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Asymmetric hydrogenation reactions mediated by a new class of bicyclic bisphosphinites

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Abstract

The bicyclic alcohol (−)-**4** was prepared from (−)-bicyclo[3.2.0]hept-2-en-6-one (−)-**1** in 50% yield. The diol (−)-**4** was coupled to selected chlorophosphines **6**–**12** to produce a series of bisphosphinites **13**–**19** in 89–95% yield. From these bisphosphinites were prepared the rhodium complexes **20**–**26** which were characterised by ^{31}P NMR and used in situ for the asymmetric hydrogenation of α-enamides **27**–**29**. Complexes **21**, **23**–**25** proved to be the superior catalysts for the production of (*R*)-*N*-acetylphenylalanine (91, 84, 90 and 87.5% ee) from **27** and (*S*)-*N*-acetylalanine methyl ester (70, 72, 68 and 71% ee) from **28**.

1. Introduction

Wilkinson reported that the complex [$Rh(Ph_3P)_3Cl$] acted as a homogeneous catalyst for the hydrogenation of olefins over 30 years ago.[1] Shortly afterwards, Horner published the first attempts to accomplish asymmetric hydrogenation reactions using Wilkinson-type catalysts.[2] Since that time various chiral bidentate bisphosphine and bisphosphinite ligands have been developed for metal-catalysed asymmetric hydrogenation reactions, some of the more popular being Achiwa's BPPM,[3] Kagan's DIOP,[4] Knowles' DiPAMP,[5] Noyori's BINAP[6] and Burk's DuPHOS.[7]

The desire for efficient routes to optically active natural and non-natural amino acids focused attention on the use of chiral bisphosphine- and bisphosphinite-rhodium catalysts for the stereoselective hydrogenation of α-(acylamino)acrylates (α-enamides), as outlined in Scheme 1.[8,9]

While chiral bisphosphine ligands are still the most commonly-used stereodirecting moieties in such asymmetric hydrogenations, there is an increasing number of bisphosphinites (Scheme 1) being used

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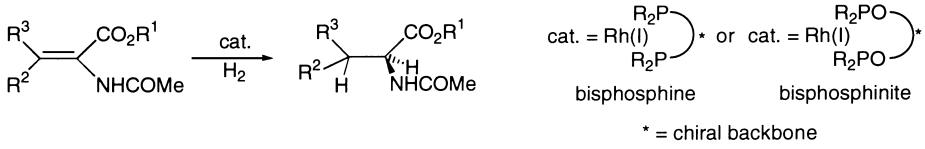


Scheme 1.

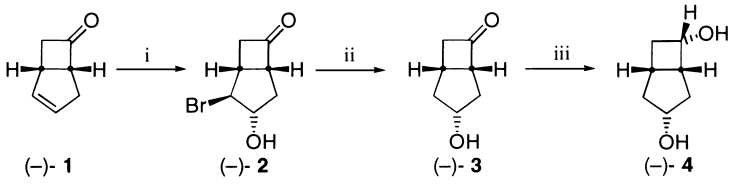
for the same purpose, for example Johnson's glucophinite,[10] Hayashi's BDPCP[11] and more recently Zhang's BICPO,[12] Selke or RajanBabu's carbohydrate phosphinites,[13,14] as well as Chan's spirOP[15] and DIMOP.[16] One reason for the increasing popularity of bisphosphinite ligands stems from the simple method of preparation (by reacting diols with chlorophosphines in the presence of a base) and the ready availability of the necessary starting materials. Thus, the preparation of the requisite chiral diols, which should be readily available in both enantiomeric forms, has received significant impetus. The hydroxyl groups must be held in space by a backbone so that, after formation of the bisphosphinite, a metal ion, for example Rh(I), is tightly chelated between the phosphorus atoms.

