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Tetrahedron: *Asymmetry*

Bis(diazaphospholidine) ligands for asymmetric hydroformylation: use of ESPHOS and derivatives based on ferrocene and diarylether backbones

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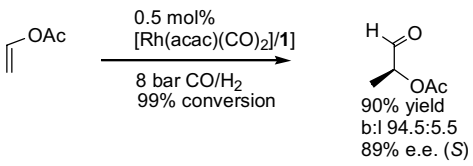
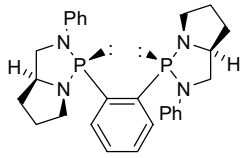
Abstract—A series of investigations have been completed on the use of the bis(diazaphospholidine) ligand ESPHOS in asymmetric hydroformylation. This study serves to confirm the optimum conditions for the use of this ligand. Two further ligands, based on ferrocene and biphenylether backbones, are also reported, but both give inferior results in hydroformylation in comparison with ESPHOS itself. The results from the hydroformylation reactions, and other studies, suggest that the ferrocene and biarylether systems are acting as monodonor ligands, rather than bidentate.

1. Introduction

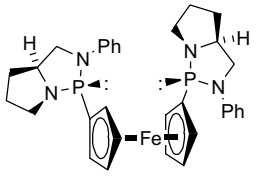
We recently reported the synthesis[1] and application to asymmetric hydroformylation[2,3] of the bis(diazaphospholidine) ligand ESPHOS **1**. In the case of vinyl acetate, this ligand gives excellent yields, branched:linear (b:l) ratios and ees for the hydroformylation product (Scheme 1). This result compares well with other systems reported for asymmetric hydroformylation,[4,5] although the substrate scope is not as broad as that observed for the well-established BINAPHOS ligand.[4] However it is significant that the ESPHOS/Rh(I) system works well at the relatively low pressure of 10 bar. In addition, extended hydroformylation times and high pressures also lead to aldehyde reduction, thus furnishing a potential asymmetric synthesis of diols. Herein we



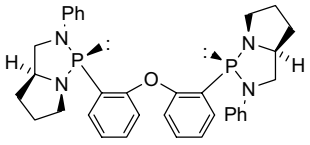
Scheme 1.



ESPHOS **1**



FerriESPHOS **2**



DiPhenESPHOS **3**

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Table 1. Asymmetric hydrogenation of vinyl acetate using Rh(I)/ESPHOS

Run	Rh concn ($mol\,dm^{-3}$)	L concn ($mol\,dm^{-3}$)	T (°C)	p (bar)	Conv. (%)	t (h)	Aldehyde (%)	$k^0 \exp(-5)$ ($mol\,dm^{-3}\,s^{-1}$)	Branched (%)	Ee (%)
1	0.001	0.001	40	10	5.5	23	3.1	0.8	92.73	22.6
2	0.005	0.005	40	10	25.5	18	22.2	1.6	94.12	71.2
2	0.005	0.005	40	10	17.4	9.5	14.6	2.4	93.68	74.0
3	0.001	0.001	100	10	3.6	7.5	1.18	—	93.61	69.5
4	0.005	0.005	100	10	55.3	1.5	43.5	—	86.98	80.7
5	0.001	0.001	40	40	10.1	8	7.9	7	95.05	21.5
6	0.005	0.005	40	40	71.5	20.5	64.1	4.1	94.55	65.7
6	0.005	0.005	40	40	30.3	9	26.26	4	94.06	53.1
7	0.001	0.001	100	40	31.4	—	24.3	—	91.40	82.7
7	0.001	0.001	100	40	4.8	2	2.2	1.9	89.58	0.0
8	0.005	0.005	100	40	98.3	2	67.7	—	90.03	84.3
9	0.001	0.002	40	10	0.3	1.75	0.1	—	97.33	n/a
10	0.005	0.01	40	10	−ppt	—	—	—	—	—
11	0.001	0.002	100	10	52.4	19.5	32.7	10	90.08	71.3
12	0.005	0.01	100	10	−ppt	—	—	—	—	—
13	0.001	0.002	40	40	−0	2	—	—	—	—
14	0.005	0.01	40	40	−ppt	—	—	—	—	—
15/1	0.001	0.002	100	40	86.8	4.5	55.7	—	90.90	82.4
15/2	0.001	0.002	100	40	87.5	2	72.3	46	91.43	83.4
16	0.005	0.01	100	40	−ppt	—	65.5	—	—	—
17	0.003	0.0045	70	25	73.3	1.5	65.5	83	92.77	88.4
18	0.003	0.0045	70	25	85.4	1.4	75.3	71	92.62	87.5
19	0.003	0.0045	70	25	99.4	3	80.9	80	92.15	87.4

Notes: Rate constants not corrected for Rh concentration or pressure. H_2/CO ratio is 2:1 in each case.

report the results of further investigations into asymmetric hydroformylations of vinyl acetate using **1**, and also the synthesis and use of the related ligands **2** and **3**.

