Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 7168–7179
Tetrahedron

# Highly enantioselective fluorination reactions of β-ketoesters and β-ketophosphonates catalyzed by chiral palladium complexes

Yoshitaka Hamashima,[a] Toshiaki Suzuki,[a] Hisashi Takano,[a] Yuta Shimura,[a] Yasunori Tsuchiya,[a] Ken-ichi Moriya,[a] Tomomi Goto[a] and Mikiko Sodeoka[a,b,*]

[a]*Institute of Multidisciplinary Research for Advanced Materials, Tohoku University, 2-1-1 Katahira, Aoba-ku, Sendai 980-8577, Japan*
[b]*RIKEN (The Institute of Physical and Chemical Research), 2-1 Hirosawa, Wako, 351-0198, Japan*

Received 11 December 2005; accepted 12 December 2005
Available online 6 May 2006

**Abstract**—Using chiral palladium enolates as key intermediates, efficient catalytic enantioselective fluorination reactions of active methine compounds have been developed. These reactions can be conducted in alcoholic solvents without any precaution to exclude water and moisture, and various β-ketoesters and β-ketophosphonates were fluorinated in a highly enantioselective manner (up to 98% ee).


## 1. Introduction

Acquisition of novel activity distinct from that of the parent compound by replacing atom(s) in a biologically active compound with other atom(s) is a very important aspect of medicinal chemistry. In particular, introduction of fluorine, which rarely occurs in natural products, into bioactive compounds sometimes leads to significant improvement of their biological activity profiles,[1] probably due to the unique properties of the fluorine atom and/or the carbon–fluorine bond (Chart 1).

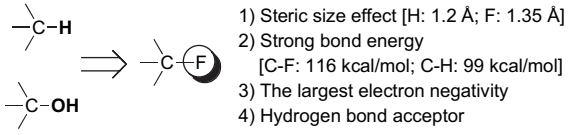


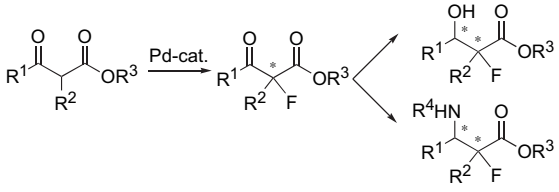

**Chart 1**. Properties of the fluorine atom and carbon–fluorine bonds.

For this reason, the effect of fluorine-substitution is often examined in the course of development of new drug candidates. Most such investigations have focused on replacement of hydrogen(s) on an aromatic ring with fluorine atom(s). The effect of substitution at $sp^3$ carbons has been less well investigated. For the synthesis of chiral fluorinated compounds, application of well-established asymmetric reactions, including hydrogenation of olefins, reduction of ketones, aldol reactions, and ene reactions, to fluorinated starting materials is an important strategy, and thus chiral compounds, which do not have a fluorine atom at a chiral carbon center can be utilized for the preparation of fluorinated drug candidates.[2,3] However, the use of optically active compounds bearing a fluorine atom at a chiral carbon center is restricted by the limited availability of effective methods for enantioselective construction of fluorinated stereogenic carbon centers. Thus, enantioselective synthesis of organofluorine compounds via direct introduction of fluorine atoms is still a highly desirable goal in synthetic organic chemistry.[4] In addition to diastereoselective fluorination reactions,[5] great efforts have been made to develop chiral fluorinating reagents.[6] Shibata et al. and Cahard et al. independently reported an ingenious procedure that allows in situ generation of a chiral fluorinating reagent from cinchona alkaloids and Selectfluor (see Chart 3).[7] Since the initial reports by Togni et al., catalytic enantioselective fluorination reactions have been attracting much attention.[8,9] In 2002, on the basis of our palladium enolate chemistry, we developed an efficient method for enantioselective fluorination reactions with high generality as regards β-ketoesters.[10] Subsequent studies from other laboratories revealed that late transition metal complexes consisting of Cu(II), Ni(II), and Zn(II) were also excellent catalysts for catalytic enantioselective fluorination reactions of active methine compounds.[11] Several groups have reported attempts at applying organocatalysis to asymmetric fluorination reactions, and catalytic enantioselective monofluorination of aldehydes having two hydrogens at the α-position has been achieved.[12,13] Although the scope of available substrates for asymmetric fluorination reactions is rapidly expanding, continuing exploitation of novel catalysts, including metal

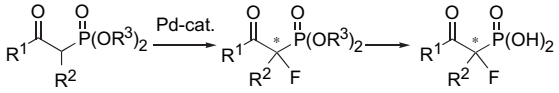
*Keywords*: Fluorination; Palladium; β-Ketoesters; β-Ketophosphonates; Asymmetric catalysis.
* Corresponding author. Tel./fax: +81 22 217 5601; e-mail addresses: sodeoka@tagen.tohoku.ac.jp; sodeoka@riken.jp

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.12.070

complexes and organic catalysts, is necessary to meet the need for various chiral fluorinated compounds, many of which are expected to find applications in the fields of medicinal chemistry, chemical biology, and material sciences. Herein, we present full details of our study on the catalytic enantioselective fluorination reactions of β-ketoesters and β-ketophosphonates (Eqs. 1 and 2).[10] Our palladium complexes were effective catalysts for such active methine compounds, affording the corresponding fluorinated products in a highly enantioselective manner (up to 98% ee). We confirmed the utility of our methods by stereoselective syntheses of fluorinated derivatives of fundamental units found in biologically active natural and unnatural compounds.



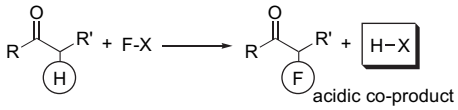

(1)



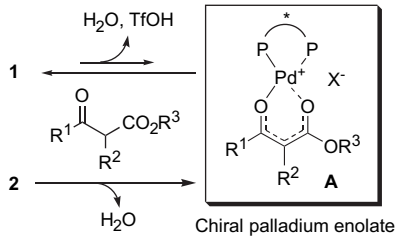

(2)

## 2. Results and discussion

In principle, electrophilic fluorination reactions of carbonyl compounds entail concomitant generation of an acidic coproduct during the reaction (Eq. 3). It seems difficult to carry out the reaction in the presence of strongly basic catalysts to remove a hydrogen atom at the α-position, because decomposition or neutralization of the catalysts might occur. Thus, activation of the nucleophiles under acidic or neutral conditions would be a promising alternative approach to carry out enantioselective electrophilic fluorination catalytically. We have already reported that the cationic palladium complexes **1** and **2** reacted with 1,3-dicarbonyl compounds, such as β-ketoesters, to form chiral palladium enolates **A** (Chart 2 and Scheme 1).[14] Because the palladium aqua and μ-hydroxo complexes are inherently acidic or neutral, this enolate formation is considered to occur under nonbasic conditions. We envisaged that this palladium enolate chemistry would be applicable to enantioselective electrophilic fluorination reactions. Development of the fluorination reactions of β-ketoesters is valuable, because optically active α-substituted α-fluoro-β-ketoesters are regarded as nonenolizable β-ketoesters. In addition, since ketone is easily converted to other functional groups, α-substituted α-fluoro-β-ketoesters would be versatile synthetic precursors of various α-fluorinated carboxylic acid derivatives. Therefore, we planned to examine the enantioselective fluorination reactions of β-ketoesters using the palladium complexes **1** and **2**.

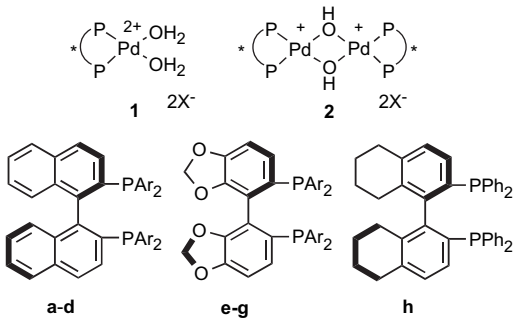



(3)




**Scheme 1**. Formation of chiral palladium enolates.

Since a bulky ester moiety was found to be essential for high asymmetric induction in our previous study on catalytic asymmetric Michael reactions,[14] we chose *tert*-butyl 2-oxo-cyclopentanecarboxylate **3a** as a model substrate. Among several electrophilic fluorinating reagents, *N*-fluorobenzenesulfonimide (NFSI) **4** was the most effective (Chart 3). While salt-type reagents, such as **5** and **6**, did not give the desired product **7a** in a detectable amount, the reaction of **3a** with **4** under the influence of **1a** (5 mol %) in THF proceeded smoothly to afford **7a** in 72% yield with 79% ee (Table 1, entry 1). It should be noted that the palladium complex retained its catalytic activity until the completion of the reaction. In contrast, a stoichiometric amount of a conventional base would be required for the reaction with NFSI, because sulfonimide [$(PhSO_2)_2NH$] with high acidity was formed during the reaction. Therefore, our reaction system was considered suitable for the development of fluorination reactions.




**a**: Ar = Ph: (*R*)-BINAP
**b**: Ar = 4-$MeC_6H_4$: (*R*)-Tol-BINAP
**c**: Ar = 4-$MeOC_6H_4$: (*R*)-MeO-BINAP
**d**: Ar = 3,5-$Me_2C_6H_3$: (*R*)-DM-BINAP
**e**: Ar = Ph: (*R*)-SEGPHOS
**f**: Ar = 3,5-$Me_2C_6H_3$: (*R*)-DM-SEGPHOS
**g**: Ar = 3,5-(*t*-Bu)$_2$-4-$MeOC_6H_2$: (*R*)-DTBM-SEGPHOS
**h**: (*R*)-$H_8$-BINAP

**Chart 2**. Chiral palladium complexes.

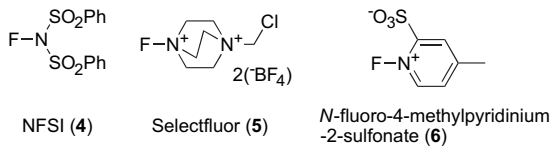
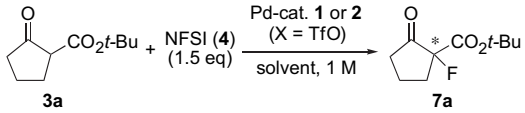



**Chart 3**. Electrophilic fluorinating reagents examined in this study.

To improve the enantioselectivity, we examined a series of chiral phosphine ligands. Among the diphosphines, bulkier ligands bearing substituents at the *meta* positions of aryl group on phosphine gave better enantioselectivity (entries

**Table 1**. Optimization of the reaction conditions




3a 7a

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

[a] **1**–**2**: Catalyst structure; **a**–**h**: chiral ligand.
[b] Catalyst amount.
[c] Isolated yield.
[d] Determined by chiral HPLC analysis.

