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Asymmetric Synthesis of Chiral Spiroketal Bisphosphine Ligands and Their Application in Enantioselective Olefin Hydrogenation

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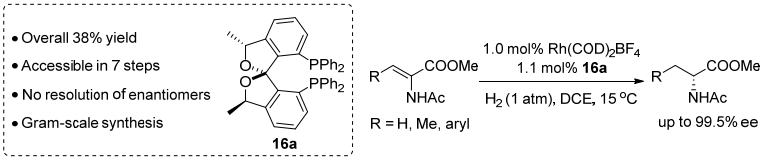
Supporting Information Placeholder



ABSTRACT: A series of chiral spiroketal bisphosphine ligands containing 1,1'-spirobi(3*H*,3'*H*)isobenzofuran backbones was accessed through asymmetric synthesis and subsequently tested in enantioselective Rh-catalyzed hydrogenation of α-dehydroamino acid esters. The ligand providing the highest enantioselectivity (up to 99.5%) was obtained in seven steps in an overall 38% yield. The synthesis could be performed on gram-scale and no kinetic resolution of enantiomers is required. Overall, the developed ligand provides an easily accessible alternative to SDP ligands as well as other chiral bisphosphine ligands.

Asymmetric catalysis is one of the most powerful and atom-economical strategies for accessing enantiopure chiral organic molecules, such as pharmaceuticals, fragrances, and agrochemicals.[1] Since asymmetric transition-metal catalysis is highly dependent on chiral non-racemic ligands, the development of new ligands, which are easily accessible in high enantiopurity and which provide high levels of enantioselectivity in catalytic reactions, is an important task. Across a range of reactions, C_2-symmetric bisphosphines, such as DIOP and BINAP, have demonstrated the ability to provide high enantioselectivities.[2,3] However, there is still a need for alternatives to the well-established ligands for further improving reaction conditions, yields, and enantioselectivities.

Since 2003, C_2-symmetric bisphosphines based on spiro-fused carbocyclic backbones have been identified as a new privileged ligand class.[4] The first example of these ligands was described by Zhou and coworkers who developed the SPINOL-based SDP ligands (Figure 1).[5] SDP ligands have since then been applied in a number of asymmetric transformations where they induced high levels of enantioselectivity.[6,7] Later, SFDP ligands based on a spirobifluorene structure was developed and applied in Ru-catalyzed asymmetric hydrogenation of unsaturated carboxylic acids (Figure 1).[8,9] Examples of related spiroketal-based ligands have also been developed and successfully applied in asymmetric catalysis. Most notable are the SKP ligands which contain a spirobichroman skeleton, as first reported by Ding et al. (Figure 1).[10] These ligands were efficient in Pd-catalyzed asymmetric allylic amination of racemic Morita–Baylis–Hillman adducts, obtaining good yields and excellent enantioselectivities. Importantly, the spiroketal moiety is stable and maintains stereochemical integrity under basic, neutral, and mildly acidic conditions.

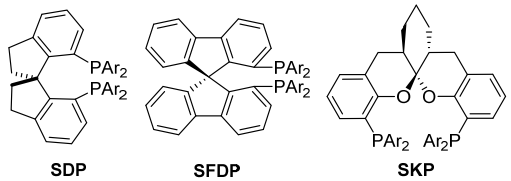


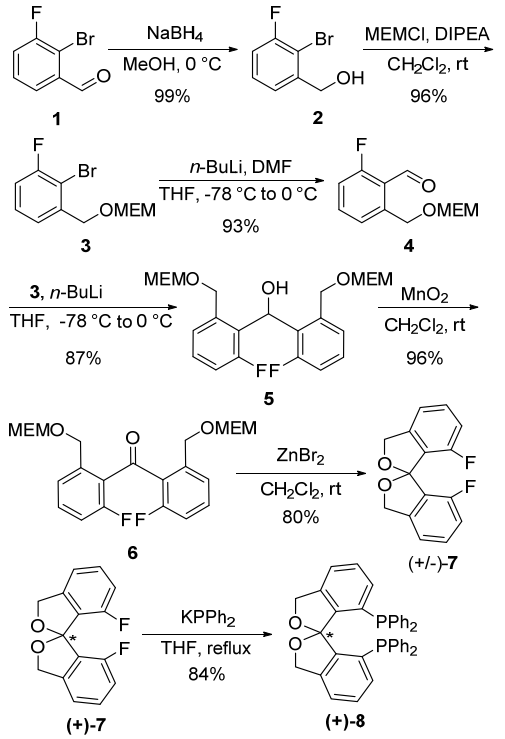
Figure 1. Examples of previously reported chiral spiro-bisphosphines.

Although SDP ligands have been highly successful in asymmetric catalysis, their high price prevents widespread use and makes large-scale applications less attractive.[11] The synthesis of SDP ligands starting from SPINOL in-

volves resolution of enantiomers and multistep synthesis.[5a,5b] Due to the ability of SDP ligands to induce high levels of enantioselectivity in combination with high price and difficult access routes, easily accessible ligand analogues are highly warranted. As a result, this year, three prominent routes to SDP analogues and precursors have been reported.[12] Ding et. al demonstrated the facile synthesis of cyclohexyl-fused spirobiindane scaffolds, which can serve as SDP-analogue precursors.[12c] Yin, Zhang, and coworkers reported a large scale synthesis of 3,3'-spirobi(2*H*,2'*H*)isobenzofuran scaffolds, which can also serve as SDP-analogue precursors.[12b] Finally, Nagorny and coworkers reported the first 1,1'-spirobi(3*H*,3'*H*)isobenzofuran analogues of the SDP-ligand in a synthesis affording 23% overall yield of the best-performing ligand.[12a,13] We had also envisioned that 1,1'-spirobi(3*H*,3'*H*)isobenzofuran analogues of the SDP-ligands could be obtained in a straightforward fashion relying on robust chemical transformations. Herein, we report the asymmetric synthesis of these chiral spiroketal bisphosphine ligands as well as their application in enantioselective rhodium-catalyzed hydrogenation of α-dehydroamino acid esters. The ligand providing the highest enantioselectivity (up to 99.5%) was obtained in just seven steps in an overall 38% yield.

Initially, the direct spiroketal analogue of SDP was targeted (Scheme 1). Starting from 2-bromo-3-fluorobenzaldehyde (**1**), sodium borohydride reduction afforded the benzylic alcohol **2**, quantitatively. Treatment of **2** with MEMCl in the presence of *N*,*N*-diisopropylethyl amine (DIPEA) afforded ether **3** in 96% yield. Compound **3** was subjected to lithium-bromide exchange, followed by formylation to give aldehyde **4** in 93% yield. In the key step, after a lithium–bromide exchange, compound **3** was reacted with the previously accessed aldehyde **4** to give the symmetrical alcohol, **5**. Oxidation with manganese dioxide provided ketone **6** in an excellent yield. In the presence of dry zinc bromide, intermediate **6** undergoes deprotection and cyclization affording racemic spiroketal difluoride **7**. At this point, enantiomerically pure isomers of **7** were obtained by separation of enantiomers using an HPLC with a chiral stationary phase. One of the enantiomers, (+)-**7**, was converted to the spiroketal-bisphosphine ligand (+)-**8** by addition of $KPPh_2$.

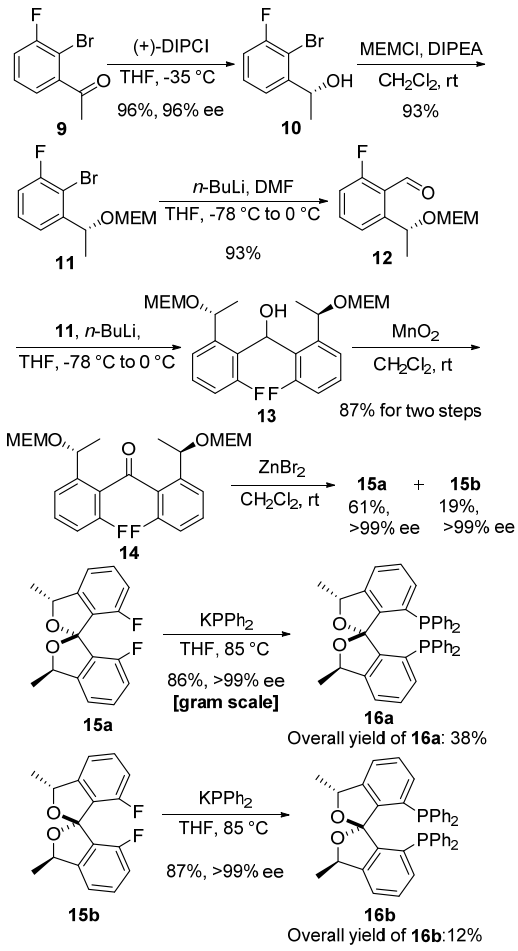
Scheme 1. Synthesis of a 1,1'-spirobi-(3*H*,3'*H*)isobenzofuran bisphosphine ligand.