2. Results and discussion

A series of reactions was carried out in order to optimise the hydroformylation reaction of vinyl acetate using a Rh(I)/ESPHOS catalyst. This was completed with the assistance of the reaction-design software MODDE to identify suitable experiments for optimisation with respect to rhodium and ligand concentration, temperature and pressure. In each experiment, 1.0 g of vinyl acetate was used, at a S/C ratio of 200. In total 19 experiments were carried out, the results of which are given in Table 1. Some of the attempts to carry out a reaction at high rhodium loading ($0.005\,mol\,dm^{-3}$) with a 1:2 Rh:L ratio were complicated by catalyst precipitation and very little activity was observed. The reaction in entry 13 was very slow and the rate was not measured. The temperature for this reaction was therefore increased and the resulting reaction is recorded as entry 15/2. Since 15/2 was a repeat of entry 15/1 it was not used in the statistical analysis, however it proved to be a useful test of the reproducibility of the reaction.

Statistical analysis of these results indicates that a high percentage of branched product is favoured at lower temperature and rhodium concentration, whilst the effects of the pressure and ligand concentration are somewhat less significant. A higher ee appears to be favoured by increasing temperature, pressure, rhodium concentration and to a lesser extent the ligand concentration, whereas the rate is increased by all parameters. On the other hand the selectivity for aldehyde (over alcohol) is favoured by increased rhodium concentration and pressure, but decreased temperature. If the data in our original communication[2] is included, the same trends are observed except that at high rhodium concentration, the ee decreases with increasing temperature. Overall the ees are higher, therefore we would predict that high ee is favoured by high rhodium concentration, high pressure and low temperature. The ligand/Rh ratio makes little difference. There is also an unexpected difference in the effect of increased temperature at high and low rhodium concentration.

From these observations, we conclude that the best ee is likely to be obtained at high rhodium concentration and low temperature but high pressure. This concurs with the results of our preliminary study, in which 93% ee was obtained under these conditions.[2] Unfortunately the reaction rate is also sharply reduced; only 24% conversion was observed after 17 h. For reactor use, however, such long reaction times are impractical, therefore we would identify the optimum conditions for use of this catalyst as those which gave a 90% yield of 1-(acetoxy)propanal in 5 h (i.e., 60 °C, 8 bar). Although the ee, at 89%, is slightly lower than the maximum possible, the conversion and b:l ratio are excellent.

The rather small dependance on ligand concentration suggests that a 1:1 complex is formed between ESPHOS and Rh(I) under all conditions (other than when the overall catalyst concentration is high and precipitation is observed). This would be expected from a bidentate ligand such as ESPHOS.

During the course of our investigations into dis(diazaphospholidine) ligands we also prepared ligands **2** and **3**, which are closely related in structure to ESPHOS.[6] The

former, based on a literature precedent,[7] was prepared via dilithiation of ferrocene **4** followed by reaction with chlorobis(dimethylamino)phosphine to give **5**. The synthesis was completed by the amine exchange of **5** with (*S*)-2-(phenylaminomethyl)pyrrolidine **6** in 77% isolated yield. The synthesis of **2** via 1,1′-dibromoferrocene was also attempted but proved to be highly troublesome; a small amount (ca. 5%) of unreacted ferrocene remained in the product and hindered its purification significantly. The low yields for the first step of the sequence reflect significant losses in purification, which was achieved by repeated recrystallisation. An X-ray crystal structure of **2** was obtained in order to confirm its structure, particularly with respect to the configuration at the phosphorus atoms (Fig. 1). As expected, and in common with X-ray crystal structures of other diazaphospholidine ligands derived from **6**, the relative configuration was that in which the three-carbon bridge on the pyrrolidine ring was *trans* to the ferrocene group on the phosphorus atom. The second ligand, **3**, was prepared through the dilithiation of diphenylether followed by trapping with $ClP(NMe_2)_2$ to give **7**, which was then reacted with 2 equiv of (*S*)-**6**.

