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Axially chiral phosphine–oxazoline ligands in silver(I)-catalyzed asymmetric Mannich reaction of *N*-Boc aldimines with trimethylsiloxyfuran

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ABSTRACT

Axially chiral phosphine–oxazoline ligand **L6** was found to be a fairly effective chiral ligand in silver(I)-catalyzed asymmetric Mannich reaction of *N*-Boc aldimines with trimethylsiloxyfuran to give the corresponding adducts in up to 97% yield, 7:1 dr and 86% ee (major diastereoisomer).

1. Introduction

Catalytic asymmetric vinylogous Mannich (AVM)-type reaction of trimethylsiloxyfuran with aldimines has been proved to be a very powerful synthetic protocol to prepare chiral γ-butenolide derivatives bearing an amino functional group in recent years.[1] Many successful examples have been reported thus far. For example, Martin and Lopez reported the first example of catalytic asymmetric addition of trialkylsilyloxyfurans to aldimines in 1999, affording the corresponding adducts in moderate ee value along with high yield.[1a] A few years late, Hoveyda and Snapper have developed a elegant asymmetric catalytic system with silver(I)-based catalyst using a 2-methyloxyphenyl group as aldimine substituent, leading to the corresponding product of AVM (asymmetric vinylogous Mannich) reaction of trimethylsiloxyfuran with aldimine in excellent diastereo- and enantioselectivity.[1b,c] Later on, a new highly diastereo- and enantioselective catalytic asymmetric vinylogous Mannich-type reaction system applicable to a wide range of aldimines, which do not possess a 2-methyloxyphenyl group, with siloxyfuran using an axially chiral phosphine–oxazoline ligand [(*R*,*S*)-*P*-Oxa-Ph]/AgOAc/CF_3CH_2OH combination has been developed by our group.[1e] During our ongoing investigation on this interesting asymmetric catalytic system, we attempted to explore the AVM reaction of trimethylsiloxyfuran with *N*-Boc (^{t}BuOC(O))-protected aldimine, which has not yet been developed. This is because asymmetric addition of nucleophiles to *N*-Boc-protected imines has provided a straightforward synthetic approach to chiral amines since its precursor ($BocNH_2$) as well as the *N*-Boc protected imine are easily available and the *N*-protecting group (*N*-Boc) can be readily cleaved under several convenient acidic conditions (HCl or TFA).[2] In this paper, we wish to report that axially chiral phosphine–oxazoline ligand **L6** derived from (*R*)-binol is a fairly effective catalyst in the silver(I)-catalyzed asymmetric Mannich reaction of *N*-Boc aldimines with trimethylsiloxyfuran under mild conditions, providing the corresponding chiral *N*-Boc-protected γ-butenolides in moderate to good enantiomeric excesses and good to high yields as well as good diastereoselectivities.

2. Results and discussion

Axially chiral phosphine–oxazoline ligands **L1**–**L6** are known compounds and were synthesized according to the previous literature.[1e,3] The new chiral phosphine–oxazoline ligands **L7**–**L12** were synthesized from (**a*R***)-**1**, which is derived from (*R*)-binol[4] and their synthetic route has been shown in Scheme 1. The spectroscopic data of these new chiral ligands are indicated in the experimental section.

With these above chiral ligands in hand, we set out to utilize the Lewis acid AgOAc (10 mol %)[5] combined with chiral phosphine–oxazoline ligands **L1**–**L12** (10 mol %) (Fig. 1) as the catalysts

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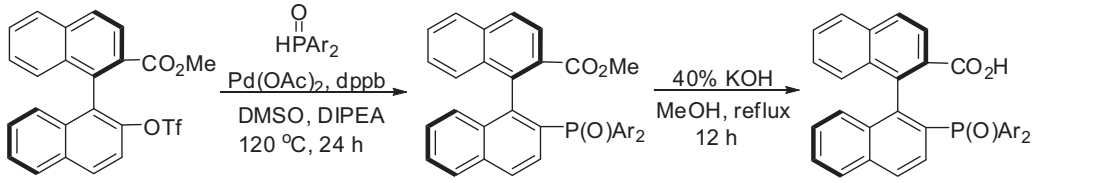
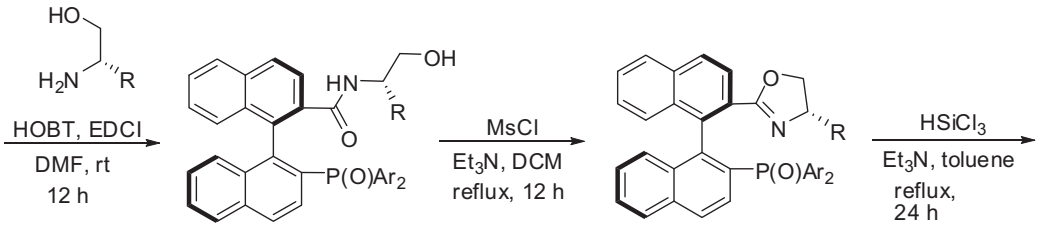


(*aR*)-**1**

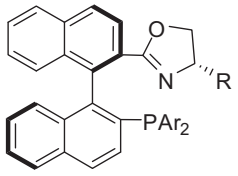
(*aR*)-**2a**: Ar = Ph (81%)
(*aR*)-**2b**: Ar = 4-FC_6H_4 (70%)
(*aR*)-**2c**: Ar = 4-$MeOC_6H_4$ (79%)
(*aR*)-**2d**: Ar = 4-MeC_6H_4 (74%)
(*aR*)-**2e**: Ar = 3,5-$Me_2C_6H_3$ (83%)

(*aR*)-**3a**: Ar = Ph (97%)
(*aR*)-**3b**: Ar = 4-FC_6H_4 (97%)
(*aR*)-**3c**: Ar = 4-$MeOC_6H_4$ (94%)
(*aR*)-**3d**: Ar = 4-MeC_6H_4 (95%)
(*aR*)-**3e**: Ar = 3,5-$Me_2C_6H_3$ (92%)



(*aR,S*)-**4a**: R = 2-naphthylmethyl, Ar = Ph (91%)
(*aR,S*)-**4b**: R = benzyl, Ar = Ph (82%)
(*aR,S*)-**4c**: R = ^{t}Bu, Ar = 4-FC_6H_4 (78%)
(*aR,S*)-**4d**: R = ^{t}Bu, Ar = 4-$MeOC_6H_4$ (85%)
(*aR,S*)-**4e**: R = ^{t}Bu, Ar = 4-MeC_6H_4 (89%)
(*aR,S*)-**4f**: R = ^{t}Bu, Ar = 3,5-$Me_2C_6H_3$ (98%)

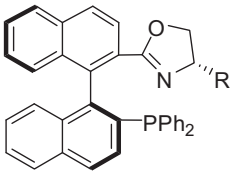
(*aR,S*)-**5a**: R = 2-naphthylmethyl, Ar = Ph (91%)
(*aR,S*)-**5b**: R = benzyl, Ar = Ph (82%)
(*aR,S*)-**5c**: R = ^{t}Bu, Ar = 4-FC_6H_4 (78%)
(*aR,S*)-**5d**: R = ^{t}Bu, Ar = 4-$MeOC_6H_4$ (85%)
(*aR,S*)-**5e**: R = ^{t}Bu, Ar = 4-MeC_6H_4 (89%)
(*aR,S*)-**5f**: R = ^{t}Bu, Ar = 3,5-$Me_2C_6H_3$ (98%)



(*aR,S*)-**L7**: R = 2-naphthylmethyl, Ar = Ph (91%)
(*aR,S*)-**L8**: R = benzyl, Ar = Ph (82%)
(*aR,S*)-**L9**: R = ^{t}Bu, Ar = 4-FC_6H_4 (78%)
(*aR,S*)-**L10**: R = ^{t}Bu, Ar = 4-$MeOC_6H_4$ (85%)
(*aR,S*)-**L11**: R = ^{t}Bu, Ar = 4-MeC_6H_4 (89%)
(*aR,S*)-**L12**: R = ^{t}Bu, Ar = 3,5-$Me_2C_6H_3$ (98%)

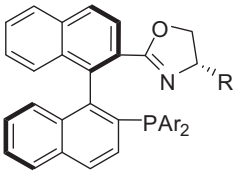
Scheme 1. Reaction procedure for the preparation of ligands **L7**–**L12**.

and the AVM reaction of readily available *N*-Boc aldimine **1a** (0.15 mmol) with siloxyfuran **2** (0.27 mmol) as a model reaction in dichloromethane (CH_2Cl_2) containing 0.27 mmol (1.8 equiv) of CH_3CH_2OH[1d,e,5a] to develop the optimal reaction conditions and the results of these experiments are summarized in Table 1. It was found that (*aR*,*S*)-*P*-Oxa-^{t}Bu (**L6**) is the best chiral ligand in this reaction to afford the corresponding product **3a** in 97% yield and 86% ee for the major diastereoisomer (dr=6:1) in CH_2Cl_2 at −78 °C for 24 h (Table 1, entry 6). Other chiral ligands **L1**–**L5** and **L7**–**L12** are not as effective as **L6** in this reaction under identical conditions



(*aS,S*)

L1: R = Ph
L2: R = ^{i}Pr
L3: R = ^{t}Bu

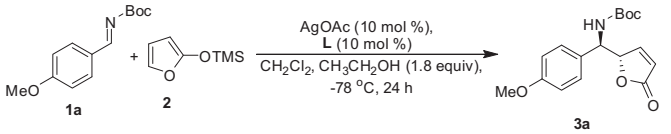


(*aR,S*)

L4: R = Ph, Ar = Ph
L5: R = ^{i}Pr, Ar = Ph
L6: R = ^{t}Bu, Ar = Ph
L7: R = 2-naphthylmethyl, Ar = Ph
L8: R = benzyl, Ar = Ph
L9: R = ^{t}Bu, Ar = 4-FC_6H_4
L10: R = ^{t}Bu, Ar = 4-$MeOC_6H_4$
L11: R = ^{t}Bu, Ar = 4-MeC_6H_4
L12: R = ^{t}Bu, Ar = 3,5-$Me_2C_6H_3$

Fig. 1. Axially chiral phosphine–oxazoline ligands **L1**–**L12**.

