Electronic Supplementary Material (ESI) for Chemical Communications.

Supporting Information

Effector enhanced enantioselective hydroformylation

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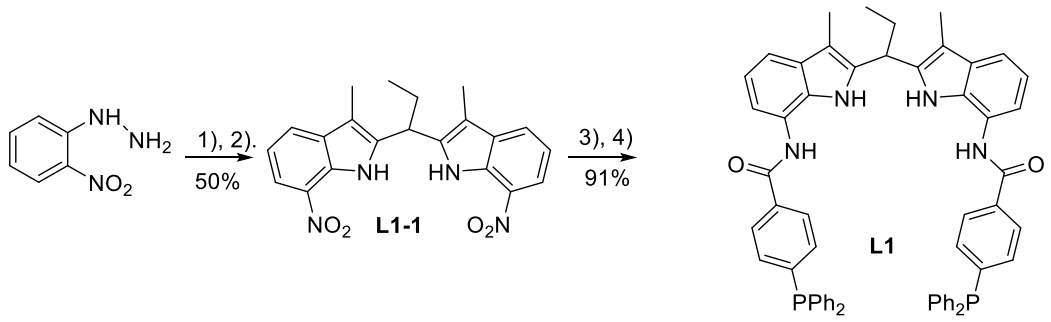
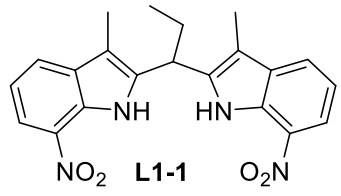
General Information

All reactions involving air- or moisture sensitive materials were carried out under nitrogen atmosphere using standard Schlenk techniques or in Glove-box. THF, pentane, hexane and toluene were distilled from sodium-benzophenone under nitrogen atmosphere; dichloromethane, methanol were distilled from CaH_2 under nitrogen atmosphere; triethylamine was distilled from KOH pellets under nitrogen. Toluene-d8, CD_2Cl_2 and *N,N*-diisopropylethylamine were dried over molecular sieves (3Å) and degassed by three freeze-pump-thaw cycles. ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, $^{1}H\{^{31}P\}$ NMR experiments were performed on Bruker AMX 300 MHz, Bruker AMX 400 MHz or Bruker AMX 500 MHz. ^{1}H NMR chemical shifts are given in ppm, and were calibrated by using the residual solvent as internal reference ($CHCl_3$ 7.26 ppm, CH_2Cl_2 5.32 ppm). ^{13}C NMR chemical shifts were reported in ppm with the solvent peaks used as internal reference ($CHCl_3$ 77.16 ppm, CH_2Cl_2 53.84 ppm). Mass spectra were collected on an AccuTOF GC v 4g, JMS-T100GCV Mass spectrometer (JEOL, Japan). If not stated otherwise, syngas referred to a 1:1 mixture of H_2 and CO, and the pressure refers to a sum pressure of both. All reagents were purchased from commercial suppliers and used without further purification, unless otherwise noted.

Synthesis of DIM-ligands L1-3



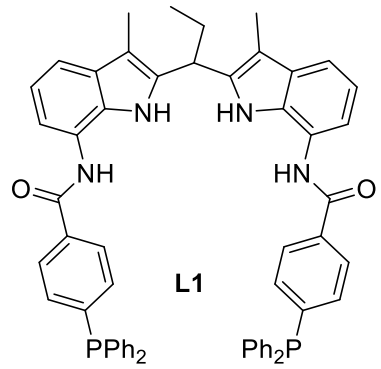
Scheme S1 Synthesis of Ligand **L1**:1) C_2H_5CHO, CH_3CO_2H, reflux 2 hours; 2) C_2H_5CHO, conc. HCl, reflux 2 hours; 3) 1 bar H_2, Pd/C, THF/MeOH, RT; 4) 4-(Diphenylphosphino)benzoic acid, 4-pyrrolidinopyridine, 4-Dimethylaminopyridine, *N,N'*-diisopropylcarbodiimide, DCM, RT.



1,1-Bis-(3-methyl-7-nitro-1H-indol-2-yl)-propane (**L1-1**)

The compound was prepared as follow based on reported procedure[1]: A mixture of 2-nitrophenylhydrazine, moistened with 30% water, as received from Sigma Aldrich (60 g, 0.38 mol, 1.0 eq.), propionaldehyde (50 mL, 0.70 mol, 1.8 eq.), acetic acid (2.0 mL, 0.03 mol, 0.09 eq.) and ethanol (0.5 L) was refluxed for 2 hours. After completion (monitored by TLC), the volatiles were removed under vacuum. The yellow solid residue was carefully suspended in concentrated aqueous HCl (35-37%, 0.6 L) by sonication for 1 hour (!!!in the fume hood). After adding 100 mL ethanol into the mixture, the suspension was carefully (!) warmed up to 100 ^{o}C while vigorously stirring. Propionaldehyde (45 mL, 0.63 mol, 1.7 eq.) was added dropwise via a syringe controlled by an injection pump while the heating was continued for 1 hour. After cooling down, the reaction mixture was poured into a beaker containing water (1 L) and $CHCl_3$ (300 mL). The reaction mixture was carefully neutralized with Na_2CO_3 until pH 7 (careful!!). After phase separation, the water phase was extracted with $CHCl_3$ (2x800 mL). The combined organic phase was dried over $MgSO_4$, filtrated and evaporated. The oil like black residue was dissolved in hot 1,2-dichloroethane (50 mL) and slowly cooled down. The solid was filtered off, washed thoroughly with hexane, until almost all the black impurities were removed (be patient!!), and then with a small amount DCM or cold methanol, yielding 50% of the desired compound **L1-1**, as orange crystals, identical to the literature[1].

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 2H, indole-NH), 8.09 (d, *J* = 8.1 Hz, 2H), 7.84 (d, *J* = 7.7 Hz, 2H), 7.18 (t, *J* = 7.9 Hz, 2H), 4.52 (t, *J* = 8.0 Hz, 1H, $CHCH_2CH_3$), 2.40 – 2.49 (m, 8H, $ArCH_3$ and $CHCH_2CH_3$), 1.07 (t, *J* = 7.3 Hz, 3H, $CHCH_2CH_3$).



L1

1-Bis-(4-(diphenylphosphino)benzoamide) of 1,1-Bis-(7-amino-3-methyl-1H-indol-2-yl)-propane (ParaDIMPhos (**L1**))

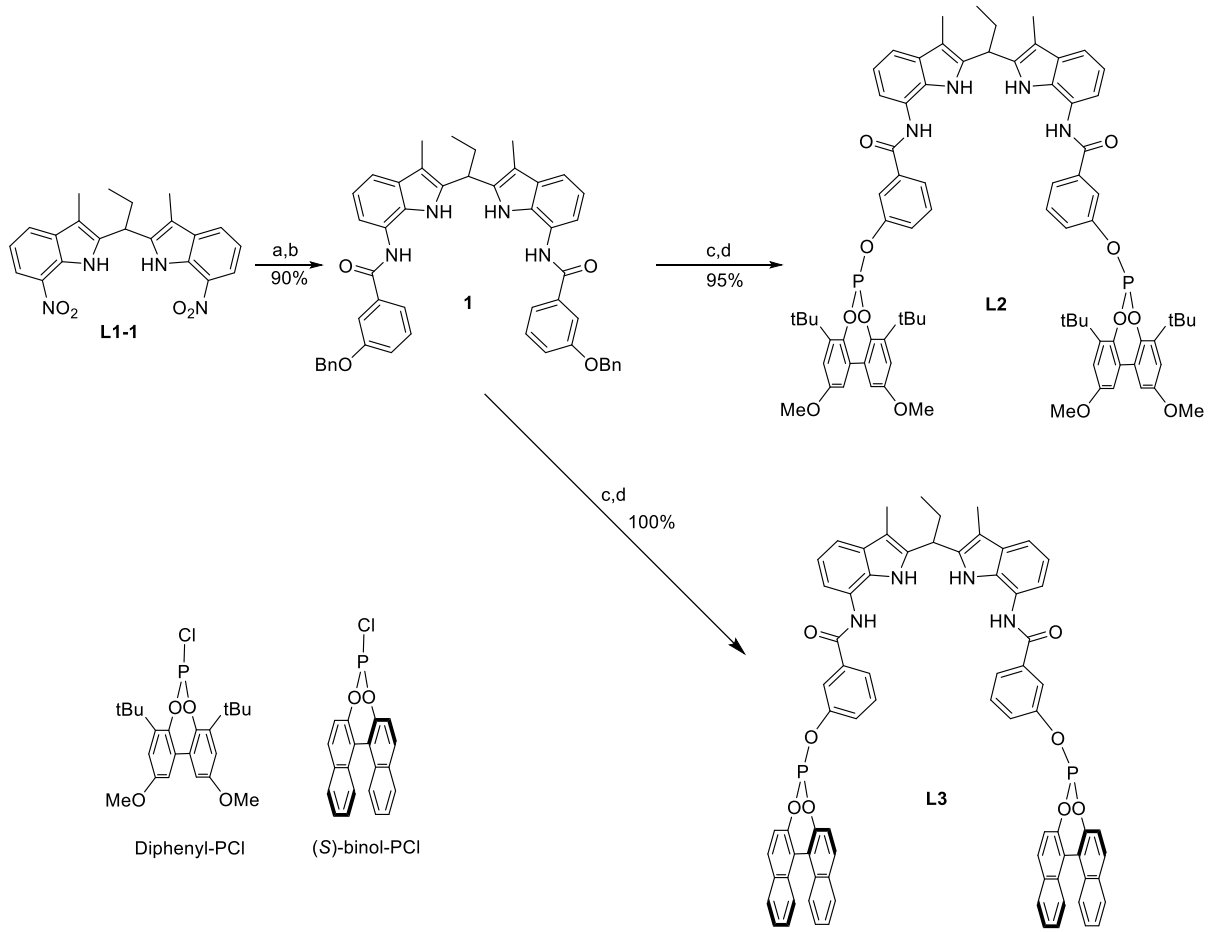
The compound was prepared as follow based on reported procedure[2]: 1,1-Bis-(3-methyl-7-nitro-1H-indol-2-yl)-propane (**L1-1**) (1.21 g, 3.08 mmol, 1.0 eq.) was suspended in methanol/THF (1/1, 50 mL) and 10% palladium on charcoal was added (0.39 g). The reaction

mixture was vigorously stirred under 1 bar of H_2 atmosphere with a balloon. The progress of the reaction was monitored by TLC, and after completion (about 2 hours), the catalyst was filtered off. The solvent was evaporated, and the crude diamine was immediately used in the subsequent reaction without further purification. To a solution of the crude diamine (300.0 mg, 1.1 mmol, 1 eq.), 4-(Diphenylphospino)benzoic acid (766.0 mg, 2.4 mmol, 2.2 eq.), 4-Dimethylaminopyridine (69.0 mg, 0.6 mmol, 0.5 eq.) and 4-pyrrolidinopyridine (68.8 mg, 0.5 mmol, 0.4 eq.) in dichloromethane (20 ml), *N*,*N*'-diisopropylcarbodiimide (1.4 ml, 8.8 mmol, 8.0 eq.) was added slowly while stirring at 0 ^{o}C under N_2, and the mixture was then stirred overnight. The precipitate was filtered off, the solvent was evaporated and the solid residue was purified by column chromatography on silica gel (100 g), with a hexane/dichloromethane (1:3) mixture to pure dichloromethane as an eluent. Then dissolve the product with a minimum amount of dichloromethane and add pentane/hexane slowly until precipitation appears, followed by crystallization under -20 ^{o}C overnight. After quickly filtration, pure compound was obtained. Yield 91%, yellow powder. Identical to the literature.[2]

