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Novel phosphinobioxazines as chiral ligands in palladium-catalyzed enantioselective allylic substitution

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Abstract

Novel C_2-symmetric chiral (4*S*,4′*S*)-bisphosphinobioxazine **2a**, a six-membered analog of (4*S*,4*S*′)-bisphosphinobioxazoline (Phos-Biox, **1**), and monophosphinobioxazine **2b** have been synthesized and used as chiral ligands for Pd-catalyzed asymmetric allylic substitutions of *rac*-1,3-diphenyl-2-propenyl acetate with dimethyl malonate. C_2-Symmetric bisphosphinobioxazine **2a** exhibited moderate enantioselectivities (63–84% ee) whereas excellent enantioselectivities (94–95% ee) were observed with monophosphinobioxazine **2b**.

1. Introduction

The design and development of efficient chiral ligands for transition metals are essential for catalytic asymmetric reactions and has become one of the most intense areas of investigation. In recent years, enantiomerically pure oxazolines have received a great deal of attention through their use in various catalytic processes. In particular, many impressive levels of enantioselectivities have been recorded in metal-catalyzed asymmetric reactions using C_2-symmetric chiral bisoxazoline[1] and phosphine–oxazoline hybrid ligands.[2,3] However, in contrast with five-membered oxazolines, the chiral oxazines as ligands have not been extensively studied to date. To the best of our knowledge, only one type of phosphino-oxazine prepared starting from (−)-β-pinene, has been used as a chiral ligand in Pd-catalyzed allylic substitution reactions.[4]

In a program directed toward the development of new C_2-symmetric chiral ligands for asymmetric catalysis,[5] we recently prepared a new type of C_2-symmetric phosphine–oxazoline hybrid, bisphosphino-bioxazoline (Phos-Biox **1**).[5b,c] The fidelity of Phos-Biox **1** as a chiral ligand holds throughout the survey of the transition metal-catalyzed asymmetric catalysis. In Rh-catalyzed asymmetric hydrosilylations[5b]

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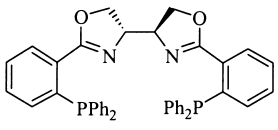
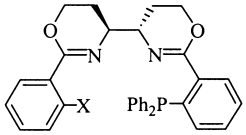
and Pd-catalyzed allylic substitutions[5c] using Phos-Biox **1** as a chiral ligand, up to 97% ee has been achieved in both asymmetric reactions. These results prompted us to investigate C_2-symmetric bisphosphinobioxazine **2a** as a potential six-membered analog of Phos-Biox **1**. The six-membered bioxazine backbone in **2a** has a less planar conformation compared with the five-membered oxazoline ring in bisphosphinobioxazoline **1**. Therefore, the results using **2a** as a chiral ligand may provide additional information on the role of backbone conformation in ligand design, and might lead to further insight into the origin of asymmetric induction. In this paper, the synthesis of phosphinobioxazines **2a**,**b** and their applications as chiral ligands in Pd-catalyzed asymmetric allylic substitutions are described.



1 (Phos-Biox)



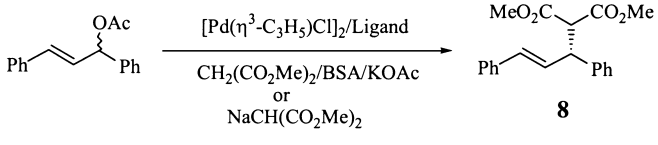
2a : X = PPh_2
2b : X = F

2. Results and discussion

For the synthesis of **2a**,**b**, commercially available *trans*-β-hydromuconic acid was chosen as a starting material, then transformed into TBDMS ether **3** by standard methods (esterification, $LiAlH_4$ reduction and silylation) in a three-step synthesis (overall 70% yield).