Table 1
Optimization of chiral ligands for the AVM reaction of *N*-Boc aldimine **1a** and siloxyfuran **2**



Entry[a]	Ligand	Yield [%][b]	*anti*:*syn*[c]	*anti*, ee [%][d]
		3a	**3a**	**3a**
1	**L1**	90	>20:1	47
2	**L2**	79	7:1	53
3	**L3**	82	5:1	52
4	**L4**	98	>20:1	46
5	**L5**	99	>20:1	51
6	***L6***	*97*	*6:1*	*86*
7	**L7**	89	9:1	61
8	**L8**	94	9:1	68
9	**L9**	85	5:1	65
10	**L10**	88	6:1	80
11	**L11**	90	7:1	79
12	**L12**	92	4:1	79

[a] Reaction conditions: **1a** (0.15 mmol), **2** (0.27 mmol), CH_3CH_2OH (0.27 mmol), AgOAc (10 mol %), ligand (10 mol %), CH_2Cl_2 (1.0 mL), and the reaction was carried out at −78 °C for 24 h.
[b] Yields of the purified *syn* and *anti* product.
[c] Determined by ^1H NMR spectroscopic data of the crude product.
[d] Determined by chiral HPLC analysis.

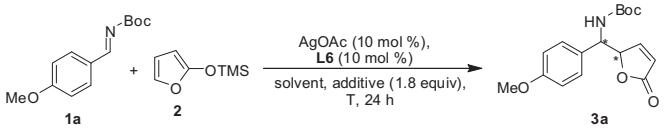
(Table 1, entries 1–5 and 7–12) although excellent yields and drs were achieved when **L1**, **L4**, and **L5** were used as the chiral ligands in this reaction (Table 1, entries 1, 4, and 5).

The effects of temperature, solvents, and additives were then investigated using the best chiral (a*R*,*S*)-*P*-Oxa-^{t}Bu ligand **L6** in the model reaction of **1a** with **2**, the results are outlined in Table 2 combined with the result obtained in DCM for comparison (Table 2, entry 5). It can be seen from Table 2, increasing the reaction temperature from −78 °C to room temperature (20 °C) caused the decrease in enantioselectivity (from 86% to 61%) although excellent drs were observed at 0 °C and at room temperature (dr>20:1) (Table 2, entries 1–5). When solvents, such as tetrahydrofuran (THF), toluene, CH_2ClCH_2Cl, and $CHCl_2CHCl_2$ were used in this reaction, lower ee value (from 77% to 57%) was realized but along with good to excellent drs (from 11:1 to >20:1) (Table 2, entries 6–9). Previous studies have revealed that the addition of alcoholic additives can enhance the reactivity and enantioselectivity in this asymmetric reaction.[6] The optimization studies on the effects of different alcoholic additives in this reaction were then performed and the results of these experiments are also summarized in Table 2 (entries 10–13). A significant decrease in enantioselectivity was observed by adding CF_3CH_2OH or BnOH (1.8 equiv) into the reaction system (Table 2, entries 10 and 11). We also examined additive effects of *i*-PrOH and ^{t}BuOH in this reaction under identical conditions, but no improvement was observed (Table 2, entries 12 and 13). Therefore, the best reaction conditions are those using 10 mol % of AgOAc along with 10 mol % of chiral ligand **L6** as the catalyst and carrying out the reaction in CH_2Cl_2 at −78 °C for 24 h in the presence of 1.8 equiv of CH_3CH_2OH.

Having established the optimal conditions, we next examined the generality of this reaction using various *N*-Boc-protected imines **1** with siloxyfuran **2** and the results are summarized in Table 3. It was found that the *N*-Boc-protected imines **1b**–**i** bearing an aromatic ring (R group=aromatic ring) could react with **2** smoothly to give the corresponding asymmetric vinylogous Mannich-type products **3b**–**i** in good to high yields (79%–97%) and good diastereoselectivities (4:1–7:1 dr) as well as moderate to good enantiomeric excesses (63%–83% ee) for the major diastereoisomers whether they have electron-rich or electron-poor aromatic groups (Table 2, entries 2–9). When R is a heteroaryl group, such as 2-furyl group, similar result was obtained, affording the desired adduct **3j** in 79% yield, 80% ee and 7:1 dr (Table 2, entry 10). As for alkyl *N*-Boc-protected imine **1k**, the reactions also proceeded smoothly to give the corresponding *N*-Boc-protected γ-butenolides **3k** in 75 yield and 75% ee along with 6:1 dr value (Table 2, entry 11).

The synthetic utility of the product can be displayed by removal of the *N*-Boc-protecting group with trifluoroacetic acid (TFA) in CH_2Cl_2 at room temperature for 4 h, affording the corresponding free amine product **4** in 92% yield (Scheme 2). The absolute

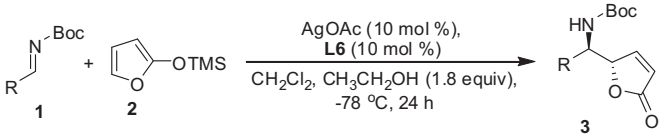
Table 2
Optimization of the temperature, solvent, and additive for the AVM reaction of *N*-Boc aldimine **1a** and siloxyfuran **2**



Entry[a]	T [°C]	Solvent	Additive	Yield [%][b]	*anti*:*syn*[c]	*anti*, ee [%][d]
				3a	**3a**	**3a**
1	rt	DCM	CH_3CH_2OH	99	20:1	61
2	0	DCM	CH_3CH_2OH	67	>20:1	67
3	−20	DCM	CH_3CH_2OH	63	5:1	73
4	−40	DCM	CH_3CH_2OH	90	8:1	64
5	−78	DCM	CH_3CH_2OH	97	6:1	86
6	−78	THF	CH_3CH_2OH	85	19:1	77
7	−78	Toluene	CH_3CH_2OH	60	>20:1	74
8	−20	CH_2ClCH_2Cl	CH_3CH_2OH	83	>20:1	78
9	−20	$CHCl_2CHC_2$	CH_3CH_2OH	77	11:1	57
10	−78	DCM	CF_3CH_2OH	80	6:1	52
11	−78	DCM	BnOH	63	3:1	65
12	−78	DCM	*i*-PrOH	82	5:1	85
13	−78	DCM	^{t}BuOH	88	11:1	74

[a] Reaction conditions: **1a** (0.15 mmol), **2** (0.27 mmol), CH_3CH_2OH (0.27 mmol), AgOAc (10 mol %), ligand (10 mol %), solvent (1.0 mL), and the reaction was carried out at rt ~ −78 °C for 24 h.
[b] Yields of the purified *syn* and *anti* product.
[c] Determined by ^1H NMR spectroscopic data of the crude product.
[d] Determined by chiral HPLC analysis.

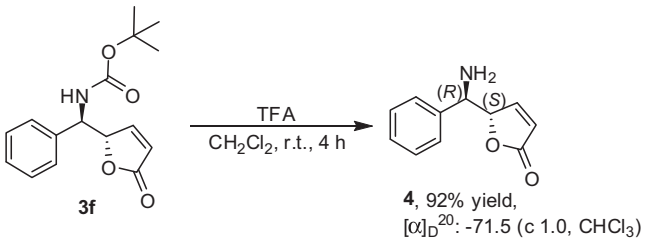
Table 3
Scope and limitations of AVM reaction of *N*-Boc aldimines **1** and siloxyfuran **2**



Entry[a]	R	Yield [%][b]	*anti*:*syn*[c]	*anti*, ee [%][d]
		3	**3**	**3**
1	*p*-$MeOC_6H_4$, **1a**	**3a**, 97 (83)	6:1	86
2	*m*-$MeOC_6H_4$, **1b**	**3b**, 95 (83)	7:1	78
3	*p*-MeC_6H_4, **1c**	**3c**, 90 (72)	4:1	83
4	*m*-MeC_6H_4, **1d**	**3d**, 92 (79)	6:1	71
5	3,4,5-$(MeO)_3C_6H_2$, **1e**	**3e**, 94 (78)	5:1	76
6	Ph, **1f**	**3f**, 82 (70)	6:1	77
7	*p*-FC_6H_4, **1g**	**3g**, 93 (80)	6:1	63
8	*p*-BrC_6H_4 **1 h**	**3h**, 88 (75)	6:1	67
9	*m*-BrC_6H_4 **1i**	**3i**, 79 (69)	7:1	73
10	2-Furyl, **1j**	**3j**, 79 (69)	7:1	80
11	Cydohexyl, **1k**	**3k**, 88 (75)	6:1	75

[a] Reaction conditions: **1a** (0.15 mmol), **2** (0.27 mmol), CH_3CH_2OH (0.27 mmol), AgOAc (10 mol %), ligand (10 mol %), CH_2Cl_2 (1.0 mL), and the reaction was carried out at −78 °C for 24 h.
[b] Yields are determined by ^1H NMR spectrum and in parentheses are isolated yields of the *anti* isomer.
[c] Determined by ^1H NMR spectroscopic data of the crude product.
[d] Determined by chiral HPLC analysis.

configuration was assigned to be (*R*,*S*) for the products **3a**–**k** by comparison of the free amine product **4**'s ^{1}H NMR and ^{13}C NMR spectra data as well as optical rotation with literature values.[1b,e]



Scheme 2. Removal of the *N*-Boc group and determination of the absolute configuratiion of **4**.