The facile synthesis of (+)-**8** demonstrated that spiroketal analogues of SDP could indeed be accesses in high yields using straightforward and robust chemical transformations. However, the route still suffers from the need for separation of enantiomers by HPLC. To avoid this resolution, we hypothesized that the installation of stereogenic, homochiral methyl groups at the 3,3'-positions, leading to diastereomers during spiroketal formation, would facilitate purification by normal column chromatography.

The synthesis the 3,3'-methyl-substituted ligand was initiated from 1-(2-bromo-3-fluorophenyl)-ethanone **9** (Scheme 2).[14] Asymmetric reduction of the ketone was effectuated by (+)-*B*-chlorodiisopinocampheylborane ((+)-DIPCl) affording the (*R*)-enantiomer of alcohol **10** in 96% ee and 96% yield.[15] Treatment of the chiral alcohol **10** with MEMCl in the presence of DIPEA produced ether **11** in 93% yield. Compound **11** was subjected to lithium bromide exchange followed by formylation to give aldehyde **12** in 93% yield. After another lithium–bromide exchange on compound **11**, it was reacted with the aldehyde **12** affording alcohol **13**, which was oxidized with manganese dioxide to ketone **14** in 87% yield over two steps. The deprotection/spiroketal formation mediated by dry zinc bromide also proceeded smoothly forming both diastereomers of spiroketal **15**. However, the cyclization is diastereoselective leading to a 3:1 ratio of **15a**:**15b**. The separation of diastereomers by column chromatography on normal silica gel was straightforward, thus avoiding the need for purification by chiral HPLC. Finally, each of the diastereomers were reacted with $KPPh_2$ affording enantiopure bisphosphine ligands **16a** and **16b** in 38% and 12% overall yield, respectively.

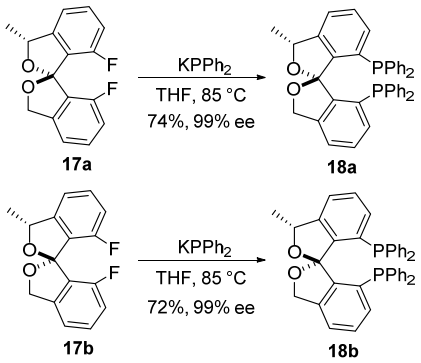
Scheme 2. Synthesis of 3,3'-dimethyl-1,1'-spirobi-(3*H*,3'*H*)isobenzofuran bisphosphine ligands.



While the installation of 3,3'-methyl groups on the 1,1'-spirobi(3*H*,3'*H*)isobenzofuran backbone was mainly done for to facilitate easy purification, the substituents could potentially also affect ketal stability as well as stereoselectivity when applied in catalysis. To investigate the latter point, the mono-methyl analogues were prepared in an analogous manner to the 3,3'-methyl substituted ligands by reacting compound **4** and **11**.[16] The spiroketal formation afforded a 2:1 ratio of diastereomers **17a**:**17b**. Finally, reaction with $KPPh_2$ provided the bisphosphine ligands **18a** and **18b**, respectively (Scheme 3).

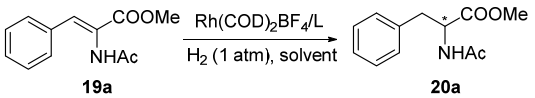
All the synthesized ligands are stable and can be stored in ambient atmosphere without oxidation or erosion of enantio- and diastereomeric purity. The absolute and relative stereochemistry of ligands **16a**, **16b**, and **18a** were confirmed by single-crystal X-ray diffraction.

Scheme 3. Synthesis of 3-methyl-1,1'spirobi(3*H*,3'*H*)isobenzofuran bisphosphine ligands.

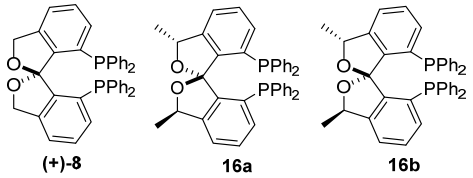


With five different new chiral ligands in hand, their ability to induce enantioselectivity in rhodium-catalyzed hydrogenation of α-dehydroamino acid esters was investigated. In order to compare the ligands, they were tested under the same reaction conditions with α-dehydroamino acid ester **19a** (Table 1). The direct spiroketal analogue of SDP, (+)-**8**, led to full conversion to hydrogenated product **20a** but with modest 59% ee (entry 1). The major diastereomer of the 3,3'-dimethyl substituted ligand, **16a**, dramatically increased the enantioselectivity to 94.5% ee (entry 2). Hence, the 3,3'-methyl substituents not only simplify the ligand synthesis, they are also highly beneficial for enantioselectivity during catalysis. However, the minor diastereomer of the 3,3'-substituted ligand, **16b**, afforded the opposite enantiomer of **20a** and only in 65% ee (entry 3). It is evident that the stereochemistry of the spiroketal stereocenter controls which enantiomer is predominantly formed; the (*S*,*R*,*R*)-configuration of **16a** provides the *R*-enantiomer of product while the (*R*,*R*,*R*)-configuration of **16b** gives the *S*-enantiomer. In addition, the spiroketal stereocenter and the methyl stereocenters must be matched in order to enhance the enantioselectivity (compare entries 2 and 3). The same trends are observed for mono-methyl ligands **18a** and **18b** which afforded 88% and 52% ee, respectively (entries 4-5). To our surprise, using the original SDP ligand under the same reaction conditions led to a sluggish reaction affording almost racemic product (entry 6).

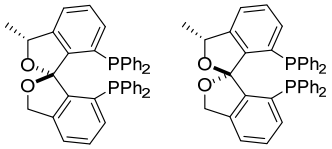
Table 1 Optimization for asymmetric hydrogenation of methyl (*Z*)-2-acetamido-3-phenylacrylate.



19a 20a



(+)-8 16a 16b



18a 18b

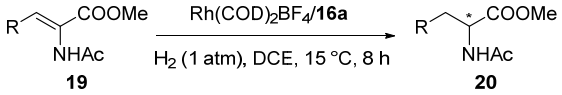
entry[a]	L	solvent	temp (°C)	time (h)[b]	conv (%)	ee (%)[c]
1	**(+)-8**[d]	DCM	rt	3	100	-59
2	**16a**	DCM	rt	3	100	94.5
3	**16b**	DCM	rt	3	100	-65
4	**18a**	DCM	rt	3	100	88
5	**18b**	DCM	rt	3	100	-52
6	**(*R*)-SDP**	DCM	rt	24	10	-10
7	**16a**	$CHCl_3$	rt	3	100	93.9
8	**16a**	DCE	rt	3	100	95.5
9	**16a**	EtOH	rt	3	100	93.6
10	**16a**	*i*-PrOH	rt	3	100	93.1
11	**16a**	THF	rt	3	100	90.2
12[e]	**16a**	DCE	rt	9	100	95.1
13	**16a**	DCE	0	24	83	98.1
14	**16a**	DCE	15	8	100	96.5

[a] The reaction was performed at room temperature with 0.5 mmol of substrate and 1 mol% of catalyst {[$Rh(COD)_2BF_4$]:L = 1:1.1} in 5 mL of solvent unless stated otherwise. [b] Time taken for 100% conversion of substrate. [c] Determined by chiral stationary phase HPLC. [d] The stereochemistry of (+)-**8** was tentatively assigned based on the stereoselectivity. [e] 0.5 mol% of catalyst {[$Rh(COD)_2BF_4$]:L = 1:1.1} was used.