The threo diol (*R*,*R*)-**4** was prepared by Sharpless asymmetric dihydroxylation (AD)[6] using $(DHQD)_2PHAL$ as a ligand in 93.5% ee. The ee of **4** was determined by HPLC analysis using a Chiralcel OD column. The diol **4** was efficiently converted into diamine **5** in a similar manner with our previous methods[5a] for **1**. The diamine **5** was transformed into diamide **6** by reaction with *o*-fluorobenzoyl chloride in 93% yield. After deprotection of the TBDMS group with HF/pyridine, the resulting diol was cyclized intramolecularly using triflic anhydride to give bisfluorobioxazine **7**. The reaction of bisfluorobioxazine **7** with potassium diphenylphosphide afforded a mixture of bisphosphinobioxazine **2a** and monophosphinobioxazine **2b** which separated by column chromatography on silica gel to give pure **2a** (33%) and **2b** (20%) (Scheme 1).

To examine the catalytic efficiency of **2a**,**b** as chiral ligands in Pd-catalyzed allylic substitution, the benchmark reaction between *rac*-1,3-diphenyl-2-propenyl acetate and dimethyl malonate has been investigated under standard reaction conditions. The results are summarized in Table 1 in which the results[5c] using Phos-Biox **1** are also included for comparison.



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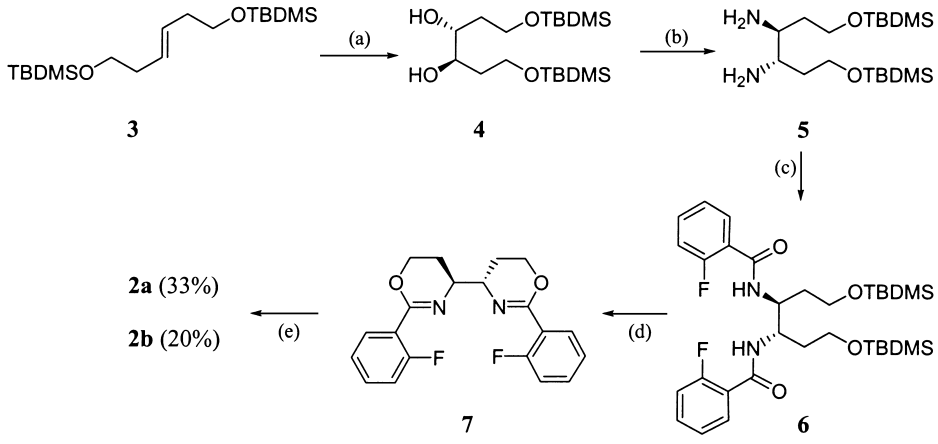
From the data in Table 1, it has been found that the enantioselectivity and reactivity are strongly dependent upon the backbone ring size. The Phos-Biox ligand **1** possessing a five-membered bioxazoline backbone exhibited excellent enantioselectivity and reactivity (entries 1–4).[5c] Whereas, the same allylic substitution reactions using C_2-symmetric phosphinobioxazine **2a** as a chiral ligand afforded lower reactivity and enantioselectivity. Moreover, the reactivity and enantioselectivity are largely dependent



Scheme 1. (a) $(DHQD)_2PHAL$, $OsO_4/K_3Fe(CN)_6/K_2CO_3/CH_3SO_2HN_2/t$-BuOH–$H_2O$ (1/1, v/v) 0°C, 19 h, 93%; (b) (i) $MsCl/Et_3N$, CH_2Cl_2, 0°C, 1 h, 95%; (ii) NaN_3, DMF, 105°C, 20 h, 88%; (iii) Pd–$CaCO_3/H_2$/EtOH, rt, 24 h, 97%; (c) *o*-F-benzoylchloride/Et_3N, CH_2Cl_2, 0°C, 5 h, 95%; (d) (i) HF/pyridine, CH_3CN, rt, 2 h, 80%; (ii) Tf_2O, *i*-Pr_2NEt, −78°C to rt, 5 h, 58%; (e) $KPPh_2$/THF, rt, 1 h, and separation

Table 1
Pd-catalyzed enantioselective allylic alkylation of *rac*-1,3-diphenyl-2-propenyl acetate with dimethyl malonate using **1** and **2a**,**b** as chiral ligands