To identify the coordination pattern between **L6** and AgOAc, we treated **L6** with AgOAc (1.0 equiv) at 25 °C in DCM-d_2 for 0.5 h, and measured their ^{31}P NMR spectroscopy at 25 °C. A significant chemical shift change of their ^{31}P NMR spectroscopic signals has been observed from −15.97 ppm (singlet) to 4.85 ppm (doublet, J=555 Hz) in comparison with that of **L6**, suggesting the coordination between **L6** and AgOAc (see the Supplementary data). On the basis of previous mechanistic studies by Hoveyda and our group,[1c,e] a transition-state model can be outlined in Fig. 2. In the activated complex, to minimize the steric interactions, the substrate is bound *anti* to the bulky substituent (^{t}Bu) on oxazoline of **L6**. The catalyst-bound imine may react with the siloxyfuran by an *endo*-type addition,[7] and consequently, the reaction of a optically active *N*-Boc imines with siloxyfuran catalyzed by AgOAc combined with **L6** provides the (*R*, *S*) stereoisomer predominantly.

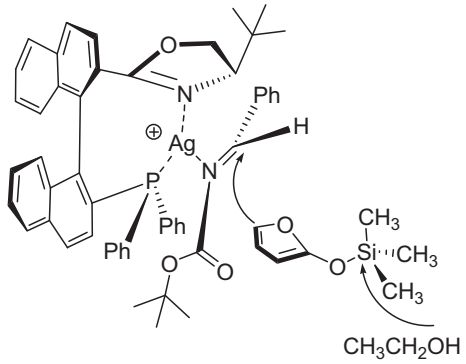


Fig. 2. Plausible transition-state model.

3. Conclusion

In summary, we have reported a silver(I)-catalyzed catalytic asymmetric Mannich reaction of *N*-Boc imines with trimethylsiloxyfuran in the presence of chiral phosphine–oxazoline ligand **L6** in CH_2Cl_2 under mild conditions, affording the corresponding adducts in good to high yields and good diastereoselectivities along with moderate to good enantioselectivities. Since the *N*-Boc group can be easily cleaved under several convenient acidic conditions (HCl or TFA),[2] the chiral *N*-Boc-protected γ-butenolides synthesized in this paper will be more useful in organic synthesis.

4. Experimental section

4.1. 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 unit of 10 deg^{-1} cm^2 g^{-1} ^{1}H NMR spectra were recorded on a Bruker AM-300 and AM-400 spectrometer for solution in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard; coupling constants J are given in hertz. ^{19}F and ^{31}P NMR spectra were recorded on a Bruker AM-300 and AM-400 spectrophotometers with complete proton decoupling spectrophotometers. Infrared spectra were recorded on a Perkin–Elmer PE-983 spectrometer with absorption in cm^{-1}. Flash column chromatography was performed using 300–400 mesh silica gel. For thin-layer chromatography (TLC), silica gel plates (Huanghai GF_{254}) were used. Chiral HPLC was performed on an SHIMADZU SPD-10A *vp* series with chiral columns (Chiralpak AD-H, OJ-H, PA-H, and IC-H columns 4.6×250 mm, (Daicel Chemical Ind., Ltd.)). Mass spectra were recorded by EI, ESI, MALDI, and HRMS was measured on an HP-5989 instrument. Organic solvents used were dried by standard methods when necessary. *N*-Boc aldimines **1a**–**k** were prepared according to the previous reports.[8] (***aR***)-**2a** and (***aR***)-**3a** are known compounds and were prepared according to literature procedures.[1e,3]

4.2. Typical reaction procedure for the preparation of (*aR*)-2

To a solution of (***aR***)-**1**[4] (115 mg, 0.25 mmol), diarylphosphine oxide (0.50 mmol), palladium diacetate (5.6 mg, 0.025 mmol), and 1,4-bis(diphenylphosphino)butane (10.7 mg, 0.025 mmol), in 1.5 mL of DMSO was added diisopropylethylamine (0.21 mL, 1.2 mmol), and the mixture was stirred at 120 °C for 24 h. After being cooled to room temperature, the reaction mixture was diluted with EtOAc, washed with H_2O, and dried over $MgSO_4$. Removal of the solvent followed by column chromatography on silica gel (elution with *n*-hexane/EtOAc=1/2) gave compound (***aR***)-**2**.

*4.2.1. Compound (**aR**)-**2b**.* Yield: 70%, 96 mg, white solid, mp 79–80 °C; IR (neat): ν 3056, 2949, 2884, 2835, 1718, 1589, 1497, 1277, 1225, 1190, 1158, 1113, 877, 828, 766, 662 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 3.55 (3H, s), 6.70–6.75 (2H, m), 6.86–6.91 (2H, m), 6.97 (1H, d, J=8.4 Hz), 7.05–7.20 (3H, m), 7.30–7.40 (3H, m), 7.45–7.51 (3H, m), 7.64 (1H, dd, J=8.8, 12.0 Hz), 7.72 (1H, d, J=8.0 Hz), 7.78 (1H, d, J=8.4 Hz), 7.89 (1H, d, J=8.4 Hz), 7.95 (1H, d, J=8.8 Hz), 8.05 (1H, d, J=8.4 Hz); ^{31}P NMR (161.94 MHz, $CDCl_3$, 85% H_3PO_4): δ 26.24; ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$): δ −107.4 to 107.5 (1F, m), −107.8 to 107.9 (1F, m); MS (ESI) m/z 549.5 (M+H$^+$, 100). HRMS (MALDI) calcd for $C_{34}H_{24}O_3F_2P$ requires (M+H$^+$) 549.1426, found: 549.1439; $[\alpha]_D^{20}$ +19.8 (*c* 0.44, CH_2Cl_2).

*4.2.2. Compound (**aR**)-**2c**.* Yield: 79%, 113 mg, white solid, mp 85–68 °C; IR (neat): ν 3057, 2976, 2885, 2836, 1719, 1595, 1501, 1277, 1244, 1177, 1115, 1023, 828, 800, 766, 695, 646 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 3.53 (3H, s), 3.71 (3H, s), 3.77 (3H, s), 6.58 (2H, dd, J=2.4, 8.8 Hz), 6.68 (1H, dd, J=2.4, 8.8 Hz), 6.97–7.02 (2H, m), 7.09–7.13 (1H, m), 7.18–7.27 (3H, m), 7.33–7.41 (3H, m), 7.49 (1H, t, J=8.0 Hz), 7.68–7.78 (3H, m), 7.90–7.95 (2H, m), 8.03 (1H, d, J=8.8 Hz); ^{31}P NMR (161.93 MHz, $CDCl_3$, 85% H_3PO_4): δ 27.44; MS (MALDI) m/z 573.5 (M+H$^+$, 100). HRMS (ESI) calcd for $C_{36}H_{30}O_5P$ requires (M+H$^+$) 573.1825, found: 573.1828; $[\alpha]_D^{20}$ +15.8 (*c* 0.40, CH_2Cl_2).

*4.2.3. Compound (**aR**)-**2d**.* Yield: 74%, 100 mg, white solid, mp 79–80 °C; IR (neat): ν 3056, 2986, 2877, 2837, 1720, 1599, 1433, 1276, 1241, 1186, 1132, 809, 765, 747, 658, 645 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 2.20 (3H, s), 2.30 (3H, s), 3.53 (3H, s), 6.83 (2H, dd, J=2.4, 7.8 Hz), 6.95–7.11 (5H, m), 7.16–7.25 (3H, m), 7.34–7.40 (3H, m), 7.48 (1H, t, J=7.8 Hz), 7.63–7.70 (2H, m), 7.76 (1H, d, J=9.0 Hz), 7.89–7.94 (2H, m), 8.02 (1H, d, J=9.0 Hz); ^{31}P NMR (121.45 MHz, $CDCl_3$, 85% H_3PO_4): δ 28.82; MS (ESI) m/z 541.6

(M+H$^+$, 100). HRMS (MALDI) calcd for $C_{36}H_{30}O_3P$ requires (M+H$^+$) 541.1927, found: 541.1918; $[\alpha]_D^{20}$ +6.0 (*c* 0.58, CH_2Cl_2).

*4.2.4. Compound (**aR**)-**2e**.* Yield: 83%, 118 mg, white solid, mp 107–110 °C; IR (CH_2Cl_2): *ν* 3048, 2948, 2918, 2859, 1724, 1597, 1455, 1433, 1276, 1243, 1190, 1132, 871, 852, 767, 733, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): *δ* 2.06 (6H, s), 2.20 (6H, s), 3.59 (3H, s), 6.70 (1H, s), 6.89 (1H, d, *J*=12 Hz), 6.95–7.02 (3H, m), 7.11–7.29 (5H, m), 7.36 (1H, td, *J*=1.2, 7.2 Hz), 7.49 (1H, t, *J*=7.2 Hz), 7.68–7.75 (3H, m), 7.90–7.95 (2H, m), 8.03 (1H, d, *J*=8.4 Hz); ^{31}P NMR (161.94 MHz, $CDCl_3$, TMS): *δ* 27.08; MS (ESI) *m*/*z* 569.4 (M+H$^+$, 100). HRMS (ESI) calcd for $C_{38}H_{33}O_3PNa$ requires (M+Na$^+$) 591.2060, found: 591.2071; $[\alpha]_D^{20}$ −8.2 (*c* 1.0, CH_2Cl_2).

4.3. Typical reaction procedure for the preparation of (*aR*)-3

To a solution of (***aR***)-**2** (0.20 mmol) in 2.5 mL of methanol (dioxane for (***aR***)-**2b**) was added 500 μL of 40% KOH solution and the mixture was refluxed for 13 h. The reaction mixture was acidified to pH=2 by addition of concd HCl at 0 °C and extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was recrystallized in CH_2Cl_2 and petroleum ether to give compound (**aR**)-**3**.