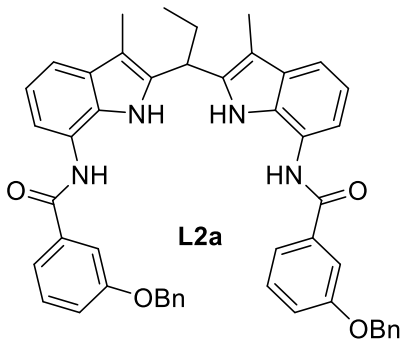
^{1}H NMR (400 MHz, CD_2Cl_2) δ 9.42 (s, 2H, indole-NH), 8.21 (s, 2H, amide-NH), 7.62 (d, *J* = 7.9 Hz, 4H), 7.43 – 7.26 (m, 22H), 7.22 (t, *J* = 7.4 Hz, 4H), 7.02 (t, *J* = 7.6 Hz, 2H), 6.94 (d, *J* = 7.6 Hz, 2H), 4.48 (t, *J* = 8.2 Hz, 1H, $\underline{CH}CH_2CH_3$), 2.30 (s, 6H, aryl-Me), 2.16 (t, *J* = 7.6 Hz, 2H, $CH\underline{CH_2}CH_3$), 0.99 (t, *J* = 7.3 Hz, 3H, $CHCH_2\underline{CH_3}$).

^{13}C NMR (126 MHz, CD_2Cl_2) δ 165.94, 136.32, 134.43, 134.37, 134.27, 134.22, 133.78, 133.64, 132.10, 129.78, 129.20, 129.15, 128.04, 127.71, 127.66, 122.38, 119.30, 116.15, 114.06, 108.20, 36.88, 27.94, 12.60, 8.86.

^{31}P NMR (162 MHz, CD_2Cl_2) δ -5.62.



Scheme S2. Synthesis of the DIMphosphite **L2** and **L3**: a. 1 bar H_2, Pd/C, THF/MeOH; b. 3-benzyloxybenzoyl chloride, TEA, DCM, RT; c. 1 bar H_2, Pd/C, THF/MeOH; d. (*S*)-binol-PCl or Diphenyl-PCl, THF, -78 ^{o}C to RT.

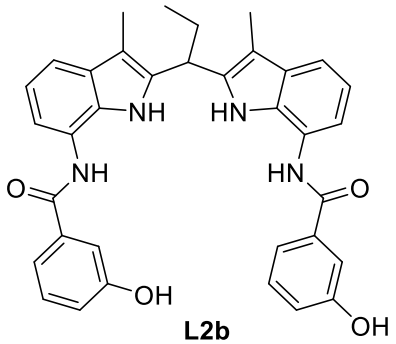


Bis-(3-(benzyloxy)benzoamide) of 1,1-bis-(-7-amino-3-methyl-1H-indol-2-yl)-propane (**L2a**)

The compound was prepared as follow based on reported procedure[3]: 1,1-Bis-(-3-methyl-7-nitro-1H-indol-2-yl)propane (1.0 g, 2.5 mmol) was suspended in methanol/tetrahydrofuran (1/1, 15 ml) and 10% palladium on charcoal was added (0.2 g). The reaction mixture was flushed with hydrogen, and then vigorously stirred under 1 bar of hydrogen with a balloon. The progress of the reaction was monitored by TLC (DCM/Methanol 10/1), and after completion (~2 hours), the catalyst was filtered off over Celite. The solvent was evaporated, and the crude diamine was immediately used in the subsequent reaction without further purification.

To the solution of the crude diamine (2.5 mmol) and triethylamine (5.0 mmol) in dichloromethane (10 ml), a solution of 3-(benzyloxy)benzoyl chloride (1.6 g, 6,5 mmol) in dichloromethane (10 ml) was slowly added while stirring, and the mixture was allowed to continue stirring overnight. After completion (TLC, pentane/ ethyl acetate 2/1), the solvent was evaporated and the crude mixture was purified by chromatography with pentane/ethyl acetate (3/1) to dichloromethane/methanol (20/1) as the eluent. The product was then dissolved in a minimum amount of chloromethane/methanol and followed by the addition of hexane to precipitate the compounds, which was filtrated through filter and washed with hexane to obtain pure compound **L2a**. Identical to the literature.[3]

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 2H, indole-NH), 8.15 (s, 2H, amide-NH), 7.40 – 7.31 (m, 16H), 7.24 – 7.14 (m, 1H), 7.03 (t, *J* = 6.8 Hz, 5H), 6.94 (d, *J* = 7.4 Hz, 2H), 5.03 – 4.89 (m, 4H, Bn-CH_2), 4.50 – 4.42 (m, 1H, $\underline{CH}CH_2CH_3$), 2.31 (s, 6H, aryl-CH_3), 2.23 – 2.14 (m, 2H $CH\underline{CH_2}CH_3$), 0.99 (t, *J* = 7.6 Hz, 3H, $CHCH_2\underline{CH_3}$).

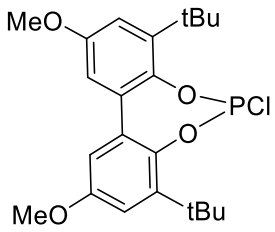


L2b

1-Bis-(3-(hydroxyl)benzoamide of 1,1-Bis-(7-amino-3-methyl-1H-indol-2-yl)-propane (**L2b**)

The compound was prepared as follow based on reported procedure[3]: Bis-(3-(benzyloxy)benzoamide) of 1,1-bis-(-7-amino-3-methyl-1H-indol-2-yl)-propane (**L2a**) (1.23 g, 1.6 mmol) was suspended in methanol (30 ml) and 10% palladium on charcoal was added (0.3 g). The reaction mixture was flushed with hydrogen, and then vigorously stirred under 1 bar hydrogen with a balloon. The progress of the reaction was monitored by TLC (DCM/Methanol 10/1), and after overnight reaction, the catalyst was filtered off over Celite. The solvent was evaporated, and the pure product was obtained by crystallization with dichloromethane and hexane. Identical to the literature.[3]

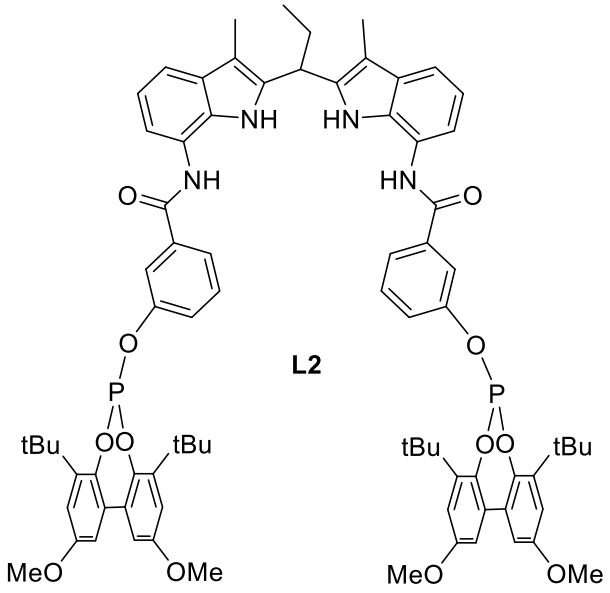
^{1}H NMR (500 MHz, Methanol-d_4) δ 7.43 – 7.32 (m, 6H), 7.30 – 7.21 (m, 4H), 7.00 (q, J = 8.0 Hz, 4H), 4.53 (t, J = 8.0 Hz, 1H, $\underline{CH}CH_2CH_3$), 2.35 – 2.17 (m, 8H, aryl-CH_3 & $CH\underline{CH_2}CH_3$), 0.99 (t, J = 7.3 Hz, 3H, $CHCH_2\underline{CH_3}$).



Diphenyl-PCl

4,8-Di-tert-butyl-6-chloro-2,10-dimethoxydibenzo[d,f][1,3,2]dioxaphosphepine (Diphenyl-PCl)

A flamed dried Schlenk flask with a Teflon stirring bar was charged with 3,3'-di-tert-butyl-5,5'-dimethoxy-[1,1'-biphenyl]-2,2'-diol (1 eq., 187.8 mg, 0.52 mmol), followed by co-evaporation with dry toluene three times. Then 5 ml dried and degassed THF was added into the flask. To this solution under -78 ^{o}C, PCl_3 (1.5 eq., 69.1 uL, 0.78 mmol) and triethylamine (3.0 eq., 221 uL, 1.56 mmol) was added dropwise. After stirring under -78 ^{o}C for 15 min, the reaction mixture was slowly warmed up to room temperature and stirred for another 45 min. After completion (monitored by ^{31}P NMR), the volatiles were evaporated under vacuum and further co-evaporated with dry toluene three times. The product was formed quantitatively and used directly.



L2

(Bis-3-((4,8-Di-tert-butyl-2,10-dimethoxydibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)oxyl)benzoamide of 1,1-bis-(7-amino-3-methyl-1H-indol-2-yl)-propane (**L2**)

A flamed dried Schlenk flask with a Teflon stirring bar was charged with bis-(3-(hydroxyl)benzoamide) of 1,1-bis-(-7-amino-3-methyl-1H-indol-2-yl)-propane **L2b** (1 eq., 150.0 mg, 0.26 mmol), followed by co-evaporation with dry toluene three times. Then 5 ml dried and degassed THF was added into the flask. To this solution under -78 ^{o}C, Diphenyl-PCl (2.0 eq., 0.52 mmol) and triethylamine (3.0 eq., 221 uL, 1.56 mmol) in THF was added dropwise. After stirring under -78 ^{o}C for 15 min, the reaction mixture was slowly warmed up to room temperature and stirred for another 45 min. After completion (monitored by ^{31}P NMR), the volatiles were evaporated under vacuum and further co-evaporated with dry toluene three times. The reaction mixture was evaporated, and to the solid residue THF (5 ml) was added. The suspension was filtered through a plug of celite, which was subsequently washed with THF (10 ml). The combined organic fractions were concentrated, hexane (10 ml) was added, followed by evaporation of all volatiles to dryness. The product was formed quantitatively without further purification.