Entry[a]	Method[c]	Ligand	solvent	Time[d]	Yield (%)[e]	% ee[f] (config)[g]
1[b]	A	**1**	CH_2Cl_2	1 h	>99	95 (*S*)
2[b]	A	**1**	THF	40 min	>99	97 (*S*)
3[b]	B	**1**	CH_2Cl_2	3 h	>99	96 (*S*)
4[b]	B	**1**	THF	4 h	96	94 (*S*)
5	A	**2a**	CH_2Cl_2	26 h	38	82 (*R*)
6	A	**2a**	THF	26 h	66	84 (*R*)
7	B	**2a**	CH_2Cl_2	26 h	<5	-
8	B	**2a**	THF	5 h	99	63 (*R*)
9	A	**2b**	CH_2Cl_2	3 h	>99	94 (*R*)
10	A	**2b**	THF	4 h	>99	95 (*R*)
11	B	**2b**	CH_2Cl_2	4 h	>99	94 (*R*)
12	B	**2b**	THF	20 h	>99	94 (*R*)

[a] The ratio of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$: ligand : substrate was 1 : 2.5 : 400. [b] Results reported in ref 5c. [c] Method A: Reaction of 1 mmol of substrate with the sodium salt prepared from 2 mmol of dimethyl malonate and 1.5 mmol of NaH in 3 mL of solvent. Method B: Reaction of 1 mmol of substrate with 3 mmol of dimethyl malonate, 3 mmol of *N,O*-bis(trimethylsilyl) acetamide(BSA) and 10 μmol of KOAc in 3 mL of solvent. [d] The reaction time in which all of the substrate was consumed. For entries 5~7, the reaction was carried out for 26 h in which the substrate was not consumed completely [e] Isolated yield. [f] Determined by ^1H NMR ($CDCl_3$) analysis with chiral shift reagent $Eu(hfc)_3$. [g] Determined by comparing the sign of the specific rotation.

on the solvent polarity and reaction conditions. The substitution reactions using sodium malonate nucleophile (method A) proceeded very slowly; thus, the reactions were not completed after 26 h in either methylene chloride or THF solvents. However, the reaction in THF afforded a higher yield (66%) than in methylene chloride (38%) with almost the same enantioselectivities (entry 5 vs 6). A more dramatic solvent dependency of the reactivity was observed in dimethyl malonate/BSA conditions (method B). In methylene chloride solvent, only a tiny amount of product **8** was detected by TLC (entry 7). The reaction rate was dramatically increased when the solvent was changed to polar THF which gave **8** in 99% yield with 63% ee within 5 h (entry 8). The large solvent dependency of the reactivity using C_2-symmetric

bisphosphinobioxazine **2a** under dimethyl malonate/BSA conditions cannot be explained simply at the present time. Nevertheless, it seems clear that the decreased reactivity with **2a** compared with Phos-Biox **1** may be related to backbone ring size. It has been found that Phos-Biox **1** formed a *P*,*N*,*N*,*P*-tetradentate complex with Pd(II) in solid and solution states.[5c] Therefore, although the chelation mode of **2a** with Pd metal is not yet clear, we assume that due to the decreased ring strain of the bioxazine, the two nitrogen atoms of the bioxazine ring could be more strongly coordinated to Pd metal than those of the bioxazoline ring in Phos-Biox **1**. Presumably, this stable *P*,*N*,*N*,*P*-tetradentate Pd-**2a** complex decreases the reactivity, since the *P*,*N*,*N*,*P*-tetradentate Pd-complex requires that two of the P,N,N,P dissociate from the Pd metal at the oxidative addition step. The results using monophosphinobioxazine **2b** may provide indirect evidence for this hypothesis. As can be seen in entries 9–12, the allylic substitutions using **2b** afforded **8** in high yields (>99%) and excellent enantioselectivities (94–95% ee).