*4.3.1. Compound (**aR**)-**3b**.* Yield: 97%, 104 mg, white solid, mp 148–150 °C; IR (neat): *ν* 3057, 2989, 2884, 2829, 1588, 1497, 1386, 1226, 1159, 1134, 1013, 807, 772, 745, 663 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): *δ* 6.28 (1H, d, *J*=8.4 Hz), 6.62–6.65 (2H, m), 6.80 (1H, t, *J*=7.2 Hz), 7.12–7.20 (5H, m), 7.26–7.34 (3H, m), 7.54 (1H, t, *J*=8.0 Hz), 7.68–7.77 (4H, m), 7.89–7.97 (3H, m); ^{31}P NMR (161.94 MHz, $CDCl_3$, 85% H_3PO_4): *δ* 33.26 (t, *J*=1.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$): *δ* −104.9 to 105.0 (1F, m), −106.2 to 106.3 (1F, m); MS (ESI) *m*/*z* 535.5 (M+H$^+$, 100). HRMS (MALDI) calcd for $C_{33}H_{21}O_3F_2PNa$ requires (M+Na$^+$) 557.1089, found: 557.1089; $[\alpha]_D^{20}$ −78.7 (*c* 1.0, CH_2Cl_2).

*4.3.2. Compound (**aR**)-**3c**.* Yield: 94%, 105 mg, white solid, mp 116–117 °C; IR (neat): *ν* 3058, 2964, 2892, 2837, 1711, 1594, 1501, 1404, 1254, 1116, 1022, 800, 746, 650 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): *δ* 3.68 (3H, s), 3.87 (3H, s), 6.18 (1H, d, *J*=8.4 Hz), 6.43 (2H, dd, *J*=2.0, 8.8 Hz), 6.68–6.72 (1H, m), 7.00–7.05 (4H, m), 7.10 (1H, d, *J*=8.4 Hz), 7.18 (1H, t, *J*=8.0 Hz), 7.24–7.28 (1H, m), 7.34 (1H, dd, *J*=8.4, 12.4 Hz), 7.51 (1H, t, *J*=8.0 Hz), 7.66–7.74 (4H, m), 7.87–7.94 (3H, m); ^{31}P NMR (161.93 MHz, $CDCl_3$, 85% H_3PO_4): *δ* 34.53; MS (ESI) *m*/*z* 559.4 (M+H$^+$, 100). HRMS (ESI) calcd for $C_{35}H_{27}NaO_5P$ requires (M+Na$^+$) 581.1488, found: 581.1507; $[\alpha]_D^{20}$ +86.4 (*c* 0.59, CH_2Cl_2).

*4.3.3. Compound (**aR**)-**3d**.* Yield: 95%, 100 mg, white solid, mp 245–246 °C; IR (neat): *ν* 3049, 2984, 2883, 2833, 1717, 1599, 1404, 1284, 1115, 1086, 1019, 826, 806, 752, 680, 649 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): *δ* 2.16 (3H, s), 2.44 (3H, s), 6.18 (1H, d, *J*=8.7 Hz), 6.63–6.73 (3H, m), 6.96–7.03 (2H, m), 7.09–7.20 (2H, m), 7.24–7.37 (4H, m), 7.51 (1H, t, *J*=7.5 Hz), 7.63–7.73 (4H, m), 7.86–7.93 (3H, m); ^{31}P NMR (121.45 MHz, $CDCl_3$, 85% H_3PO_4): *δ* 35.79; MS (ESI) *m*/*z* 527.6 (M+H$^+$, 100). HRMS (MALDI) calcd for $C_{35}H_{28}O_3P$ requires (M+H$^+$) 527.1771, found: 527.1766; $[\alpha]_D^{20}$ +119.5 (*c* 0.7, CH_2Cl_2).

*4.3.4. Compound (**aR**)-**3e**.* Yield: 92%, 102 mg, white solid, mp 325–328 °C; IR (CH_2Cl_2): *ν* 3054, 2918, 2859, 2461, 1923, 1718, 1599, 1502, 1466, 1402, 1272, 1232, 1157, 1134, 1104, 878, 852, 766, 738, 693, 644 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): *δ* 2.00 (6H, s), 2.36 (6H, s), 6.24 (1H, d, *J*=8.0 Hz), 6.62 (1H, s), 6.70 (2H, d, *J*=12.8 Hz), 6.77 (1H, t, *J*=8.0 Hz), 7.10–7.17 (2H, m), 7.24–7.30 (3H, m), 7.34–7.42 (3H, m), 7.53 (1H, t, *J*=8.0 Hz), 7.65 (1H, d, *J*=8.0 Hz), 7.72 (1H, d, *J*=8.0 Hz), 7.88–7.95 (3H, m); ^{31}P NMR (161.94 MHz, $CDCl_3$, TMS): *δ* 34.02; MS (ESI) *m*/*z* 555.4 (M+H$^+$, 100). HRMS (ESI) calcd for $C_{37}H_{31}O_3PNa$ requires (M+Na$^+$) 577.1903, found: 577.1911; $[\alpha]_D^{20}$ +127.4 (*c* 1.0, CH_2Cl_2).

4.4. Typical reaction procedure for the preparation of (*aR*)-4

A mixture of compound (***aR***)-**3** (1.0 mmol), chiral aminoalcohol (2.0 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (576 mg, 3.0 mmol), and 1-hydroxy-benzotriazole (542 mg, 4.00 mmol) in *N*,*N*-dimethylformamide (20 mL) was stirred at room temperature overnight. Then, the solvent was removed from the flask under reduced pressure. The resulting residue was diluted with CH_2Cl_2, washed with saturated NaCl solution twice, and extracted by CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel (elution with petroleum ether/EtOAc=1:1) to give compound (***aR***,***S***)-**4**.

*4.4.1. Compound (**aR**,**S**)-**4a**.* Yield: 91%, 620 mg, white solid, mp 229–230 °C; IR (neat): *ν* 3367, 3296, 3057, 3022, 2946, 2877, 2825, 1651, 1537, 1435, 1297, 1147, 1112, 872, 822, 750, 721, 687, 639 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): *δ* 1.86 (1H, dd, *J*=5.1, 13.5 Hz), 2.13 (1H, dd, *J*=10.2, 13.5 Hz), 3.32–3.40 (1H, m), 3.70–3.74 (1H, m), 4.00–4.02 (1H, m), 4.24–4.29 (1H, m), 6.66–6.73 (3H, m), 6.89–6.96 (2H, m), 7.06–7.13 (4H, m), 7.19–7.28 (2H, m), 7.34–7.38 (3H, m), 7.45 (1H, t, *J*=7.2 Hz), 7.52–7.64 (7H, m), 7.70–7.86 (4H, m), 7.91–7.98 (3H, m), 8.97 (1H, d, *J*=7.5 Hz); ^{31}P NMR (121.45 MHz, $CDCl_3$, 85% H_3PO_4): *δ* 31.41; MS (ESI) *m*/*z* 682.6 (M+H$^+$, 100). HRMS (MALDI) calcd for $C_{46}H_{37}NO_3P$ requires (M+H$^+$) 682.2506, found: 682.2510; $[\alpha]_D^{20}$ −28.3 (*c* 1.1, CH_2Cl_2).

*4.4.2. Compound (**aR**,**S**)-**4b**.* Yield: 82%, 517 mg, white solid, mp 262–263 °C; IR (neat): *ν* 3406, 3263, 3059, 2995, 2879, 2825, 1649, 1543, 1435, 1295, 1147, 1090, 943, 875, 832, 816, 753, 707, 641 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): *δ* 1.68 (1H, dd, *J*=5.1, 13.5 Hz), 1.94 (1H, dd, *J*=10.2, 13.5 Hz), 3.27–3.36 (1H, m), 3.68–3.73 (1H, m), 3.83–3.91 (1H, m), 4.22–4.26 (1H, m), 6.67–6.75 (3H, m), 6.89–6.97 (4H, m), 7.07–7.13 (6H, m), 7.20–7.33 (2H, m), 7.52–7.65 (6H, m), 7.79 (2H, dd, *J*=8.4, 30.0 Hz), 7.90–8.02 (4H, m), 8.85 (1H, d, *J*=7.8 Hz); ^{31}P NMR (121.45 MHz, $CDCl_3$, 85% H_3PO_4): *δ* 31.49; MS (ESI) *m*/*z* 632.6 (M+H$^+$, 100). HRMS (MALDI) calcd for $C_{42}H_{35}NO_3P$ requires (M+H$^+$) 632.2349, found: 632.2342; $[\alpha]_D^{20}$ −26.3 (*c* 0.74, CH_2Cl_2).

*4.4.3. Compound (**aR**)-**4c**.* Yield: 78%, 494 mg, white solid, mp 225–226 °C; IR (neat): *ν* 3431, 3224, 3065, 2965, 2880, 2836, 1647, 1591, 1495, 1397, 1227, 1184, 1093, 1058, 847, 825, 680 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): *δ* 0.24 (9H, s), 3.26–3.34 (1H, m), 3.69–3.82 (2H, m), 4.25 (1H, t, *J*=6.0 Hz), 6.36–6.43 (2H, m), 6.54 (1H, d, *J*=9.0 Hz), 6.97–7.11 (3H, m), 7.19–7.25 (3H, m), 7.30–7.43 (3H, m), 7.49–7.62 (3H, m), 7.77 (1H, d, *J*=9.0 Hz), 7.83–8.02 (4H, m), 8.12 (1H, d, *J*=8.4 Hz); ^{31}P NMR (121.45 MHz, $CDCl_3$, 85% H_3PO_4): *δ* 28.66 (t, *J*=1.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): *δ* −106.3 to 106.5 (1F, m), −108.0 to 108.1 (1F, m); MS (ESI) *m*/*z* 634.7 (M+H$^+$, 100). HRMS (MALDI) calcd for $C_{39}H_{34}NO_3F_2PNa$ requires (M+Na$^+$) 656.2137, found: 656.2126; $[\alpha]_D^{20}$ −34.0 (*c* 0.29, CH_2Cl_2).

