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HetPHOX: a new class of easily prepared modular chiral ligands

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Abstract—The synthesis of a new class of modular chiral phosphino-oxazoline ligands containing the diphenylphosphino group at different positions of the heterocyclic backbone is described. HetPHOX ligands were tested in enantioselective allylations and in transfer hydrogenation reactions. The synthesis of the ligands is facile with high enantioselectivity (99% ee) obtained in the Pd-catalyzed addition of malonate to diphenylallyl acetate using ligand **10**.

1. Introduction

Chiral phosphino-oxazoline ligands **1** (PHOX; Fig. 1) represent a class of well established ligands, which have been used in a variety of asymmetric catalytic transformations.[1] Diversity was exploited by the synthesis of different scaffolds coupled with several phosphorus groups.[2] In order to further expand the library of modular PN ligands,[3] we became interested in heterocyclic rings.[4] The advantage of having a choice between electron-rich or electron-deficient ring systems in conjunction with the facile and regioselective metallation[5] make heterocyclic scaffolds valuable.[6] We have prepared a series of heterocyclic phosphino-oxazolines (HetPHOX) and applied them in the enantioselective Ir-promoted hydrogenation of unfunctionalized alkenes[7] as well as a Pd-catalyzed Heck reaction.[8] For both of the cited examples HetPHOX ligands performed as well as PHOX and, in certain instances, the new ligands turned out to be superior. Herein, we report the use of these new ligands in two standard PHOX catalyzed reactions; (i) the asymmetric transfer hydrogenation of acetophenone and (ii) the asymmetric allylation of 1,3-diphenylallyl acetate with malonate.

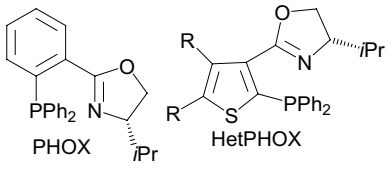

Figure 1.

2. Results and discussion

For these studies, we have selected HetPHOX ligands obtained from thiophene and benzo[*b*]thiophene as backbone templates. In addition, we were interested in changing the relative position of the phosphine and oxazoline group on the heterocyclic ring.

In the case of ligands with a thiophene backbone, we started from 2-cyano-thiophene, which was converted into oxazolines **2** and **3** as previously reported.[9] Selective metallation of **2** and **3** at the 3-position with Et_2O as solvent[10] and introduction of the Ph_2P group took place without any difficulties giving the desired ligands **4** and **5** (Scheme 1).

For the syntheses of the benzo[*b*]thiophene derivatives a different methodology was applied. Benzo[*b*]thiophene was brominated at the 3-position and converted to the corresponding benzothiophene carboxylic acid by trapping the Grignard reagent with CO_2. The latter was transformed into the 3-oxazolines **6**, **10** and **11** using standard reaction conditions (Scheme 2).[11]

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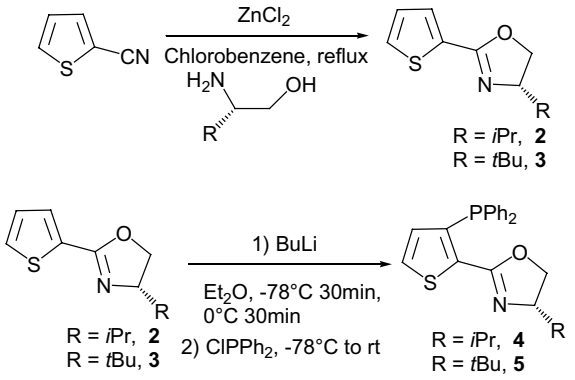
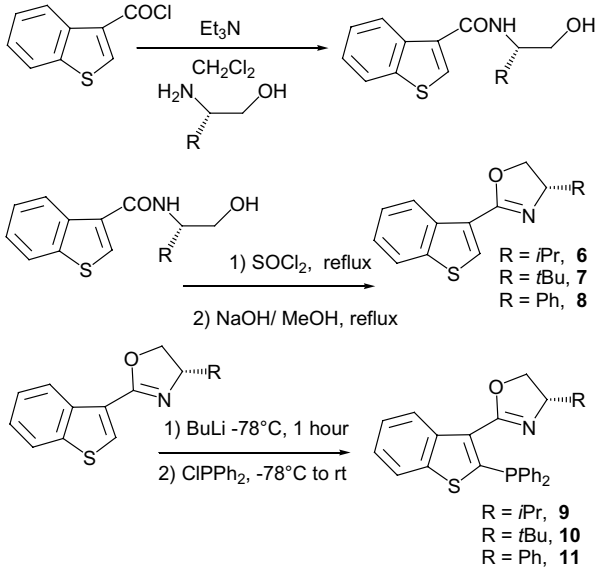