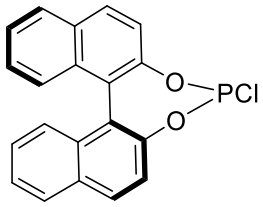
^{1}H NMR (500 MHz, CD_2Cl_2) δ 9.82 (s, 2H, indole-NH), 8.34 (s, 2H, amide-NH), 7.60 – 7.50 (m, 2H), 7.35 (dd, *J* = 6.5, 2.3 Hz, 2H), 7.25 – 7.22 (m, 3H), 7.19 – 7.15 (m, 3H), 7.07 – 6.95 (m, 8H), 6.75 – 6.73 (m, 4H), 4.49 (t, *J* = 8.0 Hz, 1H, $\underline{CH}CH_2CH_3$), 3.79 – 3.78 (m, 12H), 2.32 (s, 6H, indole-$\underline{Me}$), 2.23 (p, *J* = 7.6 Hz, 2H, $CH\underline{CH_2}CH_3$), 1.87 –

1.77 (m, 2H), 1.47 (d, *J* = 2.0 Hz, 6H, OMe), 1.44 (s, 18H), 1.42 (s, 18H), 1.00 (t, *J* = 7.6 Hz, 3H, $CHCH_2\underline{CH_3}$).

^{31}P NMR (202 MHz, CD_2Cl_2) δ 139.34.

^{13}C NMR (101 MHz, CD_2Cl_2) δ 165.23, 156.50, 152.64 (d, *J* = 6.2 Hz), 143.06 (m), 141.45 (d, *J* = 5.9 Hz), 138.38, 136.58 (d, *J* = 34.2 Hz), 134.02 (m), 132.15, 130.38, 129.37, 128.43 (d, *J* = 27.1 Hz), 125.64, 123.88 (d, *J* = 7.9 Hz), 123.38, 122.39, 119.76 (d, *J* = 7.6 Hz), 119.20, 116.14, 115.29, 114.85, 114.14, 113.36, 108.00, 55.99, 46.18, 35.74, 31.24 (m), 30.85, 25.99, 12.65, 8.90.

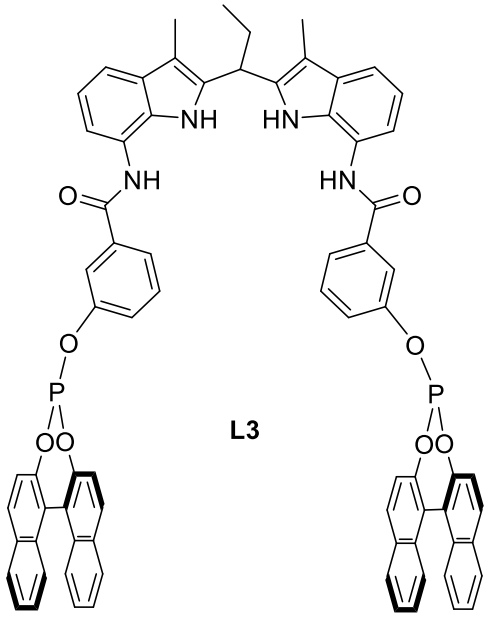
HR MS (FD+(eiFi)$^+$): calcd. for $C_{79}H_{86}N_4O_{12}P_2$ $[M]^+$ 1344.5717; found 1344.5774.



(*S*)-binol-PCl

(*S*)-1,1'-Binaphthyl-2,2-diyl phosphorochloridate, (*S*)-binol-PCl

A flamed dried Schlenk flask with a Teflon stirring bar was charged with (*S*)-binol (1 eq., 1.87 g, 5.2 mmol), followed by co-evaporation with dry toluene three times. Dried and degassed THF (20 ml) was then added into the flask. To this solution under -78 °C, PCl_3 (1.5 eq., 691 uL, 7.8 mmol) and triethylamine (3.0 eq., 2.21 mL, 15.6 mmol) was added dropwise. After stirring under -78 °C for 30 min, the reaction mixture was slowly warmed up to room temperature and stirred for another 60 min. After completion (monitored by ^{31}P NMR), the volatiles were evaporated under vacuum and further co-evaporated with dry toluene three times. The product was formed quantitatively as white solid and used directly without further purification.



(Bis-(3-((*S*)-1,1'-binaphthyl-2,2-diyl phosphito)benzoamide) of 1,1-Bis-(7-amino-3-methyl-1H-indol-2-yl)-propane (**L3**)

A flamed dried Schlenk flask with a Teflon stirring bar was charged with bis-(3-(hydroxyl)benzoamide) of 1,1-bis-(-7-amino-3-methyl-1H-indol-2-yl)-propane **L2b** (1 eq., 1.15 g, 2.0 mmol), followed by co-evaporation with dry toluene three times. Then 25 ml dried and degassed THF was added into the flask. To this solution under -78 ^{o}C, (*S*)-binol-PCl (2.0 eq., 1.40 g, 4.0 mmol) and triethylamine (3.0 eq., 0.84 mL, 6.0 mmol) in THF (20 mL) was added dropwise. After stirring under -78 ^{o}C for 15 min, the reaction mixture was slowly warmed up to room temperature and stirred for overnight. The reaction mixture was evaporated, and to the solid residue THF (40 ml) was added. The suspension was filtered through a plug of celite, which was subsequently washed with THF (40 ml). The combined organic fractions were concentrated, hexane (30 ml) was added, followed by evaporation of all volatiles to dryness, yielding 2.58g (95%) of **L3**·THF·C_6H_{14}. NOTE: Ligand **L3** is sensitive to moisture, and thus should be stored in inert conditions at low temperatures preferably.

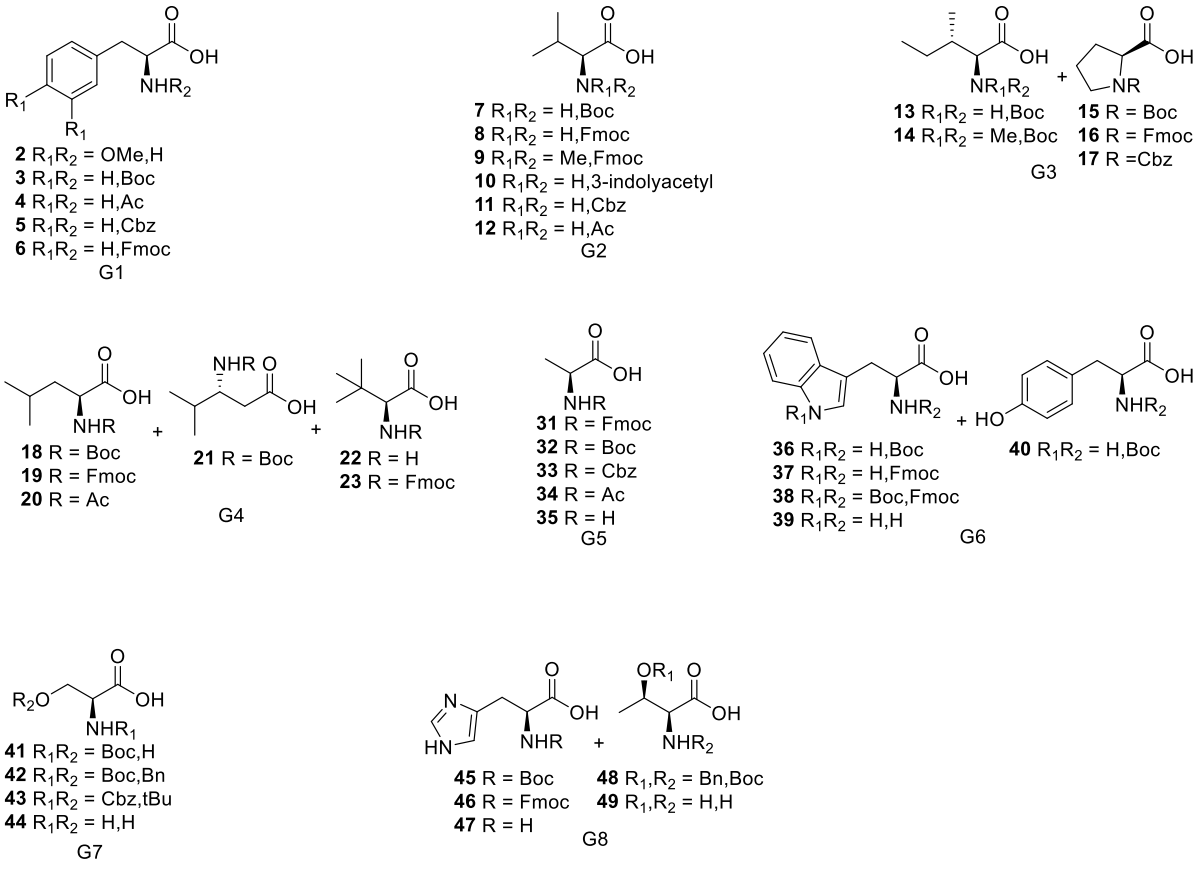
^{1}H NMR (400 MHz, CD_2Cl_2) δ 9.50 (m, 2H, indole-NH), 8.21 (s, 1H, amide-NH), 8.16 (s, 1H, amide-NH), 8.07 – 7.81 (m, 8H), 7.62 – 7.14 (m, 26H), 6.99 (t, *J* = 7.7 Hz, 1H), 6.94 – 6.77 (m, 3H), 4.49 (d, *J* = 7.9 Hz, 1H, $\underline{CH}CH_2CH_3$), 2.33 (s, 3H, aryl-Me), 2.32 (s, 3H, aryl-Me), 2.26 – 2.06 (m, 2H, $CH\underline{CH_2}CH_3$), 1.00 (t, *J* = 7.3 Hz, 3H, $CHCH_2\underline{CH_3}$).

^{31}P NMR (162 MHz, CD_2Cl_2) δ 144.08, 143.97.

