperature. The resultant solution was stirred at room temperature for 1 h. Addition of Et_2O to the solution precipitated the Pd enolate complex as a reddish orange powder. The powder was collected by filtration, and washed with Et_2O. The desired Pd enolate complex **6c** was obtained in 81% yield (94 mg), and was recrystallized from acetone/n-hexane.

^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.91–7.86 (m, 2H), 7.67–7.42 (m, 20H), 7.22–7.14 (m, 2H), 7.01–6.95 (m, 3H), 6.79–6.69 (m, 5H), 4.91 (br s, 1H), 2.39–2.26 (m, 2H), 1.99–1.91 (m, 1H), 1.78–1.72 (m, 2H), 1.70–1.61 (m, 1H), 0.54 (s, 9H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 182.1, 166.5, 135.6–120.9 (m, 44C), 96.2, 51.5, 38.0, 29.5, 28.7 (3C), 20.8; ^{31}P NMR (160 MHz, CD_2Cl_2): δ 34.3 (d, *J*=25.8 Hz), 27.7 (d, *J*=25.8 Hz); HRMS (ESI) calcd for $C_{54}H_{48}NO_2P_2Pd$ $[M]^+$ 910.2208, found 910.2218.

4.4. X-ray crystallographic analysis of Pd enolate complex 6

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-1060704 (**6a**) and CCDC-1060705 (**6c**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK [Fax: +44 1223 336 033; E-mail: deposit@ccdc.cam.ac.uk].

*4.4.1. Crystal data for **6a**.* $(C_{55}H_{49}O_2P_2Pd)(CF_3O_3S)$, Fw: 1059.35, crystal system: orthorhombic, space group: $P2_12_12_1$, unit cell dimensions; *a*=12.1411(1) Å, *b*=15.8771(2) Å, *c*=27.3220(3) Å, *V*=5266.74(10) Å^3, *Z*: 4, density (calcd): 1.336 Mg/m^3, temperature: 90 K, reflections collected: 147,680, independent reflections: 16,737, final *R* indices: $R(F)$=0.0842, $wR(F^2)$=0.2168 and *S*=1.128 (for 15,290 reflections with $I>2\sigma(I)$), $wR(F^2)$=0.2197 and *S*=1.119 (for all data, 147,680 reflections).

*4.4.2. Crystal data for **6c**.* $(C_{54}H_{48}NO_2P_2Pd)(CF_3O_3S)\cdot 2(C_3H_6O)$, Fw: 1176.50, crystal system: orthorhombic, space group: $P2_12_12_1$, unit cell dimensions; *a*=12.0980(1) Å, *b*=16.3983(2) Å, *c*=27.0237(3) Å, *V*=5361.14(10) Å^3, *Z*: 4, density (calcd): 1.458 Mg/m^3, temperature: 90 K, reflections collected: 90,610, independent reflections: 17,194, final *R* indices: $R(F)$=0.0577, $wR(F^2)$=0.1622 and *S*=1.036 (for 13,469 reflections with $I>2\sigma(I)$), $wR(F^2)$=0.1768 and *S*=1.035 (for all data, 17,194 reflections).

4.5. General procedure for catalytic enantioselective Michael reaction (condition A)

The palladium catalyst **1** (0.0055 mmol, 10 mol %) was dissolved in a solvent (0.55 mL, 0.1 M). To this solution was added β-ketoamide **5** (0.055 mmol) at ambient temperature. At the indicated temperature, methyl vinyl ketone (0.11 mmol, 2 equiv) was added. The resulting mixture was stirred at the same temperature. After completion of the reaction, saturated aqueous NH_4Cl was added for quenching. The aqueous layer was extracted with ethyl acetate (AcOEt). The combined organic layers were dried over $MgSO_4$. Removal of the solvent under reduced pressure, followed by preparative TLC (eluent: *n*-hexane/AcOEt system) afforded the product **7**.