With **16a** identified as the superior ligand, different solvents were examined and dichloroethane (DCE) afforded the highest enantioselectivity (Table 1, entry 7-11). No loss of enantioselectivity was observed when the catalyst loading was reduced to 0.5 mol% (entry 12). Reducing the temperature improved the enantioselectivity of the reaction. At 0 °C, 98.1% ee was obtained but the reaction was sluggish (entry 13). However, at 15 °C, full conversion was observed in 8 h and the product obtained in 96.5% ee (entry 14).

Next, a variety of aryl and alkyl dehydroamino acid esters were subjected to the optimized reaction conditions (Table 2). For all the substrates, the observed enantioselectivities (96.5–99.5% ee) match the best-performing ligands (e.g. DuPHOS[17]: 99–99.4%; MonoPHOS[18]: 93.2–99.8%; SIPHOS[19]: 95.6%-99.3%) and they are better than those reported for BINAP[3a] (92-93%).

Table 2 Asymmetric hydrogenation of α-dehydroamino acid esters



19 20

entry[a]	Substrate (**19**)	ee (%)[b]	Config.[c]
1	(R = Ph)	96.5	*R*
2	(R = 4-ClPh)	97.6	*R*
3	(R = 2-OMePh)	98.8	*R*
4	(R = 3-OMePh)	97.8	*R*
5	(R = 4-CH_3Ph)	97.0	*R*
6	(R = H)	99.4	*R*
7	(R = Me)	99.5	*R*

[a] The reaction was performed at 15 °C with 0.5 mmol of substrate and 1 mol% of catalyst {[$Rh(COD)_2BF_4$]:L = 1:1.1} in 5 mL of DCE; 100% conversion was observed for all substrates by ^1H NMR of the crude reaction mixture. [b] Determined by chiral stationary phase HPLC. [c] Assigned by comparing the optical rotation with reported values.

In summary, we have developed a new chiral bisphosphine ligand, **16a**, which contains a 1,1'-spirobi(3*H*,3'*H*)isobenzofuran backbone. The ligand is accessed in 7 steps in an overall 38%. The synthesis does not involve separation of enantiomers and the chemical transformations are robust and can be performed on gram-scale. The ligand was evaluated in rhodium-catalyzed hydrogenation of α-dehydroamino acid esters where it provided excellent enantioselectivities (96.5%-99.5% ee). Interestingly, when compared head-to-head under the same conditions for this reaction, ligand **16a** significantly outperforms the original SDP ligand.

EXPERIMENTAL SECTION

General Information. NMR spectra were all recorded on a Bruker AM400 (400 MHz) spectrometer. Chemical shifts are reported in δ ppm referenced to an internal $SiMe_4$ standard for ^1H NMR and chloroform-d (δ 77.16) for ^{13}C NMR. Optical rotations were measured in CH_2Cl_2 or $CHCl_3$ on a Perkin-Elmer 241MC automatic polarimeter. HRMS were recorded on a Bruker ApeXIII 7.0 TESLA FTMS (TOF) Mass Spectrometer. Flash column chromatography was performed using silica gel (300-400 mesh). Analytical thin-layer chromatography was performed using glass plates precoated with 0.25 mm 300–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure

to ultraviolet light (254 nm). Enantioselectivities were determined by high-performance liquid chromatography (HPLC) with a Aglilent-1100 or Aglilent-1260 intelligent uv/vis detector (λ = 214 nm, 220nm or 254 nm) and a Daicel IC or Daicel AD-H column. $KPPh_2$ (0.5 M in THF) was purchased from Sigma-Aldrich.

Experimental Procedures. *(2-bromo-3-fluorophenyl)methanol (**2**).* To a solution of compound **1** (6.0 g, 30.0 mmol) in MeOH (100 mL) was added $NaBH_4$ (1.1 g, 30.0 mmol) slowly at 0 °C. The mixture was stirred at 0 °C for an additional 1 h. After quenching with 10 mL of saturated aqueous solution of ammonium chloride, the mixture was concentrated and extracted with EtOAc (3×100 mL). The combined extracts were washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated to give **2** (6.0 g, 99%) as a white solid. The product was used directly for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.32 (m, 2H), 7.04-7.09 (m, 1H), 4.78 (s, 2H).

*2-Bromo-1-fluoro-3-(((2-methoxyethoxy)methoxy)methyl)benzene (**3**).* DIPEA (10.3 mL, 60 mmol) was added to a solution of compound **2** (6.0 g, 29.3 mmol) in anhydrous CH_2Cl_2 (80 mL) at 0 °C under argon. MEMCl (6.1 mL, 52.7 mmol) was added dropwise and the mixture was stirred at 0 °C for 1 h. It was then allowed to warm to room temperature and stirred for 24 h. The mixture was concentrated, and the crude product was purified by flash chromatography (silica gel, PE/EA = 7:1) to give the product **3** (8.3 g, 96%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ7.25-7.31 (m, 2H), 7.03-7.09 (m,1H), 4.87 (s, 2H), 4.71 (s, 2H), 3.76-3.78 (m, 2H), 3.57-3.59 (m, 2H), 3.40 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -106.14. ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9 (d, *J* = 246.7.2 Hz), 13.7, 128.2 (d, *J* = 8.7 Hz), 124.2 (d, *J* = 3.1 Hz), 115.1 (d, *J* = 22.2 Hz), 109.4 (d, *J* = 17.6 Hz), 95.1, 71.6, 68.4, 67.0, 58.0. HRMS: (ESI) calcd for $C_{11}H_{14}BrFNaO_3$ $(M+Na)^+$: 315.0008, found 315.0019. IR (KBr) 2927, 2886, 1602, 1578, 1467, 1445, 1263, 1173, 1055, 993, 779 cm^{-1}.

*2-Fluoro-6-(((2-methoxyethoxy)methoxy)methyl)benzaldehyde (**4**).* Compound **3** (11.8 g, 40.0 mmol) was dissolved in 85 mL THF and cooled to −78 °C under argon. *n*-BuLi (20.0 mL, 48 mmol) was added dropwise and the mixture was stirred for an additional 40 minutes. DMF (6.21 mL, 80.0 mmol) was added. The mixture was stirred for 30 minutes while the temperature rose to −70 °C. The reaction mixture was then allowed to warm to 0 °C (about 4 h). The reaction mixture was quenched with 20 mL of saturated aqueous solution of ammonium chloride and extracted with EtOAc (3×100 mL). The combined organic extracts were washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated, and the crude product was purified by flash chromatography (silica gel, PE/EA = 5:1) to give the product **4** (9.0 g, 93%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.51 (s, 1H), 7.52-7.62 (m, 2H), 7.11 (t, *J* = 9.2 Hz, 1H), 5.02 (s, 2H), 4.88 (s, 2H), 3.74-3.77 (m, 2H), 3.56-3.59 (m, 2H), 3.40 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -120.89. ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.5 (d, *J* = 10.7 Hz), 167.1, 164.5, 142.7, 135.4 (d, *J* = 10.7 Hz), 122.9, 120.9 (d, *J* = 6.1 Hz), 114.8 (d, *J* = 21.4 Hz), 95.2, 71.6, 66.9 (d, *J* = 14.6 Hz), 58.8. HRMS: (ESI+, m/z) calculated for $[C_{12}H_{15}FNaO_4]^+$ $(M+Na)^+$: 265.0852, found: 265.0868. IR (KBr) 2923, 2887, 2789, 1694, 1613, 1574, 1473, 1411, 1242, 1118, 1055, 831, 792, 519 cm^{-1}.

