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Highly Diastereo- and Enantioselective Vinylogous Mannich Reactions of Fluorinated Aldimines with Siloxyfurans

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Abstract: A highly regio- and enantioselective asymmetric vinylogous Mannich reaction of readily available fluorinated aldimines bearing a chiral auxiliary [(*S*)-1-phenylethyl group] with siloxyfurans to afford chiral fluorine-containing γ-butenolide or γ-lactone derivatives has been developed in the presence of silver acetate (10 mol%) and axially chiral phosphine-oxazoline ligand **L1** (11 mol%). In most cases, the corresponding fluorinated adducts were obtained in high yields, good to excellent enantiomeric excesses and up to >20:1 *dr*.

Keywords: asymmetric catalysis; axially chiral phosphine-oxazoline ligands; chiral auxiliary; fluorinated aldimines; Mannich reaction; siloxyfurans; silver acetate

It has been well known that incorporation of fluorine(s) into strategic positions of target molecules can significantly modify their chemical properties, biological activities and selectivities.[1] Thus far, numerous fluoro- and fluoroalkyl-substituted pharmaceuticals, agrochemicals, dyes and polymers have been successfully commercialized.[2] Among these modifications, for example, trifluoromethyl-substituted molecules have attracted much attention because of their specific properties, such as the high lipophilicity and stability against heating or photo-irradiation, brought by the CF_3 moiety. Recently, these molecules have found outstanding applications in the pharmaceutical society,[3] for instance, Efavirenz[4] (anti-HIV) and Celecoxib[5] (antiarthritic) are two famous drugs used in the treatment of human diseases. Moreover, the difluoromethylene unit, which plays a significant role in current organofluorine chemistry,[6] has been revealed as a component of some biologically interesting compounds, such as phosphotyrosine (pTyr) mimetics,[7] the anticancer agent gemcitabine,[8] and HIV-1 protease inhibitors.[9] Furthermore, α,α-difluoro-β-amino acids have also attracted much interest due to their importance in chemical biology during the past decades.[10] It is not surprising, therefore, that broad research efforts have been focused on the enantioselective construction of fluorine-containing stereogenicity[11] and the exploitation of an efficient and novel catalytic asymmetric method for the synthesis of these compounds is highly desirable.

The catalytic asymmetric vinylogous Mannich (AVM)-type reaction of trimethylsiloxyfuran with aldimines has proved to be a powerful synthetic protocol to prepare chiral γ-butenolide derivatives bearing an amine functionality in recent years.[12] However, preparing chiral fluorine-containing γ-butenolide derivatives bearing an amine functionality by using such an AVM-type reaction is still a tough challenge. Crousse and Bonnet-Delpon reported the first example of a vinylogous Mannich reaction of trifluoromethylaldimines with trimethylsiloxyfuran in the presence of Lewis acids to produce fluorine-containing γ-butenolide derivatives in high yields along with good diastereoselectivities (>98%).[13] To the best of our knowledge, a catalytic asymmetric vinylogous Mannich reaction of fluorinated aldimines with trimethylsiloxyfuran has only been reported by our group recently, in which high yields and excellent diastereoselectivities along with up to 81% *ee* have been realized.[14] It is rather difficult to obtain fluorine-containing γ-butenolide derivatives in >95% *ee*.[13,14,15] During our ongoing effects to improve the enantioselectivity of this reaction, we found that, in the silver(I)-catalyzed asymmetric vinylogous Mannich reaction of fluorinated aldimines bearing an (*S*)-Me(Ph)CH group as a chiral auxiliary with siloxyfurans, the corresponding

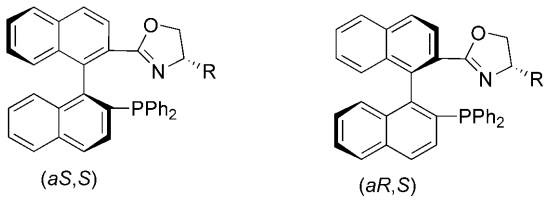


Figure 1. Axially chiral phosphine-oxazoline ligands **L1**–**L5**.

fluorinated γ-butenolides or γ-lactones could be produced in high yields, high diastereoselectivities, and high to excellent enantiomeric excesses in the presence of axially chiral phosphine-oxazoline ligand **L1** under mild conditions. To the best of our knowledge, the use of both a chiral auxiliary and a chiral catalyst in an asymmetric reaction is rarely reported, especially in the case of imines bearing a chiral auxiliary together with chiral catalyst in the AVM reaction although asymmetric reactions using optically active imines as the starting materials have been reported frequently.[16] Herein, we wish to report the details in this context.