*4.5.1. N-(tert-Butyl)-2-oxo-1-(3-oxobutyl)cyclopentanecarboxamide (**7c**).* White solid; 98%, 88% ee; $[\alpha]_D^{24}$ +27.0 (*c* 1.03, $CHCl_3$) >99% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.57 (br s, 1H), 2.57 (m, 1H), 2.43 (t, *J*=7.8 Hz, 2H), 2.34 (t, *J*=7.8 Hz, 2H), 2.13 (s, 3H), 2.02–1.95 (m, 1H), 1.91–1.71 (m, 4H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 220.9, 207.5, 167.9, 60.0, 51.4, 38.9, 38.7, 31.9, 30.6, 30.2, 28.7 (3C), 19.0; HRMS (ESI) calcd for $C_{14}H_{23}NO_3$ $[M+Na]^+$ 276.1570; found 276.1574; HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/EtOH=97:3, 0.5 mL/min, 254 nm) t_R (major)=23.8 min, t_R (minor)=32.3 min.

*4.5.2. 2-Oxo-1-(3-oxobutyl)-N-phenylcyclopentanecarboxamide (**7d**).* Colorless oil; 98%, 69% ee; $[\alpha]_D^{25}$ −49.2 (*c* 0.51, $CHCl_3$) 69% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (br s, 1H), 7.53 (d, *J*=8.6 Hz, 2H), 7.33 (dd, *J*=8.6, 7.2 Hz, 2H), 7.11 (t, *J*=7.2 Hz, 1H), 2.68–2.60 (m, 1H), 2.52 (t, *J*=7.8 Hz, 2H), 2.47–2.40 (m, 2H), 2.12 (s, 3H), 2.14–2.09 (m, 1H), 2.00–1.91 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 220.9, 207.1, 167.2, 137.6, 129.2 (2C), 124.6, 119.9 (2C), 60.0, 38.9, 38.7, 31.7, 30.5, 30.3, 18.8; HRMS (ESI) calcd for $C_{16}H_{19}NO_3$ $[M+Na]^+$ 296.1257; found 296.1258; HPLC (DAICEL CHIRALPAK AS-H, *n*-hexane/IPA=90:10, 1.0 mL/min, 254 nm) t_R (minor)=22.3 min, t_R (major)=28.9 min.

*4.5.3. N-Methyl-2-oxo-(3-oxobutyl)-N-phenylcyclopentanecarboxamide (**7e**).* Colorless oil; 77%, 61% ee; $[\alpha]_D^{26}$ +53.9 (*c* 0.48, $CHCl_3$) 61% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.33 (m, 3H), 7.16 (br d, *J*=6.8 Hz, 2H), 3.23 (s, 3H), 2.77–2.60 (m, 2H), 2.47–2.39 (m, 1H), 2.11 (s, 3H), 2.05–1.24 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.8, 208.8, 171.3, 142.3, 130.6, 129.6 (2C), 128.6 (2C), 59.4, 40.5, 39.2, 37.5, 35.9, 30.2, 28.6, 19.0; HRMS (ESI) calcd for $C_{17}H_{21}NO_3$ $[M+Na]^+$ 310.1414; found 310.1415; HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA=95/5, 1.0 mL/min, 254 nm) t_R (major)=29.8 min, t_R (minor)=33.4 min.

4.6. General procedure for catalytic enantioselective fluorination (condition B)

The palladium catalyst **2** (0.0028 mmol, 5 mol %) was dissolved in a solvent (0.55 mL, 0.1 M). To this solution was added β-ketoamide **5** (0.055 mmol) at ambient temperature. At the indicated temperature, NFSI (0.082 mmol, 1.5 equiv) was added, and the resulting mixture was stirred at the same temperature. After completion of the reaction, saturated aqueous NH_4Cl was added for quenching. The aqueous layer was extracted with AcOEt. The combined organic layers were dried over $MgSO_4$. Removal of the solvent under reduced pressure, followed by preparative TLC (eluent: *n*-hexane/AcOEt system) afforded the product **8**.