Scheme 1.



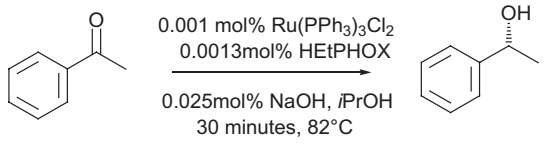
Scheme 2.

Metallation in the 2-position with *n*-BuLi proved easy and treatment of the lithiated species with Ph_2PCl afforded the desired phosphino-oxazoline ligands **9**, **10** and **11** in good yields.

It is worthy of note that the relatively high acidity of thiophene and benzo[*b*]thiophene allows the preparation of phosphino-oxazolines by direct metallation, whereas for the preparation of PHOX ligands usually required an exchange reaction between a bromo derivative. This can be a considerable advantage in the synthetic design of substituted thiophene or benzo[*b*]thiophene phosphino-oxazoline ligands.

Thiophene ligand **5** and benzo[*b*]thiophene derivatives **9**, **10** and **11** were evaluated in a catalytic enantioselective transfer hydrogenation reaction.[12] The use of PHOX ligand **1** in transfer hydrogenation reactions has previously been reported by Langer and Helmchen in 1996.[13] The catalyst was prepared in situ by mixing PHOX and $RuCl_2(PPh_3)_3$ with the complex able to reduce acetophenone within 30 min. The corresponding alcohol was isolated with an enantiomeric excess of 85%.

In order to compare HetPHOX with PHOX, we chose acetophenone as the substrate for the reduction following Helmchen's protocol. All reactions were stopped after 30 min (Scheme 3). It can be seen from the data reported in Table 1 that HetPHOX ligands derived from benzo[*b*]thiophene displayed diminished activity in this reaction when compared to PHOX ligands.



Scheme 3.

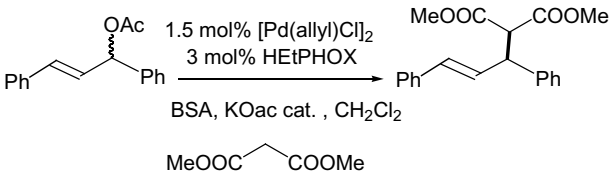
Table 1. Enantioselective reduction of acetophenone via transfer hydrogenation catalyzed by RuHetPHOX

Ligand	Yield[a]	Ee[b]
1	81	85[c]
1	84	79[c]
5	82	66
5	22	99[d]
9	47	89
10	27	81
11	24	70

[a] Isolated yields after chromatographic purification. All the reactions were stopped after 30 min.
[b] The enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OD).
[c] The reaction time was 60 min.
[d] The reaction was run at room temperature.

Although the alcohol could be isolated with an excellent enantiomeric excess, the Ru-complex derived from ligand **5** showed a low catalytic activity at room temperature. However, when the reaction was performed at reflux, the activity of the thiophene based oxazoline was similar to PHOX, but the enatiomeric excess of the product was slightly inferior.

Another comparison between the performances of our HetPHOX ligands and the PHOX ligands was studied by considering the well established palladium-catalyzed allylic alkylations of diphenylallyl acetate with dimethyl malonate (Scheme 4). As a matter of fact, PHOX ligands such as **1** have been reported to give high enantiomeric excesses in this reaction.[14] The required palladium complexes were prepared in situ by mixing $[Pd(C_3H_3)Cl]_2$ with the phosphino-oxazolines **4**, **5**, **9**, **10** and **11**, respectively, in CH_2Cl_2 at room temperature, and then allylation performed following Trost's protocol.[15]



Scheme 4.