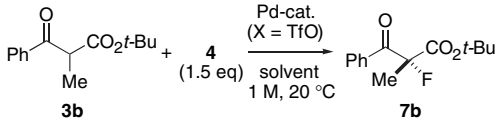
4 and 6), while substituents at the *para* position and semi-reduction of the binaphthyl scaffold did not significantly influence the reaction efficiency (entries 2, 3, and 7).[15] In contrast to the Michael reaction, the use of the Pd μ-hydroxo complex **2g** also promoted the reaction smoothly,[16] and the best selectivity of 92% ee was observed (entry 8). This difference in reactivity may be attributed to the higher electrophilicity of NFSI than that of the enone. Further optimization of the reaction conditions revealed that the reaction proceeded more rapidly in polar solvents (entries 9–12). Interestingly, an alcoholic solvent such as EtOH or *i*-PrOH was the best of those tested and the reaction time was reduced from 48 h to 18 h without any loss of enantioselectivity (entries 10 and 11). In the case of *t*-BuOH, however, the reaction was retarded and the starting material was not consumed completely after 18 h (entry 12).

A conspicuous solvent effect was observed when **3b** was tested as a substrate (Table 2). Probably because of steric repulsion derived from the phenyl ring of the substrate, the reaction did not proceed when **1g** was used (entry 1). The less bulky **1d** promoted the reaction, but the reaction in THF was sluggish, giving rise to **7b** in 63% yield with 82% ee after more than 250 h (entry 2). Fortunately, dramatic acceleration of the reaction was observed when EtOH was used as a solvent. The reaction reached completion after 48 h, affording the desired product in 96% yield with 91% ee (entries 3 and 4). Even when the concentration was reduced from 1 M to 0.1 M, **7b** was isolated in 54% yield, maintaining the same enantioselectivity (entry 5). $^1$H NMR study revealed that stoichiometric reaction of **3a** with **2b** (0.5 equiv to **3a**) was completed within 10 min in $CD_3OD$, while the same reaction in THF-$d_8$ took 2 h for completion.[14a] Thus, we speculated that alcoholic solvents played a key role for rapid formation of the chiral palladium enolates, thereby significantly accelerating the reaction.

Because the palladium complexes are stable to water, the reaction could be performed in aqueous solvent systems (entries 6–9). Interestingly, the reaction in water without co-solvents proceeded at a synthetically useful level to give **7b** in 76% yield with 89% ee (entry 9).

With the optimized reaction conditions in hand, we next examined the generality of our fluorination reaction. As summarized in Table 3, other cyclic and acyclic β-ketoesters were converted to the desired products smoothly in the presence of 2.5 mol % of the palladium complexes. Except for **3g**, the desired fluorinated compounds were obtained in a highly enantioselective manner (up to 94% ee). As in the case of **3a**, the reaction of **3c** using **2d** gave the product with 94% ee, while a slight decrease of enantioselectivity was observed when **1d** was used (entries 1 and 7). In entry 3, the isolated chemical yield was lower due to the volatility of **7e**, but the excellent ee of 91% was observed. In contrast to **3f**, the reaction of **3g**, which has a different substitution

**Table 2**. Solvent effect on the reaction of **3b**

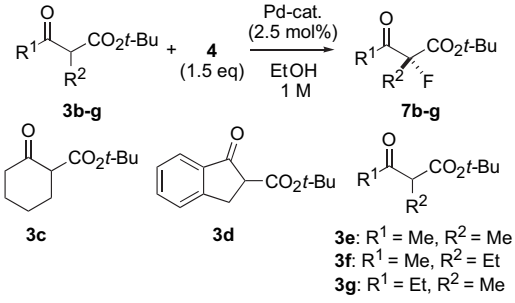



3b 7b

| Entry | Catalyst (mol %) | Solvent | Time (h) | Yield (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | **1g** (5) | THF | — | No reaction | |
| 2 | **1d** (5) | THF | 255 | 63 | 82 |
| 3 | **1d** (5) | EtOH | 48 | 96 | 91 |
| 4[a] | **2d** (2.5) | EtOH | 40 | 92 | 91 |
| 5[b] | **2d** (2.5) | EtOH | 40 | 54 | 91 |
| 6 | **2d** (2.5) | EtOH/$H_2O$ (1/1) | 66 | 57 | 78 |
| 7 | **2d** (2.5) | EtOH/$H_2O$ (4/1) | 120 | 53 | 85 |
| 8 | **2d** (2.5) | Acetone/$H_2O$ (9/1) | 96 | 73 | 88 |
| 9 | **2d** (2.5) | $H_2O$ | 75 | 76 | 89 |

[a] X=$BF_4$.
[b] 0.1 M.

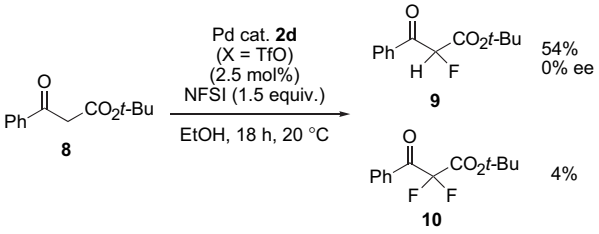
**Table 3**. Catalytic enantioselective fluorination reactions of β-ketoesters




| Entry | 3 | Catalyst (X) | Temp (°C) | Time (h) | Yield (%) | ee (%) |
|---|---|---|---|---|---|---|
| 1 | **3c** | **2d** ($BF_4$) | −10 | 20 | 91 | 94 |
| 2 | **3d** | **2d** (TfO) | −20 | 36 | 85 | 83[a] |
| 3 | **3e** | **2f** (TfO) | 20 | 72 | 49[b] | 91 |
| 4 | **3f** | **2d** (TfO) | 20 | 42 | 88 | 87 |
| 5 | **3g** | **2d** (TfO) | 20 | 72 | 47 | 69 |
| 6[c] | **3c** | **2d** ($BF_4$) | 0 | 20 | 82 | 91 |
| 7 | **3c** | **1d** (TfO) | −10 | 20 | 95 | 92 |
| 8[d] | **3b** | **1d** (TfO) | 20 | 48 | 96 | 91[a] |

[a] The absolute configuration was determined to be *R* after conversion to the known compound.
[b] Lower yield due to the volatility of **7e**.
[c] Compound **2d** (1 mol %).
[d] One gram scale.

pattern from **3f**, was slower and less enantioselective. Thus, **7g** was obtained in only 47% yield with 69% ee after 72 h. Even when the amount of catalyst was reduced to 1 mol %, comparable results were obtained (entry 6). It is also noteworthy that this reaction could be easily scaled up using reagent-grade non-distilled EtOH as a solvent (entry 8). In these reactions, we found that **2d** and **2g** were effective catalysts, and various substrates were selectively fluorinated by employing either of these two ligands according to the nature of the β-ketoesters. Notably, it is environmentally advantageous that this reaction proceeds well in alcoholic solvents and even in water. Unfortunately, the reaction of α-nonsubstituted β-ketoester **8** was unsuccessful (Scheme 2). Because the corresponding product **9** was more susceptible to enolization than **8**, no asymmetric induction was observed and a difluorinated compound **10** was obtained in 4% yield.

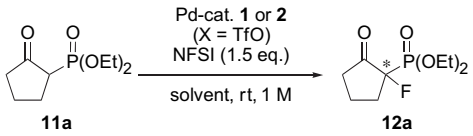



**Scheme 2**. Fluorination of α-nonsubstituted β-ketoester.

Encouraged by the success in the fluorination reactions of β-ketoesters, we next turned our attention to other active methine compounds. We envisaged that other bidentate carbonyl compounds would react with Pd complexes to form similar chiral palladium enolates. Among several candidates, we focused on β-ketophosphonates[17] because difluoro- and monofluorophosphonates have been utilized in drug design as mimics of phosphates.[18,19] Compared with non-fluorinated phosphonates and difluorophosphonates, α-monofluorophosphonates are expected to be a better surrogate of phosphates, because they show similar second p$K_a$ values (~6.5) to those of biological phosphates (~6.5).[18] Although several non-enantioselective or diastereoselective syntheses of α-monofluorophosphonates have been reported,[20] there was no example of the catalytic enantioselective synthesis of chiral α-fluoro-β-ketophosphonates before we started our investigation. Independently, Jørgensen and Kim recently reported similar reactions using Zn(II)–Ph–DBFOX complexes and Pd–BINAP complexes, respectively.[11e,f]

Similar optimization of the reaction conditions using **11a** as a model substrate revealed that the combination of **1d** as a catalyst and EtOH as a solvent was the most appropriate for the fluorination of β-ketophosphonates (Table 4). Thus, when 5 mol % of **1d** was used in EtOH, the reaction of **11a** reached completion after only 2 h to give the desired fluorinated product **12a** in 91% yield (entry 3). Gratifyingly, the ee of the product was determined to be 95% by chiral HPLC analysis. When a bulkier ligand such as DTBM-SEGPHOS was used, a higher enantioselectivity of 98% was observed (entry 5), but the reaction rate was considerably decreased, probably due to severe steric repulsion. EtOH was found to be superior to other solvents in terms of chemical yield and enantioselectivity (entries 6–9). In this fluorination of

**Table 4**. Optimization of the reaction conditions



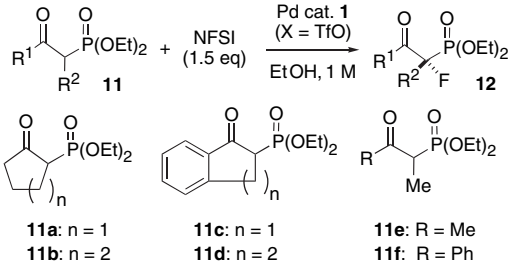

| Entry | Catalyst (mol %) | Solvent | Time (h) | Yield[a] (%) | ee[b] (%) |
|---|---|---|---|---|---|
| 1 | **1a** (5) | EtOH | 5 | 81 | 75 |
| 2 | **1b** (5) | EtOH | 5 | 82 | 79 |
| 3 | **1d** (5) | EtOH | 2 | 91 | 95 |
| 4 | **1f** (5) | EtOH | 2 | 87 | 95 |
| 5 | **1g** (5) | EtOH | 5 | 46 | 98 |
| 6 | **1d** (5) | Acetone | 3 | 70 | 93 |
| 7 | **1d** (5) | THF | 3 | 66 | 92 |
| 8 | **1d** (5) | DMF | 6 | 20 | 90 |
| 9 | **1d** (5) | $CH_2Cl_2$ | 6 | 43 | 92 |
| 10 | **2d** (2.5) | EtOH | 2 | 91 | 95 |

[a] Isolated yield.
[b] Determined by HPLC analysis.

β-ketophosphonates, the Pdμ-hydroxo complex **2d** gave results comparable to those obtained using **1d** (entry 10).