According to our previous investigation,[14] we initially utilized the Lewis acid AgOAc (10 mol%) combined with PPh_3 or chiral phosphine-oxazoline ligands **L1**–**L5** (11 mol%) (Figure 1) as the catalysts in the AVM reactions of readily available fluorinated aldimine **2a** (0.15 mmol) bearing an (*S*)-Me(Ph)CH group as a chiral auxiliary with siloxyfuran **3a** (0.27 mmol) in tetrahydrofuran (THF) containing 0.27 mmol of CH_3CH_2OH (1.8 equiv.) to develop the optimal reaction conditions, and the results of these experiments are summarized in Table 1. It was found that the corresponding fluorinated γ-butenolide **4a** was formed in 95% yield, 1:2 diastereoselectivity, and 40% *ee* for the major diastereomer in the presence of PPh_3 (Table 1, entry 1). The enantiomeric excesse of **4a** was determined by a $Pd(OH)_2$-catalyzed hydrogenation in methanol to remove the chiral auxiliary along with the reduction of the double bond, affording the corresponding fluorinated γ-lactone, which was further transformed to the fluorinated amide **5a** in 77% overall yield by the reaction with *p*-bromobenzoic acid (2.0 equiv.) in the presence of *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (3.0 equiv.) and 1-hydroxy-*N*-hydroxybenzotriazole (HOBt) (4.0 equiv.) in *N*,*N*-dimethylformamide (DMF) (Table 1). The racemic amide **5a** was synthesized using the corresponding fluorinated aldimine **2aa** (Figure 2)[17] as the substrate following the same reaction procedure mentioned above (see the Supporting Information for the detail). Further investigation of chiral ligands **L1**–**L5** revealed that the combination of AgOAc with chiral ligand (*S*,*S*)-P-Oxa-*t*-Bu (**L1**) is the more efficient catalyst in this reaction, affording the corresponding fluorinated aldi-

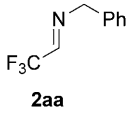
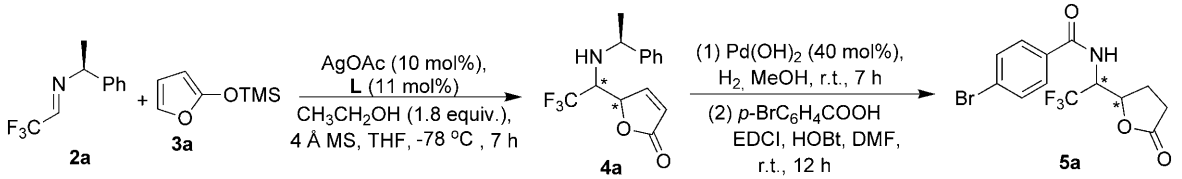


Figure 2. Fluorinated aldimine **2aa**.

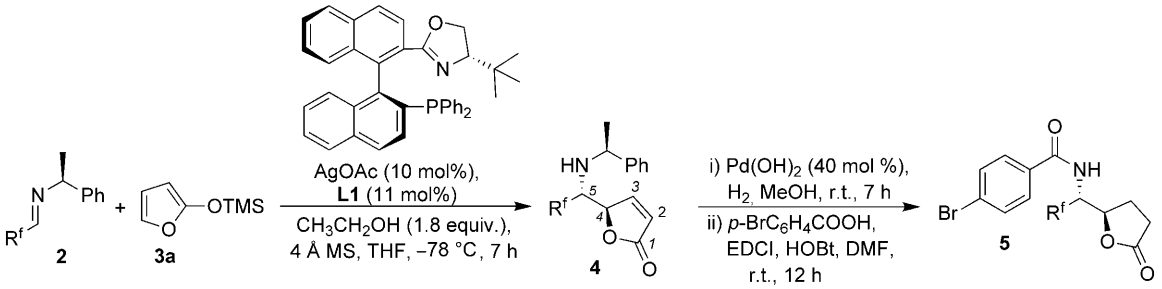
Table 1. Screening of ligands for the AVM reaction of optically active fluorinated aldimine **2a** with siloxyfuran **3a**.