From the data reported in Table 2, the HetPHOX ligands derived from thiophene or benzo[*b*]thiophene are both capable of inducing high enantiomeric excesses in this reaction.

Table 2. Catalytic enantioselective allylation promoted by HetPHOX ligands

Entry	Ligand	Yield[a]	Ee[b]	Time (h)
1	**4**	90	95	0.5
2	**5**	30	80	3
3	**5**	50	80	16
5	**9**	82	94	3
6	**10**	72	99	16
7	**11**	62	97	16

[a] Yields after chromatographic purification.

[b] The enantiomeric excess was determined by chiral HPLC analysis chiralcel OD with hexane/isopropanol 99.5:0.5 as the eluent. The absolute configuration of the product was established by comparison with reported analytical data.

Differences in the reactivity of ligands **4** and **9** can be attributed to the different electronic properties of the thiophene and benzo[*b*]thiophene moiety.[16] It is well known that it is possible to modulate the electron-donor properties of the phosphorus atom by changing the supporting heterocyclic system.[16] This tuning is also influenced by the relative positions of the phosphine and oxazoline group on the thiophene and benzo[*b*]thiophene backbone, respectively, and may be responsible for the differences in reactivity exhibited by the palladium complexes.

3. Conclusions

In conclusion, we have described a facile synthesis of a new type of phosphino-oxazoline ligands. Clearly, this new class of PN ligands needs to be further evaluated in different reactions, where the electron-rich or electron-poor nature of the heterocyclic scaffold can play a decisive role in controlling the reaction rate and enantioselectivity.[17] The large variety of heterocyclic scaffolds, which can be used to prepare tailored HetPHOX ligands adds further value to this new ligand family. Further studies on different C–C bond forming reactions are currently under investigation and will be disclosed in due time.

4. Experimental

4.1. General procedures

^{1}H NMR spectra were recorded on Varian 200 MHz, Varian 300 MHz or Brucker 300 MHz spectrometer. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: δ 7.27 ppm). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian 50 MHz or Varian 75 MHz spectrometer with proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent as internal standard (deuterochloroform: δ 77.0 ppm). Mass spectra were performed at an ionizing voltage of 70 eV. Chromatographic purification was done with 240–400 mesh silica gel (Merck). Analytical gas chromatography (GC) was performed on a Hewlett–Packard HP 6890 gas chromatograph with a flame ionization detector and split mode capillary injection system, using a Cross-linked 5% PHME Siloxane (30 m) column or a Megadex5 chiral (25 m) column. Analytical high performance liquid chromatography (HPLC) was performed on a HP 1090 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp 190–600 nm), using a Daicel Chiralcel™ OD column (0.46 cm I.D. × 25 cm). HPLC grade isopropanol and hexane were used as the eluting solvents. Elemental analyses were carried out using a EACE 1110 CHNOS analyzer. All reactions were carried out under a nitrogen atmosphere in flame-dried glassware using standard inert techniques for introducing reagents and solvents. Acetophenone was distilled prior to use. All other commercially obtained reagents were used as received. Anhydrous CH_2Cl_2, THF and Et_2O, were purchased from Fluka. BuLi 1.6 M in hexane and BuLi 2.5 M in hexane were purchased from Aldrich. Thiophene-2-yl-4-*iso*-propyl-4,5-dihydro-oxazoline **2** and thiophene-2-yl-4-*tert*-butyl-4,5-dihydro-oxazoline **3** were prepared as described in literature.[7] 4-*iso*-Propyl-2-(3-diphenyl-phosphino-thiophene-2-yl)-4,5-dihydrooxazole and 4-*tert*-butyl-2-(3-diphenylphosphino-thiophene-2-yl)-4,5-dihydrooxazole were prepared as described.[8,17]