*4.4.4. Compound (**aR**)-**4d**.* Yield: 85%, 558 mg, white solid, mp 191–192 °C; IR (neat): *ν* 3429, 3302, 3241, 3068, 2958, 2900, 2836, 1642, 1594, 1522, 1499, 1249, 1169, 1113, 1022, 799, 765, 667, 643 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): *δ* 0.25 (9H, s), 3.44 (1H, dd, *J*=6.4, 11.6 Hz), 3.64 (3H, s), 3.73–3.81 (2H, m), 3.85 (3H, s), 6.22 (2H, dd, *J*=2.4, 8.8 Hz), 6.48 (1H, d, *J*=8.4 Hz), 6.90–7.03 (5H, m), 7.20–7.31 (3H, m), 7.52–7.59 (3H, m), 7.74–7.81 (3H, m), 7.90–7.96 (3H, m), 8.09 (1H, d, *J*=8.8 Hz); ^{31}P NMR (161.93 MHz, $CDCl_3$, 85% H_3PO_4): *δ* 29.25; MS (ESI) *m*/*z* 658.6 (M+H$^+$, 100). HRMS (ESI) calcd

for $C_{41}H_{41}NO_5P$ requires ($M+H^+$) 658.2717, found: 658.2714; $[\alpha]_D^{20}$ −43.7 (*c* 0.39, CH_2Cl_2).

4.4.5. Compound (***aR***)-***4e***. Yield: 89%, 557 mg, white solid, mp 117–118 °C; IR (neat): *ν* 3425, 3305, 3239, 3055, 2973, 2950, 2877, 2830, 1645, 1550, 1502, 1308, 1165, 1113, 1093, 810, 748, 661, 646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): *δ* 0.24 (9H, s), 2.07 (3H, s), 2.41 (3H, s), 3.44 (1H, dd, *J*=6.0, 11.2 Hz), 3.74–3.82 (2H, m), 4.41 (1H, s), 6.48 (3H, d, *J*=8.4 Hz), 6.88–6.98 (3H, m), 7.19–7.33 (5H, m), 7.50–7.60 (3H, m), 7.72–7.80 (3H, m), 7.90–7.96 (3H, m), 8.08 (1H, d, *J*=8.8 Hz); ^{31}P NMR (161.93 MHz, $CDCl_3$, 85% H_3PO_4): *δ* 31.01; MS (ESI) *m*/*z* 626.7 ($M+H^+$, 100). HRMS (MALDI) calcd for $C_{41}H_{41}NO_3P$ requires ($M+H^+$) 626.2819, found: 626.2818; $[\alpha]_D^{20}$ −41.7 (*c* 0.52, CH_2Cl_2).

4.4.6. Compound (***aR***)-***4f***. Yield: 98%, 640 mg, white solid, mp 275–278 °C; IR (CH_2Cl_2): *ν* 3434, 3055, 2957, 2866, 1649, 1551, 1503, 1272, 1175, 1164, 1152, 1162, 876, 852, 718, 748, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): *δ* 0.25 (9H, s), 1.93 (6H, s), 2.36 (6H, s), 3.40–3.48 (1H, m), 3.73–3.81 (2H, m), 4.33 (1H, t, *J*=7.2 Hz), 6.45 (1H, s), 6.50 (1H, d, *J*=8.1 Hz), 6.65 (1H, d, *J*=12.6 Hz), 6.97 (1H, t, *J*=6.9 Hz), 7.16–7.31 (4H, m), 7.50–7.66 (5H, m), 7.75 (1H, d, *J*=8.7 Hz), 7.91–8.00 (3H, m), 8.10 (1H, d, *J*=8.7 Hz); ^{31}P NMR (121.45 MHz, $CDCl_3$, TMS): *δ* 24.77; MS (ESI) *m*/*z* 654.4 ($M+H^+$, 100). HRMS (ESI) calcd for $C_{43}H_{45}NO_3P$ requires ($M+H^+$) 654.3132, found: 654.3145; $[\alpha]_D^{20}$ −30.1 (*c* 1.0, CH_2Cl_2).

4.5. Typical reaction procedure for the preparation of (*aR*)-5

To a mixture of compound (***aR***)-**4** (1.0 mmol), 4-dimethylaminopyridine (1.22 mg, 0.01 mmol), and triethylamine (1.8 mL, 2.0 mmol) in dichloromethane (15 mL) was added methanesulfonyl chloride (0.4 mL, 2.0 mmol) at 0 °C, and the solution was stirred for 0.5 h at this temperature. Then another portion of triethylamine (1.4 mL, 9.0 mmol) was added to the solution, and it was refluxed until the initially formed mesylation product disappeared (checked by TLC plates). On cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2, then washed with saturated $NaHCO_3$ solution and extracted by CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel (elution with EtOAc) to give compound (***aR,S***)-**5**.

4.5.1. Compound (***aR,S***)-***5a***. Yield: 91%, 603 mg, white solid, mp 106–107 °C; IR (neat): *ν* 3050, 2986, 2888, 2836, 1631, 1504, 1435, 1363, 1308, 1189, 1113, 1057, 971, 815, 747, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): *δ* 2.45 (1H, dd, *J*=8.4, 13.8 Hz), 3.02 (1H, dd, *J*=5.4, 13.8 Hz), 3.58 (1H, t, *J*=7.8 Hz), 3.91 (1H, t, *J*=8.4 Hz), 4.25–4.36 (1H, m), 6.99–7.22 (10H, m), 7.27–7.52 (10H, m), 7.60–7.77 (6H, m), 7.84–7.89 (2H, m), 7.99 (1H, d, *J*=8.4 Hz); ^{31}P NMR (121.45 MHz, $CDCl_3$, 85% H_3PO_4): *δ* 28.41; MS (ESI) *m*/*z* 664.6 ($M+H^+$, 100). HRMS (MALDI) calcd for $C_{46}H_{35}NO_2P$ requires ($M+H^+$) 664.2400, found: 664.2399; $[\alpha]_D^{20}$ +8.0 (*c* 0.30, CH_2Cl_2).

4.5.2. Compound (***aR,S***)-***5b***. Yield: 82%, 503 mg, white solid, mp 94–95 °C; IR (neat): *ν* 3053, 2987, 2886, 2828, 1634, 1496, 1436, 1310, 1190, 1113, 1056, 973, 818, 748, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): *δ* 2.23 (1H, dd, *J*=8.8, 14.0 Hz), 2.87 (1H, dd, *J*=5.6, 14.0 Hz), 3.51 (1H, t, *J*=8.0 Hz), 3.92 (1H, t, *J*=8.8 Hz), 4.16–4.22 (1H, m), 6.94 (2H, d, *J*=6.4 Hz), 7.02–7.07 (3H, m), 7.10–7.21 (8H, m), 7.23–7.30 (2H, m), 7.34–7.39 (3H, m), 7.45 (2H, dd, *J*=8.0, 11.6 Hz), 7.53 (1H, t, *J*=7.2 Hz), 7.65–7.72 (3H, m), 7.91–7.95 (3H, m); ^{31}P NMR (161.93 MHz, $CDCl_3$, 85% H_3PO_4): *δ* 27.53; MS (ESI) *m*/*z* 614.6 ($M+H^+$, 100). HRMS (MALDI) calcd for $C_{42}H_{33}NO_2P$ requires ($M+H^+$) 614.2243, found: 614.2235; $[\alpha]_D^{20}$ +13.4 (*c* 0.57, CH_2Cl_2).

4.5.3. Compound (***aR,S***)-***5c***. Yield: 78%, 480 mg, white solid, mp 80–81 °C; IR (neat): *ν* 3059, 2978, 2953, 2838, 1640, 1589, 1498, 1355, 1236, 1158, 1099, 1058, 1112, 817, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): *δ* 0.57 (9H, s), 3.55 (1H, t, *J*=8.4 Hz), 3.70 (1H, t, *J*=9.3 Hz), 3.93 (1H, t, *J*=9.3 Hz), 6.72–6.83 (4H, m), 7.05–7.27 (4H, m), 7.31–7.43 (5H, m), 7.50 (1H, t, *J*=7.5 Hz), 7.69–7.77 (3H, m), 7.88–7.97 (3H, m); ^{31}P NMR (121.45 MHz, $CDCl_3$, 85% H_3PO_4): *δ* 27.52 (t, *J*=1.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): *δ* −108.4 to 108.5 (2F, m); MS (ESI) *m*/*z* 616.6 ($M+H^+$, 100). HRMS (MALDI) calcd for $C_{39}H_{33}NO_2F_2P$ requires ($M+H^+$) 616.2212, found: 616.2211; $[\alpha]_D^{20}$ +72.6 (*c* 0.42, CH_2Cl_2).

4.5.4. Compound (***aR,S***)-***5d***. Yield: 85%, 543 mg, white solid, mp 96–97 °C; IR (neat): *ν* 3058, 2950, 2895, 2836, 1637, 1595, 1501, 1292, 1251, 1117, 1114, 1024, 823, 750, 663 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): *δ* 0.56 (9H, s), 3.51 (1H, t, *J*=8.4 Hz), 3.69 (1H, t, *J*=8.4 Hz), 3.75 (3H, s), 3.76 (3H, s), 3.91 (1H, dd, *J*=8.4, 9.9 Hz), 6.56–6.65 (4H, m), 7.03–7.22 (4H, m), 7.26–7.39 (5H, m), 7.47 (1H, t, *J*=7.8 Hz), 7.68–7.96 (6H, m); ^{31}P NMR (121.45 MHz, $CDCl_3$, 85% H_3PO_4): *δ* 29.04; MS (ESI) *m*/*z* 640.7 ($M+H^+$, 100). HRMS (MALDI) calcd for $C_{41}H_{39}NO_4P$ requires ($M+H^+$) 640.2611, found: 640.2624; $[\alpha]_D^{20}$ +42.0 (*c* 0.28, CH_2Cl_2).