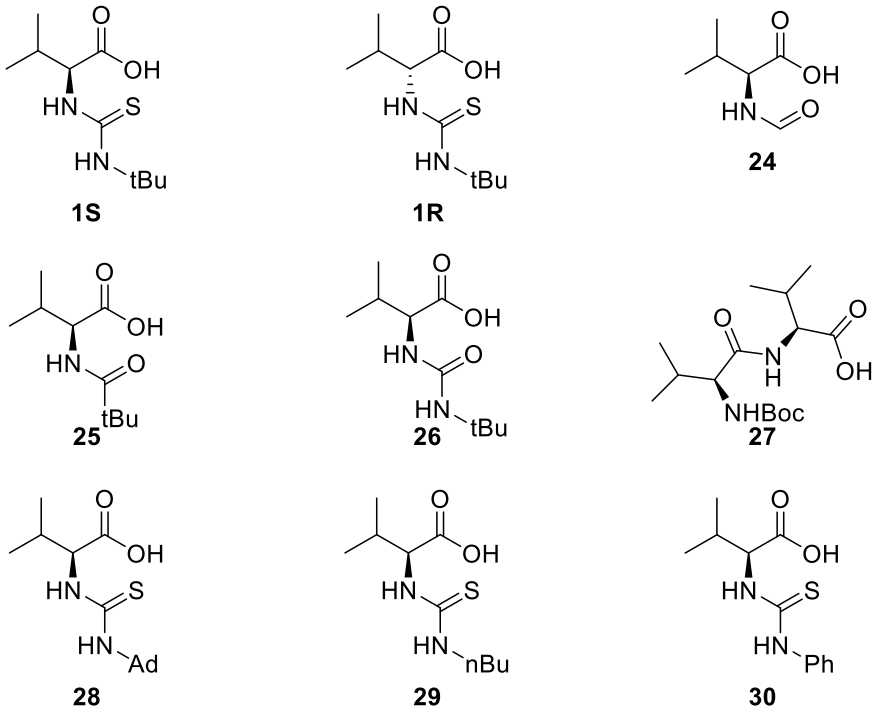
^{13}C NMR (100MHz, CD_2Cl_2): δ = 165.24 (m), 152.29 (m), 147.84 (d, *J* = 4.6 Hz), 147.22 (m), 136.74, 136.38 (d, *J* = 8.0 Hz), 133.19, 132.87, 132.36, 132.24, 131.74 (m), 131.11, 130.50 (m), 128.85 (d, *J* = 8.1 Hz), 128.27 (d, *J* = 3.0 Hz), 127.21, 127.08 (d, *J* = 3.0 Hz), 126.90 (d, *J* = 6.5 Hz), 125.73 (d, *J* = 17.1 Hz), 124.55 (m), 124.05 (d, *J* = 8.1 Hz), 123.75 (d, *J* = 8.5 Hz), 123.46 (d, *J* = 11.1 Hz), 123.21 (m), 122.17, 121.97, 119.92 (m), 119.73 (d, *J* = 7.5 Hz), 119.30 (d, *J* = 4.0 Hz), 118.15, 116.41, 114.10 (d, *J* = 16.0 Hz), 108.25 (d, *J* = 4.4 Hz), 36.86, 25.99, 12.61, 8.89.

HR MS (FD+(eiFi)$^+$): calcd. for $C_{75}H_{54}N_4O_8P_2$ $[M]^+$ 1200.34169; found 1200.33967.

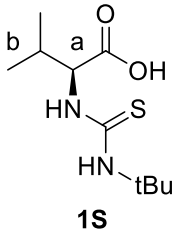
The effectors used in this study



Scheme S3. Effectors purchased from commercial source



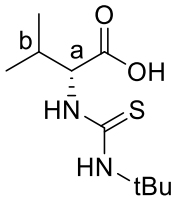
Scheme S4. Effectors prepared except **27** purchased from commercial sources



L-(tert-butylthiocarbamoyl)-*N*-valine (**1S**)

The compound was prepared as follow based on reported procedure[4]: *L*-Valine methyl ester hydrochloride (1 eq., 200 mg, 1.70 mmol) was dissolved in 0.25 M $NaHCO_3$ solution (80 mL), followed by adding the isothiocyanate (1 eq., 0.22 mL, 1.7 mmol). The mixture was heated at 80 ^oC for 3 hours and the progress of the reaction was monitored by TLC (petroleum ether/ethyl acetate, 1/1). After completion, the reaction mixture was cooling down and acidified to pH 2 with 1M HCl (3x80 mL). The products were extracted with ethyl acetate (3x100 mL). The combined organic layer was dried over $MgSO_4$. The pure product was obtained as white powder with 50% yield after crystallization. Identical to the literature.[4]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (s, 1H, thiourea-NH), 7.38 (d, J = 8.6 Hz, 1H, thiourea-NH), 4.84 (dd, J = 8.6, 4.6 Hz, 1H, Ha), 2.08 (m, 1H, Hb), 1.42 (s, 9H, tert-butyl-Me), 0.88 (m, 6H, isopropyl-Me).



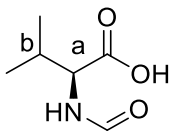
1R

D-(tert-butylthiocarbamoyl)-*N*-valine (**1S**) was prepared following the same procedures for **1R**.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.55 (s, 1H, COOH), 7.49 (s, 1H, thiourea-NH), 7.37 (d, J = 8.6 Hz, 1H, thiourea-NH), 4.83 (dd, J = 8.6, 4.6 Hz, 1H, Ha), 2.09 – 2.05 (m, 1H, Hb), 1.41 (s, 9H, tert-butyl), 0.88 -0.86 (m, 6H, isopropyl-Me).

^{13}C NMR (126 MHz, DMSO-d_6) δ 181.82, 173.42, 60.30, 52.27, 30.57, 28.89, 18.87, 18.12.

HRMS (FD+(eiFi)): calcd. for $C_{10}H_{20}N_2O_2S_1$ $[M]^+$ 232.1245; found 232.1201.

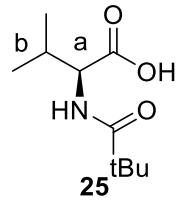


24

L-*N*-formyl-Valine (**24**)

The compound was prepared as follow based on reported procedure[4]: *L*-Valine methyl ester hydrochloride (0.3 g, 2.5 mmol), formic acid (9.52 g, 11.3 mmol) and acetic acid anhydride (1 g, 9.8 mmol) were dissolved in acetic acid (10 mL), and the reaction was stirred for 4 hours at room temperature. Afterwards, all the volatiles were removed under vacuum and the crude product was purified by recrystallization to give while power, identical to literature.[4]

^{1}H NMR (400 MHz, DMSO-d_6) 12.56 (bs, 1H, COOH), 8.41 (s, 1H, formyl-H), 7.98 (d, J = 8 Hz, 1H, amide-NH), 4.11 (dd, J = 8 Hz, J = 6 Hz, 1H, Ha), 2.02 (m, 1H, Hb) 0.87 (dd, J = 1 Hz, J = 7 Hz, 6H, isopropyl-Me).

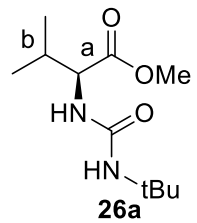


25

L-*N*-trimethylacetyl-Valine (**25**)

The compound was prepared as follow based on reported procedure[5]: A round bottom flask equipped with a magnetic stirring bar was charged with distilled water and $NaHCO_3$. The resulting reaction mixtures was cooled to 0 ^{o}C in an ice bath. *L*-Valine methyl ester hydrochloride (300 mg, 2.56 mmol) was added, and the solution was stirred until homogeneous. The flask was equipped with an addition funnel. The corresponding trimethylacetyl chloride, which was prepared from the corresponding pivalic acid, in 1,4-dioxane (4 mL) was added dropwise. The reaction mixture was then allowed to stir at room temperature overnight. Next, the reaction was extracted with Et_2O (2x20 mL) to remove the impurities. The aqueous layer was again cooled to 0 ^{o}C in an ice bath, and 1M HCl was added until pH 3. The product was extracted with ethyl acetate (3x100 mL). The organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum to give the product as white powder. Identical to the literature.[5]

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 1H, COOH), 6.24 (d, J = 8.5 Hz, 1H, amide-NH), 4.56 (dd, J = 8.5, 4.7 Hz, 1H, Ha), 2.23 (m, 1H, Hb), 1.22 (s, 9H, tert-butyl-Me), 1.06 – 0.93 (m, 6H, isopropyl-Me).

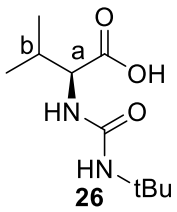


26a

L-(tert-butylcarbamoyl)-N-valine methyl ester (**26a**)

The compound was prepared as follow based on reported procedure[4]: *L*-Valine methyl ester hydrochloride (1.0 g, 7.62 mmol) was dissolved in dry DCM (100 mL), and the isocyanate was added. The mixture was stirred and the progress of the reaction was monitored by TLC (petroleum ether/ethyl acetate, 1/1). After completion, the solvents were removed under vacuum, and the crude product was dissolved in DCM (80 mL), washed with 1M HCl (3x80 mL), dried over $MgSO_4$. The pure product was obtained as white powder with 96% yield. Identical to the literature.[4]

^{1}H NMR (400 MHz, DMSO-d_6) δ 6.04 (d, J = 8.8 Hz, 1H, urea-NH), 5.94 (s, 1H, urea-NH), 4.03 (dd, J = 8.8, 5.3 Hz, 1H, Ha), 3.62 (s, 3H, OMe), 2.09 – 1.83 (m, 1H, Hb), 1.20 (s, 9H, tert-butyl), 0.83 (m, 6H, isopropyl-Me).

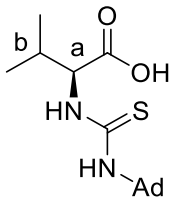


26

L-(tert-butylcarbamoyl)-*N*-valine (**26**)

The compound was prepared as follow based on reported procedure[4]: To a solution of *L*-(tert-butylcarbamoyl)-N-valine methyl ester (1 eq., 0.74 g, 3.22 mmol) in methanol/THF/water (1:1:1, 30 mL) mixture was added $LiOH{\cdot}H_2O$ (1 eq., 135 mg, 3.22 mmol). After overnight stirring at room temperature, the resulting reaction mixtures was partially concentrated under vacuum, followed by the addition of water (20 mL). The mixture was acidified with 1M HCl to pH 4, and then the product was extracted with ethyl acetate (3x30 mL). The combined organic layer was washed with brine (30 mL), dried over $MgSO_4$. The pure product was obtained as white powder with 80% yield. Identical to the literature.[4]

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.41 (s, 1H, COOH), 5.91 (s, 1H, urea-NH), 5.87 (d, J = 9.1 Hz, 1H, urea-NH), 3.99 (dd, J = 8.9, 4.8 Hz, 1H, Ha), 1.99 – 1.88 (m, 1H, Hb), 1.20 (s, 9H, tert-butyl), 0.85 - 0.81 (m, 6H, isopropyl-Me).

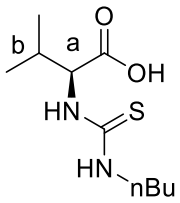


28

L-(Adamantylthiocarbamoyl)-*N*-valine (**28**)

The compound was prepared as follow based on reported procedure[4]: *L*-Valine methyl ester hydrochloride (1 eq., 0.5 g, 4.3 mmol) was dissolved in a mixture of 0.25 M $NaHCO_3$(aq) solution (50 ml) and methanol (50 ml), adamantyl isothiocyanate (0.83 g, 4.3 mmol) was added, and the reaction was heated at 80°C for 3 hours. After cooling down, the methanol was removed under vacuum and the reaction was acidified with 1 M HCl to reach pH = 2. The product was extracted with ethyl acetate (3 x 100ml). The combined organic layers were dried over $MgSO_4$, and the solvent was removed under vacuum. The crude product was dissolved in a small amount of hot DCM, precipitated with hexane, and filtered off, providing 0.4510 g (34%) of pure product. Identical to the literature. [4]

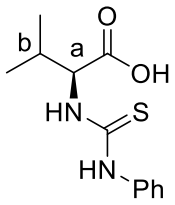
^{1}H NMR (400 MHz, DMSO-d_6) 12.56 (bs, 1H, COOH), 7.40 (d, *J*= 8 Hz, 1H, thiourea-NH), 7.36 (s, 1H, thiourea-NH), 4.77 (dd, *J*= 3 Hz, *J*= 8Hz, 1H, Ha), 2.15 (m, 6H), 2.08 (m, 1H, Hb), 2.02 (m, 3H), 1.61 (m, 6H,), 0.86 (m, 6H, isopropyl-Me).