Entry[a]	Ligand	Yield [%][b] **4a/5a**[c]	*dr*[d] **4a** (or **5a**)	*ee* [%][e] **5a**
1	Ph_3P	95/77	1:2	40
2	**L1**	95/75	>20:1	97
3	**L2**	98/75	>20:1	89
4	**L3**	97/74	>20:1	88
5	**L4**	99/76	6:1	65
6	**L5**	96/74	6:1	52

[a] *Reaction conditions:* **2a** (0.15 mmol), **3a** (0.27 mmol), CH_3CH_2OH (0.27 mmol), AgOAc (10 mol%), ligand (11 mol%), 4 Å MS (50 mg), THF (1.0 mL), and the reaction was carried out at −78 °C for 7 h.
[b] Isolated yields after column chromatography.
[c] Overall yields of two steps.
[d] Determined by analysis of ^1H NMR spectroscopic data of **4**.
[e] Determined by chiral HPLC analysis of the major diastereoisomer of **5a**.

Table 2. Substrate scope of AVM reaction of optically active fluorinated aldimines **2** with siloxyfuran **3a**



Entry[a]	**2** (R_f)	Yield [%][b] **4**/**5**[c]	*dr*[d] **4** (or **5**)	*ee* [%][e] **5**
1	**2a** (CF_3)	**4a**, 95/**5a**, 75	>20:1	97 (4*R*, 5*R*)
2	**2b** (CF_2H)	**4b**, 99/**5b**, 77	>20:1	92 (4*R*, 5*R*)
3[f]	**2c** (CF_2Br)	**4c**, 98/**5c**, 65	>20:1	96 (4*R*, 5*R*)
4	**2d** (CF_2Cl)	**4d**, 96/**5d**, 70	20:1	96 (4*R*, 5*R*)
5	**2e** (CF_3CF_2)	**4e**, 98/**5e**, 69	>20:1	97 (4*R*, 5*R*)
6	**2f** ($C_6H_5CF_2$)	**4f**, 95/**5f**, 66	>20:1	98 (4*R*, 5*R*)
7[g]	**2g** (*p*-$BrC_6H_4CF_2$)	**4g**, 95/**5g**, 67	>20:1	95 (4*R*, 5*R*)[h]
8[g]	**2h** (*p*-$ClC_6H_4CF_2$)	**4h**, 98/**5h**, 79	>20:1	96 (4*R*, 5*R*)
9	**2i** ($PMPCF_2$)	**4i**, 98/**5i**, 70	>20:1	87 (4*R*, 5*R*)
10	**2j** (*p*-$MeC_6H_4CF_2$)	**4j**, 99/**5j**, 52	>20:1	92 (4*R*, 5*R*)

[a] *Reaction conditions:* **2** (0.15 mmol), **3** (0.27 mmol), CH_3CH_2OH (0.27 mmol), AgOAc (10 mol%), ligand (11 mol%), 4 Å MS (50 mg), THF (1.0 mL), and the reaction was carried out at −78 °C for 7 h.
[b] Isolated yields after column chromatography.
[c] Overall yields of two steps.
[d] Determined by analysis of ^{1}H NMR spectroscopic data of **4**.
[e] Determined by chiral HPLC analysis of **5**.
[f] R_f was hydrogenated to CF_2H.
[g] R_f was hydrogenated to $C_6H_4CF_2$.
[h] Absolute configuration was determined by X-ray crystallography of **4g** (see the Supporting Information).