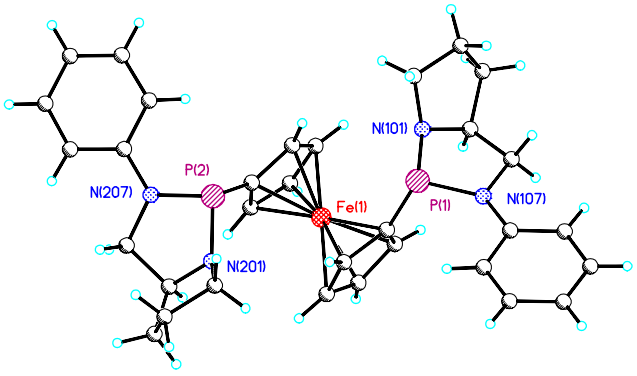
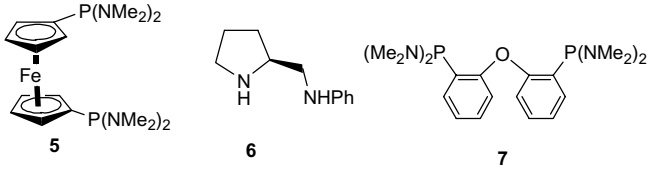


Figure 1. X-ray crystal structure of **2**.



Ligands **2** and **3** were tested in the asymmetric hydroformylation reaction of vinyl acetate and of styrene using the optimised conditions for **1** (Table 2). The results were disappointing, although also informative. In the case of vinyl acetate, both ligands proved to be poor in this application, both in terms of conversion and ee. In the case of **2** the major enantiomer was of (*S*)-configuration, whilst in the second case it was of (*R*)-configuration. In the case of styrene the conversions were better, however the pattern of low and inverted enantio- selectivities was mirrored.

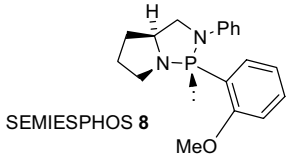
Table 2. Hydroformylation of vinyl acetate and styrene using **2** and **3**

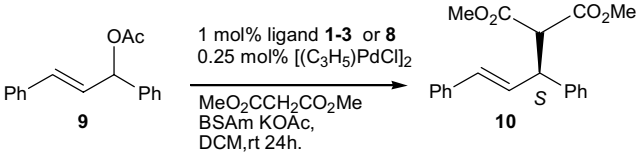
Substrate	Ligand	Conversion (%)	Ee (%)	Branched
Vinyl acetate	**2**	14.5	32 (*S*)	—
Vinyl acetate	**3**	8.3	13 (*R*)	—
Styrene	**2**	66.7	15 (*R*)	77%
Styrene	**3**	92.1	10 (*S*)	93%

Note: Reactions carried out at 60 °C, 8 bar, 3.5–5 h, S/C = 200.

The results obviously indicate that **2** and **3** are significantly inferior for the vinyl acetate hydroformylation compared to ESPHOS **1**, despite a strong structural similarity. One explanation for the difference may be that the two new ligands are acting in a monodentate manner.[8] This can be inferred from a comparison with the result obtained from monodonor SEMI-ESPHOS **8**, which also furnishes an essentially racemic product. Whilst this comparison alone cannot allow us to confirm the mono versus bidentate nature of the ligands, it may suggest that **2** and **3** cannot chelate the rhodium(I) in the same manner as ESPHOS.

In order to gain further insight into the mode of action of the two new ligands, we employed them in the allylic substitution reaction of **9** with dimethylmalonate. Although a venerable reaction of limited synthetic utility, the transformation provides a useful method for the comparison of new ligands. The results of our study (Scheme 2, Table 3) revealed, to our surprise, that both **2** and **3** gave product **10** of *S* configuration in good yields and ees of 91.8% and 90.4%, respectively. The product configuration matches that obtained using monodonor **8** (and similar compounds)[1,8] and is opposed to that of product obtained from the use of **1** as a ligand. Again this indirectly supports the proposition that both new ligands **2** and **3** may be acting in a *monodentate* manner.





Scheme 2.