*4.6.1. 1-Fluoro-2-oxo-N-(tert-butyl)cyclopentanecarboxamide (**8c**).* White solid; 72%, 90% ee; $[\alpha]_D^{22}$ +96.4 (*c* 0.90, $CHCl_3$) >99% ee; ^1H NMR (400 MHz, $CDCl_3$): δ 6.21 (br s, 1H), 2.71–2.61 (m, 1H), 2.52–2.37 (m, 2H), 2.26–2.02 (m, 3H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.0 (d, J_{C-F}=16.2 Hz), 166.9 (d, J_{C-F}=21.0 Hz), 96.4 (d, J_{C-F}=201.4 Hz), 51.9, 36.1, 33.3 (d, J_{C-F}=20.0 Hz), 28.7 (3C), 18.4 (d, J_{C-F}=3.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −158.5 (dd, *J*=22.9, 22.9 Hz); HRMS (ESI) calcd for $C_{10}H_{16}FNO_2$ $[M+Na]^+$ 224.1057; found 224.1058; HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA=99:1, 0.8 mL/min, 254 nm) t_R (major)=12.5 min, t_R (minor)=16.3 min.

*4.6.2. 1-Fluoro-2-oxo-N-phenylcyclopentanecarboxamide (**8d**).* White solid; 86%, 66% ee; $[\alpha]_D^{25}$ +53.1 (*c* 0.43, $CHCl_3$) 66% ee; ^1H NMR (400 MHz, $CDCl_3$): δ 8.07 (br s, 1H), 7.54 (d, *J*=8.8 Hz, 2H), 7.34 (dd, *J*=8.8, 7.2 Hz, 2H), 7.16 (t, *J*=7.2 Hz, 1H), 2.85–2.74 (m, 1H), 2.63–2.45 (m, 2H), 2.37–2.23 (m, 2H), 2.19–2.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.0 (d, J_{C-F}=16.1 Hz), 165.6 (d, J_{C-F}=21.9 Hz), 136.5, 129.2 (2C), 125.4, 120.2 (2C), 96.8 (d, J_{C-F}=201.4 Hz), 36.1, 33.4 (d, J_{C-F}=20.0 Hz), 18.4 (d, J_{C-F}=3.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −159.5 (dd, *J*=22.9, 22.9 Hz); HRMS (ESI) calcd for $C_{12}H_{12}FNO_2$ $[M+Na]^+$ 244.0744; found 244.0745; HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA=95:5, 1.0 mL/min, 254 nm) t_R (major)=12.6 min, t_R (minor)=16.9 min.

*4.6.3. 1-Fluoro-2-oxo-N-methyl-N-phenylcyclopentanecarboxamide (**8e**).* Colorless oil; 81%, 59% ee; $[\alpha]_D^{25}$ +43.4 (*c* 0.43, $CHCl_3$) 59% ee; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (dd, *J*=7.6, 7.2 Hz, 2H), 7.33 (t, *J*=7.2 Hz, 1H), 7.25 (d, *J*=7.6 Hz, 2H), 3.30 (br s, 3H), 2.76–2.55 (m, 1H), 2.54–2.30 (m, 2H), 2.23–2.04 (m, 2H), 2.03–1.88 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 209.4 (d, J_{C-F}=17.3 Hz), 167.3 (d, J_{C-F}=21.6 Hz), 142.6, 129.1 (2C), 127.6, 126.7 (2C), 96.9 (d, J_{C-F}=206.6 Hz), 38.8, 35.6, 34.7, 17.6; ^{19}F NMR (376 MHz, $CDCl_3$): δ −153.9 (br s); HRMS (ESI) calcd for $C_{13}H_{14}FNO_2$ $[M+Na]^+$ 258.0901 found 258.0901; HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA=95:5, 1.0 mL/min, 254 nm) t_R (major)=13.1 min, t_R (minor)=14.4 min.

*4.6.4. N-(tert-Butyl)-3-fluoro-2-oxotetrahydro-3-furancarboxamide (**8f**).* White solid; 96%, 79% ee; $[\alpha]_D^{24}$ −8.02 (*c* 0.38, $CHCl_3$) 79% ee; ^1H NMR (400 MHz, $CDCl_3$): δ 6.32 (br s, 1H), 4.59–4.48 (m, 2H), 3.03–2.94 (m, 1H), 2.64–2.51 (m, 1H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2 (d, J_{C-F}=23.8 Hz), 165.0 (d, J_{C-F}=21.0 Hz), 92.7 (d, J_{C-F}=206.2 Hz), 66.4 (d, J_{C-F}=4.8 Hz), 52.4, 32.8 (d, J_{C-F}=20.0 Hz), 28.6 (3C); ^{19}F NMR (376 MHz, $CDCl_3$): δ −159.6 (ddd, *J*=26.3, 10.4, 4.7 Hz); HRMS (ESI) calcd for $C_9H_{14}FNO_3$ $[M+Na]^+$ 226.0850; found 226.0853. HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA=95:5, 1.0 mL/min, 254 nm) t_R (major)=9.22 min, t_R (minor)=11.4 min.