29

L-(n-butylthiocarbamoyl)-*N*-valine (**29**) was prepared following the same procedures for **28**.

^{1}H NMR (400 MHz, DMSO-d_6) 10.34 (bs, 1H, COOH), 4.15 (d, *J*= 3 Hz, 1H, Ha), 3.67 (m, 2H), 2.08 (m, 1H, Hb), 1.52 (m, 2H), 1.27 (m, 2H), 0.94 - 0.81 (m, 6H, isopropyl-Me), 0.88 (t, *J*= 7 Hz, 3H).



30

L-(phenylthiocarbamoyl)-N-valine (**30**) was prepared following the same procedures for **28**.

^{1}H NMR (400 MHz, DMSO-d_6) 10.59 (bs, 1H, COOH), 7.48 (dd, *J* = 7 Hz, *J* = 7 Hz, 2H), 7.43 (d, *J* = 7 Hz, 1H), 7.23 (d, *J* = 7 Hz, 2H), 4.33 (d, *J*= 3 Hz, 1H, Ha), 2.19 (m, 1H, Hb), 1.04 - 0.91 (m, 6H, isopropyl-Me).

General procedures for the hydroformylation reaction

General procedures: A stock solution for the hydroformylation experiments was prepared by charging a flame-dried Schlenk flask with Rh(acac)$(CO)_2$, ligand, effectors and *N*,*N*-diisopropylethylamine (if stated), internal standard (1,3,5-trimethoxylbenzene) and dried and degassed toluene with standard Schlenk technique or in the Glove-Box. The solution was stirred for 30 minutes and then the 1.5 mL reaction vials (pre-dried in oven overnight) equipped with mini Teflon stir bars were charged with proper amount of substrates followed by the addition of a proper amount of catalyst stock solution in the Glove-Box. The vials were placed in a stainless steel autoclave (250 mL) charged with an insert suitable for 15 reaction vials for conducting parallel reactions. The autoclave was closed properly and then purged three times with 30 of bar syngas followed by pressurized at 40 bar of syngas. The reaction mixtures were stirred at the appropriate temperature for the required reaction time. Thereafter, the pressure was released and the yield, regioselectivity and enantioselectivity were determined by ^{1}H NMR analysis and GC or HPLC analysis. For NMR analysis, usually 100 uL reaction mixture were diluted with a proper amount of $CDCl_3$. For GC analysis, usually 50 uL reaction mixture was dilute to 1 mL with dichloromethane and injected to GC for measurements with beta DEX 225 column. For HPLC analysis, usually 30 uL reaction mixture was evaporated under vacuum and re-dissolved in isopropyl alcohol and n-heptane and then injected to HPLC for measurements.

For vinyl acetate, vinyl benzoate and vinyl pivalate, the enantiomeric ratio was analyzed by Chiral GC (Supelco's Beta Dex 225).

Hydroformylation of vinyl acetate. Initial temperature = 100 °C for 10 min, then 4 °C/min to 140 °C, then 40 °C/min to 200 °C. Retention time: t_R(*R*) = 4.022 min, and t_R (*S*)= 5.277 min.[6]

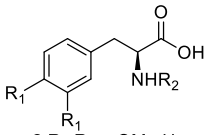
Hydroformylation of vinyl benzoate. Initial temperature= 135 °C for 22 min, then 20 °C/min to 220 °C. Retention time: t_R(*R*) = 14.687 min, and t_R(*S*) = 15.340 min.[6,7]

Hydroformylation of vinyl pivalate. Initial temperature= 77 °C for 22 min, then 40 °C/min to 220 °C for 5 min. Retention time: t_R(*R*)= 11.561 min, and t_R(*S*)= 12.01 min. [6]

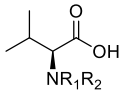
For *N*-vinyl phthalimide, the enantiomeric ratio was analyzed by HPLC (Chiralcel OJ-H, 3% iPrOH/n-heptane, 0.8 mL/min, λ=220 nm). Retention time: t_R(major) = 30.3 min, t_R(minor) = 32.3 min.[8]

Hydroformylation results

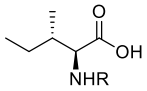
Table S1. Evaluation of the effector in succeed groups in the hydroformylation of vinyl acetate[a]



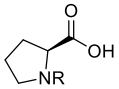
2 R_1,R_2 = OMe,H
3 R_1,R_2 = H,Boc
4 R_1,R_2 = H,Ac
5 R_1,R_2 = H,Cbz
6 R_1,R_2 = H,Fmoc



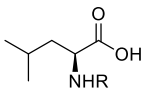
7 R_1,R_2 = H,Boc
8 R_1,R_2 = H,Fmoc
9 R_1,R_2 = Me,Fmoc
10 R_1,R_2 = H,3-indolyacetyl
11 R_1,R_2 = H,Cbz
12 R_1,R_2 = H,Ac



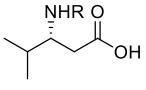
13 R_1,R_2 = H,Boc
14 R_1,R_2 = Me,Boc



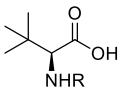
15 R = Boc
16 R = Fmoc
17 R =Cbz



18 R = Boc
19 R = Fmoc
20 R = Ac



21 R = Boc

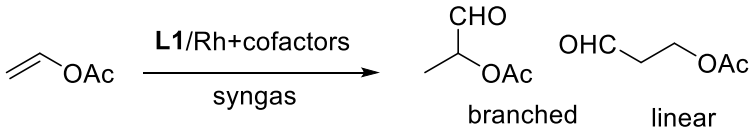


22 R = H
23 R = Fmoc

entry	Effector	Conv./%	ee/%	b/l
1	**2** R_1,R_2 = OMe, H	72	17(*R*)	>99
2	**3** R_1,R_2 = H,Boc	88	43(*R*)	>99
3	**4** R_1,R_2 = H,Ac	97	60(*R*)	>99
4	**5** R_1,R_2 = H,Cbz	93	58(*R*)	>99
5	**6** R_1,R_2 = H,Fmoc	96	57(*R*)	>99
6	**7** R_1,R_2 = H,Boc	89	50(*R*)	>99
7	**8** R_1,R_2 = H,Fmoc	75	41(*R*)	>99
8	**9** R_1,R_2 = Me,Fmoc	76	54(*R*)	>99
9	**10** R_1,R_2 = H,3-indolyacetyl	55	26(*R*)	>99
10	**11** R_1,R_2 = H,Cbz	89	49(*R*)	>99
11	**12** R_1,R_2 = H,Ac	94	62(*R*)	>99
12	**13** R_1,R_2 = H,Boc	95	51(*R*)	>99
13	**14** R_1,R_2 = Me,Boc	77	30(*R*)	>99
14	**15** R = Boc	92	49(*R*)	>99
15	**16** R = Fmoc	99	49(*R*)	>99
16	**17** R = Cbz	93	54(*R*)	>99
17	**18** R = Boc	95	40(*R*)	>99
18	**19** R = Fmoc	95	51(*R*)	>99
19	**20** R = Ac	87	47(*R*)	>99
20	**21** R = Boc	80	29(*R*)	>99
21	**22** R = H	99	23(*R*)	>99
22	**23** R = Fmoc	99	53(*R*)	>99

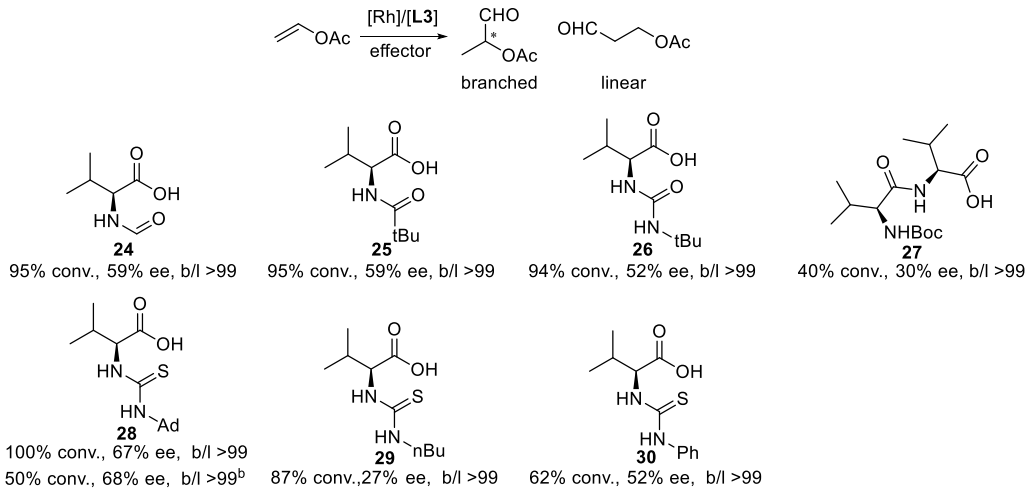
[a]Conditions: 0.5% Cat. $[Rh(acac)(CO)_2]$/L = 1/1.3, 0.2 M vinyl acetate, 10 mol% effector, 8 mol% DIPEA, 1 ml toluene as the solvent, 40 bar syngas, 40 ^oC, 96 hours. Conversion and regioselectivity were determined by ^1H NMR analysis. ee was determined by GC analysis.

Table S2. Evaluation of mixtures of effectors of subgroups in the hydroformylation of vinyl acetate [a]



entry	Sub	Effectors	Conv./%	ee/%	b/l
1	vinylacetate	G1(**2-6**)	80	45(*R*)	>99
2	vinylacetate	G2(**7-12**)	80	42(*R*)	>99
3	vinylacetate	G3(**13-17**)	95	51(*R*)	>99
4	vinylacetate	G4(**18-23**)	95	52(*R*)	>99
5	vinylacetate	G5(**31-35**)	99	55(*R*)	>99
6	vinylacetate	G6(**36-40**)	63	34(*R*)	>99
7	vinylacetate	G7(**41-44**)	75	24(*R*)	>99
8	vinylacetate	G8(**45-49**)	79	35(*R*)	>99
9	vinylacetate	no	100	1	27

Conditions: 0.5% Cat. [Rh(acac)$(CO)_2$]/L = 1/1.3, 0.2 M Vinylacetate, 2 mol% of per effector, 10 mol% DIPEA, 1 ml toluene as the solvent, 40 bar syngas, 40 °C, 96 hours. Conversion and regioselectivity were determined by ^{1}H NMR analysis. ee was determined by GC analysis.