Table 3

Ligand	Yield (%)	Ee (%)	Configuration
1	77	81	*R*
2	87	92	*S*
3	53	91	*S*
8	91	81	*S*

3. Conclusion

In conclusion, we have completed a series of further studies into the optimisation of the asymmetric hydroformylation of vinyl acetate with ESPHOS/Rh(I). In this study the optimal practical conditions mirror those used in our earlier paper to give a product of 89% ee. In addition we have prepared and evaluated two new ligands, based on ferrocene and diphenylether

backbones, however these gave greatly inferior results in the model reaction. Further tests suggest that, out of the bis(diazaphospholidine) ligands we have prepared, ESPHOS may be unique in being able to form an active chelate structure with the rhodium(I) metal in order to deliver a suitable catalyst for asymmetric hydroformylation.

4. Experimental section

All reactions were performed in oven dried glassware in an atmosphere of dry nitrogen or argon. Ether and tetrahydrofuran were distilled under nitrogen from sodium benzophenone ketyl. Chalcone was purified by recrystallisation from methanol. Heated experiments were performed using standard thermostatically controlled oil baths. Room temperature refers to ambient temperature (20–22 °C), 0 °C refers to an ice slush bath, −78 °C refers to a dry ice acetone bath, −20 °C refers to a 25% by weight sodium chloride/ice bath. Reactions were monitored using thin layer chromatography on silica gel 60_{F254} plates and visualised using $UV_{254\,nm}$. Flash column chromatography was performed by the method of Still, Kahn and Mitra[2] using Merck silica gel 60. Solution phase NMR experiments were performed using a Bruker DPX-300 Spectrospin (300 MHz) spectrometer and run as a 30 mg solution of compound in 0.6 mL of deuterated chloroform (0.03% Me_4Si), unless otherwise stated. Chemical shifts are reported in δ units, parts per million from Me_4Si. Coupling constants (J) are measured in hertz. Infrared spectra were obtained using a Nicolet Avatar 320 FTIR with Specac golden gate single reflection diamond attenuated total reflection (ATR) top plate. Optical rotations were taken using a Perkin Elmer 241 Polarimeter. Mass spectra are courtesy of The EPSRC National Mass Spectrometry Service Centre University of Wales Swansea or Warwick University mass spectrometry service. Elemental analyses were performed by Warwick Analytical Services. Melting points were recorded on a Stuart Scientific melting point apparatus and are uncorrected. Hydroformylation experiments, and the determination of the conversion and ee of these, were carried out by the St. Andrews CATS service using the instruments and procedure given in a previous paper.[2]

4.1. Synthesis of 1,1′-bis[bis-(dimethylamino)phosphino]-ferrocene 5

A two-neck oven dried 250 mL round bottom flask equipped with a magnetic stirrer bar and a reflux condenser with nitrogen/vacuum adapter was charged with ferrocene **4** (4.25 g, 0.023 mol) and dried for 2 h at high vacuum. Freshly distilled diethylether (40 mL) was added with rapid and efficient stirring. The resulting orange suspension was cooled to −78 °C in a dry ice/acetone bath and *n*-butyllithium (0.05 mol, 20 mL of a 2.5 M solution) was added in one portion followed by freshly distilled tetramethylethylenediamine (3.19 g, 0.0275 mol, 4.125 mL) *very slowly* dropwise via nitrogen purged syringe whilst maintaining the suspension at −78 °C with the addition of fresh dry ice. The resulting mixture was gradually allowed to room temperature over 2 h and was consequently refluxed under an atmosphere of dry nitrogen for 16 h. The resulting red suspension was allowed to cool to ambient temperature and then further cooled to −78 °C. Chlorobis(dimethylamino)phosphine (7.82 g, 0.05 mol, 7.38 mL) added *very slowly* dropwise via nitrogen purged syringe and the reaction was allowed to warm to ambient temperature with rapid and efficient stirring for 4 h. The resulting orange suspension was diluted with dry degassed diethylether (300 mL), washed with saturated degassed sodium hydrogen carbonate solution (150 mL) and the organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give a viscous deep red oil. The crude oil was placed under high vacuum for 1 h to remove traces of solvent. The oil was dissolved in boiling anhydrous acetonitrile (60 mL) under an atmosphere of inert gas and allowed to crystallise at −30 °C in a freezer to give slightly impure orange yellow needles. The supernatant liquor was syringed off and the solids re-dissolved in boiling anhydrous acetonitrile (60 mL) and allowed to crystallise overnight at ambient temperature under an atmosphere of dry nitrogen furnishing the pure product **5** as large highly crystalline orange/red transparent needles (2.73 g, 28% yield); mp 66 °C (single crystal); (found: C, 50.90; H, 7.55; N, 13.34. $C_{18}H_{32}N_4P_2Fe$ requires C, 51.20; H, 7.64; N, 13.27); ν_{max} solid/cm^{-1} 2855, 2824, 2774, 1443, 1260, 1174, 1155, 984, 816; δ_H (400 MHz, $CDCl_3$, Me_4Si); 4.27 (4H, m, $H_{3,3\prime,4,4\prime}$), 4.20 (4H, m, $H_{2,2\prime,5,5\prime}$), 2.67 (24H, d, J_{P-H} 9.3, CH_3; δ_C (100 MHz, $CDCl_3$, Me_4Si): 80.6 (d, J_{P-C} 11.5, *ipso* $C_{1,1\prime}$), 72.7 (dd, J_{P-C} 1.9, 10.4, $C_{3,3\prime,4,4\prime}$), 72.0 (t, J_{P-C} 3.1, $C_{2,2\prime,5,5\prime}$), 41.8 (d, J_{P-C} 14.9, CH_3); δ_P (121 MHz, $CDCl_3$): 95.3 m/z (EI) 422 (M^+), 378, 335, 291, 246, 119; m/z (EI) 422.146851 (M^+) $C_{18}H_{32}N_4P_2Fe$ requires 422.14516.