2. Results and discussion

We realised that the bicyclo[3.2.0]heptane framework with its relatively inflexible superstructure has established chemistry available for appending hydroxy substituents at positions which, when modified to provide phosphinite units, would give the requisite bite-angles for complexation to rhodium(I). In this article we describe the synthesis of the appropriate bisphosphinites, complexation to the metal and the stereoselective hydrogenation of α-enamides using these new catalysts.[17]

2.1. Preparation of chiral phosphinite ligands based on the bicyclo[3.2.0]heptane ring system

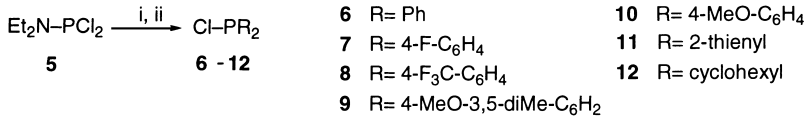
Bicyclo[3.2.0]hept-2-en-6-one (±)-**1** is readily prepared[18] and may be resolved by preparation of the bisulfite adduct and formation of diastereomeric salts with (*S*)-α-phenethylamine (ABAC).[19,20] Treatment of the less water-soluble salt with aqueous hydrochloric acid afforded (−)-**1** (Scheme 2). Bromohydrin formation using *N*-bromosuccinimide in aqueous acetone furnished the bromohydrin (−)-**2**[21] which was hydrodehalogenated[22] giving (−)-**3**, and reduced with sodium borohydride to give the diol (−)-**4** in 50% overall yield from the ketone (−)-**1**. It is noteworthy that (−)-**4** or (+)-**4** may also be prepared by biotransformations using baker's yeast[17] or lipase-catalysed reactions.[23,24] In short, the diol **4** is readily available in both enantiomeric forms.



Scheme 2. Reagents and conditions: (i) *N*-bromosuccinimide, H_2O, 20 h (91%); (ii) *n*Bu_3SnH, toluene, AIBN, 80°C, 1 h (76%); (iii) $NaBH_4$, MeOH, −78°C, 2 h (70%)

Contemporaneously *N*,*N*-diethylphosphoramidous dichloride **5**[25,26] was reacted with the appropriate Grignard reagent (RMgX), then dry HCl gas, to produce a series of chlorophosphines **6**–**12** (Scheme 3).[13,25,27,28]

Coupling of the diol (−)-**4** to the chlorophosphines **6**–**12** in tetrahydrofuran by addition of triethylamine gave the crude bisphosphinites **13**–**18** in 89–95% yield. The purity of the bisphosphinites was assessed by

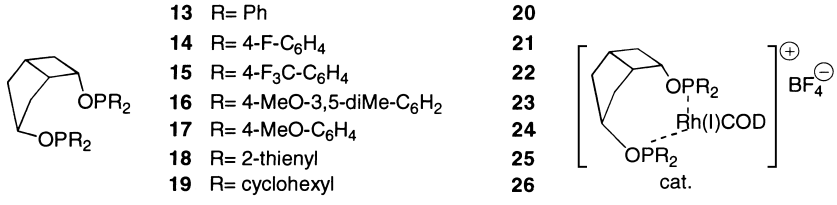


Scheme 3. Reagents and conditions: (i) 2 equiv. RMgX, THF, 0°C; (ii) HCl_g, pentane, 0°C; overall yields 20–56%

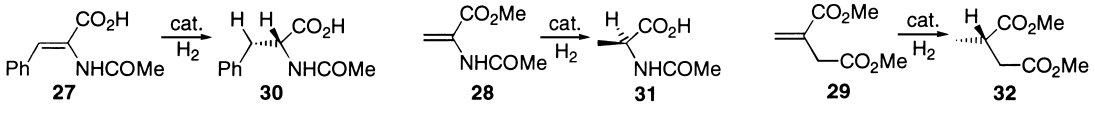
^{31}P NMR spectroscopy and by using this method the purities of the crude bisphosphinites were judged to be 58, 66, 78, 65 and 98%, respectively, and were used in this purity for hydrogenation. The cyclohexyl compound **19** was difficult to prepare (56% yield) and was produced only in a relatively impure state (43% pure by ^{31}P NMR) (in all cases material of higher purity has been obtained for analysis, by filtration of the crude material through neutral alumina under an atmosphere of an inert gas using diethyl ether as eluant).