4.5.5. Compound (***aR,S***)-***5e***. Yield: 89%, 540 mg, white solid, mp 83–84 °C; IR (neat): *ν* 3050, 2973, 2898, 2868, 2836, 1635, 1600, 1359, 1186, 1112, 1055, 973, 808, 749, 658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): *δ* 0.56 (9H, s), 2.25 (3H, s), 2.26 (3H, s), 3.51 (1H, t, *J*=8.4 Hz), 3.67 (1H, t, *J*=9.6 Hz), 3.90 (1H, dd, *J*=8.4, 9.6 Hz), 6.88–6.91 (4H, m), 7.03–7.11 (3H, m), 7.17–7.37 (6H, m), 7.47 (1H, t, *J*=8.0 Hz), 7.66–7.77 (3H, m), 7.86–7.93 (3H, m); ^{31}P NMR (161.93 MHz, $CDCl_3$, 85% H_3PO_4): *δ* 28.46; MS (ESI) *m*/*z* 608.7 ($M+H^+$, 100). HRMS (MALDI) calcd for $C_{41}H_{39}NO_2P$ requires ($M+H^+$) 608.2713, found: 608.2714; $[\alpha]_D^{20}$ +41.9 (*c* 0.45, CH_2Cl_2).

4.5.6. Compound (***aR,S***)-***5f***. Yield: 98%, 622 mg, white solid, mp 121–126 °C; IR (CH_2Cl_2): *ν* 3050, 2954, 2865, 1640, 1600, 1477, 1360, 1271, 1191, 1124, 978, 870, 853, 824, 749, 669, 642 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): *δ* 0.55 (9H, s), 2.13 (6H, s), 2.14 (6H, s), 3.54 (1H, t, *J*=9.3 Hz), 3.72 (1H, t, *J*=9.3 Hz), 3.98 (1H, t, *J*=8.7 Hz), 6.85 (2H, d, *J*=13.2 Hz), 6.96–7.22 (8H, m), 7.36 (1H, t, *J*=7.5 Hz), 7.47 (1H, t, *J*=7.5 Hz), 7.66–7.78 (3H, m), 7.86–7.93 (3H, m); ^{31}P NMR (121.45 MHz, $CDCl_3$, TMS): *δ* 23.80; MS (EI) *m*/*z* (%): 635 [M^+] (7.6), 578 (22.7), 378 (79.0), 365 (45.6), 257 (91.5), 210 (100.0), 209 (31.5), 183 (76.3), 91 (42.1), 57 (25.7), 43 (18.2); HRMS (EI) calcd for $C_{43}H_{42}NO_2P$ requires (M^+) 635.2953, found: 635.2956; $[\alpha]_D^{20}$ +41.7 (*c* 1.0, CH_2Cl_2).

4.6. Typical reaction procedure for the preparation of L7–L12

To a mixture of compound (***aR,S***)-**5** (1.0 mmol) and triethylamine (4.2 mL, 30 mmol) in toluene (20 mL) was added trichlorosilane (1.0 mL, 10.0 mmol) at 0 °C, and the solution was stirred for 0.5 h at this temperature. It was then refluxed for 24 h under nitrogen atmosphere. After cooling to room temperature, the mixture was diluted with EtOAc and quenched with small amount of saturated $NaHCO_3$. The resulting suspension was filtered through Celite and the filter cake was washed with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (elution petroleum ether/EtOAc=4:1) to give chiral ligands **L7**–**L12**.

L7. 589 mg, Yield: 91%, white solid, mp 67–68 °C; IR (neat): *ν* 3049, 2973, 2889, 2837, 1632, 1504, 1477, 1432, 1308, 1261, 1091, 1055, 1024, 815, 741, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): *δ* 2.26 (1H, dd, *J*=8.8, 13.6 Hz), 2.91 (1H, dd, *J*=5.2, 13.6 Hz), 3.36 (1H, t, *J*=8.0 Hz), 3.60 (1H, t, *J*=8.8 Hz), 4.05–4.14 (1H, m), 6.96–7.29 (15H, m), 7.34 (1H, s), 7.40–7.49 (5H, m), 7.65–7.69 (2H, m), 7.75 (1H, d, *J*=8.0 Hz), 7.83–7.91 (3H, m), 8.02 (1H, d, *J*=8.4 Hz), 8.16 (1H, d, *J*=8.4 Hz); ^{31}P NMR (161.93 MHz, $CDCl_3$, 85% H_3PO_4): *δ* −15.38; MS (MALDI) *m*/*z* 648.6 ($M+H^+$, 100). HRMS (ESI) calcd for

$C_{46}H_{35}NOP$ requires ($M+H^+$) 648.2451, found: 648.2457; $[\alpha]_D^{20}$ −29.9 (*c* 0.54, CH_2Cl_2).

L8. 490 mg, Yield: 82%, white solid, mp 65–66 °C; IR (neat): *ν* 3050, 2975, 2885, 2831, 1633, 1495, 1478, 1432, 1262, 1093, 1054, 1025, 971, 816, 741, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): *δ* 2.08 (1H, dd, *J*=8.8, 13.6 Hz), 2.75 (1H, dd, *J*=4.2, 13.6 Hz), 3.30 (1H, t, *J*=8.0 Hz), 3.62 (1H, t, *J*=8.8 Hz), 3.95–4.03 (1H, m), 6.89 (2H, d, *J*=6.8 Hz), 6.95–7.05 (4H, m), 7.10–7.27 (13H, m), 7.39–7.49 (3H, m), 7.84–7.91 (3H, m), 8.01 (1H, d, *J*=8.8 Hz), 8.13 (1H, d, *J*=8.8 Hz); ^{31}P NMR (161.93 MHz, $CDCl_3$, 85% H_3PO_4): *δ* −15.32; MS (ESI) *m*/*z* 598.6 ($M+H^+$, 100). HRMS (MALDI) calcd for $C_{42}H_{33}NOP$ requires ($M+H^+$) 598.2294, found: 598.2274; $[\alpha]_D^{20}$ −24.1 (*c* 0.61, CH_2Cl_2).

L9. 467 mg, Yield: 78%, white solid, mp 59–60 °C; IR (neat): *ν* 3058, 2958, 2899, 2867, 1639, 1586, 1493, 1359, 1224, 1158, 1097, 1054, 1014, 811, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): *δ* 0.52 (9H, s), 3.45 (1H, t, *J*=8.0 Hz), 3.61 (1H, t, *J*=8.0 Hz), 3.71 (1H, t, *J*=8.8 Hz), 6.78–6.83 (3H, m), 6.93–7.00 (5H, m), 7.21–7.24 (4H, m), 7.35–7.45 (3H, m), 7.84–7.88 (3H, m), 7.99 (1H, d, *J*=8.8 Hz), 8.10 (1H, d, *J*=8.8 Hz); ^{31}P NMR (161.93 MHz, $CDCl_3$, 85% H_3PO_4): *δ* −17.54 (t, *J*=4.5 Hz); ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): *δ* −112.9 to 113.0 (1F, m), −113.4 to 113.5 (1F, m); MS (ESI) *m*/*z* 600.6 ($M+H^+$, 100). HRMS (MALDI) calcd for $C_{39}H_{33}NOF_2P$ requires ($M+H^+$) 600.2262, found: 600.2268; $[\alpha]_D^{20}$ +11.9 (*c* 0.31, CH_2Cl_2).

L10. 530 mg, Yield: 85%, white solid, mp 68–69 °C; IR (neat): *ν* 3059, 2960, 2899, 2834, 1635, 1592, 1496, 1282, 1244, 1176, 1093, 1028, 821, 796, 649 cm^{-1}; ^1H NMR (400 MHz, CDCl3, TMS): *δ* 0.52 (9H, s), 3.44 (1H, t, *J*=8.0 Hz), 3.57 (1H, dd, *J*=8.0, 10.0 Hz), 3.70 (1H, dd, *J*=8.0, 10.0 Hz), 3.71 (3H, s), 3.77 (3H, s), 6.64 (2H, d, *J*=8.0 Hz), 6.81–6.86 (3H, m), 6.90–6.97 (3H, m), 7.16–7.24 (4H, m), 7.33–7.46 (3H, m), 7.81–7.86 (3H, m), 7.97 (1H, d, *J*=8.8 Hz), 8.11 (1H, d, *J*=8.4 Hz); ^{31}P NMR (161.94 MHz, $CDCl_3$, 85% H_3PO_4): *δ* −18.36; MS (ESI) *m*/*z* 624.7 ($M+H^+$, 100). HRMS (MALDI) calcd for $C_{41}H_{39}NO_3P$ requires ($M+H^+$) 624.2662, found: 624.2661; $[\alpha]_D^{20}$ −18.1 (*c* 0.32, CH_2Cl_2).

L11. 526 mg, Yield: 89%, white solid, mp 71–72 °C; IR (neat): *ν* 3047, 2971, 2896, 2836, 1634, 1496, 1359, 1262, 1099, 1054, 972, 804, 746, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): *δ* 0.52 (9H, s), 2.25 (3H, s), 2.32 (3H, s), 3.42 (1H, t, *J*=8.4 Hz), 3.54 (1H, t, *J*=9.6 Hz), 3.67 (1H, dd, *J*=8.4, 9.6 Hz), 6.90–6.91 (5H, m), 6.95–7.00 (1H, m), 7.08 (2H, d, *J*=7.6 Hz), 7.14–7.20 (4H, m), 7.35–7.43 (2H, m), 7.48 (1H, dd, *J*=2.8, 8.4 Hz), 7.82 (2H, d, *J*=8.4 Hz), 7.87 (1H, d, *J*=8.0 Hz), 7.98 (1H, d, *J*=8.8 Hz), 8.11 (1H, d, *J*=8.8 Hz); ^{31}P NMR (161.93 MHz, $CDCl_3$, 85% H_3PO_4): *δ* −17.06; MS (MALDI) *m*/*z* 592.7 ($M+H^+$, 100). HRMS (ESI) calcd for $C_{41}H_{39}NOP$ requires ($M+H^+$) 592.2764, found: 592.2762; $[\alpha]_D^{20}$ −11.2 (*c* 0.5, CH_2Cl_2).