This catalytic system was also applicable to various substrates including cyclic and acyclic β-ketophosphonates (Table 5). All the substrates examined were fluorinated in a highly enantioselective manner (up to 97% ee). As shown in entries 1 and 6, the reactions smoothly proceeded in the presence of as little as 1 mol % of the catalyst without deterioration of the reaction efficiency. When the reaction was carried out at 0 °C, the ee was improved to 97% ee (entry 5). In contrast to cyclic β-ketophosphonates, the reaction of acyclic substrates was found to be slow (entries 7 and 8). The starting materials **11e** and **11f** were not consumed at 40 °C even after 48 h. Although the chemical yield was modest to good, the ees of the products were found to be excellent (94 and 95% ee, respectively). For these reactions, **1f** gave

**Table 5**. Catalytic enantioselective fluorination of β-ketophosphonates

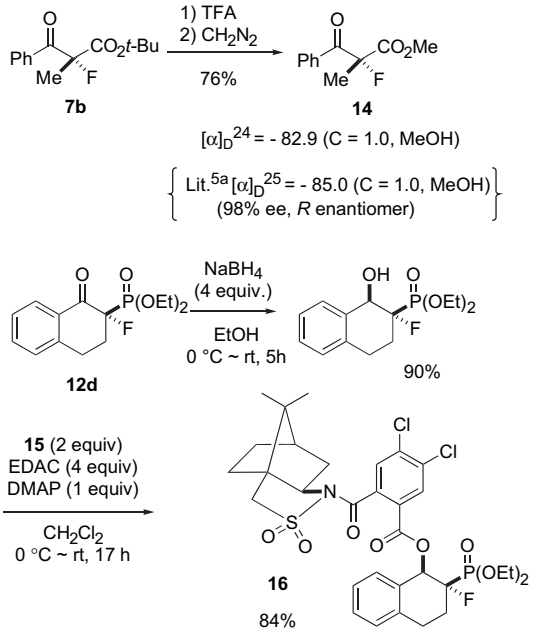



| Entry | 11 | Catalyst (mol %) | Temp (°C) | Time (h) | Yield[a] (%) | ee[b] (%) |
|---|---|---|---|---|---|---|
| 1 | **11a** | **1d** (1) | rt | 12 | 82 | 95 |
| 2 | **11b** | **1d** (5) | rt | 8 | 93 | 96 |
| 3 | **11c** | **1d** (5) | rt | 3 | 84 | 95 |
| 4 | **11d** | **1d** (5) | rt | 3 | 97 | 94[c] |
| 5 | **11d** | **1d** (5) | 0 | 24 | 90 | 97 |
| 6 | **11d** | **1d** (1) | rt | 7 | 83 | 95 |
| 7 | **11e** | **1f** (10) | 40 | 48 | 57 | 94[d] |
| 8 | **11f** | **1f** (10) | 40 | 48 | 38 | 95 |

[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] The absolute configuration was determined by X-ray analysis.
[d] The ee was determined after conversion to the corresponding 2,4-dinitrophenylhydrazone **13**.

a slightly better selectivity than **1d**. Similarly decreased reaction rates in the case of acyclic substrates were noted in Kim's report.[11e] They examined various acyclic β-ketophosphonates employing Pd complexes similar to our Pd aqua complexes **1**, and longer reaction times (58–94 h) were required to obtain the products in yields ranging from 50–79%.

To establish the absolute configuration of these fluorinated products, the following conversion of **7b** and **12d** was carried out (Scheme 3). As described previously,[21] the absolute configuration of **7b** was determined to be *R* by comparison of optical rotation of **14** with the reported value.[5a] In addition, *R* configuration was observed in the case of **7d** after conversion to 2-fluoro-2-methyl indanone, whose optically active form was previously synthesized by Shibata and Takeuchi.[6c,7a,21] To determine the absolute stereochemistry of the fluorinated β-ketophosphonate **12d**, we planned to attach a chiral auxiliary in some way, because no appropriate reference compound could be found in the literature. Thus, stereoselective reduction with $NaBH_4$, followed by esterification with *N*-(2-carboxy-4,5-dichlorobenzoyl)-(−)-10, 2-camphorsultam (**15**) gave **16** in good yield.[22] Recrystallization of **16** from hexane/ethyl acetate (3/1) gave a single crystal suitable for X-ray structural analysis. As shown in Figure 1, on the basis of the known structure of (−)-camphorsultam, the absolute configuration of **12d** was unequivocally determined to be *S*.




**Scheme 3**. Determination of the absolute configuration of the products.

Because formation of the chiral palladium enolates was observed using $^1H$ NMR in the cases of both β-ketoesters and β-ketophosphonates,[10,14] we believe that these enolates are key intermediates in the fluorination reactions. If structurally similar enolates are generated in the reaction mixture, the absolute configuration observed in these reactions indicates that the fluorinating reagent reacts from the less hindered side of the enolates with the same sense of enantioselection (Fig. 2). In the case of β-ketoesters, a bulky *tert*-butyl group would be located at one enolate face to avoid steric repulsion

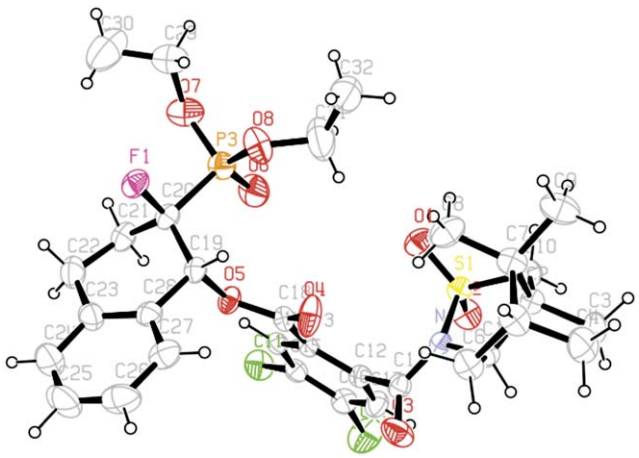


**Figure 1**. X-ray structure of **16**.

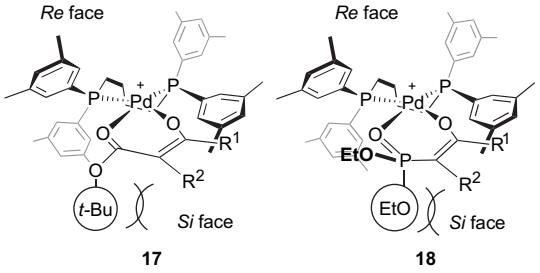
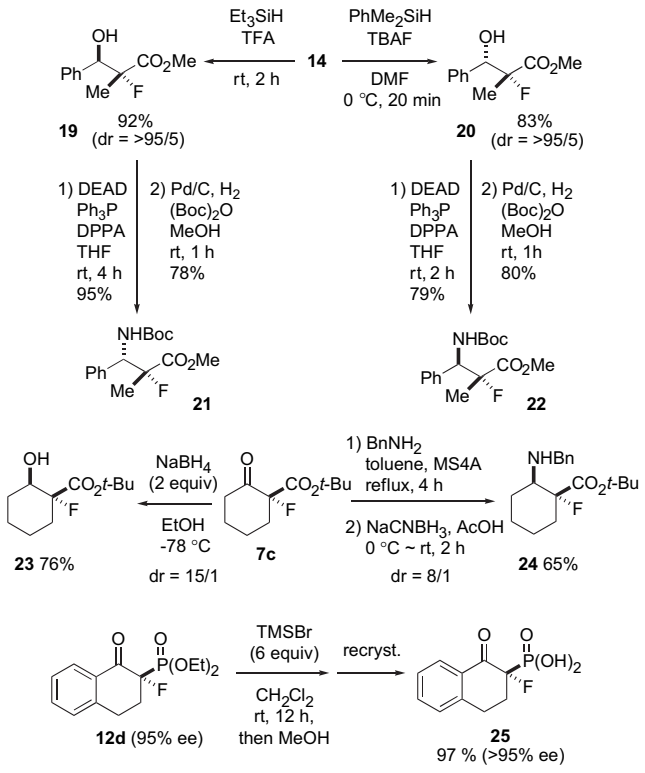



**Figure 2**. Plausible transition state models.

with the 3,5-dimethylphenyl group of the ligand. Thus, the *si*-face of the enolate **17** might be effectively shielded by the *tert*-butyl group and the aryl group on phosphine, forcing NFSI to approach from the *re*-face of the enolate. The face discrimination in the case of β-ketophosphonates can also be explained by postulating involvement of a similar intermediate. But, the structure of the corresponding enolate would be more complex because of the $sp^3$-hybridization of the phosphorus atom of the substrate. Likewise, the two ethoxy groups of the β-ketophosphonates **11** would be positioned to cause minimum steric repulsion with the aryl group on phosphine. Comparing **18** with **17**, the *si*-face of the enolate **18** seems more crowded than that of **17**, since one of the ethoxy groups should be oriented much closer to the reactive center. This speculation is in accord with the better enantioselectivity observed in the case of β-ketophosphonates than that of β-ketoesters.

Finally, to confirm the synthetic utility of our fluorination reactions, transformation of the fluorinated products was investigated (Scheme 4). Because β-hydroxy or β-amino acids are fundamental units in various natural or unnatural compounds, their α-fluorinated derivatives are of particular interest. First, conventional reduction with $NaBH_4$ in the presence of Lewis acids was examined, but it gave only a mixture of the reduced products **19** and **20** (~1/6). According to the reported procedure,[23] we next tried reduction with silanes. Although the use of $AlCl_3$ as an activator of the ketone was unsuccessful, the reaction in TFA afforded **19** in a highly diastereoselective manner. We previously reported that reduction with $Ph_3SiH$ afforded **19** in 75% yield. When this silane was switched to $Et_3SiH$, the chemical yield

was improved to 92%. The relative configuration can be explained by assuming a chelation model. In addition, Lewis base activation of $PhMe_2SiH$ was found to be effective for stereoselective reduction (dr≥95/5).[23] This reaction is likely to proceed according to a Felkin–Anh model, and another diastereomer **20** was produced in 83% isolated yield. These compounds were subjected to azidation with inversion of configuration. Reduction of the azide group, followed by protection of the amino group, afforded the α-fluoro-β-amino esters **21** and **22** in good yields. Enantioenrichment of **21** by recrystallization from ethyl acetate was possible, and optically pure **21** was obtained (>99% ee). In addition, the cyclic fluorinated product **7c** was also converted to **23** as a major diastereomer in 76% yield. Relative stereochemistry of **23** was deduced from a comparison of the coupling constants of the methine proton adjacent to the hydroxyl group against the fluorine atom, which are larger than those between protons (**23**: $J_{H-F}$=10.0 Hz; minor isomer: $J_{H-F}$=24.0 Hz).[24] In the presence of benzylamine and $NaCNBH_3$, **7c** underwent reductive amination to give **24** as the major product in 65% yield (coupling constants of the methine protons; **24**: $J_{H-F}$=12.7 Hz; minor: $J_{H-F}$=27.6 Hz).[24] A further example is as follows. To evaluate the ability of the fluorinated phosphonates to act as phosphate mimics, dealkylation of **12d** is essential. When **12d** was treated with 6 equiv of TMSBr in $CH_2Cl_2$, removal of two ethyl groups occurred readily, affording the desired phosphonic acid **25** in excellent yield.[25]




**Scheme 4**. Conversion of the fluorinated products.

## 3. Conclusion

Using chiral palladium enolates as key intermediates, highly enantioselective fluorination reactions of β-ketoesters and β-ketophosphonates have been developed. Our reactions are operationally convenient because special precautions to exclude air and moisture are unnecessary, and reagent-grade non-distilled alcoholic solvents could be used as reaction media. In addition, transformation of the fluorinated products was successfully demonstrated, and the availability of these fluorinated fundamental units should be valuable in medicinal chemistry. Further studies to expand the scope of the fluorination reactions and their application for the development of enzyme inhibitors are under way in our laboratory.