*Bis(2-fluoro-6-(((2-methoxyethoxy)methoxy)methyl)phenyl)methanol (**5**).* Compound **3** (2.2 g, 7.6 mmol) was dissolved in 40 mL THF and cooled to −78 °C under argon. *n*-BuLi (4.8 mL, 7.6 mmol) was added dropwise and the mixture was stirred for an additional 1 h. A solution of compound **4** (1.5 g, 6.3 mmol) in THF (10 mL) was added dropwise. After completed addition, the mixture was stirred for 1.5 h while the temperature rose to −60 °C. The reaction mixture was then allowed to warm to 0 °C (about 4 h). The reaction mixture was treated with 10 mL of saturated aqueous solution of ammonium chloride and extracted with EtOAc (3×30 mL). The combined organic extracts were washed with 20 mL of brine, dried over Na_2SO_4, filtered, and concentrated and the crude product was purified by flash chromatography (silica gel, PE/EA = 2:1) to give the product **5** (2.5 g, 87%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17-7.26 (m, 4H), 6.87-6.92 (m, 2H), 6.54 (d, *J* = 5.6 Hz, 1H), 4.93 (q, *J* = 12.4 Hz, 4H), 4.78 (s, 4H), 4.20 (d, *J* = 5.6 Hz, 1H), 3.69-3.72 (m, 4H), 3.56 – 3.44 (m, 4H), 3.35 (s, 6H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -114.26. ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.9, 159.4, 138.2, 128.6, 128.5, 128.4, 128.3, 125.5, 115.7, 115.4, 94.6, 71.6, 67.4, 67.0, 65.9 (t, *J* = 3.8 Hz), 58.9. HRMS: (ESI+, m/z) calculated for $[C_{23}H_{30}F_2NaO_7]^+$ $(M+Na)^+$: 479.1857, found: 479.1851. IR (KBr) 2931, 2886, 1696, 1614, 1579, 1468, 1243, 1113, 1048, 851, 786 cm^{-1}.

*Bis(2-fluoro-6-(((2-methoxyethoxy)methoxy)methyl)phenyl)methanone (**6**).* To a solution of compound **5** (2.5 g, 5.5 mmol) in anhydrous CH_2Cl_2 (30 mL) was added activated manganese dioxide (6.2 g, 71.7 mmol). The mixture was stirred at room temperature overnight. The reaction mixture was filtered and the retained solid rinsed with 50 mL of CH_2Cl_2. The combined filtrates were concentrated to give the crude product **6** (2.4 g, 97%) as a pale yellow oil. The crude product was used directly for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.48 (m, 4H), 6.99 (t, *J* = 8.8 Hz, 2H), 4.79 (s, 4H), 4.74 (s, 4H), 3.71 (t, *J* = 4.8 Hz, 4H), 3.54 (t, *J* = 4.4 Hz, 4H), 3.37 (s, 6H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -113.51. ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.4, 161.9, 159.4, 140.0, 132.3, 132.2, 127.1, 127.0, 123.9, 115.0, 114.7, 94.8, 71.5, 66.8, 66.3, 58.7. HRMS: (ESI+, m/z) calculated for $[C_{23}H_{28}F_2NaO_7]^+$ $(M+Na)^+$: 477.1701, found: 477.1695. IR (KBr) 2927, 2886, 2815, 1673, 1611, 1577, 1469, 1251, 1115, 1052, 924, 794 cm^{-1}.

*(+)-7,7'-Difluoro-3H,3'H-1,1'-spirobi[isobenzofuran] ((+)-**7**).* To a solution of compound **6** (2.4 g, 5.3 mmol) in anhydrous CH_2Cl_2 (30 mL) was added extra dry $ZnBr_2$ (3.6 g, 32.0 mmol). The mixture was stirred at room temperature overnight. Then, the reaction mixture was filtered, the retained solid washed with 30 mL of CH_2Cl_2, and the combined filtrates concentrated to give the crude product which was purified by flash chromatography (silica gel, PE/EA = 15:1) to give the racemic product **7** (1.1 g, 80%)

as a white solid. Resolution of the enantiomers was performed by HPLC using a chiral column. (Separation conditions: Daicel Chiralpak OJ-H column, EtOH=100%, flow rate 0.5 mL/min, λ = 214 nm: t_{R1} = 7.62 min., t_{R2} = 9.95 min. (+)-**7**: $[\alpha]^{20}_D$ = 19 (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.42 (m, 2H), 7.10 (d, *J* = 7.2 Hz, 2H), 6.95 (t *J* = 8.8 Hz, 2H), 5.34 (d, *J* = 12.8 Hz, 2H), 5.23 (d, *J* = 12.8 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -121.31. ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 156.8, 143.0, 142.9, 131.9, 131.4, 125.4, 125.2, 116.9, 116.8, 116.7, 114.7, 114.5, 72.1. HRMS: (ESI+, m/z) calculated for $[C_{15}H_{11}F_2O_2]^+$ $(M+H)^+$: 261.0727, found: 261.0733. IR (KBr) 2953, 2873, 1629, 1597, 1475, 1364, 1294, 1256, 1023, 968, 932, 776, 735, 588 cm^{-1}. HPLC: Daicel OJ-H column (EtOH = 100%), flow rate = 0.5 mL/min; λ = 214 nm; $t_{R(minor)}$ = 7.62min, $t_{R(major)}$ = 9.95 min, ee = 99%.

*(+)-7,7'-Bis(diphenylphosphanyl)-3H,3'H-1,1'-spirobi[isobenzofuran] ((+)-**8**)*. To a 15 mL pressure tube equipped with magnetic stirring bar were added compound (+)-**7** (130 mg, 0.5 mmol) and $KPPh_2$ (3.0 mL, 1.5 mmol, 0.5 M in THF), and the tube sealed under argon. The mixture was heated to reflux for 6 h and then cooled and filtered. The retained solid was washed with CH_2Cl_2 and the combined filtrates were concentrated to give the crude product which was purified by flash chromatography (silica gel, PE/EA/CH_2Cl_2 = 20:1:1) to give the product (+)-**8** (250 mg, 84%, > 99% ee) as a white solid. m. p. 212 ~ 214 °C. $[\alpha]^{20}_D$ = 255(c = 1.0, CH_2Cl_2). m. p. 212 ~ 214 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (t *J* = 8.8 Hz, 2H), 7.21-7.26 (m, 10H), 7.18 (t *J* = 7.2 Hz, 4H), 7.03-7.13 (m, 4H), 6.91-6.95 (m, 2H), 6.88 (t *J* = 7.6 Hz, 4H), 5.12 (d, *J* = 12.4 Hz, 2H), 4.71 (d, *J* = 12.4 Hz, 2H). ^{31}P NMR (162 MHz, $CDCl_3$): δ -18.60. ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.2, 143.9, 140.9, 140.8, 137.7, 137.6, 136.7, 136.6, 134.0, 133.8, 133.7, 133.4, 133.2, 133.0, 129.5, 128.3, 128.2, 128.1, 128.0, 121.5, 120.7, 71.3. HRMS: (ESI+, m/z) calculated for $[C_{39}H_{31}O_2P_2]^+$ $(M+H)^+$: 593.1799, found: 593.1791. IR (KBr) 3067, 2912, 2860, 1584, 1479, 1433, 1357, 1281, 1091, 1025, 947, 744, 695, 506 cm^{-1}. HPLC: Daicel IA column (hexane/i-PrOH = 95/05), flow rate = 1.0 mL/min; λ = 254 nm; $t_{R(major)}$ = 7.52min, $t_{R(minor)}$ = 10.72 min.

*R)-1-(2-Bromo-3-fluorophenyl)ethan-1-ol (**10**)*. With reference to the known literature[15], (+)-DIPCl (50.0 mL, 84 mmol) was dissolved in 400 mL THF and cooled to –35 °C under argon. A solution of compound **9** (14.0 g, 64.4 mmol) in 140 mL THF was added dropwise. After completed addition, the mixture was stirred for 18 h at –35 °C. Then, diethanolamine (20.2 g, 193.2 mmol) was added and the reaction mixture stirred for 3 h. The mixture was concentrated, solvent added (400 mL, *n*-hexane/MTBE = 7:1), and the mixture filtered, rinsing the retained solid with 100 mL *n*-hexane. The concentrated filtrates were purified by flash chromatography (silica gel, PE/EA = 10:1) to give the product **10** (13.5 g, 96%, 96% ee) as a colorless oil. $[\alpha]^{20}_D$ = 60 (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.40 (m, 1H), 7.30 (dt, *J* = 5.6 Hz, *J* = 8.0 Hz, 1H), 7.03 (dt, *J* = 1.6 Hz, *J* =9.6 Hz, 1H), 5.22-5.28 (m, 1H), 2.22 (d, *J* = 3.2 Hz, 1H), 1.47 (d, *J* = 6.4 Hz, 3H).