3. Conclusion

Novel C_2-symmetric bisphosphinobioxazine **2a**, a six-membered analog of bisphosphinobioxazoline **1**, and monophosphinobioxazine **2b** have been successfully synthesized, and their catalytic efficiency for Pd-catalyzed allylic substitutions of *rac*-1,3-diphenyl-2-propenyl acetate have been examined. Our results demonstrated how the reactivity and enantioselectivity of Pd-catalyzed allylic substitutions can be changed by modification of the backbone ring size of the ligand. The concepts used for the design of ligands **2a**,**b** may serve as a guideline for the development of new ligands for asymmetric catalysis. Current efforts are directed toward elucidation of the coordination mode and application of these new chiral phosphinobioxazines to other metal-catalyzed asymmetric catalysis reactions.

4. Experimental

4.1. General procedures

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer with TMS as internal reference. IR spectra were recorded on a MIDAC 101025 FT-IR spectrometer and optical rotations were measured with an Autopol® polarimeter. Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Chemical analyses were carried out by the Advanced Analysis Center at the Korea Institute of Science and Technology. HRMS (FAB) analysis was carried out by the Mass Spectrometry Analysis Group at the Korea Basic Science Institute. All solvents were distilled prior to use. Column chromatography was performed on Kieselgel 60 (230–400 mesh) and TLC was carried out using glass sheets precoated with silica gel 60F 254 purchased from Merck.

4.2. (3R,4R)-1,6-Bis(tert-butyldimethylsilyloxy)-3,4-dihydroxyhexane **4**

In a double jacketed reaction flask attached to a cooling system was placed a mixture of $(DHQD)_2PHAL$ (2.26 g, 2.9 mmol), $K_3Fe(CN)_6$ (28.7 g, 87.1 mmol), K_2CO_3 (12.03 g, 87.1 mmol), methanesulfonamide (2.76 g, 29.0 mmol) in *tert*-butanol:water (70:70 mL). The mixture was stirred at 0°C for 1 h. Osmium tetroxide (1.85 mL, 0.29 mmol, 4% OsO_4 in water) was added. After 30 min stirring, *trans*-1,6-bis(*tert*-butyldimethylsilyloxy)-3-hexene (10.0 g, 29.0 mmol) was added, and then stirred for a further 19 h. The reaction was quenched with sodium metabisulfite. After stirring for

an additional 2 h at room temperature, the organic layer was extracted with ethyl acetate, dried, filtered, and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate:*n*-hexane=1:4, v/v) giving **4** (10.2 g, 93%) with 93.5% ee. The enantiomeric excess was determined by HPLC analysis of the corresponding (3*R*,4*R*)-1,6-bis(*tert*-butyldiphenylsilyloxy)-3,4-dihydroxyhexane (in order to use the UV detector, the TBDMS group was converted to the TBDPS group) using a Chiralcel OD chiral column [eluent: *n*-hexane:*i*-propanol=97:3; flow rate: 0.8 mL/min; retention times (3*S*,4*S*)-isomer: 10.9 min, (3*R*,4*R*)-isomer: 14.2 min]. R_f 0.2; $[\alpha]_D$=+19.4 (*c* 1.05, CH_3OH); mp 32–33°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (m, 4H), 3.72 (m, 2H), 3.41 (d, *J*=3.2 Hz, 2H), 1.74 (m, 4H), 0.90 (s, 18H), 0.08 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 72.77, 61.12, 35.48, 25.81, 18.04, −5.56; IR (KBr) 3424, 1472, 1256, 1094, 836 cm^{-1}.