4.1.1. 2-Benzo[*b*]thiophene-3-yl-4-*iso*-propyl-4,5-dihydro-oxazole 6. A solution of (*S*)-valinol (4.41 g, 42.7 mmol) and triethylamine (6.63 mL, 47.0 mmol) in CH_2Cl_2 (120 mL) was cooled to 0 °C, and then a solution of benzo[*b*]thiophene-3-carboxylchloride (8.40 g, 42.7 mmol) in CH_2Cl_2 (120 mL) added dropwise within 30 min. The mixture was stirred at room temperature overnight. The formed precipitate was dissolved completely by adding 700 mL of CH_2Cl_2, and then washed with a solution of 1 M HCl (500 mL). The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The crude solid was re-crystallized from CH_2Cl_2/hexane to give a colourless product (9.30 g, 83%). The amide (9.30 g, 35.5 mmol) was dissolved in CH_2Cl_2 (145 mL) and $SOCl_2$ (6.33 mL, 86.1 mmol) then added. The solution was stirred for 2 h at 70 °C and then allowed to cool to room temperature. A saturated solution of $NaHCO_3$ (150 mL) was added and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 80 mL) and the organic phases combined, dried over Na_2SO_4 and evaporated under reduced pressure to give a colourless solid (9.68 g, 97%). The benzo[*b*]thiophene 3-(1-chloromethyl-2-methyl-propyl)carboxyamide (9.68 g, 34.4 mmol) was dissolved in MeOH (200 mL) and then a solution of NaOH (1.44 g, 36.1 mmol) in MeOH (50 mL) added. The resulting mixture was stirred for 2 h at 70 °C. The MeOH was then evaporated under reduced pressure and

the residue treated with CH_2Cl_2 (300 mL). The resulting solution was extracted with a saturated solution of $NaHCO_3$ (150 mL). The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure to give an oil, which was purified by chromatography (hexane/AcOEt 7:3). Yield 7.4 g, 84%. $C_{14}H_{15}NOS$ Fw = 245.34. $[\alpha]_D = -45.0$ (*c* 1.09, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 0.99 (d, 3H, $J = 6.7$ Hz); 1.11 (d, 3H, $J = 6.7$ Hz); 1.90 (sept, 1H, $J = 6.7$ Hz); 4.11 (dd, 1H, $J = 7.6$, 15.2 Hz); 4.16–4.23 (m, 1H); 4.38 (dd, 1H, $J = 7.4$, 9.1 Hz); 7.37–7.52 (m, 2H); 7.82–7.90 (m, 1H); 8.07 (s, 1H); 8.78–8.83 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.7; 19.2; 33.3; 69.4; 73.3; 122.6; 125.1; 125.3; 125.5; 131.9; 137.1; 140.3; 159.3. GC–MS: 245 (M^+, 15); 202 (100); 174 (28); 147 (32). Element. Anal. Calcd for $C_{14}H_{15}NOS$: C, 68.54; H, 6.16; N, 5.71. Found: C, 68.51; H, 6.13; N, 5.68.

4.1.2. 2-Benzo[*b*]thiophene-3-yl-4-*tert*-butyl-4,5-dihydrooxazole 7. Compound **7** was prepared following the procedure described for compound **6**. Yield 0.8 g, 70%. $C_{15}H_{17}NOS$ Fw = 259.37. $[\alpha]_D = -56.1$ (*c* 0.9, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 1.02 (s, 9H); 4.11–4.23 (m, 2H); 7.37–7.52 (m, 2H); 7.87 (d, 2H, $J = 8.2$ Hz); 8.08 (s, 1H); 8.79 (d, 1H, $J = 7.9$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 26.2; 34.3; 67.8; 122.6; 124.7; 125.1; 125.3; 125.5; 131.8; 137.2; 140.3; 159.1. GC–MS 260 ($[M+1]^+$, 100); 386 (61); 358 (100); 239 (30). Element. Anal. Calcd for $C_{15}H_{17}NOS$: C, 69.46; H, 6.61; N, 5.40. Found: C, 69.43; H, 6.58; N, 5.38.