*(R)-2-Bromo-1-fluoro-3-(1-((2-methoxyethoxy)methoxy)ethyl)benzene (**11**)*. DIPEA (21.3 mL, 123.2 mmol) was added to a solution of compound **10** (13.5 g, 61.6 mmol) in anhydrous CH_2Cl_2 (200 mL) at 0 °C under argon. MEMCl (12.7 mL, 110.9 mmol) was added dropwise and the mixture was stirred at 0 °C for 1 h. It was then allowed to warm to room temperature and stirred for 24 h. The mixture was concentrated, and the crude product was purified by flash chromatography (silica gel, PE/EA = 10:1) to give the product **11** (17.6 g, 93%) as a colorless oil. $[\alpha]^{20}_D$ = 143 (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.32 (m, 2H)，7.00-7.05 (m,1H)，5.18 (q, *J* = 6.4 Hz, 1H), 4.75 (d, *J* = 7.2 Hz, 1H), 4.63 (d, *J* = 6.8 Hz, 1H), 3.77-3.82 (m, 1H), 3.59-3.65 (m, 1H), 3.47-3.64 (m, 2H), 3.38 (s, 3H), 1.44 (d, *J* = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -105.31. ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7 (d, *J* = 45.2 Hz), 145.4, 128.6 (d, *J* = 7.7 Hz), 123.3 (d, *J* = 3.1 Hz), 114.8 (d, *J* = 22.2 Hz), 109.2 (d, *J* = 20.7 Hz), 93.7, 72.7 (d, *J* = 3.1 Hz), 71.7, 67.1, 59.0, 22.3. HRMS: (ESI+, m/z) calculated for $[C_{12}H_{20}BrFNO_3]^+$ $(M+NH_4)^+$: 324.0611, found: 324.0604. IR (KBr) 2930, 2887, 1674, 1575, 1465, 1261, 1119, 1041, 929, 848, 791, 715 cm^{-1}.

*(R)-2-Fluoro-6-(1-((2-methoxyethoxy)methoxy)ethyl)benzaldehyde (**12**).* Compound **11** (9.0 g, 29.3 mmol) was dissolved in 130 mL THF and cooled to –78 °C under argon. *n*-BuLi (22.0 mL, 35.2 mmol) was added dropwise and the mixture was stirred for an additional 40 minutes. DMF (4.6 mL, 58.6 mmol) was added. The mixture was stirred for 30 minutes while the temperature rose to –70 °C. The reaction mixture was then allowed to warm to 0 °C (about 4 h). The reaction mixture was quenched with 20 mL of saturated aqueous solution of ammonium chloride and extracted with EtOAc (3×60 mL). The combined organic extracts were washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated, and the crude product was purified by flash chromatography (silica gel, PE/EA = 5:1) to give the product **12** (7.0 g, 93%) as a pale yellow oil. $[\alpha]^{20}_D$ = 205 (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.47 (s, 1H), 7.41-7.61 (m, 2H), 6.93-7.12 (m, 1H), 5.60 (q, *J* = 5.6 Hz, 1H), 4.70 (d, *J* = 6.8 Hz, 1H), 4.56 (d, *J* = 5.6 Hz, 1H), 3.65-3.79 (m, 1H), 3.40-3.58 (m, 1H), 3.32 (s, 3H), 1.41 (d, *J* = 8.4 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -120.79. ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.8 (d, *J* = 11.5 Hz), 165.6 (d, *J* = 256.6 Hz), 148.7, 135.5 (d, *J* = 9.9 Hz), 122.1 (d, *J* = 3.8 Hz), 121.2 (d, *J* = 6.2 Hz), 114.6 (d, *J* = 21.5 Hz), 93.8, 71.5, 70.2 (d, *J* = 2.3 Hz), 67.0, 58.9, 23.6. HRMS: (ESI+, m/z) calculated for $[C_{13}H_{21}FNO_4]^+$ $(M+NH_4)^+$: 274.1455, found: 274.1468. IR (KBr) 2931, 2886, 1697, 1611, 1573, 1470, 1241, 1118, 1038, 801, 730 cm^{-1}.

*Bis(2-fluoro-6-((R)-1-((2-methoxyethoxy)methoxy)ethyl)phenyl)methanone (**14**)*. Compound **11** (8.6 g, 28.0 mmol) was dissolved in 130 mL THF and cooled to –78 °C under argon. *n*-BuLi (17.5 mL, 28.0 mmol) was added dropwise and the mixture was stirred for an additional 1 h. A solution of compound **12** (6.0 g, 23.3 mmol) in 50 mL THF was added dropwise. After completed addition, the mixture was stirred for 1.5 h while the temperature rose to –60 °C. The reaction mixture

was then allowed to warm to 0 °C (about 4 h). The reaction mixture was treated with 10 mL of saturated aqueous solution of ammonium chloride and extracted with EtOAc (3×100 mL). The combined organic extracts were washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated to give 12.5 g of the crude product **13**, which was used directly for the next step without further purification: To a solution of compound **13** (12.5 g, 23.3 mmol) in anhydrous CH_2Cl_2 (150 mL) was added activated manganese dioxide (30.5 g, 349.5 mmol). The mixture was stirred at room temperature overnight. Then, the mixture was filtered, the retained solid rinsed with 100 mL of CH_2Cl_2, and the combined filtrates concentrated to give the crude product which was purified by flash chromatography (silica gel, PE/EA = 3:1) to give the product **14** (9.8 g, 87%) as a colorless viscous liquid. $[\alpha]^{20}_D$ = 170 (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ7.42-7.53 (m, 4H), 6.92 (t, *J* = 8.8 Hz, 2H), 5.01 (q, *J* = 6.4 Hz, 2H), 4.67 (d, *J* = 6.8 Hz, 2H), 4.59 (d, *J* = 6.8 Hz, 2H), 3.71-3.77 (m, 2H), 3.56-3.62 (m, 2H), 3.43-3.53 (m, 4H), 3.33 (s, 6H), 1.58 (d, *J* = 6.4 Hz, 6H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -113.31. ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.0, 161.5, 158.9, 146.8, 132.6, 132.5, 127.8, 127.7, 122.6, 114.4, 114.1, 93.6, 71.6, 70.9, 66.9, 58.8, 24.5. HRMS: (ESI+, m/z) calculated for $[C_{25}H_{36}F_2NO_7]^+$ $(M+NH_4)^+$: 500.2460, found: 500.2459. IR (KBr) 2931, 2887, 1668, 1612, 1574, 1470, 1294, 1245, 1119, 1035, 922, 805 cm^{-1}.

*(1S,3R,3'R)-7,7'-Difluoro-3,3'-dimethyl-3H,3'H-1,1'-spirobi[isobenzofuran]**(15a)** and (1R,3R,3'R)-7,7'-difluoro-3,3'-dimethyl-3H,3'H-1,1'-spirobi[isobenzofuran] **(15b)***. To a solution of compound **14** (9.0 g, 18.6 mmol) in anhydrous CH_2Cl_2 (90 mL) was added extra dry $ZnBr_2$ (30.0 g, 130.2 mmol). The mixture was stirred at room temperature overnight. Then, the reaction mixture was filtered, the retained solid rinsed with 100 mL of CH_2Cl_2, and the combined filtrates concentrated to give the crude product which was purified by flash chromatography (silica gel, PE/EA = 25:1) to obtain two diastereoisomers **15a** and **15b**. **15a**: 3.3 g (61%, > 99% ee), white solid. m. p. 141 ~ 143 °C. $[\alpha]^{20}_D$ = 32 (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.43 (m, 2H), 7.04 (d, *J* = 7.2 Hz, 2H), 6.95 (t *J* = 8.8 Hz, 2H), 5.57 (q, *J* = 6.4 Hz, 2H), 1.58 (d, *J* = 6.4 Hz, 6H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -121.13. ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1, 156.6, 147.6, 147.6, 132.0, 132.0, 126.0, 125.4, 116.6, 116.6, 114.9, 114.7, 114.0, 79.1, 21.0. HRMS: (ESI+, m/z) calculated for $[C_{17}H_{15}F_2O_2]^+$ $(M+H)^+$: 289.1040, found: 289.1028. IR (KBr) 2986, 2865, 1626, 1601, 1478, 1351, 1301, 1253, 1084, 1013, 944, 779, 744 cm^{-1}. HPLC: Daicel Chiralpak IC column, hexane/i-PrOH 99:01, flow rate 0.7 mL/min, λ = 220 nm: $t_{R(minor)}$ = 8.66 min., $t_{R(major)}$ = 10.17 min. **15b**: 1.0 g (19%, > 99% ee), white solid. m. p. 149 ~ 152 °C. $[\alpha]^{20}_D$ = -43 (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.40 (m, 2H), 7.03 (d, *J* = 7.6 Hz, 2H), 6.93 (t, *J* = 8.8 Hz, 2H), 5.48 (q, *J* = 6.4 Hz, 2H), 1.64 (d, *J* = 6.4 Hz, 6H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -121.15. ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 156.5, 147.4, 147.3, 131.8, 131.7, 125.7, 125.5, 116.7, 116.6, 114.8, 114.6, 113.0, 79.5, 21.0. HRMS: (ESI, m/z) calculated for $[C_{17}H_{15}F_2O_2]^+$ $(M+H)^+$: 289.1040, found: 289.1051. IR (KBr) 2984, 2894, 1627, 1598, 1476, 1368, 1285, 1245, 1076, 1009, 935, 794, 745 cm^{-1}. HPLC: Daicel Chiralpak IC column, hexane/i-PrOH 99:01, flow rate 0.7 mL/min, λ = 220 nm: $t_{R(minor)}$= 7.49 min., $t_{R\ (major)}$ = 9.18 min.