## 4. Experimental

### 4.1. General

All asymmetric reactions were carried out without precautions to exclude air and moisture. Catalysts used in this paper were prepared according to the reported procedure.[10a,26] NMR spectra were recorded on a JEOL JNM-LA400 spectrometer, operating at 400 MHz for $^1$H NMR and 100.4 MHz for $^{13}$C NMR. Chemical shifts were reported downfield from TMS (=0) for $^1$H NMR. For $^{13}$C NMR, chemical shifts were reported relative to the solvent used as an internal reference. $^{19}$F NMR was measured at 400 or 376 MHz, and $CF_3COOH$ was used as an external standard. FAB–LRMS and FAB–HRMS were taken on JEOL JMS GCmate II using *m*-nitrobenzyl alcohol (*m*NBA) as a matrix. Optical rotations were measured on a JASCO DIP-370 polarimeter. Column chromatography was performed with silica gel 60 (40–100 μm) purchased from Kanto Chemical Co. The enantiomeric excesses (ees) were determined by HPLC or GC analysis. HPLC analysis was performed on Shimadzu HPLC systems consisting of the following components: pump, LC-10AD; detector, SPD-10A set at 254 or 280 nm; column, DAICEL CHIRALPAK AS, AD-H, and CHIRALCEL OJ-H; mobile phase, hexane/2-propanol (IPA). GC analysis was performed on Shimadzu GC-17A with Tokyo Kasei CHIRALDEX G-TA (0.25 mm i.d. ×30 m ×0.125 μm). Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. EtOH was distilled from calcium hydride. Other reagents were purified by usual methods.

### 4.2. General procedure for the catalytic enantioselective fluorination of β-ketoesters

To a solution of the palladium complex **2** (0.005 mmol) in EtOH (0.2 mL) was added a β-ketoester (0.2 mmol) at room temperature. At the indicated temperature, NFSI (95 mg, 0.3 mmol) was added. The resulting mixture was stirred for the time given in Table 3. After the completion of the reaction (TLC, hexane/ether=10/1), saturated aqueous $NH_4Cl$ was added for quenching. The aqueous layer was extracted with $Et_2O$ (3×10 mL). The combined organic layers were washed with water and brine. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure. Further purification was performed by flash column chromatography on $SiO_2$ (hexane/$Et_2O$=10/1) to give the pure product as a colorless oil. The ees of the products were determined by chiral HPLC or GC analysis. In this study, decoupled $^{19}$F NMR spectra were obtained for all the products.

**4.2.1. *tert*-Butyl 1-fluoro-2-oxocyclopentanecarboxylate (7a).** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.49 (s, 9H), 2.07–2.15 (m, 2H), 2.21–2.34 (m, 1H), 2.44–2.57 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 18.0 (d, $J$=4.1 Hz), 27.9, 33.8 (d, $J$=20.6 Hz), 35.7, 84.0, 94.4 (d, $J$=199.1 Hz), 166.4 (d, $J$=27.9 Hz), 208.1 (d, $J$=16.4 Hz); $^{19}$F NMR (400 MHz, $CDCl_3$) $\delta$ −163.2; FABMS (*m*NBA) *m/z* 202 $(M)^+$, 146 $(M-t\text{-Bu})^+$; $[\alpha]_D^{31}$ +72.7 (*c* 1.27, $CHCl_3$) (92% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane/IPA=99/1, 0.40 mL/min, 280 nm) $t_r$ (minor)=20.3 min, $t_r$ (major)=24.7 min; FAB–HRMS (*m*NBA) Calcd for $C_{10}H_{15}O_3F$ $(M)^+$ 202.1005. Found 202.1002. Calcd for $C_{10}H_{16}O_3F$ $(M+1)^+$ 203.1084. Found 203.1082; IR (neat) $\nu$ 2978, 2927, 1764, 1746, 1458, 1395, 1370, 1145, 840 cm$^{-1}$.

**4.2.2. (*R*)-*tert*-Butyl 2-fluoro-2-methyl-3-oxo-3-phenylpropionate (7b).** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.37 (s, 9H), 1.82 (d, $J$=22.4 Hz, 3H), 7.43–7.48 (m, 2H), 7.56–7.60 (m, 1H), 8.02–8.06 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 20.6 (d, $J$=23.9 Hz), 27.6, 84.0, 96.6 (d, $J$=193 Hz, 1H), 128.5, 129.5, 133.6, 167.5 (d, $J$=25.5 Hz), 191.7 (d, $J$=25.5 Hz); $^{19}$F NMR (400 MHz, $CDCl_3$) $\delta$ −151.2; FABMS (*m*NBA) *m/z* 253 $(M+1)^+$, 197 $(M+2H-t\text{-Bu})^+$; $[\alpha]_D^{33}$ +74.0 (*c* 1.3, $CHCl_3$) (91% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane/IPA=200/1, 0.40 mL/min, 254 nm) $t_r$ (major)=17.7 min, $t_r$ (minor)=19.1 min; FAB–HRMS (*m*NBA) Calcd for $C_{14}H_{18}O_3F$ $(M+1)^+$ 253.1240. Found 253.1240; IR (neat) $\nu$ 2981, 2935, 1754, 1700, 1449, 1395, 1370, 1288, 1247, 1145, 1123, 979, 696 cm$^{-1}$.

**4.2.3. *tert*-Butyl 1-fluoro-2-oxocyclohexanecarboxylate (7c).** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.53 (s, 9H), 1.82–2.12 (m, 5H), 2.40–2.74 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 21.2 (d, $J$=6.6 Hz), 26.5, 27.8, 36.0 (d, $J$=21.4 Hz), 39.9, 83.8, 96.3 (d, $J$=195 Hz), 165.7 (d, $J$=23.9 Hz), 202.2 (d, $J$=19.0 Hz); $^{19}$F NMR (400 MHz, $CDCl_3$) $\delta$ −159.6; FABMS (*m*NBA) *m/z* 217 $(M+1)^+$, 161 $(M+2-t\text{-Bu})^+$; $[\alpha]_D^{33}$ −88.6 (*c* 1.39, $CHCl_3$) (94% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane/IPA=99/1, 1.0 mL/min, 280 nm) $t_r$ (minor)=14.0 min, $t_r$ (major)=16.6 min; FAB–HRMS (*m*NBA) Calcd for $C_{11}H_{18}O_3F$ $(M+1)^+$ 217.1240. Found 217.1243; IR (neat) $\nu$ 2937, 2865, 1736, 1726, 1452, 1395, 1370, 1291, 1252, 1144,1095, 838 cm$^{-1}$.

**4.2.4. (*R*)-*tert*-Butyl 2-fluoro-1-oxoindane-2-carboxylate (7d).** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.43 (s, 9H), 3.40 (dd, $J$=17.6, 23.0 Hz, 1H), 3.73 (dd, $J$=10.7, 17.6 Hz, 1H), 7.43–7.50 (m, 2H), 7.67–7.71 (m, 1H), 7.83 (d, $J$=7.6 Hz 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 27.8, 38.3 (d, $J$=23.9 Hz), 84.1, 95.4 (d, $J$=201 Hz), 125.4, 126.4, 128.4, 133.6, 136.4, 150.9 (d, $J$=3.3 Hz), 166.2 (d, $J$=27.2 Hz), 195.8 (d, $J$=18.1 Hz); $^{19}$F NMR (400 MHz, $CDCl_3$) $\delta$ −164.4; FABMS (*m*NBA) *m/z* 251 $(M+1)^+$, 195 $(M+2H-t\text{-Bu})^+$; $[\alpha]_D^{34}$ +3.8 (*c* 0.86, $CHCl_3$) (83% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane/IPA=150/1, 0.75 mL/min, 254 nm) $t_r$ (minor)=24.1 min, $t_r$ (major)=33.7 min; FAB–HRMS (*m*NBA) Calcd for $C_{14}H_{16}O_3F$ $(M+1)^+$ 251.1084. Found 251.1083; IR (neat) $\nu$ 2980, 2927, 1758, 1725, 1466, 1395, 1370, 1214, 1151, 1073, 922, 834, 741 cm$^{-1}$.

**4.2.5. *tert*-Butyl 2-fluoro-2-methyl-3-oxobutyrate (7e).** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.48 (s, 9H), 1.63 (d, $J$=22.2 Hz, 3H), 2.30 (d, $J$=4.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 19.5 (d, $J$=23.1 Hz), 24.9, 27.5, 83.8, 97.7 (d, $J$=192 Hz), 165.9 (d, $J$=25.5 Hz), 202.5 (d, $J$=28.8 Hz); $^{19}$F NMR (400 MHz, $CDCl_3$) $\delta$ −156.6; FABMS (*m*NBA) *m/z* 191 $(M+1)^+$; $[\alpha]_D^{34}$ −44.0 (*c* 0.91, $CHCl_3$) (89% ee); GC (Tokyo Kasei CHIRALDEX G-TA; 0.25 mm i.d. ×30 m ×0.125 μm; temp 70 °C, inj. temp 300 °C, det. temp 250 °C) $t_r$ (minor)=21.0 min, $t_r$ (major)=21.7 min; FAB–HRMS (*m*NBA) Calcd for $C_9H_{15}O_3F$ $(M)^+$ 190.1005. Found 190.1000; IR (neat) $\nu$ 2981, 2935, 1753, 1736, 1458, 1395, 1370, 1291, 1256, 1134, 1106, 840 cm$^{-1}$.