*4.3. (3*R,*4*R*)-1,6-Bis(*tert*-butyldimethylsilyloxy)-3,4-[*O,O′*-di(methanesulfonyl)]dihydroxyhexane*

To a stirred solution of triethylamine (7.2 mL, 5.5 mmol) and dihydroxyhexane **4** (8.47 g, 22.4 mmol) in dry methylene chloride (130 mL) was added methanesulfonyl chloride (3.64 mL, 43.0 mmol) in a dropwise manner using a syringe at −76°C for 1 h and the mixture was stirred for 16 h at room temperature. The reaction mixture was diluted with ethyl ether, and washed with saturated NH_4Cl solution. The organic layer was dried ($MgSO_4$), and concentrated. The residue was solidified in *n*-hexane, then purified by recrystallization with *n*-hexane:ethyl acetate (2:1, v/v) to give dimesylate (11.4 g, 95%) as a white crystal. R_f 0.5; $[\alpha]_D$=+4.1 (*c* 1.01, CH_3OH); mp 99–100°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (m, 2H), 3.78 (m, 4H), 3.07 (s, 6H), 1.95 (m, 4H), 0.88 (s, 18H), 0.06 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 78.18, 57.96, 38.26, 33.27, 25.69, 18.18, −5.47; IR (KBr) 2958, 1348, 1184, 1098, 938, 832, 774, 538 cm^{-1}; HRMS (FAB, *m*-nitrobenzyl alcohol matrix) calcd for $C_{20}H_{47}O_8S_2Si_2$: $[M+H]^+$ (base peak): 535.2251. Found: 535.2245.

*4.4. (3*S,*4*S*)-1,6-Bis(*tert*-butyldimethylsilyloxy)-3,4-diazidohexane*

A stirred mixture of dimesylate (3*R*,4*R*)-1,6-bis(*tert*-butyldimethylsilyloxy)-3,4-[*O,O′*-di(methanesulfonyl)]dihydroxyhexane (7.82 g, 14.6 mmol) and NaN_3 (4.75 g, 73.1 mmol) in DMF (40 mL) was reacted at 100–105°C for 20 h. The reaction mixture was allowed to cool to room temperature and diluted with ethyl ether. The precipitated white solid was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate:*n*-hexane=1:20) to afford diazide (5.5 g, 88%) as a colorless oil. R_f 0.8; $[\alpha]_D$=−53.1 (*c* 1.26, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (t, *J*=5.9 Hz, 4H), 3.61 (m, 2H), 1.84 (m, 4H), 0.90 (s, 18H), 0.08 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.24, 59.19, 34.21, 25.73, 18.23, −5.49; IR (KBr) 2956, 2108, 1472, 1258, 1106, 838 cm^{-1}.

*4.5. (3*S,*4*S*)-1,6-Bis(*tert*-butyldimethylsilyloxy)-3,4-diaminohexane **5***

To a solution of diazide (3*S*,4*S*)-1,6-bis(*tert*-butyldimethylsilyloxy)-3,4-diazidohexane (2.91 g, 6.8 mmol) in ethanol (45 mL) was added the Lindlar catalyst (2 g, 5% $Pd/CaCO_3$). The mixture was hydrogenated under atmosphere pressure at room temperature for 5 h. The catalyst was then removed by filtration over Celite, and the filtrate was evaporated under reduced pressure to afford diamine **5** (2.5 g, 97%). $[\alpha]_D$=−10.9 (*c* 1.1, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (m, 4H), 2.83 (m, 2H), 2.17 (s, 2H), 1.70 (m, 2H), 1.56 (m, 2H), 0.89 (s, 18H), 0.057 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$)

δ 60.85, 53.27, 37.13, 26.24, 18.07, −5.47; IR (KBr) 2954, 1471, 1255 1096, 836 cm^{-1}; HRMS (FAB, PEG matrix) calcd for $C_{18}H_{45}N_2O_2Si_2$: $[M+H]^+$ (base peak): 377.3023. Found: 377.3020.