*((1S,3R,3'R)-3,3'-dimethyl-3H,3'H-1,1'-spirobi[isobenzofuran]-7,7'-diyl)bis(diphenylphosphane) **(16a)**.* To a 48 mL pressure tube was added compound **15a** (0.500 g, 1.74 mmol) and $KPPh_2$ (12.0 mL, 6.00 mmol, 0.5 M in THF), and the tube sealed under argon. The mixture was heated at 85 °C for 30 h and then cooled to room temperature. The mixture was filtered, the retained solid rinsed with CH_2Cl_2, and the combined filtrates concentrated to give the crude product which was purified by flash chromatography (silica gel, PE/EA/CH_2Cl_2 = 25:1:1) to give the product **16a** (0.930 g, 86%, >99% ee) as a white solid. $[\alpha]^{20}_D$ = -318 (c = 1.0, CH_2Cl_2). m. p. 264 ~ 266 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (t, *J* = 7.6 Hz, 2H), 7.18-7.30 (m, 14H), 6.93-7.03 (m, 10H), 5.36 (q, *J* = 6.4 Hz, 2H), 1.06 (d, *J* = 6.4Hz, 6H). ^{31}P NMR (162 MHz, $CDCl_3$): δ -20.47. ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.2, 145.1, 144.6, 144.3, 138.0, 137.9, 137.4, 137.2, 134.5, 134.1, 134.0, 133.9, 133.2, 133.1, 133.0, 132.4, 132.2, 129.5, 128.3, 128.2, 128.2, 128.2, 128.1, 128.0, 128.0, 128.0, 127.7, 121.6, 117.4, 77.3, 18.7.HRMS: (ESI+, m/z) calculated for $[C_{41}H_{35}O_2P_2]^+$ $(M+H)^+$: 621.2112, found: 621.2119. IR (KBr) 3050, 2924, 2854, 1583, 1480, 1432, 1371, 1322, 1280,1092, 1032, 998, 948, 775, 695, 511 cm^{-1}. HPLC: Daicel Chiralpak IC column, hexane/*i*-PrOH 99:01, flow rate 0.7 mL/min, λ = 220 nm: $t_{R(minor)}$ = 6.03 min., $t_{R\ (major)}$ = 7.48 min.

*((1R,3R,3'R)-3,3'-dimethyl-3H,3'H-1,1'-spirobi[isobenzofuran]-7,7'-diyl)bis(diphenylphosphane) **(16b)**.* To a 15 mL pressure was added compound **15b** (144 mg, 0.5 mmol) and $KPPh_2$ (4.0 mL, 2.0 mmol, 0.5 M in THF), and the tube sealed under argon. The mixture was heated at 85 °C for 30 h and then cooled to room temperature. The mixture was filtered, the retained solid rinsed with with CH_2Cl_2, and the combined filtrates concentrated to give the crude product which was purified by flash chromatography (silica gel, PE/EA/CH_2Cl_2 = 25:1:1) to give the product **16b** (270 mg, 87%, >99% ee) as a white solid. m. p. 168 ~ 171 °C. $[\alpha]^{20}_D$ = 230 (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (t, *J* = 7.2 Hz, 2H), 7.19-7.26 (m, 10H), 7.05-7.14 (m, 8H), 6.93-6.96 (m, 2H), 6.78 (t, *J* = 7.6 Hz, 4H), 5.19 (q, *J* = 6.4 Hz, 2H), 1.52 (d, *J* = 6.4Hz, 6H). ^{31}P NMR (162 MHz, $CDCl_3$): δ -19.14. ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.6, 145.5, 145.0, 144.8, 138.1, 138.0, 136.9, 136.7, 134.0, 133.8, 133.1, 133.0, 132.7, 132.5, 129.3, 128.3, 128.1, 128.0, 128.0, 127.9, 121.5, 119.1, 78.7, 78.6, 23.3. HRMS: (ESI+, m/z) calculated for $[C_{41}H_{35}O_2P_2]^+$ $(M+H)^+$: 621.2112, found: 621.2121. IR (KBr) 3050, 2968, 2921, 1584, 1478, 1433, 1343, 1268, 1027, 946, 742, 695, 502 cm^{-1}. HPLC: Daicel Chiralpak IC column, hexane/*i*-PrOH 99.6:0.4, flow rate 0.4 mL/min, λ = 220 nm: $t_{R(major)}$ = 11.23 min., $t_{R\ (minor)}$ = 12.41 min.

*(R)-(2-fluoro-6-(((2-methoxyethoxy)methoxy)methyl)phenyl)(2-fluoro-6-(1-((2-methoxyethoxy)methoxy)ethyl)phenyl)methanone **(22)**.* Compound **11** (11.0 g, 36.0 mmol) was dissolved in 160 mL THF and cooled to –78 °C under argon. *n*-BuLi (15.0 mL, 36.0 mmol) was added dropwise and the mixture was

stirred for an additional 1 h. A solution of compound **4** (7.3 g, 30.0 mmol) in 50 mL THF was added dropwise. After completed addition, the mixture was stirred for 1.5 h while the temperature rose to –60 °C. The reaction mixture was then allowed to warm to 0 °C (about 4 h). The reaction mixture was treated with 10 mL of saturated aqueous solution of ammonium chloride and extracted with EtOAc (3×100 mL). The combined organic extracts were washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated to give 15.9 g of the crude product **21**. The crude product was used directly for the next step without further purification: To a solution of compound **21** (15.9 g, 30.0 mmol) in anhydrous CH_2Cl_2 (150 mL) was added activated manganese dioxide (39.2 g, 450.0 mmol). The mixture was stirred at room temperature overnight. Then, the reaction mixture was filtered, the retained solid rinsed with 100 mL of CH_2Cl_2, and the combined filtrates concentrated to give the crude product which was purified by flash chromatography (silica gel, PE/EA = 3:1) to give the product **22** (12.0 g, 85%) as a colorless viscous liquid. $[\alpha]^{20}_D$ = 71 (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.48 (m, 4H), 6.92-7.00 (m,2H), 5.03 (q, *J* = 6.4 Hz, 1H), 4.85 (s, 2H), 4.80 (s, 2H), 4.61 (dd, *J* = 6.8 Hz, *J* = 18.4 Hz, 2H), 3.70-3.75 (m, 3H), 3.54-3.60 (m, 3H), 3.47 (t, *J* = 4.8 Hz, 2H), 3.37 (s, 3H), 3.32 (s, 3H) 1.51 (d, *J* = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -112.69, -114.16. ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.8, 161.7 (d, *J* = 98.1 Hz), 159.2 (d, *J* = 95.8 Hz), 146.1, 140.5, 132.6 (d, *J* = 9.2 Hz), 132.2 (d, *J* = 9.2 Hz), 127.7 (d, *J* = 13.8 Hz), 126.9 (d, *J* = 12.3 Hz), 124.0 (d, *J* = 2.3 Hz), 122.4 (d, *J* = 3.1 Hz), 114.9 (d, *J* = 22.2 Hz), 114.2 (d, *J* = 21.5 Hz), 94.9, 93.4, 71.6, 71.5, 70.7, 66.9, 66.8, 66.3, 58.8, 58.7, 24.1. HRMS: (ESI+, m/z) calculated for $[C_{24}H_{34}F_2NO_7]^+$ $(M+NH_4)^+$: 486.2303, found: 486.2323. IR (KBr) 2930, 2887, 1671, 1611, 1576, 1470, 1247, 1116, 1042, 923, 803 cm^{-1}.