**4.2.6. *tert*-Butyl 2-ethyl-2-fluoro-3-oxobutyrate (7f).** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.95 (t, $J$=7.4 Hz, 3H), 1.49 (s, 9H), 1.94–2.20 (m, 2H), 2.29 (d, $J$=4.64 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 7.00, 25.7, 26.9 (d, $J$=21.4 Hz), 27.8, 83.8, 100.6 (d, $J$=194 Hz), 165.3 (d, $J$=26.3 Hz), 202.4 (d, $J$=32.9 Hz); FABMS (*m*NBA) *m/z* 205 $(M+1)^+$, 147 $(M-t\text{-Bu})^+$, 148 $(M+2-t\text{-Bu})^+$; $[\alpha]_D^{31}$ −12.6 (*c* 1.45, $CHCl_3$) (87% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane/IPA=150/1, 0.40 mL/min, 280 nm) $t_r$ (minor)=11.6 min, $t_r$ (major)=12.5 min; FAB–HRMS (*m*NBA) Calcd for $C_{10}H_{18}O_3F$ $(M+1)^+$ 205.1240. Found 205.1244; IR (neat) $\nu$ 2920, 2850, 1736, 1709, 1459, 1446, 1376, 1280, 1261, 1168, 1084, 797 cm$^{-1}$.

**4.2.7. *tert*-Butyl 2-fluoro-2-methyl-3-oxopentanoate (7g).** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.09 (t, $J$=7.3 Hz, 3H), 1.47 (s, 9H), 1.63 (d, $J$=22.2 Hz, 3H), 2.65–2.70 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 7.2, 19.0 (d, $J$=23.0 Hz), 24.7, 27.5, 83.8, 97.7 (d, $J$=195 Hz), 164.9 (d, $J$=25.2 Hz), 201.5 (d, $J$=28.8 Hz); FABMS (*m*NBA) *m/z* 205 $(M+1)^+$, 147 $(M-t\text{-Bu})^+$, 148 $(M+2-t\text{-Bu})^+$; $[\alpha]_D^{31}$ −55.5 (*c* 2.28, $CH_2Cl_2$) (69% ee); HPLC (DAICEL CHIRALPAK AS, hexane/IPA=150/1, 0.20 mL/min, 280 nm) $t_r$ (minor)=19.7 min, $t_r$ (major)=22.3 min.

**4.2.8. *tert*-Butyl 2-fluoro-3-oxo-3-phenylpropionate (9).** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.42 (s, 9H), 5.75 (d, $J$=49.2 Hz, 1H), 7.45 (t, $J$=7.6 Hz, 2H), 7.63 (t, $J$=8.7 Hz, 1H), 8.02 (d, $J$=8.5 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 27.7, 84.5, 90.1 (d, $J$=195.8 Hz), 1287.7, 129.4 (d, $J$=3.3 Hz), 133.6, 134.2, 163.6, 190.0; HPLC (DAICEL CHIRALPAK AD-H, hexane/IPA=200/1, 0.40 mL/min, 254 nm) $t_r$=18.9 min, $t_r$=20.3 min.

### 4.3. General procedure for the catalytic enantioselective fluorination of β-ketophosphonates

To a stirred solution of the Pd complex **1** (0.01 mmol) in EtOH (0.2 mL), **11** (0.2 mmol) and NFSI (94.8 mg, 0.3 mmol) were added successively at ambient temperature. The reaction was monitored by TLC (hexane/ethyl acetate=1/1). After completion of the reaction, saturated aqueous $NH_4Cl$ was added for quenching. The aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine and dried over $Na_2SO_4$. After evaporation of the solvent, the obtained crude product was purified by flash column chromatography (hexane/ethyl acetate=1/1) to afford **12** as a colorless oil. The ees of the products were determined by chiral HPLC analysis. In this study, coupling constants against protons and phosphorus atoms were recorded in $^{19}$F NMR.

**4.3.1. Diethyl 1-fluoro-2-oxocyclopentylphosphonate (12a).** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.36 (t, $J$=7.1 Hz, 3H), 1.39 (t, $J$=7.1 Hz, 3H), 2.03–2.56 (m, 5H), 2.68–2.81 (m, 1H), 4.19–4.30 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 16.2 (d, $J$=5.7 Hz), 16.3 (d, $J$=5.7 Hz), 16.8 (dd, $J$=4.2, 5.8 Hz), 32.0 (dd, $J$=2.5, 18.1 Hz), 35.4 (d, $J$=2.5 Hz), 64.0 (d, $J$=6.2 Hz), 64.1 (d, $J$=6.2 Hz), 96.2 (dd, $J$=160.0, 200.8 Hz), 209.0 (dd, $J$=3.3, 13.2 Hz); $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −98.1 (ddd, $J$=11.7, 25.2, 85.0 Hz); FAB–LRMS (*m*NBA) *m/z* 239 (M+1)$^+$; $[\alpha]_D^{28}$ +130.2 (*c* 0.75, $CHCl_3$) (96% ee); HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA=95/5, 1.0 mL/min, 280 nm) $t_r$ (major)=10.6 min, $t_r$ (minor)=11.7 min; FAB–HRMS (*m*NBA) Calcd for $C_9H_{17}FO_4P$ (M+1)$^+$ 239.0849. Found 239.0855; IR (neat) $\nu$ 1756, 1259, 1047, 1022 cm$^{-1}$.

**4.3.2. Diethyl 1-fluoro-2-oxocyclohexylphosphonate (12b).** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.32 (t, $J$=7.1 Hz, 3H), 1.37 (t, $J$=7.1 Hz, 3H), 1.64–1.72 (m, 1H), 1.85–2.23 (m, 4H), 2.58–2.70 (m, 2H), 2.85–2.93 (m, 1H), 4.11–4.30 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 16.3 (d, $J$=6.6 Hz), 16.4 (d, $J$=5.7 Hz), 21.7 (d, $J$=8.2 Hz), 26.7, 36.1 (d, $J$=19.0 Hz), 40.8, 64.1 (d, $J$=6.5 Hz), 64.4 (d, $J$=6.6 Hz), 98.1 (dd, $J$=154.7, 196.6 Hz), 203.0 (dd, $J$=4.9, 14.0 Hz); $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −91.0 (dd, $J$=18.4, 80.1 Hz); FAB–LRMS (*m*NBA) *m/z* 253 (M+1)$^+$; $[\alpha]_D^{28}$ +164.2 (*c* 1.0, $CHCl_3$) (96% ee); HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA=99/1, 1.0 mL/min, 280 nm) $t_r$ (major)=47.7 min, $t_r$ (minor)=50.4 min; FAB–HRMS (*m*NBA) Calcd for $C_{10}H_{19}FO_4P$ (M+1)$^+$ 253.1005. Found 253.1009; IR (neat) $\nu$ 1726, 1257, 1013 cm$^{-1}$.

**4.3.3. Diethyl 2-fluoro-2,3-dihydro-1-oxo-1*H*-inden-2-yl-2-phosphonate (12c).** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.22 (t, $J$=7.1 Hz, 3H), 1.38 (t, $J$=7.1 Hz, 3H), 3.97 (ddd, $J$=9.3, 14.6, 17.9 Hz, 1H), 3.35–3.48 (m, 1H), 4.12–4.25 (m, 2H), 4.30 (quint, $J$=7.3 Hz, 2H), 7.42–7.48 (m, 2H), 7.67 (td, $J$=1.3, 7.7 Hz, 1H), 7.81 (d, $J$=7.6 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 16.2 (d, $J$=5.8 Hz), 16.3 (d, $J$=5.7 Hz), 36.5 (dd, $J$=3.3, 21.4 Hz), 64.3 (d, $J$=6.6 Hz), 95.9 (dd, $J$=162.9, 199.9 Hz), 125.1, 126.4, 128.5, 134.1 (d, $J$=3.3 Hz), 136.4, 149.8 (t, $J$=4.6 Hz), 196.4 (dd, $J$=3.3, 14.8 Hz); $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −101.1 (ddd, $J$=9.0, 26.4, 104.9 Hz); FAB–LRMS (*m*NBA) *m/z* 287 (M+1)$^+$; $[\alpha]_D^{28}$ +71.2 (*c* 0.85, $CHCl_3$) (95% ee); HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA=95/5, 1.0 mL/min, 254 nm) $t_r$ (major)=19.5 min, $t_r$ (minor)=24.3 min; FAB–HRMS (*m*NBA) Calcd for $C_{13}H_{17}FO_4P$ (M+1)$^+$ 287.0848. Found 287.0852; IR (neat) $\nu$ 1725, 1260, 1018 cm$^{-1}$.

**4.3.4. (*S*)-Diethyl 2-fluoro-1,2,3,4-tetrahydro-1-oxonaphthalen-2-yl-2-phosphonate (12d).** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.12 (t, $J$=7.1 Hz, 3H), 1.37 (t, $J$=7.1 Hz, 3H), 2.44–2.64 (m, 1H), 2.81–2.91 (m, 1H), 3.06–3.11 (m, 1H), 3.44–3.53 (m, 1H), 4.00–4.16 (m, 2H), 4.25–4.34 (m, 2H), 7.26 (d, $J$=7.8 Hz, 1H), 7.34 (d, $J$=7.6 Hz, 1H), 7.53 (td, $J$=1.5, 7.6 Hz, 1H), 8.06 (dd, $J$=1.2, 7.8 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 16.0 (d, $J$=6.6 Hz), 16.3 (d, $J$=4.9 Hz), 26.0 (d, $J$=10.7 Hz), 31.6 (d, $J$=19.7 Hz), 63.8 (d, $J$=6.6 Hz), 64.6 (d, $J$=6.6 Hz), 95.5 (dd, $J$=156.3, 192.5 Hz), 126.9, 127.9, 128.6, 131.1, 134.2, 143.1, 190.6 (dd, $J$=3.3, 14.4 Hz); $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −93.9 (ddd, $J$=6.8, 13.9, 83.1 Hz); FAB–LRMS (*m*NBA) *m/z* 301 (M+1)$^+$; $[\alpha]_D^{27}$ +49.1 (*c* 1.1, $CHCl_3$) (94% ee); HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA=9/1, 1.0 mL/min, 254 nm) $t_r$ (major)=10.2 min, $t_r$ (minor)=13.6 min; FAB–HRMS (*m*NBA) Calcd for $C_{14}H_{19}FO_4P$ (M+1)$^+$ 301.1005. Found 301.1000; IR (neat) $\nu$ 1694, 1259, 1014, cm$^{-1}$.