Scheme S5. Application of various modified effectors in [Rh]/[**L3**] catalyzed asymmetric hydroformylation. Conditions: 0.5% Cat. [Rh(acac)$(CO)_2$]/L = 1/1.3, 0.2 M substrate, 10 mol% effector, 8 mol% DIPEA, 1 ml toluene as the solvent, 40 bar syngas, 40 °C, 96 hours.

Conversion and regioselectivity were determined by ^{1}H NMR analysis. ee was determined by GC and HPLC analysis. [b] Performed at room temperature with 120 hours of reaction time.

Spectra

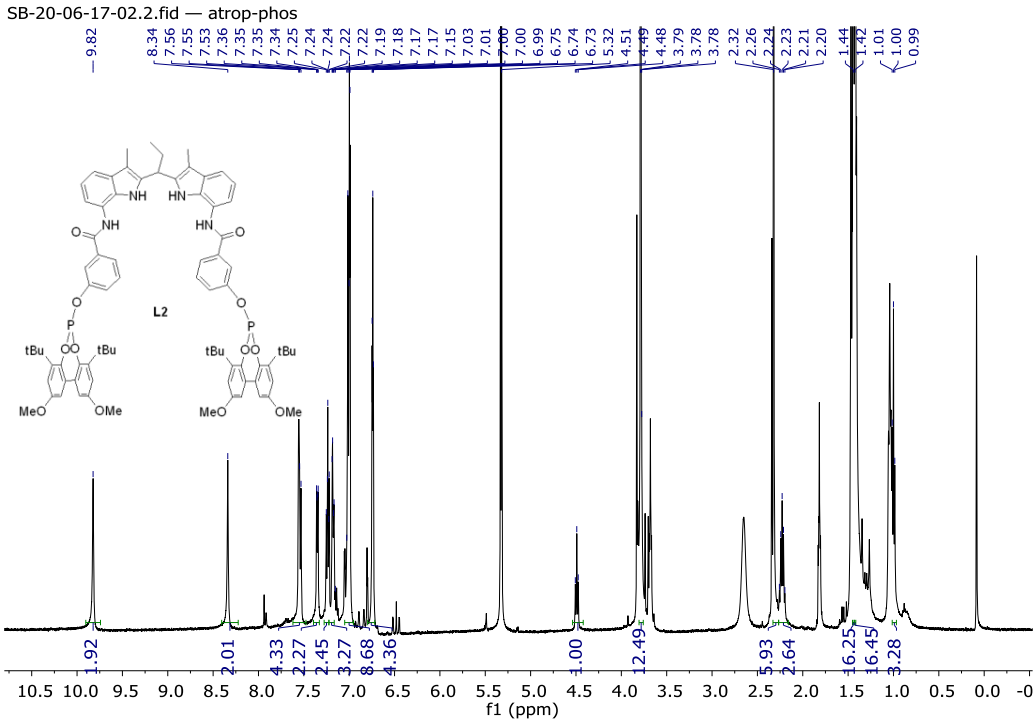


Figure S1. ^{1}H NMR spectrum of (Bis-3-((4,8-Di-tert-butyl-2,10-dimethoxydibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)oxyl)benzoamide of 1,1-bis-(7-amino-3-methyl-1H-indol-2-yl)-propane (**L2**)

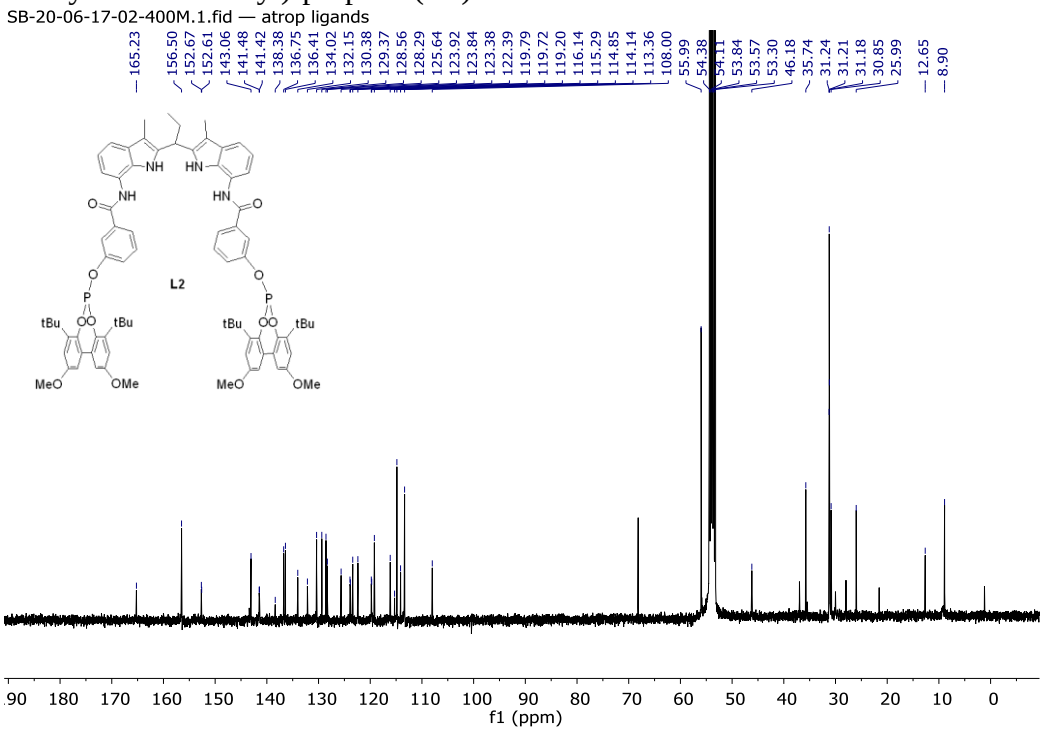


Figure S2. ^{13}C NMR spectrum of (Bis-3-((4,8-Di-tert-butyl-2,10-dimethoxydibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)oxyl)benzoamide of 1,1-bis-(7-amino-3-methyl-1H-indol-2-yl)-propane (**L2**)

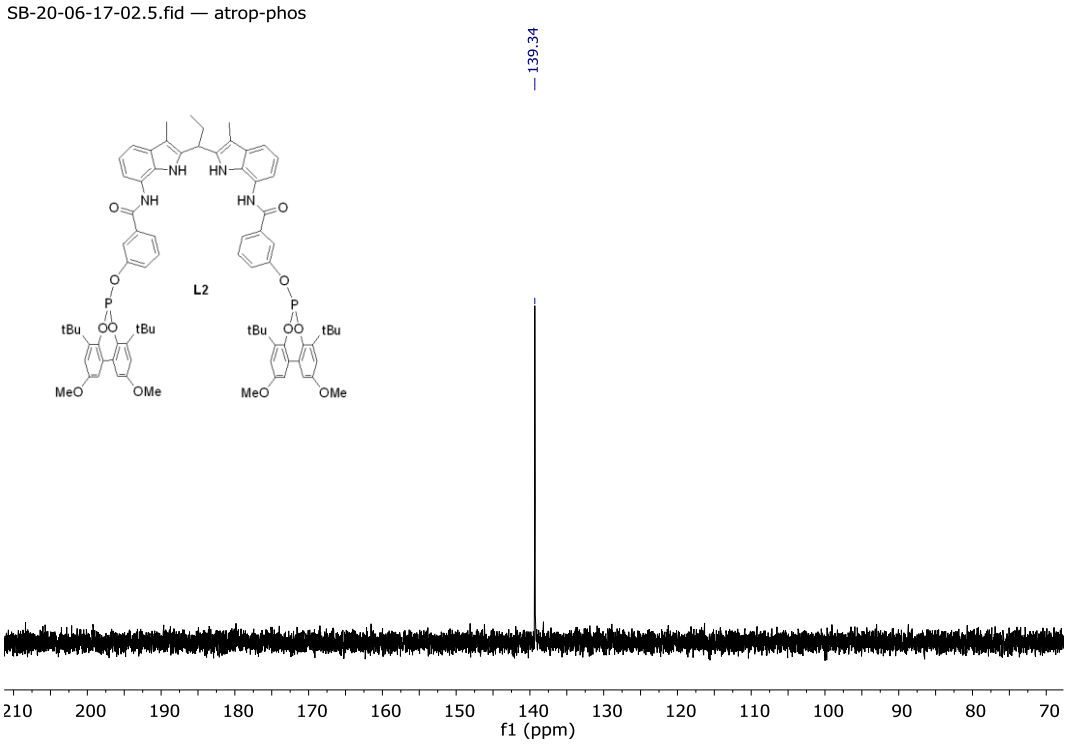


Figure S3. ^{13}P NMR spectrum of (Bis-3-((4,8-Di-tert-butyl-2,10-dimethoxydibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)oxyl)benzoamide of 1,1-bis-(7-amino-3-methyl-1H-indol-2-yl)-propane (**L2**)

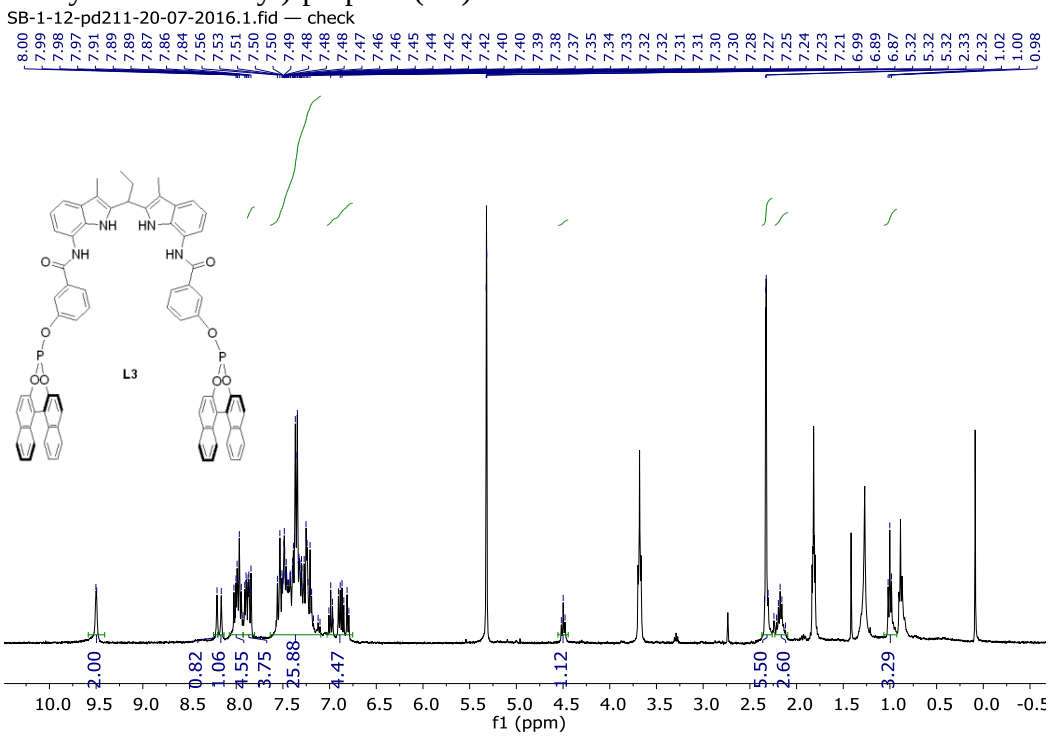


Figure S4. ^{1}H NMR spectrum of (Bis-(3-((*S*)-1,1'-binaphthyl-2,2-diyl phosphito)benzoamide) of 1,1-Bis-(7-amino-3-methyl-1H-indol-2-yl)-propane (**L3**)