4.6. *(3*S*,4*S*)-1,6-Bis(*tert*-butyldimethylsilyloxy)-3,4-[*N,N′*-di(*o*-fluorobenzoyl)]diaminohexane **6**

A solution of (3*S*,4*S*)-1,6-bis(*tert*-butyldimethylsilyloxy)-3,4-diaminohexane **5** (3.38 g, 9.0 mmol) and triethylamine (3.2 mL, 122.6 mmol) in dry methylene chloride was cooled to −76°C under nitrogen. *o*-Fluorobenzoyl chloride (3.57 g, 22.5 mmol) was added dropwise over 30 min, then the reaction mixture was allowed to warm to room temperature. After stirring for 12 h at room temperature, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution. The organic layer was separated and dried with $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (ethyl acetate:*n*-hexane=1:4) to give the white solid (5.3 g, 95%). $[\alpha]_D$=−36.3 (*c* 1.0, $CHCl_3$); mp 64–65°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (m, 2H), 7.37 (m, 2H), 7.21–6.99 (m, 6H), 4.46 (m, 2H), 3.76 (t, *J*=5.8 Hz, 4H), 2.03 (m, 2H), 1.85 (m, 2H), 0.83 (s, 18H), 0.01 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.01, 161.94, 158.65, 132.86, 131.54, 124.50, 121.94, 116.16, 115.82, 60.11, 51.18, 35.03, 25.92, 18.25, −5.46.

4.7. *(3*S*,4*S*)-3,4-[*N,N′*-Bis(*o*-fluorobenzoyl)]diamino-1,6-hexanediol*

A solution of **6** (2 g, 3.2 mmol) and HF–pyridine (30%, v/v) in CH_3CN (15 mL) was stirred at room temperature for 2 h. After completion of the reaction, the reaction mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by recrystallization with *n*-hexane to give the diol (1.0 g, 80%). $[\alpha]_D$=−76.6 (*c* 1.02, CH_3OH); mp 153–154°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (m, 2H), 7.72 (m, 2H), 7.48 (m, 2H), 7.27 (t, *J*=8.1 Hz, 2H), 7.18 (m, 2H), 4.52 (m, 2H), 3.77 (m, 4H), 2.98 (s, 2H), 2.09 (m, 2H), 1.77 (m, 2H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 165.49, 160.78 (d, J_{C-F}=248.7 Hz), 133.59 (d, *J*=8.5 Hz), 131.58, 125.32, 124.14 (d, *J*=13.4 Hz), 116.83 (d, *J*=23.3 Hz), 59.29, 51.51, 36.01.

4.8. *(4*S*,4′*S*)-2,2′-Bis(*o*-fluorophenyl)-5,5′,6,6′-tetrahydro-4,4′-bi(1,3-ozazine) **7***

To a stirred solution of (3*S*,4*S*)-3,4-[*N*,*N′*-bis(*o*-fluorobenzoyl)]diamino-1,6-hexanediol (1.88 g, 4.8 mmol) in dry methylene chloride (150 mL) was added *N*,*N*-diisopropyl ethyl amine (1.86 mL, 10.7 mmol), and the reaction temperature was cooled to −78°C. To this solution was added Tf_2O (1.71 mL, 10.2 mmol) in a dropwise manner using a syringe pump for 30 min. The mixture was stirred for 4 h at the same temperature. After stirring for an additional 5 h at room temperature, the reaction was quenched by addition of 1% aqueous HCl solution. The organic layer was washed with saturated aqueous $NaHCO_3$ solution, dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel to give bisfluorobioxazine **7** (0.99 g, 58%). $[\alpha]_D$=−62.9 (*c* 0.68, $CHCl_3$); mp 71–72°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (t, *J*=7.6 Hz, 2H), 7.39 (m, 2H), 7.14 (m, 4H), 4.52 (m, 2H), 4.37 (ddd, *J*=3.5, 3.8, 3.2 Hz, 2H), 4.03 (m, 2H), 2.05 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.66 (d, J_{C-F}=252.66 Hz), 154.35, 131.54 (d, *J*=9.1 Hz), 130.54, 123.73, 123.09 (d, *J*=11.3 Hz), 116.44 (d, *J*=22.4 Hz), 65.48, 56.13, 22.20.