4.2. Synthesis of FerriESPHOS 2

In oven dried glassware using standard cannula techniques a solution of (*S*)-2-phenylaminomethyl pyrrolidine **6** in anhydrous toluene (50 mL) was added to a solution of 1,1′-bis[bis(dimethylaminophosphino]-ferrocene **5** dissolved in anhydrous toluene (20 mL) and the resulting mixture heated at reflux for 72 h under a stream of dry nitrogen. The reaction was cooled to ambient temperature and concentrated in vacuo to give an orange/red oil, which was dried under high vacuum at 40 °C for 4 h to give the crude product as an orange solid, which was boiled in anhydrous propan-2-ol (50 mL) with rapid and efficient stirring for 15 min and then hot filtered to give the pure product **2** as an orange yellow powder, which was dried at 40 °C for 4 h to remove all traces of solvent (5.429 g, 77% yield); mp 159–161 °C; $[\alpha]_D^{17} = -96.2$ (c 1.0, chloroform); (found: C, 64.66; H, 6.09; N, 9.21. $C_{32}H_{36}FeN_4P_2$ requires C, 64.66; H, 6.10; N, 9.43); ν_{max} solid/cm^{-1} 3058, 2964, 2929, 2844, 1590, 1485, 1310, 1197, 1155, 1088, 1018, 987, 905, 839, 824, 761, 688, 668, 629; δ_H (300 MHz, $CDCl_3$, Me_4Si) 7.21 (4H, t, J 7.9, Ar–H); 6.98 (4H, d, J 7.5, Ar–H), 6.73 (2H, t, J 7.4, Ar–H), 4.33 (2H, s, Fc–H), 4.28 (2H, s, Fc–H), 4.18 (2H, s, Fc–H), 4.09 (2H, p, J 6.59, NCH),

4.00 (2H, s, Fc–H), 3.45–3.35 (4H, m, CH_2), 3.30–3.16 (2H, m, CH*H*), 3.04–3.02 (2H, m, CH*H*), 2.12–2.01 (2H, m, CH*H*), 1.88–1.80 (4H, m, CH_2), 1.73–1.64 (2H, m, CH*H*), δ_C (75 MHz, $CDCl_3$, Me_4Si) 146.4, 117.3, 115.3, 112.5, 82.5, 71.1, 70.7, 70.5, 64.8, 52.7, 52.4, 31.9, 35.7; δ_P (121 MHz, $CDCl_3$) 98.68; m/z (EI) 594 (M^+), 511, 482, 420, 389, 307, 245, 205, 136; found (EI) 594.176856 (M^+) $C_{32}H_{36}N_4P_2Fe$ requires 594.17646.