mine **4a** in 95% yield along with 97% *ee* (*dr* > 20:1) in THF at −78 °C for 7 h, which was determined by transformation of **4a** into the corresponding amide **5a** in 75% yield (Table 1, entry 2). Other chiral ligands **L2**–**L5** are not as effective as **L1** in this reaction under identical conditions (Table 1, entries 3–5). Using PPh_3 as the ligand cannot significantly interact with the substrates and the chiral auxiliary [(*S*)-1-phenylethyl group] in this reaction, giving the product in poor diastereoselectivity (Table 1, entry 1). The reversal of the diastereoselectivities in PPh_3 and **L1** was caused by the sterically different interactions among the substrates, chiral auxiliary and the chiral catalysts (Table 1, entries 1 and 2). The difference of the diastereoselectivity between ligands **L1** and **L4** clearly suggested a match/mismatch effect.

With optimal reaction conditions in hand, we next examined the generality of this reaction with various optically active fluorinated aldimines **2** bearing an (*S*)-1-phenylethyl group with siloxyfuran **3a** and the results are summarized in Table 2. As can be seen from Table 2, a series of difluoromethylated optically active aldimines **2b**–**2d** having a variety of substituents such as bromo, chloro or hydrogen atom on their R_f groups could react with **3a** smoothly to give the corresponding fluorinated products **4b**–**4d** in high yields along with 92–96% enantiomeric excesses and ≥20:1 *dr* (Table 2, entries 2–4). When R_f is a perfluoroalkyl group such as pentafluoroethyl group, a similar result was obtained, the reaction affording **4e** in 98% yield, 97% *ee* and >20:1 *dr* (Table 2, entry 5). As for the optically active difluorinated aldimines **2f**–**2j** bearing an aromatic ring on the R_f group, the reactions also proceeded smoothly to give the corresponding difluorinated γ-butenolides **4f**–**4j** in high yields (95–99%) and good to excellent enantiomeric excesses (87–98% *ee*) as well as high diastereoselectivities (*dr* >20:1) irrespective of whether they have electron-rich or electron-poor aromatic groups (Table 2, entries 6–10). Only in the case of difluorinated aldimine **2i** having an electron-rich *p*-methoxyphenyl group (PMP), was the corresponding adduct **4i** formed in 87% *ee*, presumably due to the electronic properties (Table 2, entry 9). The fluorinated adducts were formed in the *anti*-configuration and their absolute configurations have been unambiguously determined as 4*R*,5*R* by the X-ray crystallographic analysis of **4g**. Its ORTEP drawing is shown in Figure 3 and its

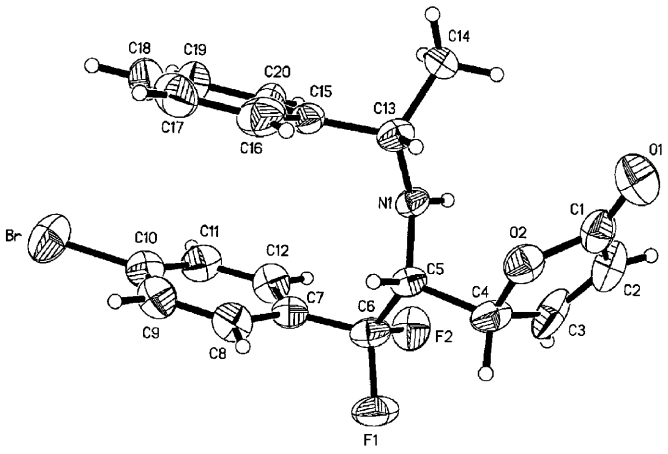
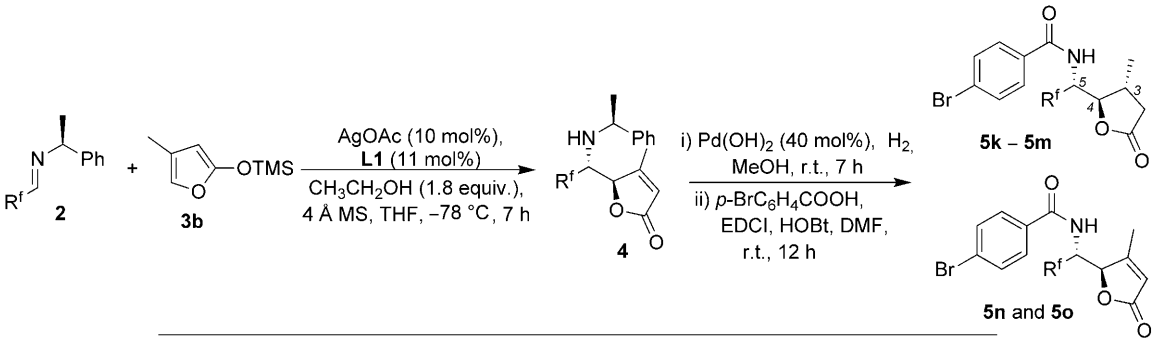