4.9. (4S,4′S)-2,2′-Bis(o-diphenylphosphinophenyl)-5,5′,6,6′-tetrahydro-4,4′-bi(1,3-ozazine) **2a** and (4S,4′S)-2-(o-diphenylphosphinophenyl)-2′-(o-fluorophenyl)-5,5′,6,6′-tetrahydro-4,4′-bi(1,3-ozazine) **2b**

To a solution of bisfluorobioxazine **7** (0.68 g, 1.9 mmol) in dry THF (8 mL) was added a solution of potassium diphenylphosphide (0.5 M in THF, 7.6 mL, 3.82 mmol) at 0°C. After 1 h stirring at room temperature, the reaction was quenched by addition of water (25 mL), and extracted with methylene chloride (50 mL×2). The combined organic layer was dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by chromatography on silica gel (*n*-hexane:ethyl acetate=3:1) to give bisphosphinobioxazine **2a** (0.43 g, 33%) and monophosphinobioxazine **2b** (0.2 g, 20%). **2a**: R_f 0.34; $[\alpha]_D^{24}$ −122.6 (*c* 0.53, $CHCl_3$); mp 134–135°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75–7.69 (m, 2H), 7.38–7.20 (m, 24H), 6.85–6.78 (m, 2H), 4.10–4.04 (m, 2H), 3.77 (td, *J*=11.0, 3.8 Hz, 2H), 3.60–3.52 (m, 2H), 1.30–1.11 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.82, 139.60–128.10 (aromatic carbon signals), 65.37, 55.84, 21.00; ^{31}P NMR (121 MHz, $CDCl_3$, triphenylphosphine as an external standard) δ −2.61; HRMS (FAB) calcd for $C_{44}H_{39}N_2O_2P_2$ [(M+H)$^+$]: 689.2487. Found: 689.2499. **2b**: R_f 0.17; $[\alpha]_D^{24}$ −104.2 (*c* 0.52, $CHCl_3$); mp 64–65°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84–7.81 (m, 1H), 7.69–7.64 (m, 1H), 7.50–7.20 (m, 13H), 7.15–7.0 (m, 2H), 6.95–6.85 (m, 1H), 4.40–4.20 (m, 2H), 3.9–3.7 (m, 2H), 1.90–1.80 (m, 1H), 1.75–1.50 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.32, 158.95, 156.20, 154.21, 139.54–116.28 (aromatic carbon signals), 65.70, 65.20, 56.12, 55.80, 21.68, 21.51; ^{31}P NMR (121 MHz, $CDCl_3$, triphenylphosphine as an external standard) δ −2.35; HRMS (FAB) calcd for $C_{32}H_{29}FN_2O_2P$ [(M+H)$^+$]: 523.1951. Found: 523.1957.

4.10. General procedure for the palladium-catalyzed allylic substitutions of rac-1,3-diphenyl-2-propenyl acetate with dimethyl malonate

In a Schlenk tube, 4 mol of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ and 10 μmol of phosphinobioxazine ligand **2** were dissolved in solvent (1 mL) as indicated in Table 1, degassed, and then stirred for 1 h at 25°C under an atmosphere of argon. To this solution were successively added *rac*-1,3-diphenyl-2-propenyl acetate (100 mg, 0.4 mmol) and a solution of nucleophile, generated in situ from dimethyl malonate (100 mg, 0.8 mmol) and base [NaH (35 mg, 0.87 mmol) or BSA (240 mg, 1.2 mmol)] in a solvent (1 mL) at 25°C. After completion of the reaction, the reaction mixture was diluted with methylene chloride (20 mL) and poured into a cold saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with methylene chloride (3×10 mL). The combined organic layer was dried over anhydrous $MgSO_4$, and the solvent was evaporated. The crude product was purified by preparative TLC (ethyl acetate:*n*-hexane=1:4, R_f 0.4) to give the pure product. The enantiomeric purities were determined by the ^{1}H NMR spectra measured in the presence of Eu(hfc)$_3$. When 0.8 equiv. of Eu(hfc)$_3$ was added, one of the two methyl ester signals appearing at δ 3.70 was split into two peaks: (*R*)-enantiomer at δ 3.99, (*S*)-enantiomer at δ 3.93. The yields and enantioselectivities are given in Table 1.

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