L12. 607 mg, Yield 98%, white solid, mp 86–91 °C; IR (CH_2Cl_2): *ν* 3050, 2953, 2866, 1640, 1598, 1582, 1477, 1359, 1264, 1124, 1101, 1055, 974, 846, 818, 746, 693, 524; ^1H NMR (300 MHz, $CDCl_3$, TMS): *δ* 0.51 (9H, s), 2.10 (6H, s), 2.23 (6H, s), 3.48 (1H, t, *J*=7.8 Hz), 3.63 (1H, t, *J*=9.6 Hz), 3.77 (1H, dd, *J*=7.8, 9.6 Hz), 6.60 (2H, d, *J*=7.8 Hz), 6.76 (1H, s), 6.83–6.98 (5H, m), 7.19–7.21 (2H, m), 7.35–7.45 (2H, m), 7.54 (1H, dd, *J*=5.7, 8.4 Hz), 7.85 (3H, t, *J*=8.4 Hz), 7.98 (1H, d, *J*=8.4 Hz), 8.10 (1H, d, *J*=8.4 Hz); ^{31}P NMR (121.45 MHz, $CDCl_3$, TMS): *δ* −13.69; MS (EI) *m*/*z* (%): 619 [M^+] (27.9), 535 (100.0), 493 (49.4), 430 (50.4), 408 (84.7), 378 (22.2), 362 (27.7), 281 (20.4), 241 (29.3), 57 (45.2), 41 (23.3); HRMS (EI) calcd for $C_{43}H_{42}NOP$ (M^+): 619.3004, found: 619.3010; $[\alpha]_D^{20}$ −8.0 (*c* 1.0, $CHCl_3$).

4.7. General procedure for the reaction of *N*-Boc aldimines 1 with siloxyfuran 2 in the presence of AgOAc and chiral phosphine–oxazoline ligand L6

AgOAc (2.50 mg, 0.015 mmol) and chiral phosphine–oxazoline ligand **L6** (8.4 mg, 0.015 mmol) were added into a Schlenk tube and then DCM (0.5 mL) was added into the reaction vessel. The resulting solution was stirred for 0.5 h at room temperature. *N*-Boc aldimine **1** (0.15 mmol), CH_3CH_2OH (16 μL, 0.27 mmol) was added followed by another 0.5 mL of DCM. The mixture was cooled to −78 °C, and stirred for 0.5 h, then 2-trimethylsiloxyfuran (**2**) (46 μL, 0.27 mmol) was added. The mixture was allowed to stir at −78 °C for 24 h, 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 $MgSO_4$, 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 **3**.

*4.7.1. Compound anti-**3a**.* Yield: 83%, 40 mg, white solid, mp 138–139 °C; IR (neat): *ν* 3364, 2990, 2938, 2841, 1767, 1693, 1506, 1282, 1242, 1152, 1091, 1030, 906, 826, 787, 634 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): *δ* 1.43 (9H, s), 3.77 (3H, s), 5.01–5.02 (1H, m), 5.39–5.41 (2H, m), 5.97 (1H, s), 6.84 (2H, d, *J*=8.4 Hz), 7.15 (2H, d, *J*=8.4 Hz), 7.34 (1H, d, *J*=5.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 28.2, 55.1, 55.8, 80.2, 84.6, 114.0 (2C), 122.8, 127.5, 128.2 (2C), 153.2, 154.9, 159.4, 172.4; MS (ESI) *m*/*z* 337.2 ($M+NH_4^+$, 100). HRMS (ESI) calcd for $C_{17}H_{21}NO_5Na$ requires ($M+Na^+$) 342.1312, found: 342.1318; $[\alpha]_D^{20}$ −100.7 (*c* 1.0, CH_2Cl_2, 86% ee). Enantiomeric excess was determined by HPLC with a Chiralcel PA-H column (*n*-hexane/*i*-PrOH=50/50, 0.7 mL/min, 214 nm, t_{minor}=21.02 min, t_{major}=16.99 min).

*4.7.2. Compound anti-**3b**.* Yield: 83%, 40 mg, white solid, mp 128–129 °C; IR (neat): *ν* 3389, 2977, 2934, 2836, 1748, 1687, 1599, 1516, 1494, 1249, 1161, 1101, 1039, 884, 830, 750, 663 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): *δ* 1.39 (9H, s), 3.81 (3H, s), 5.06–5.13 (2H, m), 5.33 (1H, s), 6.15 (1H, dd, *J*=2.0, 6.0 Hz), 6.86 (1H, dd, *J*=2.0, 8.0 Hz), 6.94–6.99 (2H, m), 7.27–7-31 (1H, m), 7.53 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 28.1, 55.1, 55.2, 80.2, 85.1, 113.0, 113.5, 119.3, 122.2, 129.9, 139.4, 154.4, 155.2, 159.9, 172.9; MS (ESI) *m*/*z* 342.3 ($M+Na^+$, 100). HRMS (ESI) calcd for $C_{17}H_{21}NO_5Na$ requires ($M+Na^+$) 342.1312, found: 342.1320; $[\alpha]_D^{20}$ −83.6 (*c* 1.0, CH_2Cl_2, 78% ee). Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (*n*-hexane/*i*-PrOH=70/30, 0.6 mL/min, 214 nm, t_{minor}=12.77 min, t_{major}=10.15 min).

*4.7.3. Compound anti-**3c**.* Yield: 72%, 33 mg, white solid, mp 153–154 °C; IR (neat): *ν* 3377, 2977, 2925, 2854, 1770, 1696, 1511, 1361, 1277, 1248, 1160, 1089, 1049, 909, 815, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): *δ* 1.43 (9H, s), 2.31 (3H, s), 5.03 (1H, s), 5.31 (1H, d, *J*=8.4 Hz), 5.41 (1H, s), 5.96 (1H, s), 7.09–7.13 (4H, m), 7.32 (1H, d, *J*=6.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 21.0, 28.2, 56.0, 80.3, 84.6, 122.9, 126.9 (2C), 129.3 (2C), 132.4, 138.1, 153.1, 154.9, 172.4; MS (ESI) *m*/*z* 326.3 ($M+Na^+$, 100). HRMS (ESI) calcd for $C_{17}H_{21}NO_4Na$ requires ($M+Na^+$) 326.1363, found: 326.1362; $[\alpha]_D^{20}$ −101.6 (*c* 1.0, CH_2Cl_2, 83% ee). Enantiomeric excess was determined by HPLC with a Chiralcel OJ-H column (*n*-hexane/*i*-PrOH=80/20, 0.7 mL/min, 230 nm, t_{minor}=14.18 min, t_{major}=11.63 min).

*4.7.4. Compound syn-**3c**.* Yield: 18%, 9 mg, white solid, mp 144–145 °C; IR (neat): *ν* 3384, 2981, 2923, 2851, 1748, 1687, 1509, 1367, 1246, 1161, 1099, 1040, 888, 815, 750, 651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): *δ* 1.39 (9H, s), 2.35 (3H, s), 4.97 (1H, d, *J*=9.2 Hz), 5.03–5.05 (1H, m), 5.32 (1H, s), 6.15 (1H, dd, *J*=2.0, 5.6 Hz), 7.18 (2H, d, *J*=8.0 Hz), 7.29 (2H, d, *J*=8.0 Hz), 7.53 (1H, d, *J*=4.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 21.1, 28.2, 54.9, 80.2, 85.3, 122.2, 127.0 (2C), 129.5 (2C), 134.9, 138.2, 154.5, 155.2, 172.9; MS (ESI) *m*/*z* 326.3 ($M+Na^+$, 100). HRMS (ESI) calcd for $C_{17}H_{21}NO_4Na$ requires ($M+Na^+$) 326.1363, found: 326.1367; $[\alpha]_D^{20}$ −1.7 (*c* 0.50, CH_2Cl_2, 7% ee). Enantiomeric excess was determined by HPLC with a Chiralcel IC-H column (*n*-hexane/*i*-PrOH=80/20, 1.0 mL/min, 214 nm, t_{minor}=22.73 min, t_{major}=10.58 min).

*4.7.5. Compound anti-**3d**.* Yield: 79%, 36 mg, white solid, mp 146–147 °C; IR (neat): *ν* 3374, 2984, 2922, 2851, 1780, 1755, 1690, 1514, 1362, 1246, 1151, 1091, 885, 832, 703, 641 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$, TMS): δ 1.43 (9H, s), 2.32 (3H, s), 5.02 (1H, s), 5.36–5.39 (2H, m), 5.97 (1H, d, *J*=2.1 Hz), 7.01–7.03 (2H, m), 7.09 (1H, d, *J*=7.5 Hz), 7.18–7-23 (1H, m), 7.34 (1H, d, *J*=5.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.3, 28.2, 56.3, 80.3, 84.5, 122.8, 124.0, 127.7, 128.5, 129.1, 135.5, 138.4, 153.0, 154.9, 172.3; MS (ESI) *m*/*z* 326.3 (M+Na^+, 100). HRMS (ESI) calcd for $C_{17}H_{21}NO_4Na$ requires (M+Na^+) 326.1363, found: 326.1360; $[\alpha]_D^{20}$ −79.5 (*c* 1.0, CH_2Cl_2, 71% ee). Enantiomeric excess was determined by HPLC with a Chiralcel IC-H column (*n*-hexane/*i*-PrOH=70/30, 0.7 mL/min, 214 nm, t_{minor}=29.48 min, t_{major}=12.13 min).

*4.7.6. Compound anti-**3e**.* Yield: 78%, 44 mg, white solid, mp 68–69 °C; IR (neat): ν 3366, 2972, 2930, 2851, 1751, 1697, 1595, 1509, 1461, 1286, 1237, 1160, 1124, 1094, 1054, 1109, 828, 683 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.45 (9H, s), 3.81 (3H, s), 3.84 (6H, s), 4.98 (1H, s), 5.33 (1H, d, *J*=7.2 Hz), 5.45 (1H, s), 6.00 (1H, s), 6.45 (2H, s), 7.32 (1H, d, *J*=5.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.2, 56.1 (2C), 56.5, 60.7, 80.5, 84.4, 104.1 (2C), 122.9, 131.3, 137.9, 153.0, 153.4 (2C), 154.9, 172.4; MS (ESI) *m*/*z* 402.4 (M+Na^+, 100). HRMS (ESI) calcd for $C_{19}H_{25}NO_7Na$ requires (M+Na^+) 402.1523, found: 402.1527; $[\alpha]_D^{20}$ −30.1 (*c* 1.0, CH_2Cl_2, 76% ee). Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (*n*-hexane/*i*-PrOH=90/10, 0.5 mL/min, 214 nm, t_{minor}=13.89 min, t_{major}=11.64 min).