Figure 3. ORTEP drawing of **4g**.

CIF data are presented in the Supporting Information.[18]

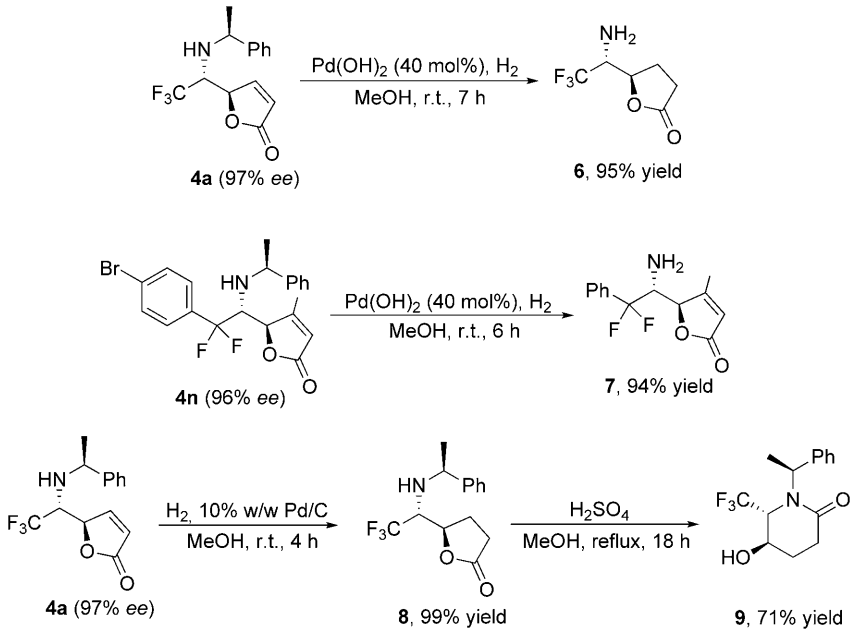
Asymmetric vinylogous Mannich reactions of fluorinated aldimines with 4-Me-substituted siloxyfuran **3b**, prepared from the reaction of commercially available 4-methyl-2(5*H*)-furanone with TMSCl and Et_3N at 0 °C, have also been examined under the standard conditions. As shown in Table 3, as for fluorinated aldimines **2a**, **2g** and **2h**, the corresponding fluorinated amide **4k**, **4n** and **4o** were obtained in high yields, good to excellent enantiomeric excesses and >20:1 *dr* (Table 3, entries 1, 4 and 5). Using fluorinated aldimines **2f** and **2i** having an electron-neutral aromatic group (phenyl group) and an electron-rich aromatic group (PMP) as the substrates the reactions afforded the corresponding fluorinated adducts **4l** and **4m** in high yields, but moderate *ee* and *dr* values, presumably due to the electronic properties in these two particular cases (Table 3, entries 2 and 3). The enantiomeric excesses of **4k**–**4o** were also determined after transformation into products **5k**–**5o**. As for products **5k**–**5m**, the newly generated stereogenic center at the C-3 position was assigned as 3*R* on the basis of the NOESY spectrum of **5k** (see the Supporting Information for the details). Interestingly, the double bond of **4n** and **4o** remained unchanged upon hydrogenation with H_2 in the presence of $Pd(OH)_2$, probably due to the electronic effect of the R_f group and the steric hindrance of the methyl group at the C-3 position, affording the corresponding fluorinated adducts **5n** and **5o** in 57% and 67% yields, respectively.