**4.3.5. Diethyl 2-fluoro-3-oxobutan-2-ylphosphonate (12e).** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.36 (dt, $J$=0.48, 7.1 Hz, 3H), 1.37 (t, $J$=0.48, 7.1 Hz, 3H), 1.71 (dd, $J$=15.4, 23.7 Hz, 3H), 2.38 (dd, $J$=0.72, 5.6 Hz, 3H), 4.18–4.28 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 16.3 (d, $J$=5.8 Hz), 16.3 (d, $J$=5.7 Hz), 19.3 (d, $J$=21.4 Hz), 26.2, 64.0 (d, $J$=7.4 Hz), 64.2 (d, $J$=7.5 Hz), 99.1 (dd, $J$=159.6, 190.0 Hz), 205.3 (dd, $J$=3.3, 25.5 Hz); $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ 93.6 (qqd, $J$=4.5, 25.0, 84.5 Hz); FAB–LRMS (*m*NBA) *m/z* 227 [M+1]$^+$; $[\alpha]_D^{28}$ −80.8 (*c* 0.47, $CHCl_3$) (94% ee); IR (neat) $\nu$ 1724, 1261, 1012 cm$^{-1}$. The ee was determined after conversion to the corresponding 2,4-dinitrophenylhydrazone **13**.[27]

Compound **13**: yellow solid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.33–1.38 (m, 1H), 1.90 (dd, $J$=13.9, 24.6 Hz, 3H), 2.24 (dd, $J$=1.2, 2.4 Hz, 3H), 4.16–4.28 (m, 4H), 7.95 (d, $J$=9.5 Hz, 1H), 8.34–8.37 (m, 1H), 9.15 (d, $J$=2.7 Hz, 1H), 11.14 (s, 1H); FAB–LRMS (*m*NBA) *m/z* 407 (M+1)$^+$; HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA=9/1, 1.0 mL/min, 254 nm) $t_r$ (major)=21.0 min, $t_r$ (minor)=25.6 min; FAB–HRMS (*m*NBA) Calcd for $C_{14}H_{21}FN_4O_7P$ (M+1)$^+$ 407. 1132. Found 407.1131.

**4.3.6. Diethyl 2-fluoro-1-oxo-1-phenylpropan-2-yl-phosphonate (12f).** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.27 (t, $J$=7.1 Hz, 3H), 1.29 (t, $J$=7.1 Hz, 3H), 1.85 (dd, $J$=15.2, 24.2 Hz, 3H), 4.10–4.26 (m, 4H), 7.38 (d, $J$=7.7 Hz, 2H), 7.48–7.52 (m, 1H), 7.99–8.02 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 16.4 (d, $J$=4.9 Hz), 16.4 (d, $J$=4.9 Hz), 21.5 (d, $J$=22.2 Hz), 64.1 (d, $J$=4.1 Hz), 64.2 (d, $J$=4.1 Hz), 100.5 (dd, $J$=161.7, 193.7 Hz), 128.2, 130.0 (d, $J$=7.4 Hz), 133.4, 134.7 (d, $J$=3.3 Hz), 197.6 (dd, $J$=4.1, 23.0 Hz); $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −85.3 (ddd, $J$=24.1, 48.1, 83.8 Hz); FAB–LRMS (*m*NBA) *m/z* 289 (M+1)$^+$; $[\alpha]_D^{25}$ −36.3 (*c* 0.37, $CHCl_3$) (90% ee); HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA=9/1, 1.0 mL/min, 254 nm) $t_r$ (minor)=7.3 min, $t_r$ (major)=7.9 min; FAB–HRMS (*m*NBA) Calcd for $C_{13}H_{19}FO_4P$ (M+1)$^+$ 289.1005. Found 289.1011; IR (neat) $\nu$ 1681, 1260, 1048, 1014 cm$^{-1}$.

### 4.4. Synthesis of 16

To a stirred solution of $NaBH_4$ (50 mg, 1.33 mmol) in EtOH (3 mL) was added a solution of the optically active **12d** (100 mg, 0.33 mmol, 95% ee) in EtOH (7 mL) under ice-bath cooling. The mixture was stirred at room temperature for 5 h, then saturated aqueous $NH_4Cl$ was added to destroy the excess reagent. The aqueous layer was extracted with ether several times and the combined organic layers were washed with brine and dried over $Na_2SO_4$. Short column chromatography on silica gel (hexane/ethyl acetate=1/3–1/20) afforded the desired product in 90% yield (90 mg)

as a colorless oil. This reaction was stereoselective and no stereoisomer was detected in $^1$H NMR of the crude products. Subsequently, the obtained alcohol (39 mg, 0.13 mmol) was mixed with the acid **15** (110 mg, 0.26 mmol) and DMAP (16 mg, 0.13 mmol) in $CH_2Cl_2$ (5 mL). After 5 min, EDAC (97.4 mg, 0.52 mmol) was added under ice-bath cooling, and the resulting mixture was stirred for 17 h at room temperature. After completion of the reaction, 1 N HCl was added and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous $NaHCO_3$, water, and brine, then dried over $Na_2SO_4$. Removal of the solvent, followed by flash column chromatography (hexane/ethyl acetate=1/1) afforded **16** as a white solid in 84% yield. Recrystallization from hexane/ethyl acetate (3/1) at ambient temperature gave colorless pillars in 76% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.98 (s, 3H), 1.21 (t, $J$=7.1 Hz, 3H), 1.25 (s, 3H), 1.26 (t, $J$=7.1 Hz, 3H), 1.33–1.48 (m, 2H), 1.87–1.97 (m, 3H), 1.98–2.15 (m, 1H), 2.35–2.7 (m, 3H), 2.97–3.14 (m, 2H), 3.34 (d, $J$=13.9 Hz, 1H), 3.43 (d, $J$=13.9 Hz, 1H), 3.88 (m, 1H), 4.05–4.25 (m, 4H), 6.47 (t, $J$=9.5 Hz, 1H), 7.16 (d, $J$=7.6 Hz, 1H), 7.19 (t, $J$=7.6 Hz, 1H), 7.27 (dt, $J$=1.5, 7.5 Hz, 1H), 7.44 (d, $J$=7.5 Hz, 1H), 7.53 (s, 1H), 8.15 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 16.2 (d, $J$=5.7 Hz), 1.63 (d, $J$=5.8 Hz), 20.0, 20.8, 24.3 (d, $J$=7.5 Hz), 26.1 (d, $J$=20.6 Hz), 26.5, 33.0, 37.5, 44.7, 47.7, 48.4, 53.0, 63.3 (d, $J$=6.6 Hz), 63.7 (d, $J$=5.7 Hz), 65.5, 71.0 (d, $J$=31.3 Hz), 77.2, 93.7 (d, $J$=175, 182 Hz), 126.6, 127.6, 128.2, 128.7, 130.0, 131.1 (d, $J$=7.4 Hz), 132.4, 134.5, 135.3, 135.6, 137.0, 162.0, 164.9; $[\alpha]_D^{27}$ −134.65 ($c$ 0.73, $CHCl_3$).

### 4.5. Conversion of the fluorinated products

**4.5.1. (2*R*,3*R*)-Methyl 2-fluoro-3-hydroxy-2-methyl-3-phenylpropanoate (19).** To a stirred solution of **14** (125.8 mg, 0.598 mmol, 91% ee) in TFA (2 mL) was added $Et_3SiH$ (0.3 mL, 1.79 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The mixture was diluted with ether (5 mL) and saturated aqueous $NaHCO_3$ was added under ice-bath cooling to neutralize the mixture. The separated aqueous layer was extracted with ether (2×10 mL). The combined organic layers were washed with water and brine. Concentration, followed by flash column chromatography (hexane/ethyl acetate=8/1) afforded the desired product **19** as a colorless oil in 92% yield (117.1 mg). $^1$H NMR of the crude products indicated high diastereoselectivity (>95/5). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.60 (d, $J$=22.2 Hz, 3H), 3.70 (s, 3H), 4.98 (d, $J$=15.6 Hz, 1H), 7.30–7.44 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 19.3 (d, $J$=11.5 Hz), 52.6, 76.2 (d, $J$=23.0 Hz), 96.2 (d, $J$=190.1 Hz), 127.3, 127.4, 128.2, 128.6, 137.5, 171.3 (d, $J$=23.9 Hz); FABMS (*m*NBA) $m/z$ 213 $(M+1)^+$, 212 $(M)^+$; $[\alpha]_D^{30}$ +2.68 ($c$ 2.44, $CHCl_3$); FAB–HRMS (*m*NBA) Calcd for $C_{11}H_{14}O_3F$ $(M+1)^+$ 213.0927. Found 213.0922. Calcd for $C_{11}H_{13}O_3F$ $(M)^+$ 212.0849. Found 212.0844; IR (solid) $\nu$ 3465, 3001, 2953, 1737, 1452, 1375, 1291, 1182, 1109, 1051, 1027, 727, 700 cm$^{-1}$.

**4.5.2. (2*R*,3*S*)-Methyl 2-fluoro-3-hydroxy-2-methyl-3-phenylpropanoate (20).** To a stirred solution of **14** (40 mg, 0.19 mmol, 91% ee) in DMF (0.2 mL) were added $PhMe_2SiH$ (120 μL, 0.76 mmol) and TBAF (380 μL, 1 M in THF, 0.38 mmol) at 0 °C. Saturated aqueous $NH_4Cl$ (3 mL) was added after 20 min. The aqueous layer was extracted with ether (5×10 mL). The combined organic layers were dried over $Na_2SO_4$. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (hexane/ethyl acetate=12/1). The desired product **20** was obtained in 83% yield as a colorless oil. The diastereoselectivity of this reaction was found to be more than 95% by $^1$H NMR. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.39 (d, $J$=21.7 Hz, 3H), 3.83 (s, 3H), 4.94 (d, $J$=20.6 Hz, 1H), 7.32–7.39 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 20.4 (d, $J$=23.0 Hz), 52.8, 77.4 (d, $J$=19.7 Hz), 96.6 (d, $J$=192.5 Hz), 127.8, 127.8, 128.4, 128.7, 137.4, 171.6 (d, $J$=24.7 Hz); FABMS (*m*NBA) $m/z$ 213 $(M+1)^+$, 212 $(M)^+$; $[\alpha]_D^{30}$ +22.9 ($c$ 1.45, $CHCl_3$); FAB–HRMS (*m*NBA) Calcd for $C_{11}H_{13}O_3F$ $(M)^+$ 212.0849. Found 212.0844; IR (solid) $\nu$ 3483, 2992, 2957, 1741, 1453, 1375, 1295, 1188, 1135, 1113, 1053, 710 cm$^{-1}$.