*4.7.7. Compound anti-**3f**.* Yield: 70%, 30 mg, white solid, mp 159–160 °C; IR (neat): ν 3385, 2984, 2924, 2852, 1751, 1686, 1513, 1498, 1355, 1246, 1165, 1102, 889, 825, 804, 702, 653, 680 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 1.39 (9H, s), 5.02–5.12 (2H, m), 5.36 (1H, s), 6.17 (1H, dd, *J*=1.8, 5.7 Hz), 7.34–7.41 (5H, m), 7.56 (1H, d, *J*=5.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.1, 55.1, 80.3, 85.2, 122.2, 127.1 (2C), 128.3, 128.9 (2C), 137.8, 154.5, 155.2, 172.9; MS (ESI) *m*/*z* 312.2 (M+Na^+, 100). HRMS (ESI) calcd for $C_{16}H_{19}NO_4Na$ requires (M+Na^+) 312.1206, found: 312.1212; $[\alpha]_D^{20}$ −71.3 (*c* 1.0, CH_2Cl_2, 77% ee). Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (*n*-hexane/*i*-PrOH=80/20, 0.6 mL/min, 214 nm, t_{minor}=13.53 min, t_{major}=10.93 min).

*4.7.8. Compound anti-**3g**.* Yield: 80%, 37 mg, white solid, mp 151–152 °C; IR (neat): ν 3387, 2983, 2920, 2851, 1754, 1682, 1504, 1349, 1277, 1249, 1226, 1158, 1102, 888, 822, 805, 680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.39 (9H, s), 5.03–5.08 (2H, m), 5.32 (1H, s), 6.17 (1H, dd, *J*=1.2, 6.0 Hz), 7.07 (2H, t, *J*=8.4 Hz), 7.38–7.42 (2H, m), 7.54 (1H, d, *J*=2.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.1, 54.4, 80.4, 85.0, 115.7 (2C, d, *J*=20.9 Hz), 122.3, 128.9 (2C, d, *J*=8.2 Hz), 133.8 (d, *J*=3.1 Hz), 154.3, 155.1, 162.4 (d, *J*=246.2 Hz), 172.8; ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$): δ −113.9 to 114.0 (1F, m); MS (ESI) *m*/*z* 330.3 (M+Na^+, 100). HRMS (ESI) calcd for $C_{16}H_{18}FNO_4Na$ requires (M+Na^+) 330.1112, found: 330.1113; $[\alpha]_D^{20}$ −65.7 (*c* 1.0, CH_2Cl_2, 63% ee). Enantiomeric excess was determined by HPLC with a Chiralcel OJ-H column (*n*-hexane/*i*-PrOH=90/10, 0.7 mL/min, 230 nm, t_{minor}=24.37 min, t_{major}=28.97 min).

*4.7.9. Compound anti-**3h**.* Yield: 75%, 41 mg, white solid, mp 165–166 °C; IR (neat): ν 3347, 2978, 2924, 2852, 1752, 1683, 1517, 1494, 1367, 1276, 1167, 1063, 1018, 922, 886, 833, 797, 655 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 1.39 (9H, s), 5.04–5.07 (2H, m), 5.31 (1H, s), 6.18 (1H, dd, *J*=2.1, 5.4 Hz), 7.29 (2H, d, *J*=8.4 Hz), 7.49–7.52 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.1, 54.5, 80.5, 84.8, 122.3, 122.5, 128.9 (2C), 132.0 (2C), 137.0, 154.1, 155.1, 172.7; MS (ESI) *m*/*z* 366.2 (M−H^+, 100). HRMS (ESI) calcd for $C_{16}H_{17}NO_4Br$ requires (M−H^+) 366.0346, found: 366.0359; $[\alpha]_D^{20}$ −40.5 (*c* 0.5, CH_2Cl_2, 67% ee). Enantiomeric excess was determined by HPLC with a Chiralcel IC-H column (*n*-hexane/*i*-PrOH=70/30, 0.6 mL/min, 230 nm, t_{minor}=36.59 min, t_{major}=32.47 min).

*4.7.10. Compound anti-**3i**.* Yield: 69%, 38 mg, white solid, mp 161–162 °C; IR (neat): ν 3347, 2960, 2923, 2849, 1754, 1685, 1518, 1490, 1368, 1245, 1168, 1060, 1010, 922, 888, 833, 797, 650 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 1.40 (9H, s), 4.98–5.07 (2H, m), 5.33 (1H, s), 6.19 (1H, dd, *J*=2.0, 5.6 Hz), 7.24–7.28 (1H, m), 7.34–7.36 (1H, m), 7.46–7.49 (1H, m), 7.52–7.57 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.2, 54.5, 80.6, 84.8, 122.6, 125.8, 130.2, 130.5, 131.5, 133.9, 140.2, 154.1, 155.1, 172.6; MS (ESI) *m*/*z* 390.3 (M+Na^+, 100). HRMS (ESI) calcd for $C_{16}H_{18}NO_4BrNa$ requires (M+Na^+) 390.0311, found: 390.0315; $[\alpha]_D^{20}$ −71.7 (*c* 0.34, CH_2Cl_2, 73% ee). Enantiomeric excess was determined by HPLC with a Chiralcel IC-H column (*n*-hexane/*i*-PrOH=70/30, 0.6 mL/min, 230 nm, t_{minor}=14.66 min, t_{major}=12.26 min).

*4.7.11. Compound anti-**3j**.* Yield: 69%, 29 mg, white solid, mp 136–137 °C; IR (neat): ν 3385, 2956, 2923, 2852, 1758, 1690, 1520, 1362, 1290, 1156, 1092, 1053, 1005, 894, 833, 778, 756, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.45 (9H, s), 5.20–5.21 (2H, m), 5.36 (1H, s), 6.10 (1H, d, *J*=3.2 Hz), 6.27 (1H, d, *J*=2.8 Hz), 6.32 (1H, s), 7.34 (1H, s), 7.42 (1H, dd, *J*=1.2, 6.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.2, 50.5, 80.7, 83.5, 108.3, 110.5, 123.1, 142.5, 149.1, 152.6, 154.8, 172.2; MS (ESI) *m*/*z* 302.1 (M+Na^+, 100). HRMS (ESI) calcd for $C_{14}H_{17}NO_5Na$ requires (M+Na^+) 302.0999, found: 302.1013; $[\alpha]_D^{20}$ −42.7 (*c* 0.5, CH_2Cl_2, 80% ee). Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (*n*-hexane/*i*-PrOH=70/30, 0.7 mL/min, 214 nm, t_{minor}=12.48 min, t_{major}=11.02 min).

*4.7.12. Compound anti-**3k**.* Yield: 75%, 33 mg, white solid, mp 163–164 °C; IR (neat): ν 3366, 2981, 2920, 2852, 1740, 1694, 1518, 1366, 1285, 1163, 1094, 1039, 1021, 901, 836, 779, 703, 616 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.16–1.191 (H, m), 1.27–1.31 (1H, m), 1.45 (9H, s), 1.61–1.80 (9H, m), 3..60–3.65 (1H, m), 4.57 (1H, d, *J*=9.2 Hz), 5.00 (1H, d, *J*=7.6 Hz), 6.17 (1H, dd, *J*=1.6, 5.6 Hz), 7.49 (1H, d, *J*=5.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.8, 25.9, 26.0, 27.0, 28.2, 30.3, 38.6, 56.8, 80.0, 83.0, 122.0, 154.9, 155.5, 172.6; MS (ESI) *m*/*z* 318.3 (M+Na^+, 100). HRMS (ESI) calcd for $C_{16}H_{25}NO_4Na$ requires (M+Na^+) 318.1676, found: 318.1681; $[\alpha]_D^{20}$ −40.0 (*c* 0.5, CH_2Cl_2, 75% ee). Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (*n*-hexane/*i*-PrOH=90/10, 0.6 mL/min, 214 nm, t_{minor}=25.72 min, t_{major}=18.54 min).

4.8. General procedure for the removal of *N*-Boc group

A solution of *anti*-**3f** (233 mg, 0.81 mmol) in dichloromethane (25 mL) and TFA (5 mL) was stirred at ambient temperature for 4 h and then the solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (elution with petroleum ether/EtOAc=4:1) to provide the title compound **4** (141 mg, 92%).

This is a known compound.[1b,e] 141 mg, Yield: 92%, orange oil; IR (CH_2Cl_2): ν 3381, 3318, 1754, 1600, 1494, 1453, 1331, 1161, 1089, 1029, 897, 825, 764, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.64 (2H, s), 4.45 (1H, d, *J*=4.8 Hz), 5.22 (1H, ddd, *J*=1.2, 2.0, 4.8 Hz), 6.13 (1H, dd, *J*=2.0, 6.0 Hz), 7.31 (1H, dd, *J*=1.2, 6.0 Hz), 7.32–7.40 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 56.9, 87.0, 123.2, 126.6, 128.1, 128.8, 139.3, 153.2, 172.7; $[\alpha]_D^{20}$ −71.5 (*c* 1.0, $CHCl_3$); MS (EI) *m*/*z* (100): 172 [M^+−NH_3] (6.2), 144 (1.8), 115 (4.6), 107 (8.6), 106 (100), 104 (7.8), 79 (30.7), 77 (16.3); HRMS (EI) calcd for $C_{11}H_{11}NO_2$ (M^+): 189.0790, found: 189.0792.

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Supplementary data

Spectroscopic data and chiral HPLC traces of the compounds shown in Tables 1–3 are included in the Supplementary data. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.03.046.

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