*(1S,3R)-7,7'-difluoro-3-methyl-3H,3'H-1,1'-spirobi[isobenzofuran] (**17a**) and (1R,3R)-7,7'-difluoro-3-methyl-3H,3'H-1,1'-spirobi[isobenzofuran] (**17b**).* To a solution of compound **22** (6.0 g, 12.8 mmol) in anhydrous CH_2Cl_2 (90 mL) was added extra dry $ZnBr_2$ (17.3 g, 76.8 mmol). The mixture was stirred at room temperature overnight. Then, the mixture was filtered, the retained solid rinsed with 50 mL of CH_2Cl_2, and the combined filtrates concentrated to give the crude product which was purified by flash chromatography (silica gel, PE/EA = 30:1) to obtain two diastereoisomers (dr = 2:1). **17a**: 1.3 g (recrystallization from hexane, 38% yield, > 99% ee), white solid. m. p. 109 ~ 111 °C. $[\alpha]^{20}_D$ = 5 (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.43 (m, 2H), 7.07 (dd, *J* = 7.6 Hz, *J* = 21.6 Hz, 2H), 6.95 (t, *J* = 8.4 Hz, 2H), 5.58 (q, *J* = 6.0 Hz, 1H), 5.32 (d, *J* = 12.8 Hz, 1H), 5.19 (d, *J* = 12 .8Hz, 1H), 1.59 (d, *J* = 6 .4Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -121.13, -121.28. ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3 (d, *J* = 27.5 Hz), 156.7 (d, *J* = 27.4 Hz), 147.5 (d, *J* = 2.8 Hz), 143.2 (d, *J* = 2.8 Hz), 132.0 (d, *J* = 6.3 Hz), 131.9 (d, *J* = 7.1 Hz), 125.5 (d, *J* = 8.5 Hz), 125.3 (d, *J* = 9.1 Hz), 116.8 (d, *J* = 3.5 Hz), 116.6 (d, *J* = 3.5 Hz), 115.3, 114.8 (d, *J* = 19.7 Hz), 79.3, 71.9, 20.9. HRMS: (ESI+, m/z) calculated for $[C_{16}H_{13}F_2O_2]^+$ $(M+H)^+$: 275.0884, found: 275.0879. IR (KBr) 2974, 2929, 2869, 1626, 1600, 1477, 1359, 1299, 1256, 1083, 1022, 950, 794, 738 cm^{-1}. HPLC: Daicel Chiralpak IC column, hexane/i-PrOH 97:03, flow rate 0.7 mL/min, λ = 254 nm: $t_{R(major)}$ = 10.02 min., $t_{R(minor)}$ = 12.83 min. **17b**: 737 mg (recrystallization from hexane, 21% yield, > 99% ee), white solid. m. p. 103 ~ 104 °C. $[\alpha]^{20}_D$ = -12 (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.42 (m, 2H), 7.06 (dd, *J* = 7.6 Hz, *J* = 18.8 Hz, 2H), 6.91-6.96 (m, 2H), 5.49 (q, *J* = 6.4 Hz, 1H), 5.37 (d, *J* = 12.8 Hz, 1H), 5.23 (d, *J* = 12 .8Hz, 1H), 1.64 (d, *J* = 6 .4Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -121.28, -121.45. ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2 (d, *J* = 13.8 Hz), 156.7 (d, *J* = 13.8 Hz), 147.3 (d, *J* = 3.1 Hz), 142.9 (d, *J* = 3.8 Hz), 132.0 (d, *J* = 6.9 Hz), 131.8 (d, *J* = 6.9 Hz), 125.6 (d, *J* = 13.7 Hz), 125.4 (d, *J* = 13.8 Hz), 116.9 (d, *J* = 3.8 Hz), 116.7 (d, *J* = 3.8 Hz), 115.8, 114.8 (d, *J* = 13.8 Hz), 114.6 (d, *J* = 14.6 Hz), 79.6, 72.2, 22.9. HRMS: (ESI+, m/z) calculated for $[C_{16}H_{13}F_2O_2]^+$ $(M+H)^+$: 275.0884, found: 275.0887. IR (KBr) 2987, 2869, 1630, 1599, 1477, 1363, 1334, 1246, 1082, 994, 937, 797, 742 cm^{-1}. HPLC: Daicel Chiralpak IC column, hexane/i-PrOH 97:03, flow rate 0.7 mL/min, λ = 254 nm: $t_{R(minor)}$= 8.79 min., $t_{R(major)}$ = 12.86 min.

*((1S,3R)-3-methyl-3H,3'H-1,1'-spirobi[isobenzofuran]-7,7'-diyl)bis(diphenylphosphane) (**18a**).* To a 15 mL pressure tube was added compound **17a** (137 mg, 0.5 mmol) and $KPPh_2$ (4.0 mL, 2 mmol, 0.5 M in THF), and the tube sealed under argon. The mixture was heated at 85 °C for 8 h and then cooled, filtered, and concentrated to give the crude product which was purified by flash chromatography (silica gel, PE/EA/CH_2Cl_2 = 20:1:1) to give the product **18a** (225 mg, 74%, >99% ee) as a white solid. m. p. 249 ~ 251 °C. $[\alpha]^{20}_D$ = -217 (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87-7.39 (m, 26H), 5.39 (q, *J* = 6.4 Hz, 1H), 4.99 (d, *J* = 12.4 Hz, 1H), 4.16 (d, *J* = 12.8Hz, 1H), 1.21 (d, *J* = 6.4Hz, 3H). ^{31}P NMR (162 MHz, $CDCl_3$): δ -17.60, -20.89. ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.7, 144.6, 143.2, 142.9, 141.6, 141.5, 138.0, 137.9, 137.5, 137.4, 137.2, 137.1, 136.7, 136.5, 134.7, 134.1, 134.0, 133.9, 133.8, 133.2, 133.0, 132.8, 132.5, 132.3, 129.7, 129.3, 128.3, 128.2, 128.2, 128.2, 128.0, 128.0, 127.9, 127.6, 121.7, 121.3, 118.9, 77.8, 70.8, 1.8. HRMS: (ESI+, m/z) calculated for $[C_{40}H_{33}O_2P_2]^+$ $(M+H)^+$: 607.1956, found: 607.1976. IR (KBr) 3051, 2923, 2855, 1583, 1479, 1433, 1353, 1281, 1089, 1025, 946, 774, 695, 505 cm^{-1}. HPLC: Daicel Chiralpak IC column, hexane/i-PrOH 97:03, flow rate 0.7 mL/min, λ = 220 nm: $t_{R(minor)}$= 6.62 min., $t_{R(major)}$ = 8.99 min.

*((1R)-3-Methyl-3H,3'H-1,1'-spirobi[isobenzofuran]-7,7'-diyl)bis(diphenylphosphane) (**18b**).* To a 15 mL pressure tube was added compound **17b** (137 mg, 0.5 mmol) and $KPPh_2$ (4.0 mL, 2 mmol, 0.5 M in THF), and the tube sealed under argon. The mixture was heated at 85 °C for 8 h and then cooled, filtered, and concentrated to give the crude product which was purified by flash chromatography (silica gel, PE/EA/CH_2Cl_2 = 20:1:1) to give the product **18b** (218 mg, 72%, >99% ee) as a white solid. m. p. 182 ~ 183 °C. $[\alpha]^{20}_D$ = 205 (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.89-7.36 (m, 22H), 6.83 (q, *J* = 7.2 Hz, 4H), 5.20 (d, *J* = 12.4 Hz, 1H), 5.04 (q, *J* = 6.4 Hz, 1H), 4.88 (d, *J* = 12.4 Hz, 1H), 1.49 (d, *J* = 6.4Hz, 3H). ^{31}P NMR (162 MHz, $CDCl_3$): δ -18.81. ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.4, 144.6, 144.3, 140.9, 137.9, 137.8, 136.7, 136.6, 134.0, 133.8, 133.2, 133.0,

132.8, 132.6, 129.5, 129.4, 128.3, 128.3, 128.1, 128.1, 128.0, 128.0, 121.5, 121.4, 119.9, 78.6, 71.4, 23.2. HRMS: (ESI+, m/z) calculated for $[C_{40}H_{33}O_2P_2]^+$ $(M+H)^+$: 607.1956, found: 607.1976. IR (KBr) 3050, 2923, 2863, 1583, 1458, 1433, 1351, 1271, 1091, 1026, 947, 742, 695, 503 cm^{-1}. HPLC: Daicel Chiralpak IB column, hexane/*i*-PrOH 99:01, flow rate 0.7 mL/min, λ = 254 nm: $t_{R\ (minor)}$= 9.50 min., $t_{R(major)}$ = 11.03 min.