*4.6.5. N-(tert-Butyl)-3-fluoro-1-methyl-2-oxo-3-pyrrolidine carboxamide (**8g**).* White solid; 66%, 83% ee; $[\alpha]_D^{25}$ +17.2 (*c* 0.26, $CHCl_3$) 83% ee; ^1H NMR (400 MHz, $CDCl_3$): δ 6.39 (br s, 1H), 3.57–3.50 (m, 1H), 3.44–3.39 (m, 1H), 2.94 (s, 3H), 2.86–2.77 (m, 1H), 2.33–2.19 (m, 1H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5 (d, J_{C-F}=23.8 Hz), 166.9 (d, J_{C-F}=22.0 Hz), 95.7 (d, J_{C-F}=199.5 Hz), 52.0, 46.3 (d, J_{C-F}=3.8 Hz), 30.6, 29.4 (d, J_{C-F}=21.0 Hz), 28.7 (3C); ^{19}F NMR (376 MHz, $CDCl_3$): δ −155.7 to −155.8 (m); HRMS (ESI) calcd for $C_{10}H_{17}FN_2O_2$ $[M+Na]^+$ 239.1166; found 239.1194. HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA=95:5, 1.0 mL/min, 254 nm) t_R (major)=9.45 min, t_R (minor)=14.4 min.

*4.6.6. N-(tert-Butyl)-2-fluoro-2-methyl-3-oxo-3-phenylpropanamide (**10c**).* White solid; 95%, 65% ee; $[\alpha]_D^{24}$ +77.5 (*c* 0.80, $CHCl_3$) 65% ee; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J*=8.4 Hz, 2H), 7.56 (t, *J*=7.6 Hz, 1H), 7.44 (dd, *J*=8.4, 7.6 Hz, 2H), 6.28 (br s, 1H), 1.84 (d, J_{H-F}=23.3 Hz, 3H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.9 (d, J_{C-F}=23.9 Hz), 167.5 (d, J_{C-F}=20.1 Hz), 134.1, 133.6, 129.6 (d, J_{C-F}=3.8 Hz, 2C), 128.6 (2C), 99.0 (d, J_{C-F}=194.7 Hz), 52.0, 28.7 (3C), 21.8 (d, J_{C-F}=22.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −148.3 (q, *J*=23.3 Hz); HRMS (ESI) calcd for $C_{14}H_{18}FNO_2$ $[M+Na]^+$ 274.1214; found 274.1214. HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA=99:1, 0.8 mL/min, 254 nm) t_R (major)=15.7 min, t_R (minor)=18.7 min.

*4.6.7. 2-Fluoro-2-methyl-3-oxo-3-phenyl-N-phenylpropanamide (**10d**).* White solid; >99%, 56% ee; $[\alpha]_D^{25}$ −45.0 (*c* 0.50, $CHCl_3$) 56% ee; ^1H NMR (400 MHz, $CDCl_3$): δ 8.20 (br s, 1H), 8.04 (d, *J*=8.4 Hz, 2H), 7.58 (d, *J*=8.0 Hz, 2H), 7.58 (t, *J*=7.8 Hz, 1H), 7.45 (dd, *J*=8.4, 7.8 Hz, 2H), 7.36 (dd, *J*=8.0, 7.6 Hz, 2H), 7.18 (t, *J*=7.6 Hz, 1H), 1.99 (d, J_{H-F}=25.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.7 (d, J_{C-F}=23.9 Hz), 166.5 (d, J_{C-F}=21.0 Hz), 136.6, 134.0, 133.8 (d, J_{C-F}=2.9 Hz), 129.7 (d, J_{C-F}=3.9 Hz, 2C), 129.4 (2C), 128.8 (2C), 125.4, 120.2 (2C), 99.4 (d, J_{C-F}=195.7 Hz), 22.2 (d, J_{C-F}=22.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −149.5 (q, *J*=25.0 Hz); HRMS (ESI) calcd for $C_{16}H_{14}FNO_2$ $[M+Na]^+$ 294.0901; found 294.0904. HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA=95:5, 1.0 mL/min, 254 nm) t_R (minor)=20.0 min, t_R (major)=23.8 min.