Table 3. Substrate scope of AVM reaction of optically active fluorinated aldimines **2** with siloxyfuran **3b**.



Entry[a]	**2** (R_f)	Yield [%][b] **4**/**5**[c]	*dr*[d] **4** (or **5**)	*ee* [%][e] **5**
1	**2a** (CF_3)	**4k**, 97/**5k**, 61	>20:1	99 (3*R*, 4*R*, 5*R*)[g]
2	**2f** ($C_6H_5CF_2$)	**4l**, 93/**5l**, 80	14:1	78 (3*R*, 4*R*, 5*R*)
3	**2i** (PMPCF_2)	**4m**, 99/**5m**, 68	10:1	77 (3*R*, 4*R*, 5*R*)
4[f]	**2g** (*p*-Br$C_6H_4CF_2$)	**4n**, 88/**5n**, 57	>20:1	96 (4*R*, 5*R*)
5[f]	**2h** (*p*-Cl$C_6H_4CF_2$)	**4o**, 98/**5o**, 67	>20:1	88 (4*R*, 5*R*)

[a] *Reaction conditions:* **2** (0.15 mmol), **3b** (0.27 mmol), CH_3CH_2OH (0.27 mmol), AgOAc (10 mol%), ligand (11 mol%), 4 Å MS (50 mg), THF (1.0 mL), and the reaction was carried out at −78 °C for 7 h.
[b] Isolated yields after column chromatography.
[c] Overall yields of two steps.
[d] Determined by analysis of ^{1}H NMR spectroscopic data of **4**.
[e] Determined by chiral HPLC analysis of **5**.
[f] The reaction time for hydrogenation was controlled within 6 h and R_f was hydrogenated to $C_6H_4CF_2$. The product is **5n** or **5o**.
[g] Relative configuration of H-C-3 and H-C-4 was assigned as *trans* by NOESY spectrum of **5k**. The absolute configurations of C-4 and C-5 were assigned in analogy with **4g** (see the Supporting Information).



Scheme 1. Removal of chiral auxiliary [(*S*)-1-phenylethyl group] and the transformation of AVM fluorinated product.

The synthetic utility of these fluorinated products **4** could be displayed by removal of the chiral auxiliary [(*S*)-1-phenylethyl group] with $Pd(OH)_2/H_2$ in MeOH under mild conditions, affording the corresponding free fluorinated amine products **6** in 95% yield and **7** in 94% yield (Scheme 1). Upon hydrogenation of **4a** with Pd/C in methanol for 4 h, the corresponding product **8** was produced in 99% yield, which could be further transformed to the functionalized fluorine-containing piperidin-2-one derivative **9** in 71% yield in the presence of sulfuric acid under reflux (Scheme 1).[13]

Based on previous mechanistic studies by Hoveyda and co-workers,[12b] a transition state model can be proposed, as shown in Figure 4. In the activated complex, to minimize steric interactions, the substrate is bound *anti* to the bulky substituent (*t*-Bu) on the oxazoline of **L1**. The catalyst-bound imine may react with the siloxyfuran by an *endo*-type addition,[19] and consequently, the reaction of an optically active fluorinated aldimine with siloxyfuran catalyzed by AgOAc combined with **L1** provides the (4*R*,5*R*) stereoisomer predominantly.

In summary, the first example of a highly regio- and enantioselective AVM reaction of readily available fluorinated aldimines having a chiral auxiliary [(*S*)-1-phenylethyl] with siloxyfurans to produce chiral fluorine-containing γ-butenolide and γ-lactone derivatives has been developed in the presence of AgOAc (10 mol%), EtOH (1.8 equiv.) and axially chiral phosphine-oxazoline ligand **L1** (11 mol%) in THF at −78 °C. In most cases, the corresponding fluorinated adducts were afforded in high yields, good to excellent enantiomeric excesses and up to >20:1 *dr*. Since the catalytic asymmetric reaction using fluorine-containing substrates is always a tough task, this finding and the method of introducing some chiral auxiliaries into the substrate in some organic catalytic asymmetric reactions can give us a new way to carry out the asymmetric catalysis in F-containing compounds.