2.2. Formation of the chiral rhodium(I) catalysts and asymmetric hydrogenation of selected alkenes

The bisphosphinites **13**–**19** (B[3.2.0]DPO) were converted into the rhodium(I) complexes **20**–**26** using an established procedure (Eq. 1).[13,14] ^{31}P NMR spectra on complexes **20**–**26** showed J_{RhP} in the range 175–182 and J_{PP} in the range 0–32 Hz. Each of the catalyst precursors was used, in situ, to promote the hydrogenation of three substrates, namely α-acetamidocinnamic acid **27**, methyl 2-acetamidoacrylate **28** and dimethyl itaconate **29** to give **30**, **31** and **32**, respectively (Scheme 4).



(1)



Scheme 4.

The reactions were conducted in methanol at room temperature under hydrogen (200 psi)[†] and were complete within 3 h when employing 1 mol% of catalyst and GC/MS monitoring indicated quantitative conversion of the α-enamide. Previous studies were carried out under atmospheric pressure of hydrogen and gave a half-life time of 3 min (i.e. reaction is complete after 30 min), showing a good activity of these catalyst precursors. Each experiment was carried out in triplicate and the results are reported in Table 1.

The compounds **20**, **21**, **23**–**25** catalysed the efficient reduction of *N*-acetylcinnamic acid **27** to give (*R*)-*N*-acetylphenylalanine **30** (ee >80%). The catalysts **21**–**25** performed less well in the hydrogenation of methyl 2-acetamidoacylate **28**, yielding (*S*)-*N*-acetylalanine methyl ester **31** in good (66–72%) but not excellent enantiomeric excess. None of the catalysts displayed a high degree of control in the asymmetric

[†] The hydrogenations were performed in a multiwell bomb rated for high pressure; the lowest pressure which could be read reliably on the gauge (200 psi) was used.

Table 1
Enantiomeric excess of asymmetric hydrogenation of substrates **27–29**

Entry	Catalyst	% Enantiomeric Excess (Absolute configuration) [a]					
		N-acetylphenylalanine **30**		*N*-acetyl alanine methyl ester **31**		dimethyl 2-methylsuccinate **32**	
1[b]	(**20**)	81 ± 3	(*R*)				
2	(**21**)	91 ± 1	(*R*)	70 ± 2	(*R*)	21 ± 1	(*S*)
3	(**22**)	67 ± 6	(*R*)	66 ± 0.5	(*R*)	3 ± 1	(*S*)
4	(**23**)	84 ± 3	(*R*)	72 ± 3	(*R*)	33 ± 0.5	(*S*)
5	(**24**)	90 ± 2	(*R*)	68 ± 1	(*R*)	17 ± 0.5	(*R*)
6	(**25**)	87.5 ± 0.5	(*R*)	71 ± 0.5	(*R*)	4 ± 0.5	(*S*)
7	(**26**)	55 ± 0.5	(*S*)	26 ± 2	(*S*)	21 ± 0.5	(*R*)

(a) Determined by comparison of chiral chromatogram (HPLC & GC) with trace of an authentic sample.
(b) This experiment was carried out in methanol under a H_2 pressure of one atmosphere.

hydrogenation of dimethyl itaconate **29**.[29] Contrarywise, the bis(dicyclohexyl)phosphinite **26** produced (*S*)-*N*-acetylphenylalanine (55% ee) and (*R*)-*N*-acetylalanine methyl ester (26% ee).

It is noteworthy that, for the conversion of *N*-acetylcinnamic acid **27** into (*R*)-*N*-acetyl phenylalanine, bisphosphinites with electron releasing aryl moieties such as *para*-fluoro **14**, *para*-methoxy **17** and 2-thienyl (**18**) perform better than the bisphosphinite (**15**) with an electron-withdrawing substituent (trifluoromethyl) in the *para*-position. However, the sulfur atom of the thienyl bisphosphinite **18** does not interfere, in a manner that has been observed in heterogeneous catalysis. Interestingly, the electron-donating cyclohexyl groups in compound **26** give rise, not to a higher enantiomeric excess for the (*R*)-enantiomer of *N*-acetylphenylalanine but, instead, this catalyst furnishes the (*S*)-enantiomer of the product (albeit in modest enantiomeric excess) due, no doubt, to the different steric environment provided by the bulky, six-membered saturated rings.