**4.5.3. *tert*-Butyl (1*S*,2*R*)-2-(methoxycarbonyl)-2-fluoro-1-phenylpropylcarbamate (21).** The alcohol **19** (25 mg, 0.118 mmol) was dissolved in THF (0.3 mL). To this solution were added $Ph_3P$ (49 mg, 0.19 mmol), DEAD (82 μL, 40% in toluene), and DPPA (33 μL, 0.15 mmol) successively in this order. After stirring for 2 h at room temperature, saturated aqueous $NH_4Cl$ was added, and the resulting mixture was stirred for 5 min. The aqueous layer was extracted with ether (3×10 mL) and the combined organic layers were washed with water and brine, and dried over $Na_2SO_4$. Further purification was performed by flash column chromatography (hexane/ethyl acetate=15/1) to give the azide in 95% yield (26.7 mg). *Azide*: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.36 (d, $J$=21.2 Hz, 3H), 3.88 (s, 3H), 4.85 (d, $J$=24.7 Hz, 1H), 7.37–7.48 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 20.8 (d, $J$=23.0 Hz), 53.0, 69.4 (d, $J$=18.9 Hz), 95.7 (d, $J$=197.5 Hz), 128.8, 129.1, 129.1, 129.4, 132.9, 170.8 (d, $J$=25.5 Hz).

To a solution of this azide (160 mg, 0.598 mmol) in MeOH (8 mL) were added $(Boc)_2O$ (156.8 mg, 0.72 mmol) and 10% Pd–C (63 mg). The reaction mixture was stirred under a hydrogen atmosphere (balloon) for 1 h at room temperature, then passed through Celite to remove Pd–C, and the residue was washed with $CH_2Cl_2$. After the removal of solvent, the crude product was purified by flash column chromatography (hexane/ethyl acetate=12/1) to give the *N*-protected β-amino ester **21** in 78% yield (146 mg) as a white solid. Recrystallization from ethyl acetate enhanced the enantioselectivity to >99%. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.38 (d, $J$=21.8 Hz, 3H), 1.39 (s, 9H), 3.80 (s, 3H), 5.07 (dd, $J$=9.6, 25.9 Hz, 1H), 5.55 (d, $J$=9.6 Hz, 1H), 7.29–7.38 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 21.5 (d, $J$=23.1 Hz), 28.2, 52.8, 59.3 (d, $J$=19.0 Hz), 80.0, 96.5 (d, $J$=190.1 Hz), 128.3, 128.3, 128.5, 136.4, 154.6, 171.1 (d, $J$=26.3 Hz); FABMS (*m*NBA) $m/z$ 312 $(M+1)^+$; $[\alpha]_D^{30}$ +13.8 ($c$ 0.73, $CHCl_3$); HPLC (DAICEL CHIRALCEl OJ-H, *n*-hexane/IPA=9/1, 1.0 mL/min, 254 nm) $t_r$ (minor)=7.2 min, $t_r$ (major)=13.5 min; FAB–HRMS (*m*NBA) Calcd for $C_{16}H_{23}NO_3F$ $(M+1)^+$ 312.1611. Found 312.1616; IR (solid) $\nu$ 3382, 2972, 2935, 1754, 1693, 1513, 1453, 1388, 1367, 1324, 1311, 1264, 1242, 1159, 1113, 1042, 1015, 980, 948, 910 cm$^{-1}$.

**4.5.4. *tert*-Butyl (1*R*,2*R*)-2-(methoxycarbonyl)-2-fluoro-1-phenylpropylcarbamate (22).** According to the same procedure described above, **20** was converted to **22**. *Azide*: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.76 (d, $J$=21.5 Hz, 3H), 3.63 (s, 3H), 4.80 (d, $J$=30.0 Hz, 1H), 7.32–7.43 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 20.7 (d, $J$=23.8 Hz), 52.6, 68.7 (d, $J$=20.6 Hz), 95.9 (d, $J$=195.0 Hz), 128.6, 128.6, 128.6, 129.2, 133.7, 169.9 (d, $J$=23.8 Hz). Compound **22**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.43 (s, 9H), 1.70 (d, $J$=21.7 Hz, 3H), 3.54 (s, 3H), 5.11 (dd, $J$=10.0, 27.1 Hz, 1H), 5.31 (d, $J$=10.0 Hz, 1H), 7.26–7.39 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 21.4 (d, $J$=23.9 Hz), 28.3, 52.3, 58.6 (d, $J$=17.3 Hz), 80.2, 97.2 (d, $J$=192.5 Hz), 127.8, 128.2, 128.5, 135.8, 137.4, 155.3, 170.3 (d, $J$=23.9 Hz); FABMS (*m*NBA) *m*/*z* 312 $(M+1)^+$, 311 $(M)^+$; $[\alpha]_D^{29}$ −30.5 (*c* 0.51, $CHCl_3$); FAB–HRMS (*m*NBA) Calcd for $C_{12}H_{15}NO_4F$ $(M+2H-t\text{-Bu})^+$ 256.0985. Found 256.0990. Calcd for $C_{12}H_{15}NO_4F$ $(M+2H-Boc)^+$ 212.1087. Found 212.1090; IR (solid) $\nu$ 3329, 2977, 2931, 1766, 1702, 1493, 1453, 1367, 1276, 1246, 1166, 1046, 1021, 982, 947, 882, 755, 703, 576 cm$^{-1}$.

**4.5.5. *tert*-Butyl 1-fluoro-2-hydroxycyclohexanecarboxylate (23).** To a stirred solution of **7c** (22 mg, 0.101 mmol, 94% ee) in EtOH (1 mL) was added $NaBH_4$ (9 mg, 0.24 mmol) at −78 °C. The reaction mixture was concentrated and the residue was diluted with ethyl acetate (10 mL). The organic layer was washed with water and brine. Further purification was performed by flash column chromatography (hexane/ethyl acetate=7/1) to give **23** in 81% yield (major: 76%, minor: 5%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.33–1.46 (m, 1H), 1.52 (s, 9H), 1.58–1.90 (m, 6H), 2.09 (dddd, $J$=5.6, 8.3, 13.9, 27.6 Hz, 1H), 3.08 (br s, 1H), 3.91–3.96 (ddd, $J$=3.9, 6.6, 10.0 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 20.1, 20.9 ($J$=4.1 Hz), 28.0, 28.8 ($J$=2.5 Hz), 29.7 ($J$=20.6 Hz), 70.1 ($J$=26.3 Hz), 28.8 ($J$=2.5 Hz), 83.2, 94.4 ($J$=185.9 Hz), 170.7 ($J$=23.8 Hz); $[\alpha]_D^{27}$ −18.7 (*c* 2.1, $CHCl_3$); FABMS (*m*NBA) *m*/*z* 219 $(M+1)^+$, 163 $(M+2-t\text{-Bu})^+$; FAB–HRMS (*m*NBA) Calcd for $C_{11}H_{18}FO_3$ $(M)^+$ 218.1318. Found 218.1318. *Minor isomer*: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.30–1.94 (m, 16H), 2.01–2.09 (m, 1H), 3.87 (ddd, $J$=4.6, 9.5, 24.0 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 19.8, 23.7, 28.0, 30.2, 32.2 ($J$=22.3 Hz), 72.0 ($J$=20.6 Hz), 82.6, 96.0 ($J$=187.6 Hz), 169.9 ($J$=26.3 Hz); FABMS (*m*NBA) *m*/*z* 219 $(M+1)^+$, 163 $(M+2-t\text{-Bu})^+$; $[\alpha]_D^{27}$ 17.9 (*c* 0.25, $CH_3CN$).

**4.5.6. *tert*-Butyl 2-benzylamino-1-fluorocyclohexanecarboxylate (24).** To a solution of **7c** (26 mg, 0.12 mmol, 94% ee) in toluene (2 mL) was added $BnNH_2$ (14 μL, 0.132 mmol) at room temperature. The reaction mixture was stirred under reflux in the presence of a catalytic amount of TsOH (5 mg, 0.026 mmol) using MS4A as a dehydrating agent. After 4 h, the solvent was removed under reduced pressure. To this crude mixture were added AcOH (0.5 mL) and $NaCNBH_3$ (25 mg, 0.4 mmol) at room temperature. The mixture was stirred for an additional 2 h. After dilution with ether (10 mL), 1 N NaOH was added until the reaction mixture reached pH 9. The aqueous layer was extracted with ether (2×10 mL) and the combined organic layers were washed with water and brine. Evaporation of the solvent and flash column chromatography (hexane/ether=20/1) of the residue afforded the desired product **23** (major: 65%, minor: 8%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.25–1.40 (m, 1H), 1.45–1.78 (m, 5H), 1.51 (s, 9H), 1.80–1.88 (m, 1H), 1.99–2.11 (m, 1H), 2.95 (ddd, $J$=4.6, 8.6, 12.7 Hz, 1H), 3.83 (d, $J$=13.2 Hz, 1H), 3.87 (d, $J$=13.2 Hz, 1H), 7.20–7.34 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 21.7 (d, $J$=7.4 Hz), 22.1, 27.6 (d, $J$=5.0 Hz), 28.1, 31.6 (d, $J$=21.4 Hz), 52.0, 59.8 (d, $J$=21.4 Hz), 82.0, 96.9 (d, $J$=183 Hz), 126.7, 128.0, 128.3, 140.7, 169.7 (d, $J$=26.3 Hz); FAB–LRMS (*m*NBA) *m*/*z* 308 $(M+1)^+$, 252 $(M+2H-t\text{-Bu})^+$; $[\alpha]_D^{26}$ −8.92 (*c* 1.44, $CHCl_3$). FAB–HRMS (*m*NBA) Calcd for $C_{18}H_{27}NO_2$ F $(M+1)^+$ 308.2026. Found 308.2016; *Minor*: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.51 (s, 9H), 1.55–2.10 (m, 8H), 2.90 (ddd, $J$=4.4, 11.4, 27.6 Hz, 1H), 3.72 (d, $J$=13.2 Hz, 1H), 3.91 (d, $J$=13.2 Hz, 1H), 7.19–7.34 (m, 5H).

**4.5.7. (*S*)-2-Fluoro-1,2,3,4-tetrahydro-1-oxonaphthalen-2-yl-2-phosphonic acid (25).** TMSBr (354 μL, 2.68 mmol) was added to a solution of **12d** (134 mg, 0.447 mmol, 95% ee) in $CH_2Cl_2$ (5 mL) under ice-bath cooling. The resulting mixture was stirred for 12 h at room temperature. After evaporation, MeOH (2 mL) was added and the mixture was stirred for an additional 2 h. Gradual removal of the solvent by leaving this solution still at ambient temperature gave a brownish solid. Washing this solid with $CHCl_3$ afforded pure **25** in 97% yield (106 mg). $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 2.30–2.49 (m, 1H), 2.62–2.75 (m, 1H), 3.01 (dt, $J$=2.8, 17.3 Hz, 1H), 3.43 (ddd, $J$=4.9, 12.7, 21.0 Hz, 1H), 7.24 (d, $J$=7.5 Hz, 1H), 7.25 (t, $J$=7.8 Hz, 1H), 7.46 (dt, $J$=1.2, 7.5 Hz, 1H), 7.89 (dd, $J$=1.2, 8.1 Hz, 1H); $^{13}$C NMR (100 MHz, $CD_3OD$) 27.2 (d, $J$=10.7 Hz), 32.9 (d, $J$=10.2 Hz), 96.8 (dd, $J$=153, 191 Hz), 127.8, 128.5 (d, $J$=1.7 Hz), 130.0, 132.9, 135.4, 145.3, 193.7 (dd, $J$=3.2, 13.1 Hz); $[\alpha]_D^{27}$ 58.9 (*c* 1.01, EtOH).