4.1.3. 2-Benzo[*b*]thiophene-3-yl-4-phenyl-4,5-dihydrooxazole 8. Compound **8** was prepared following the procedure described for compound **6**. Yield 1.35 g, 84%. $C_{17}H_{13}NOS$ Fw = 279.36. $[\alpha]_D = -55$ (*c* 0.67, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 4.24 (dd, 1H, $J = 8.1$, 8.1Hz); 4.77 (dd, 1H, $J = 8.2$, 10.1 Hz); 5.51 (dd, 1H, $J = 8.2$, 10.0 Hz); 7.30–7.35 (m, 7H); 7.82–7.92 (m, 1H); 8.22 (s, 1H); 8.87–8.92 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 70.7; 74.0; 126.2; 124.3; 125.3; 125.4; 125.6; 127.0; 127.8; 129.0; 132.8; 137.0; 140.3; 142.8; 160.8. GC–MS 280 ($[M+1]^+$. Element. Anal. Calcd for: $C_{17}H_{13}NOS$: C, 73.09; H, 6.08; N, 5.01. Found: C, 73.05; H, 6.10; N, 5.66.

4.1.4. 2-(2-Diphenylphosphino)-benzo[*b*]thiophene-3-yl-4-*iso*-propyl-4,5-dihydrooxazole 9. To a solution of benzo[*b*]thiophene oxazoline **6** (0.92 g, 3.83 mmol.) in Et_2O (10 mL) at −78 °C, a solution of 1.6 M BuLi in hexane (2.63 mL, 4.20 mmol) was added and the resulting suspension agitated at −78 °C for 1.5 h. Diphenylchlorophosphine (0.69 mL, 3.83 mmol) was added at −78 °C, and the reaction mixture warmed to room temperature and stirred for 30 min. The reaction was quenched by adding water (30 mL) and pentane (40 mL). The organic layer was separated, dried over Na_2SO_4 and purified by chromatography (hexane/ether 9:1). Yield 0.754 g, 79%. $C_{26}H_{24}NOPS$ Fw = 429.51. $[\alpha]_D = -74.0$. (*c* 0.96, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 0.8 (d, 3H, $J = 6.8$ Hz); 0.90 (d, 3H, $J = 6.8$, 7.6 Hz); 1.69 (sept, 1H, $J = 6.8$ Hz); 3.88 (dd, 1H, $J = 7.6$, 7.8 Hz);. 3.95–4.04 (m, 1H); 4.16 (dd, 1H, $J = 7.6$, 8.9 Hz); 7.28–7.49 (m, 12H); 7.65–7.69 (m, 1H); 8.57 (d, 1H, $J = 8.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.7; 19.0; 32.9; 69.5; 72.5; 121.8; 124.6; 124.7 (d, $J = 1.4$ Hz); 124.9; 128.0 (d, $J = 16.3$ Hz); 128.3 (d, $J = 7.5$ Hz); 128.4 (d, $J = 7.5$ Hz); 129.1; 129.2; 133.5 (d, $J = 21.2$ Hz); 134.0 (d, $J = 21.2$ Hz); 136.9 (d, $J = 39.4$ Hz); 137.0 (d, $J = 40.1$ Hz); 139.5; 141.8; 147.6 (d, $J = 42.1$ Hz); 159.54. ^{31}P (124 MHz, $CDCl_3$): δ −12.4. GC–MS 429 (M^+, 4); 358 (100); 338 (48); 239 (40); 41 (50). Element. Anal. Calcd for $C_{26}H_{24}NOPS$: C, 72.71; H, 5.63; N, 3.26. Found: C, 72.68; H, 5.60; N, 3.28.