4.3. Crystal structure data for 2

Yellow plate, $0.28\times0.24\times0.05$ mm, $C_{32}H_{36}FeN_4P_2$, M = 594.44, Orthorhombic, space group $P2_12_12_1$; $a = 9.4202(4)$, $b = 16.5029(5)$, $c = 18.1981(7)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 2829.09(18)$ Å^3 (by least squares refinement on 3686 reflection positions), $T = 180(2)$ K, $\lambda = 0.71073$ Å, $Z = 4$, D(calcd) = 1.396 g/cm^3, $F(000) = 1248$. μ(Mo-Kα) = 0.676 mm^{-1}. Data Collection and Processing: Siemens SMART (Siemens, 1994) three-circle system with CCD area detector. The crystal was held at 180(2) K with the Oxford Cryosystem Cryostream Cooler (Cosier & Glazer, 1986). Maximum theta was 29.12°. The *hkl* ranges were −12/12, −21/19, −20/23. 18,168 reflections measured, 6812 unique [R(int) = 0.1213]. Absorption correction by semi-empirical from equivalents; minimum and maximum transmission factors: 0.74; 0.93. The structure was solved by direct methods using SHELXS (Sheldrick, 1990) and all nonhydrogen atoms refined anisotropically. Hydrogen atoms were added at calculated positions and given isotropic displacement parameters 1.2 times that of the atom attached. The chirality was established from the known chirality of the compound and checked by refinement of the delta-f multiplier. Absolute structure parameter $x = -0.01(2)$. The data has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 233164.

4.4. Synthesis of bis 2-[bis(2-dimethylamino)phosphino]-diphenylether 7

An oven dried three-neck 250 mL round bottom flask equipped with a stirrer bar and a condenser fitted with a nitrogen/vacuum adaptor was charged with diphenylether (1.63 g, 9.58 mmol), which was dried at high vacuum for 2 h. The dried diphenylether was dissolved in freshly distilled diethylether (80 mL) and the mixture cooled to −78 °C in a dry ice/acetone bath. *n*-Butyllithium (21.1 mmol, 8.43 mL of a 2.5 M solution) was added slowly dropwise followed by freshly distilled tetramethylethylenediamine (2.45 g, 21.1 mmol, 3.18 mL) *slowly dropwise over 30 min* and the solution allowed to warm to room temperature. The diphenylether lithiated tetramethylethylenediamine adduct solution was then refluxed at 40 °C for 1 h under a positive pressure of dry nitrogen and then cooled to −78 °C in a dry ice/acetone bath. Chlorobis(dimethylamino)phosphine (3.26 g, 21.08 mmol, 3.07 mL) was added *very slowly dropwise*. The reaction removed from the cooling bath and allowed to achieve ambient temperature over 3 h with rapid and efficient stirring. The resulting white suspension was diluted with degassed diethylether (250 mL) and washed with saturated degassed sodium hydrogen carbonate solution (150 mL), the etherial layer separated and dried over excess magnesium sulfate, filtered and concentrated in vacuo to give a clear oil. The crude product was purified by crystallisation from boiling anhydrous acetonitrile (50 mL) under dry nitrogen, which was allowed to cool to ambient temperature after dissolution and seeded with a small homogeneous crystal of 5-oxoprolinanilide, sealed under inert gas and placed in a freezer overnight at −30 °C to furnish the pure product **7** as small white crystals (715 mg, 18% yield) mp 37 °C sharp (single crystal); ν_{max} solid/cm^{-1} 3077, 2968, 2871, 2816, 2774, 1579, 1559, 1450, 1431, 1248, 1221, 972, 944, 750, 652; δ_H (300 MHz, $CDCl_3$, Me_4Si) 7.46 (2H, ddd, J 1.9, 4.0, 7.5, Ar–H); 7.26–7.05 (4H, m, Ar–H); 6.75 (2H, dd, J 3.6, 8.1, Ar–H), 2.73 (24H, d, J 18, Me); δ_C (75 MHz, $CDCl_3$, Me_4Si) 158.43 (*ipso* C), 132.39 (d, J_{P-H} 6.0), 131.0 (*ipso* C), 129.3, 124.05, 118.38, 41.56 (d, J_{P-H} 18.0, Me); δ_P (121 MHz, $CDCl_3$) 96.70; m/z (CI) 405 ($M-H^+$); 319, 287, 244, 199, 119, 76; found (EI) 405.197373 ($M-H^+$) $C_{20}H_{32}N_4OP_2$ requires 405.197314.