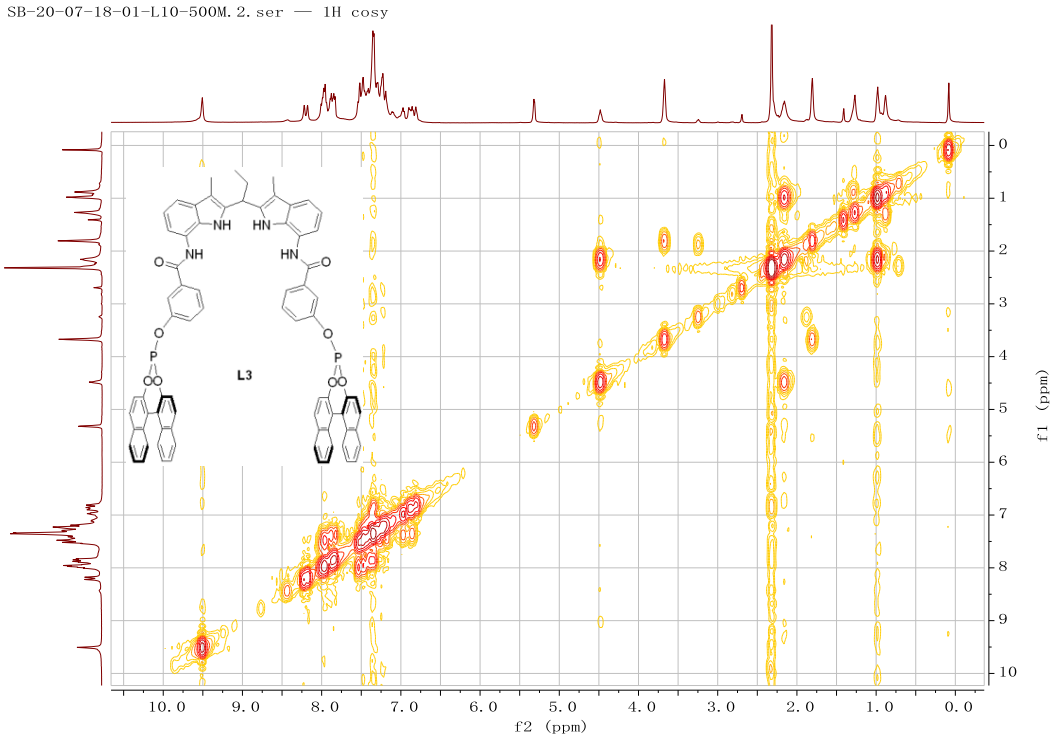


Figure S5. ^{1}H-^{1}H COSY NMR spectrum of (Bis-(3-((*S*)-1,1'-binaphthyl-2,2-diyl phosphito)benzoamide) of 1,1-Bis-(7-amino-3-methyl-1H-indol-2-yl)-propane (**L3**)

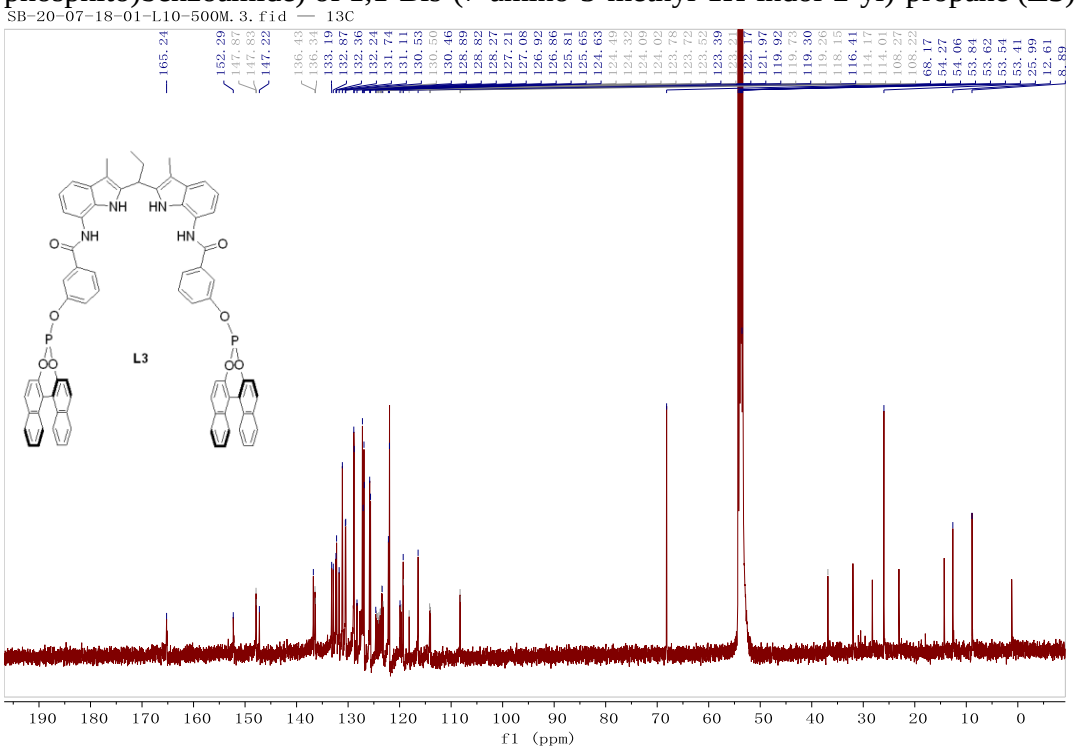


Figure S6. ^{13}C NMR spectrum of (Bis-(3-((*S*)-1,1'-binaphthyl-2,2-diyl phosphito)benzoamide) of 1,1-Bis-(7-amino-3-methyl-1H-indol-2-yl)-propane (**L3**)

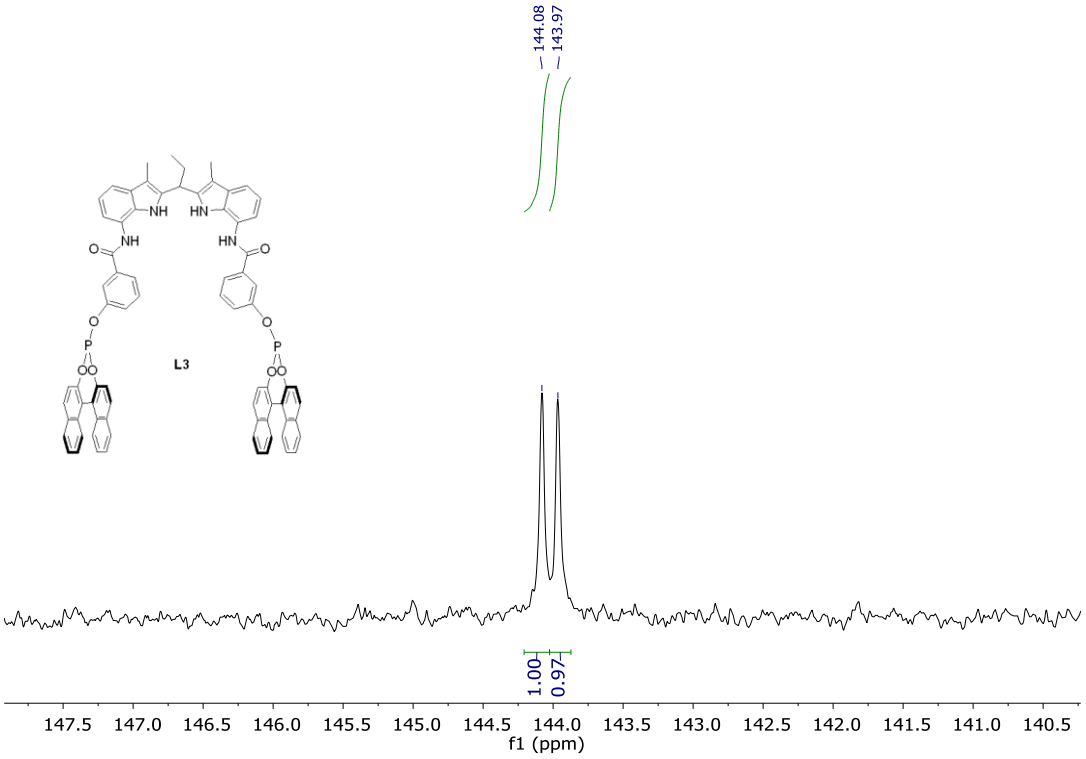


Figure S7. ^{31}P NMR spectrum of (Bis-(3-((*S*)-1,1'-binaphthyl-2,2-diyl phosphito)benzoamide) of 1,1-Bis-(7-amino-3-methyl-1H-indol-2-yl)-propane (**L3**)

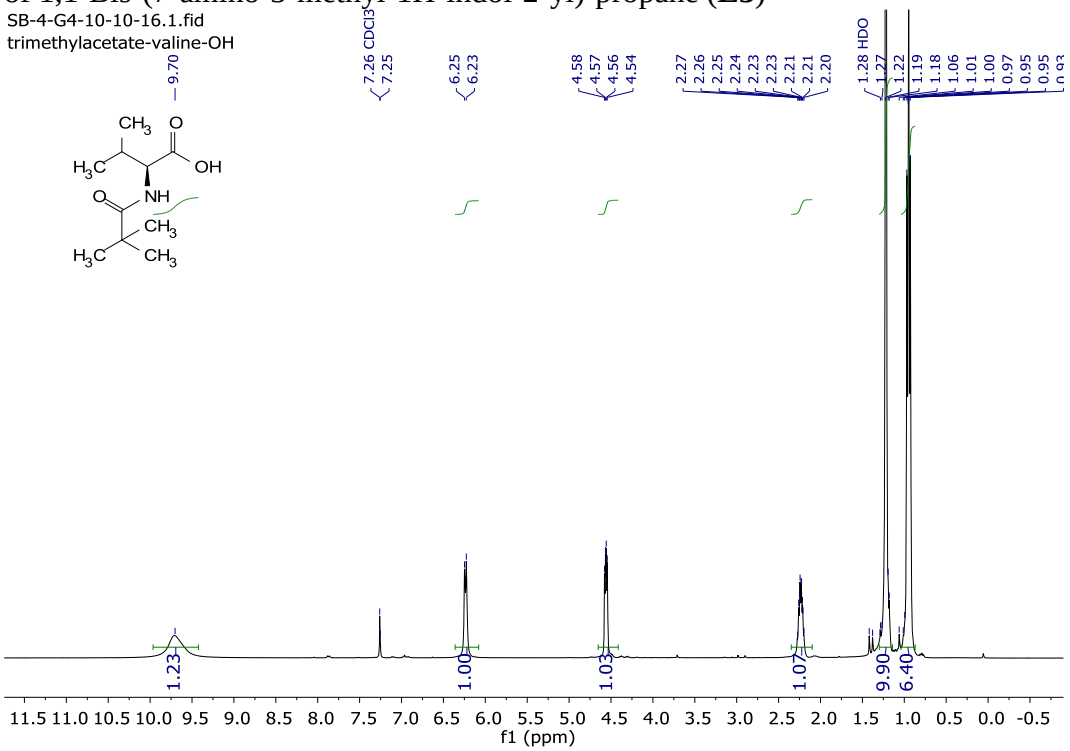


Figure S8. ^{1}H NMR spectrum of *L*-*N*-trimethylacetyl-Valine (**25**)