4.1.5. 2-(2-Diphenylphosphino)-benzo[*b*]thiophene-3-yl-4-*tert*-butyl-4,5-dihydrooxazole 10. Compound **10** was prepared following the procedure described for compound **9**. Yield 0.638 g, 52%. $C_{27}H_{26}NOPS$ Fw = 443.54. $[\alpha]_D = -52.9$ (*c* 1.04, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 0.81 (s, 9H); 3.90–5.15 (m, 3H); 7.27–7.46 (m, 12H); 7.64–7.69 (m, 1H); 8.56–8.62 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.0; 34.0; 68.2; 76.3; 121.8; 124.9; 125.0; 125.1; 125.2; 128.6 (d, $J = 7.7$ Hz); 129.4 (d, $J = 15.5$ Hz); 133.7 (d, $J = 20.7$ Hz); 134.2 (d, $J = 20.7$ Hz); 137.1 (d, $J = 29.4$ Hz); 137.5 (d, $J = 30.4$ Hz); 139.8; 142.1; 147.9; (d, $J = 42.5$ Hz); 159.8. ^{31}P (124 MHz, $CDCl_3$): δ −12.4. GC–MS 443 (M^+, 6); 386 (61); 358 (100); 239 (30). Element. Anal. Calcd for $C_{27}H_{26}NOPS$: C, 73.11; H, 5.91; N, 3.16. Found: C, 73.13; H, 5.92; N, 3.15.

4.1.6. 2-(2-Diphenylphosphino)-benzo[*b*]thiophene-3-yl-4-phenyl-4,5-dihydrooxazole 11. Compound **11** was prepared following the procedure described for compound **9**. Yield 0.89 g, 52%. $C_{29}H_{22}NOPS$ Fw = 463.54. $[\alpha]_D = -5.4$ (*c* 0.92, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 3.96 (dd, 1H, $J = 8.3$, 8.3 Hz); 4.56 (dd, 1H, $J = 8.3$, 10.3 Hz); 5.34 (dd, 1H, $J = 8.8$, 10.3 Hz); 7.04–7.09 (m, 2H); 7.22–7.52 (m, 15H); 7.58–7.72 (m, 1H); 8.60–8.66 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 70.1; 74.1; 121.7; 125.0; 125.1; 125.3; 126.9; 127.5; 127.8; 128.7; 128.8 (d, $J = 7.7$ Hz); 129.6 (d, $J = 10.9$ Hz); 133,9 (d, $J = 21.3$ Hz); 134.3 (d, $J = 1.3$ Hz); 137.0 ($J = 20.6$ Hz); 137.2 (d, $J = 16.6$ Hz); 139.8; 142.0; 142.6; 148.9 (d, $J = 42.8$ Hz); 161.3. ^{31}P (124 MHz, $CDCl_3$): δ −12.4. GC–MS 463 (M^+, 4); 358 (100); 296 (12); 239 (18). Element. Anal. Calcd for $C_{27}H_{22}NOPS$: C, 75.14; H, 4.78; N, 3.02. Found: C, 75.15; H, 4.80; N, 3.06.

4.1.7. Catalytic enantioselective reduction of acetophenone with Ru(HetPHOX). $Ru(PPh)_3Cl_2$ (9 mg, 0.01 mmol) and the HetPHOX ligand (0.013 mmol) were dissolved under an inert atmosphere in a flask containing dried and degassed *i*PrOH (5 mL). The flask was heated at reflux for 30 min, and then a solution of acetophenone (10 mmol) in *i*PrOH (3 mL) added. The mixture was stirred for 15 min and then a solution of NaOH (10 mg, 0.25 mmol) in 2 mL of *i*PrOH added and the mixture stirred for 30 min. The solvent was evapo-

rated under reduced pressure and the residue purified by column chromatography (hexane/ethylacetate 9:1).

4.1.8. Catalytic enantioselective allylation reaction. $[Pd(allyl)Cl]_2$ (3.6 mg, 0.01 mmol) and the HetPHOX ligand (0.025 mmol) were added to a reaction flask, which contained degassed CH_2Cl_2. The mixture was stirred at room temperature for 30 min. 1,3-Diphenyl-allyl acetate (1 mmol), BSA (3 mmol) and dimethyl malonate (3 mmol) were added to the reaction flask, followed by a catalytic amount of CH_3COOK (1 mg). The mixture was degassed through a freezing-pump cycle and then the reaction mixture stirred at room temperature for 3–16 h. The solvent was evaporated and the reaction mixture purified directly by chromatography (cyclohexane/ethylacetate 9:1) to give a clear oil.

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