General procedure for asymmetric hydrogenation of α-dehydroamino acid derivatives. Standard procedure at S/C = 100: To a 25 mL Schlenk tube was added compound **19a** (110 mg, 0.5 mmol), $Rh(COD)_2BF_4$ (2 mg, 5 μmol) and ligand **16a** (3.8 mg, 6 μmol) under argon in a glove box. After four vacuum/hydrogen cycles, 5 mL of 1,2-dichloroethane was added and the reaction mixture was stirring at 15 °C under ambient H_2 pressure for 8 h. The conversion was determined by ^1H NMR. The resulting mixture was filtered through a short silica gel column and concentrated under reduced pressure to give hydrogenation product in quantitative yield.

*Methyl acetyl-D-phenylalaninate (**20a**).*[20,21] 100% conversion and 96.5% ee. $[\alpha]^{20}_D$ = -105 (c = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.24-7.31 (m, 3H), 7.09 (d, *J* = 7.2 Hz, 2H), 6.00 (br s, 1H), 4.86-4.91 (m, 1H), 3.73 (s, 3H), 3.06-3.17 (m, 2H), 1.98 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 169.6, 135.8, 129.2, 128.6, 127.1, 53.1, 52.3, 37.8, 23.1. HPLC: Daicel IA column (hexane/i-PrOH = 90/10), flow rate = 1.0 mL/min; λ = 220 nm; $t_{R(major)}$ = 10.10min, $t_{R(minor)}$ = 12.87 min.

*Methyl (R)-2-acetamido-3-(p-tolyl)propanoate (**20b**).*[22,23] 100% conversion and 97.0% ee. $[\alpha]^{20}_D$ = -100 (c = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.09 (d, *J* = 7.6 Hz, 2H), 6.97 (d, *J* = 7.6 Hz, 2H), 5.98 (br d, *J* = 6.4 Hz, 1H), 4.83-4.88 (m, 1H), 3.73 (s, 3H), 3.10 (dd, *J* = 14.0 Hz, *J* = 6.0 Hz, 1H), 3.05 (dd, *J* = 14.0 Hz, *J* = 6.0 Hz, 1H), 2.31 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 169.7, 136.7, 132.6, 129.3, 129.1, 53.1, 52.2, 37.3, 23.1, 21.0. HRMS: (ESI+, m/z) calculated for $[C_{13}H_{18}NO_3]$ $(M+H)^+$: 236.1287, found: 236.1313. HPLC: Daicel IA column (hexane/i-PrOH = 90/10), flow rate = 1.0 mL/min; λ = 220 nm; $t_{R(major)}$ = 9.79min, $t_{R(minor)}$ = 12.72 min.

*Methyl (R)-2-acetamido-3-(3-methoxyphenyl)propanoate (**20c**).*[20] 100% conversion and 97.8% ee. $[\alpha]^{20}_D$ = -105 (c = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.21 (t, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.63-6.68 (m, 2H), 5.93 (br s, 1H), 4.85-4.91 (m, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.04-3.15 (m, 2H), 2.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 169.8, 159.4, 137.3, 129.3, 121.3, 114.8, 112.1, 54.9, 53.0, 52.0, 37.4, 22.7. HRMS: (ESI+, m/z) calculated for $[C_{13}H_{18}NO_4]$ $(M+H)^+$: 252.1236, found: 252.1238. HPLC: Daicel IA column (hexane/i-PrOH = 90/10), flow rate = 1.0 mL/min; λ = 220 nm; $t_{R(major)}$ = 27.13min, $t_{R(minor)}$ = 32.35 min.

*Methyl (R)-2-acetamido-3-(2-methoxyphenyl)propanoate (**20d**).*[23] 100% conversion and 98.8% ee. $[\alpha]^{20}_D$ = -64 (c = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.24 (t, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 7.2 Hz, 1H), 6.86-6.92 (m, 2H), 6.23 (br d, *J* = 6.0 Hz, 1H), 4.75 (dt, *J* = 10.4 Hz, *J* = 7.2 Hz, 1H), 3.84 (s, 3H), 3.71 (s, 3H), 3.11 (d, *J* = 6.4 Hz, 2H), 1.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 169.8, 157.5, 130.9, 131.1, 128.6, 124.5, 120.8, 55.3, 53.0, 52.1, 32.3, 22.9. HRMS: (ESI+, m/z) calculated for $[C_{13}H_{18}NO_4]$ $(M+H)^+$: 252.1236, found: 252.1241. HPLC: Daicel IA column (hexane/i-PrOH = 90/10), flow rate = 1.0 mL/min; λ = 220 nm; $t_{R(major)}$ = 11.94 min, $t_{R(minor)}$ = 16.36 min.

*Methyl (R)-2-acetamido-3-(4-chlorophenyl)propanoate (**20e**).*[22] 100% conversion and 97.0% ee. $[\alpha]^{20}_D$ = -110 (c = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 7.6 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 5.93 (br d, *J* = 6.4 Hz, 1H), 4.84-4.90 (m, 1H), 3.73 (s, 3H), 3.14 (dd, *J* = 14.0 Hz, *J* = 6.0 Hz, 1H), 3.06 (dd, *J* = 14.0 Hz, *J* = 6.0 Hz, 1H), 2.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 169.5, 134.3, 133.0, 130.5, 128.7, 53.0, 52.4, 37.2, 23.0. HRMS: (ESI+, m/z) calculated for $[C_{12}H_{15}ClNO_3]$ $(M+H)^+$: 256.0740, found: 256.0748. HPLC: Daicel IA column (hexane/i-PrOH = 90/10), flow rate = 1.0 mL/min; λ = 220 nm; $t_{R(major)}$ = 12.17min, $t_{R(minor)}$ = 14.73 min.

*Methyl (R)-2-acetamidobutanoate (**20f**).*[21] 100% conversion and 99.5% ee. $[\alpha]^{20}_D$ = -29 (c = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 6.47 (br s, 1H), 4.54-4.59 (m, 1H), 3.75 (s, 3H), 2.04 (s, 3H), 1.82-1.91 (m, 1H), 1.66-1.77 (m, 1H), 0.92 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 170.0, 53.2, 52.1, 25.3, 22.9, 9.4. HRMS: (ESI+, m/z) calculated for $[C_7H_{13}NNaO_3]$ $(M+Na)^+$: 182.0793, found: 182.0795. HPLC: Daicel IA column (hexane/i-PrOH = 95/05), flow rate = 1.0 mL/min; λ = 220 nm; $t_{R(major)}$ = 12.7 min, $t_{R(minor)}$ = 16.94 min.

*Methyl acetyl-D-alaninate (**20g**).*[24] 100% conversion and 99.4% ee. $[\alpha]^{20}_D$ = -8 (c = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 6.60 (br s, 1H), 4.54-4.62 (m, 1H), 3.75 (s, 3H), 2.02 (s, 3H), 1.40 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 169.7, 52.2, 47.8, 22.8, 18.0. HRMS: (ESI+, m/z) calculated for $[C_6H_{11}NNaO_3]$ $(M+Na)^+$: 168.0637, found: 168.0628. HPLC: Daicel IA column (hexane/i-PrOH = 95/05), flow rate = 1.0 mL/min; λ = 214 nm; $t_{R(major)}$ = 15.57min, $t_{R(minor)}$ = 21.21 min.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

HPLC traces and NMR spectra for all new compounds (PDF)

X-ray data for compound **16a**, **16b**, **18a** (CIF)

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Notes

The authors declare no competing financial interest.

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