4.7. Determination of absolute configurations of Michael adduct 7c and fluorinated β-ketoamide (8c)

*4.7.1. (R)-N-(tert-Butyl)-2-oxo-1-(3-oxyobuthyl)cyclopentanecarboxamide ((R)-**7c**) from (R)-**7b**.* (*R*)-**7b** (11.2 mg, 0.0440 mmol, 90% ee) was dissolved in TFA (0.2 mL), and the solution was stirred at ambient temperature for 20 min. The solvent was evaporated under reduced pressure to give the carboxylic acid, which was used directly in the synthesis of the *tert*-butyl amide. To the solution of carboxylic acid in DMF (0.1 mL) were added HATU (33.2 mg, 0.0873 mmol), DIPEA (38 μL, 0.221 mmol), and *tert*-butyl amine (9.5 μL, 0.088 mmol). The solution was stirred under a N_2 atmosphere at ambient temperature for 1.5 h, and then the reaction mixture was purified by flash column chromatography on silica gel (*n*-hexane/AcOEt=1:1) to give the desired product (*R*)-**7c** (8.8 mg, 0.0347 mmol, 78%, two steps). $[\alpha]_D^{25}$ +20.9 (*c* 0.44, $CHCl_3$); HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/EtOH=97:3, 0.5 mL/min, 254 nm) t_R=23.7 min. The spectra of ^1H NMR, ^{13}C NMR, and HRMS were consistent with compound **7c**.

*4.7.2. (R)-N-(tert-Butyl)-1-fluoro-2-oxocyclopentanecarboxylate (**8b**).* To a solution of **5b** (101 mg, 0.547 mmol) in IPA (0.55 mL) were added (*R*)-DTBM-SEGPHOS Pd μ-hydroxo complex **2c** (39.6 mg, 0.0137 mol) and NFSI (260 mg, 0.821 mmol). The solution was stirred under a N_2 atmosphere at ambient temperature for 27 h, and then the reaction mixture was purified by flash column chromatography on silica gel (CH_2Cl_2) to give the desired product (*R*)-**8b** (103 mg, 0.509 mmol, 93%). $[\alpha]_D^{25}$ +81.4 (*c* 1.04, $CHCl_3$) 90% ee; HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA=99:1, 0.4 mL/min, 280 nm) t_R (minor)=21.8 min, t_R (major)=27.6 min. The spectra of ^1H NMR were consistent with the literature.[3b]

*4.7.3. (R)-N-(tert-Butyl)-1-fluoro-2-oxocyclopentanecarboxamide ((R)-**8c**) from (R)-**8b**.* (*R*)-**8b** (28.2 mg, 0.139 mmol, 90% ee) was dissolved in TFA (0.3 mL), and the solution was stirred at ambient temperature for 40 min. The solvent was evaporated under reduced pressure to give the carboxylic acid, which was used directly in the synthesis of the *tert*-butyl amide. To the solution of carboxylic acid in DMF (0.1 mL) were added HATU (82.0 mg, 0.216 mmol), DIPEA (95.6 μL, 0.558 mmol), and *tert*-butyl amine (30.2 μL, 0.279 mmol). The solution was stirred under a N_2 atmosphere at ambient temperature for 21 h, and then the reaction mixture was purified by flash column chromatography on silica gel (CH_2Cl_2) to give the

desired product (*R*)-**8c** (19.9 mg, 0.0989 mol, 71%, two steps). $[\alpha]_D^{23}$ +88.2 (*c* 0.98, $CHCl_3$); HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA=99:1, 0.8 mL/min, 254 nm) t_R=12.9 min. The spectra of ^1H NMR, ^{13}C NMR, and HRMS were consistent with compound **8c** derived from **5c**.

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Supplementary data

Details of synthesis of substrates and copies of ^1H and ^{13}C NMR spectra and HPLC charts of compounds. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.07.002.

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