4.5. Synthesis of DiphenESPHOS 3

In oven dried glassware under an atmosphere of dry nitrogen (*S*)-2-phenylaminomethypyrrolide **6** (0.217 g, 1.230 mmol) dissolved in anhydrous toluene (20 mL) was added via cannula to a solution of 1,1′-bis (bis-(dimethylamino)phosphino) diphenylether **7** dissolved in anhydrous toluene (20 mL). The resulting colourless solution was refluxed for 72 h under a stream of dry nitrogen cooled to room temperature, concentrated in vacuo, washed with cold acetonitrile and dried under high vacuum to give a quantitative yield of the pure product **3** as a white powder. mp 152–154 °C; $[\alpha]_D^{18} = -397.5$ (c 1.0, chloroform); ν_{max} solid/cm^{-1} 3027, 3046, 2933 (m), 2871, 2816, 1587, 1559, 1489, 1458, 1427, 1306, 1252, 1209, 1116, 1021, 894, 738, 689; δ_H (300 MHz, $CDCl_3$, Me_4Si) 7.25–7.22 (2H, m, Ar–H), 7.15 (6H, t, J 7.5, Ar–H), 7.0–6.87 (6H, m, Ar–H), 6.77–6.66 (4H, m, Ar–H), 4.09–4.02 (2H, m, NCH), 3.59 (2H, t, J 8.5, CH), 3.24–3.08 (6H, m, CH), 2.08–1.99 (2H, m, CH), 1.90–1.73 (6H, m, CH); δ_C (75 MHz, $CDCl_3$, Me_4Si) 160.08 (d, J_{P-C} 18.0, *ipso* C), 147.4 (d, J_{P-C} 16.1, *ipso* C), 133.63 (d, J_{P-C} 29.9, *ipso* C), 130.87, 130.65, 129.37, 123.13, 119.48, 117.85, 115.85, 115.69, 115.60, 115.21, 64.62, 54.02, 52.68, 52.26, 31.71, 26.43; δ_P (121 MHz, $CDCl_3$) 95.21; m/z (CI) 577 ($M-H^+$); 373, 205, 199, 136, 77; found (EI) 577.227191 ($M-H^+$) $C_{34}H_{36}N_4OP_2$ requires 577.228614.

4.6. General procedure for asymmetric allylic substitution reaction of racemic-(*E*)-1,3-diphenyl-2-enyl-1-acetate with dimethylmalonate

A solution of allyl palladium chloride dimer (0.25 mol%) and ligand (1 mol%) in anhydrous dichloromethane (1 mL) were stirred for 45 min at room

temperature in an atmosphere of argon. Sequentially was added racemic-(*E*)-1,3-diphenyl-2-enyl-1-acetate **9** (0.2, 0.79 mmol, 1 equiv) dissolved in anhydrous dichloromethane (1 mL), dimethylmalonate (0.12 g, 0.87 mmol, 1.1 equiv), bis-[trimethylsilyl] acetamide (0.18 g, 0.87 mmol, 1.1 equiv) and potassium acetate (1 mg). The resulting suspension was stirred overnight, diluted with diethylether, washed with ice-cold, saturated ammonium chloride solution (2×20 mL), dried over magnesium sulfate, filtered, concentrated in vacuo and dried at high vacuum for several hours to remove excess dimethylmalonate. Flash column chromatography [gradient elution (5–10% EtOAc/hexane)] gave the addition product **10** as a slightly yellow oil.

4.7. NMR enantiomeric excess determination of allylic substitution products

A sample of the allylation adduct (5–10 mg) was weighed accurately into a screw top vial. $Eu(HFC)_3$ (0.4–0.45 equiv) was weighed out avoiding undue exposure to atmospheric moisture into another screw top vial. The original allylation sample was dissolved in 0.6 mL of dry $CDCl_3$ and transferred into the vial containing the shift reagent. After approximately 30 s of vigorous shaking the shift reagent dissolved and the homogeneous solution was transferred into an NMR tube. The ^1H NMR spectrum of the sample shows a doublet and two singlets at approximately 4 ppm (depending on the amount of shift reagent used). The singlets are the signal given by each antipode for one of the methyl groups in the product. The doublet is the unresolved signal for the other methyl group in the product. The integral of the doublet and sum of the integrals of the two singlets should thus give an approximately similar numerical value. The relative integrals of the two singlets can be used to give the enantiomeric excess of the sample analysed. Using the (+) antipode of the shift reagent, the singlet with the highest ppm value corresponds to the (*R*) enantiomer.

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