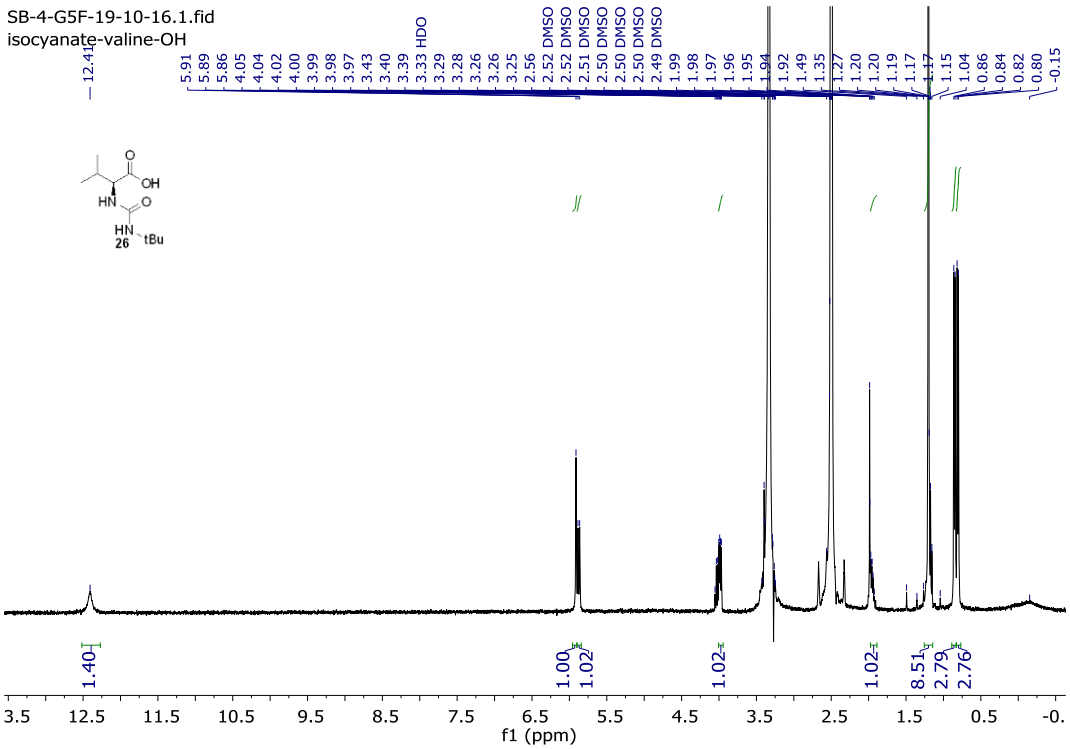


Figure S9. ^{1}H NMR spectrum of *L*-(tert-butylcarbamoyl)-*N*-valine (**26**)

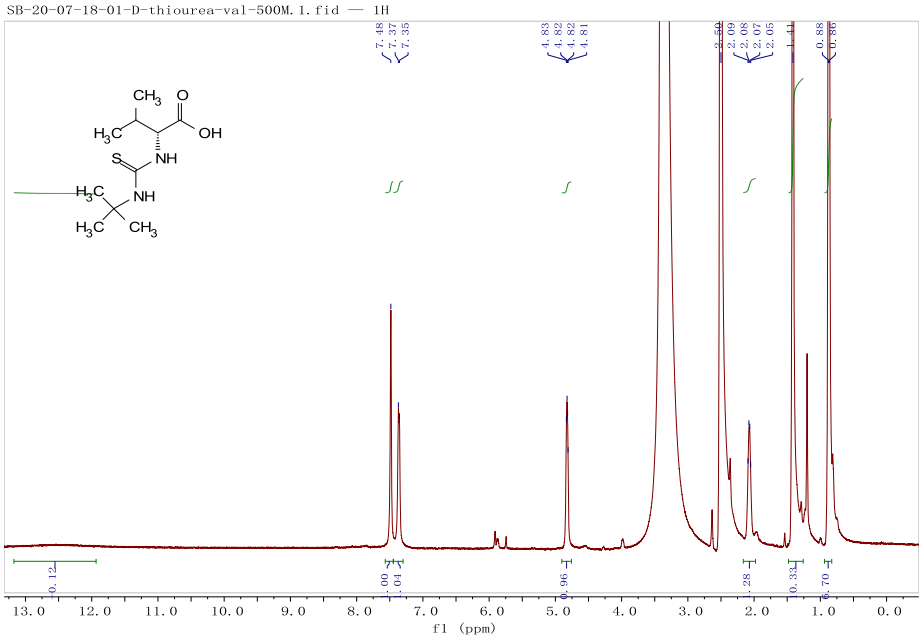


Figure S10. ^{1}H NMR spectrum of effector **1S**

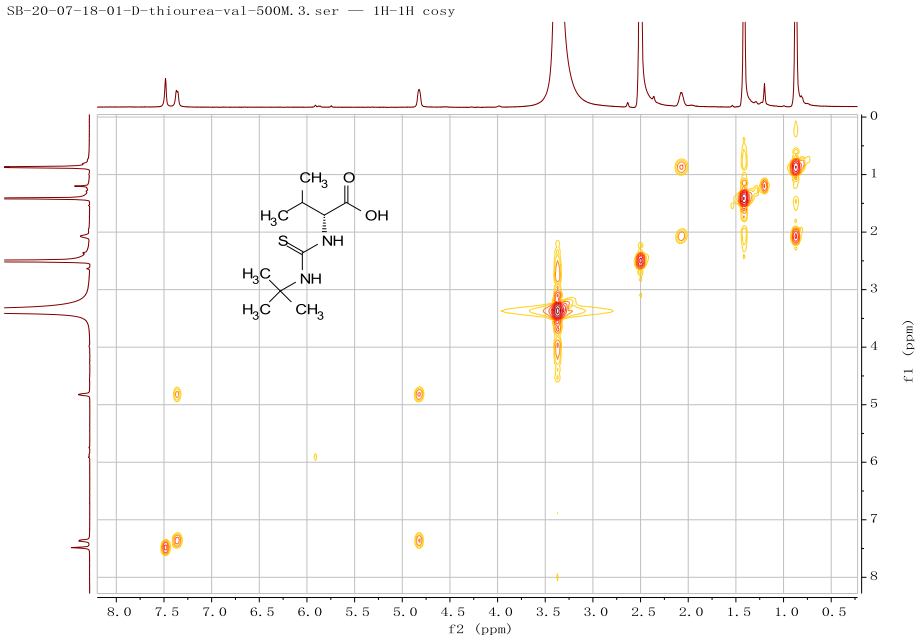


Figure S11. ^{1}H-^{1}H COSY NMR spectrum of effector **1S**

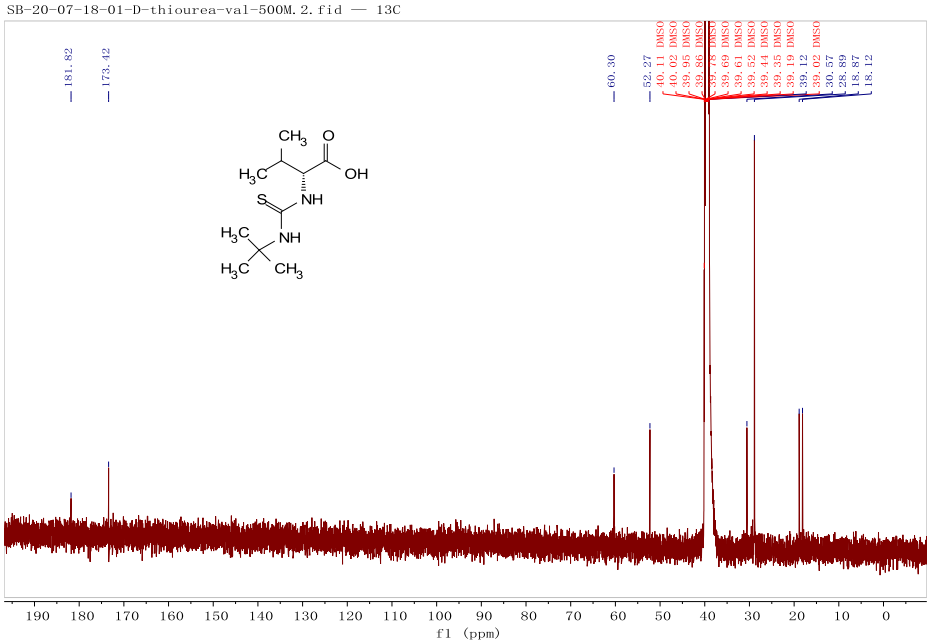


Figure S12. ^{13}C NMR spectrum of effector **1S**

References:

1 P. Dydio, D. Lichosyt, T. Zieliński and J. Jurczak, *Chem. Eur. J.*, 2012, **18**, 13686–13701.

2 P. Dydio, R. J. Detz and J. N. H. Reek, *J. Am. Chem. Soc.*, 2013, **135**, 10817–10828.

3 P. Dydio, R. J. Detz, B. de Bruin and J. N. H. H. Reek, *J. Am. Chem. Soc.*, 2014, **136**, 8418–8429.

4 P. Dydio, C. Rubay, T. Gadzikwa, M. Lutz and J. N. H. Reek, *J. Am. Chem.*

Soc., 2011, **133**, 17176–17179.
5 K. M. Engle, D. H. Wang and J. Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 14137–14151.
6 X. Zhang, B. Cao, Y. Yan, S. Yu, B. Ji and X. Zhang, *Chem. Eur. J.*, 2010, **16**, 871–877.
7 K. C. Miles, M. L. Abrams, C. R. Landis and S. S. Stahl, *Org. Lett.*, 2016, **18**, 3590–3593.
8 R. I. McDonald, G. W. Wong, R. P. Neupane, S. S. Stahl and C. R. Landis, *J. Am. Chem. Soc.*, 2010, **132**, 14027–14029.