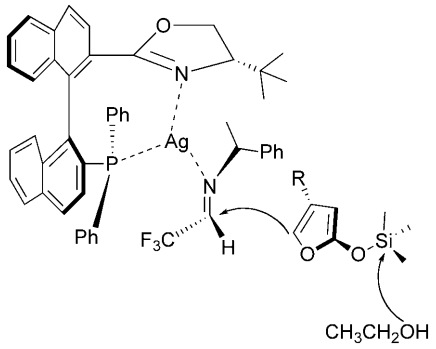


Figure 4. Plausible transition state model.

Experimental Section

General Remarks

Melting points were determined on a digital melting point apparatus and temperatures were uncorrected. Optical rotations were determined at 589 nm (sodium D line) by using a Perkin–Elmer-341 MC digital polarimeter; $[\alpha]_D$ values are

given in units of 10 $deg^{-1} cm^2 g^{-1}$. ^1H NMR spectra were recorded on Bruker AM-300 and AM-400 spectrometers for solutions in $CDCl_3$ or $(CD_3)_3CO$; coupling constants *J* are given in Hz. ^{19}F and ^{31}P NMR spectra were recorded on Bruker AM-300 and AM-400 spectrometers with complete proton decoupling. Infrared spectra were recorded on a Perkin–Elmer PE-983 spectrometer with absorptions given in cm^{-1}. Flash column chromatography was performed using 300–400 mesh silica gel. For thin-layer chromatography (TLC), silica gel plates (Huanghai GF254) were used. Chiral HPLC was performed on a Shimadzu SPD-10 A *vp* series with chiral columns [Chiralpak AD-H, OD-H, PA-H and IC-H columns 4.6×250 mm, (Daicel Chemical Ind., Ltd.)]. Mass spectra were recorded by EI, ESI, MALDI and HR-MS were measured on an HP-5989 instrument. Organic solvents used were dried by standard methods when necessary. Ligands **L1**, **L4** and **L5** are known compounds and were synthesized according to the previous literature. Compounds **1c–1o** were commercially available or prepared according to the previous literature. Fluorinated aldimines **2a**, **2b**, **2f**, **2aa**, **2bb**, **2cc** and **2dd** were prepared according to the previous reports. Racemic **4aa**, **4bb**, **4cc** and **4dd** are known compounds.

Typical Procedure

A dried Schlenk tube was charged with AgOAc (2.50 mg, 0.015 mmol), **L1** (9.30 mg, 0.017 mmol), and 4 Å MS (50 mg). Then, freshly distilled THF and optically active fluorinated aldimine **2** (**2a**–**2j**) (0.15 mmol) were added successively, and following addition of CH_3CH_2OH (16 μL, 0.27 mmol), the resulting solution was allowed to cool to −78 °C with stirring. At −78 °C, compound **3** (**3a** or **3b**) (0.27 mmol) was added and the resulting solution was kept at −78 °C for 7 h before addition of HOAc (15.4 μL, 0.27 mmol) in MeOH (0.2 mL) to quench the reaction. The quenched reaction solution was allowed to stir at −78 °C for an additional two hours, and then it was allowed to warm to room temperature (22 °C). A saturated aqueous solution of $NaHCO_3$ was added and the aqueous layer was washed with EtOAc (3×5 mL), dried over anhydrous $MgSO_4$, and the volatiles were removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (elution with petroleum ether/EtOAc = 4:1) to give the corresponding compound **4** (**4a–4o**).

Supporting Information

Experimental procedures and spectroscopic data for all new compounds, X-ray crystal structure and CIF data for **4g** areavailable free of charge as Supporting Information.

Acknowledgements

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