### 4.6. X-ray structural analysis of 16

Molecular formula: $C_{32}H_{37}Cl_2FNO_8PS$; molecular weight: 716.56; unit-cell dimensions: $a$=11.015(3) Å, $\alpha$=90°, $b$=14.875(3) Å, $\beta$=98.092(1)°, $c$=21.073(5) Å, $\gamma$=90°; $U$=3452.6(15) Å$^3$, $Z$=4, $d$=1.379 g/cm$^3$; crystal system: orthorhombic; space group: $P$ 21 21 21; type of diffractometer: Rigaku R-AXIS-CS, crystal size, 0.50×0.25×0.21 mm$^3$; temperature: 296 K; theta range: 3.01–24.69°; reflections collected: 29,415; independent reflections: 5830 [$R$(int)=0.0379]; absorption coefficient: 0.350 mm$^{-1}$; max and min transmission: 0.9301 and 0.7093; solution method: direct; refinement method: full-matrix least-squares on $F^2$; goodness of fit indicator: 1.206, $R1$=0.0511, $wR2$=0.1014. Crystallographic data for the structure reported in this paper have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 288122. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK [Fax: int. code +44 1223 336 033; E-mail: deposit@ccdc.cam.ac.uk].

## Acknowledgements

This work was supported in part by a Grant-in Aid for Encouragement of Young Scientists (B) from J.S.P.S. We

thank Dr. D. Hashizume of RIKEN for X-ray analysis, and Ms. K. Harata of RIKEN for MS measurements. We also thank Dr. Takao Saito of Takasago International Corp. for a generous gift of chiral phosphine ligands.

## References and notes


1. (a) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, 2004; (b) Hiyama, T.; Kanie, K.; Kusumoto, T.; Morizawa, Y.; Shimizu, M. *Organofluorine Compounds: Chemistry and Applications*; Springer: Berlin, 2000; (c) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996; For reviews: (d) O'Hagan, D.; Rzepa, H. S. *Chem. Commun.* **1997**, 645–652; (e) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3–11; (f) Ismail, F. M. D. *J. Fluorine Chem.* **2002**, *118*, 27–33.
2. (a) *Asymmetric Fluoroorganic Chemistry: Synthesis, Application, and Future Directions*; Ramachandran, P. V., Ed.; ACS Symposium Series 746; American Chemical Society: Washington, DC, 2000; (b) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenge and Biomedicinal Targets*; Soloshonok, V. A., Ed.; Wiley: New York, NY, 1999.
3. (a) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1–16; (b) Iseki, K. *Tetrahedron* **1998**, *54*, 13887–13914.
4. Reviews of enantioselective fluorination reactions: (a) Ibrahim, H.; Togni, A. *Chem. Commun.* **2004**, 1147–1155; (b) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119–6146; For a review of catalytic asymmetric α-halogenation reactions: (c) France, S.; Weatherwax, A.; Lectka, T. *Eur. J. Org. Chem.* **2005**, 475–479.
5. For representative examples: (a) Iwaoka, T.; Murohashi, T.; Sato, M.; Kaneko, C. *Tetrahedron: Asymmetry* **1992**, *3*, 1025–1028; (b) Davis, F. A.; Kasu, P. V. N. *Tetrahedron Lett.* **1998**, *39*, 6135–6138; (c) Enders, D.; Faure, S.; Potthoff, M.; Runsink, J. *Synthesis* **2001**, *15*, 2307–2319.
6. (a) Differding, E.; Lang, R. E. *Tetrahedron Lett.* **1988**, *29*, 6087–6090; (b) Davis, F. A.; Zhou, P.; Murphy, C. K.; Sundarababu, G.; Qi, H.; Han, W.; Przeslawski, R. M.; Chen, B.-C.; Carroll, P. *J. Org. Chem.* **1998**, *63*, 2273–2280; (c) Liu, Z.; Shibata, N.; Takeuchi, Y. *J. Org. Chem.* **2000**, *65*, 7583–7587.
7. (a) Shibata, N.; Suzuki, E.; Asahi, T.; Shiro, M. *J. Am. Chem. Soc.* **2001**, *123*, 7001–7009; (b) Mohar, B.; Baudoux, J.; Plaquevent, J.-C.; Cahard, D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4214–4216; (c) Shibata, N.; Ishimaru, T.; Suzuki, E.; Kirk, K. L. *J. Org. Chem.* **2003**, *68*, 2494–2497; (d) Zoute, L.; Audouard, C.; Plaquevent, J.-C.; Cahard, D. *Org. Biomol. Chem.* **2003**, *1*, 1833–1834; (e) Greedy, B.; Paris, J.-M.; Vidal, T.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 3291–3294; (f) Thierry, B.; Audouard, C.; Plaquevent, J.-C.; Cahard, D. *Synlett* **2004**, 856–860.
8. (a) Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4359–4362; (b) Piana, S.; Devillers, I.; Togni, A.; Rothlisberger, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 979–982; (c) Frantz, R.; Hintermann, L.; Perseghini, M.; Broggini, D.; Togni, A. *Org. Lett.* **2003**, *5*, 1709–1712.
9. Kim, D. Y.; Park, E. J. *Org. Lett.* **2002**, *4*, 545–547.
10. (a) Hamashima, Y.; Yagi, K.; Takano, H.; Tamás, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530–14531; (b) Hamashima, Y.; Takano, H.; Hotta, D.; Sodeoka, M. *Org. Lett.* **2003**, *5*, 3225–3228; (c) Hamashima, Y.; Suzuki, T.; Shimura, Y.; Shimizu, T.; Umebayashi, N.; Tamura, T.; Sasamoto, N.; Sodeoka, M. *Tetrahedron Lett.* **2005**, *46*, 1447–1450.
11. For β-ketoesters: (a) Ma, J.-A.; Cahard, D. *Tetrahedron: Asymmetry* **2004**, *15*, 1007–1011; (b) Shibata, N.; Ishimaru, T.; Nagai, T.; Kohno, J.; Toru, T. *Synlett* **2004**, 1703–1706; (c) Shibata, N.; Kohno, J.; Takai, K.; Ishimaru, T.; Nakamura, S.; Toru, T.; Kanemasa, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 4204–4207; For cyanoesters: (d) Kim, H. R.; Kim, D. Y. *Tetrahedron Lett.* **2005**, *46*, 3115–3117; For β-ketophosphonates: (e) Bernardi, L.; Jørgensen, K. A. *Chem. Commun.* **2005**, 1324–1326; (f) Kim, S. M.; Kim, H. R.; Kim, D. Y. *Org. Lett.* **2005**, *7*, 2309–2311.
12. (a) Enders, D.; Hüttl, M. R. M. *Synlett* **2005**, 991–993; (b) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703–3706; (c) Steiner, D. D.; Mase, N.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2005**, *44*, 3706–3710; (d) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826–8828; (e) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051–15053.
13. For catalytic enantioselective monofluorination of oxindoles: Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2005**, *127*, 10164–10165.
14. (a) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240–11241; (b) Hamashima, Y.; Hotta, D.; Umebayashi, N.; Tsuchiya, Y.; Suzuki, T.; Sodeoka, M. *Adv. Synth. Catal.* **2005**, *347*, 1576–1586; (c) Sodeoka, M.; Hamashima, Y. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 941–956.
15. Kumobayashi, H.; Miura, T.; Sayo, N.; Saito, T.; Zhang, X. *Synlett* **2001**, 1055–1064.
16. In the case of the Michael reaction, no reaction occurred with the Pd complexes **2**. The addition of a strong protic acid, such as TfOH, which promotes the reaction cooperatively with the Pd enolate as an activator of the enone, was necessary.
17. For the preparation of β-ketophosphonates: Calogeropoulou, T.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1987**, *52*, 4185–4190.
18. α-Fluorophosphonates have been used as mimics of a phosphate moiety. For a general review: Berkowitz, D. B.; Bose, M. *J. Fluorine Chem.* **2001**, *112*, 13–33.
19. For example: (a) Nieschalk, J.; O'Hagan, D. *J. Chem. Soc., Chem. Commun.* **1995**, 719–720; (b) Li, C.; Wu, L.; Otaka, A.; Smyth, M. S.; Roller, P. P.; Burke, T. R., Jr.; den Hertog, J.; Zhang, Z.-Y. *Biochem. Biophys. Res. Commun.* **1995**, *216*, 976–984; (c) Yokoyama, T.; Yamagishi, T.; Matsumoto, K.; Shibuya, S. *Tetrahedron* **1996**, *52*, 11725–11738; (d) Berkowitz, D. B.; Bose, M.; Pfannenstiel, T. J.; Doukov, T. *J. Org. Chem.* **2000**, *65*, 4498–4508.
20. (a) Kotoris, C. C.; Wen, W.; Lough, A.; Taylor, S. D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1271–1281; (b) Ruiz, M.; Ojea, V.; Quintela, J. M.; Guillín, J. J. *Chem. Commun.* **2002**, 1600–1601.
21. For details, see Supporting Information of Ref. 10a.
22. (a) Harada, N.; Koumura, N.; Feringa, B. L. *J. Am. Chem. Soc.* **1997**, *119*, 7256–7264; (b) Watanabe, M.; Kuwahara, S.; Harada, N.; Koizumi, M.; Ohkuma, T. *Tetrahedron: Asymmetry* **1999**, *10*, 2075–2078.

23. (a) Fujita, M.; Hiyama, T. *J. Am. Chem. Soc.* **1985**, *107*, 8294–8296; (b) Kitazume, T.; Kobayashi, T.; Yamamoto, T.; Yamazaki, T. *J. Org. Chem.* **1987**, *52*, 3218–3223.
24. The difference in coupling constants of the methine proton against the fluorine atom is derived from axial–equatorial and axial–axial relationships on the assumption that the ester group is at the equatorial position, as seen in the case of cyclohexane derivatives. The unambiguous stereochemistry observed in the reduction of **12d** under similar reaction conditions supports the predominant formation of **21**.
25. For phosphonate ester dealkylation: McKenna, C. E.; Schmidhauser, J. *J. Chem. Soc., Chem. Commun.* **1979**, 739.
26. Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450–5458.
27. Gori, G.; Bartolucci, G. B.; Sturaro, A.; Pavoli, G.; Doretti, L.; Troiano, R.; Casetta, B. *J. Chromatogr., B* **1995**, 165–172.