The reduction of α-acetylamidocinnamic acid using the parent catalyst **20** was explored at different temperatures and different concentrations (Table 2). Conducting the reaction at low temperature in a concentrated solution led to an improvement in the enantiomeric excess of the product.

Table 2
Asymmetric hydrogenation of **27** using rhodium complex **20**[a]

Temperature (°C)	Volume of solvent (mL)	Ee of product **30** (%)
25	15	81.0
12	15	83.5
2	15	87.5
25	10	88.0
25	5	91.5
2	5	92.5

(a) The acid **27** (205 mg) and the complex **20** (8 mg) dissolved in degassed methanol were stirred vigorously under an atmosphere of hydrogen for 10 min.

3. Conclusions

The rhodium(I) complexes **20**–**26** catalyse the asymmetric hydrogenation of α-acetamidocinnamic acid to *N*-acetylphenylalanine, methyl 2-acetamidoacrylate to *N*-acetylalanine methyl ester and, less efficiently, dimethyl itaconate to dimethyl 2-methylsuccinate. The relevant ligands **13**–**19** provide the chiral framework that leads to the observed asymmetric reduction reactions. The effectiveness of this new type of catalyst, in this highly competitive field,[30] is good but not outstanding. However, the significant positive points emanating from this research are as follows:

– the bicyclo[3.2.0]heptane framework can provide useful ligands for organometallic catalysts;
– bicyclo[3.2.0]heptane-3-*endo*-6-*endo*-diol is readily prepared in both enantiomeric forms. When derivatised as a bisphosphinite and complexed to Rh(I), new catalysts for asymmetric hydrogenation reactions can be readily prepared.

We are investigating the use of the complexes **20**–**26** as catalysts for other reactions and, at the same time, we are preparing other types of ligand based on the bicyclo[3.2.0]heptane ring system.

4. Experimental

4.1. General methods

Manipulations of air and moisture sensitive materials were conducted under a nitrogen atmosphere using standard Schlenk techniques. Tetrahydrofuran (THF), ether, pentane, toluene, methanol and petroleum ether, bp 40–60°C (PE), were distilled prior to use. Flash chromatography was performed using Merck 60 silica gel (40–63 μm). Thin layer chromatography (TLC) was carried out using aluminium sheets coated with Merck 60 F_{254} silica gel, R_f values are quoted with the ratio of the eluant system in v/v and visualisation was achieved using ethanolic *p*-anisaldehyde followed by heating or by using a UV lamp (254 nm). Melting points are uncorrected. NMR spectra (^{1}H, ^{13}C, ^{31}P and ^{19}F) were recorded using Bruker AMX400, DRX400, AC300, WM250 and Varian 300 Gemini 2000 spectrometers. The absolute value of the coupling constants (*J*) in hertz and assignments of ^{1}H and ^{13}C peaks were determined using COSY, HETCOR and DEPT135 experiments where necessary. Mass spectra were recorded on Kratos profile HV3, CIPOS, Fisons TRIO1000 solid probe and VG7070E spectrometers and relative intensity is quoted. Optical rotations were measured using an Optical Activity LTD AA-1000 polarimeter operating at 589 nm. Elemental analyses were recorded on a Carlo Erba Strumentazione mod. 1106 CHN analyser. Enantiomeric excess (ee) was determined by chiral gas chromatography or chiral HPLC and retention times (t_R) are quoted in minutes. Chiral GC separations were accomplished using a Lipodex® E (25 m×0.25 mm×0.2 μm film thickness) column from Macherey–Nagel unless otherwise stated. The carrier gas was helium. Chiral HPLC separations were carried out on a Chiralpak AD HPLC column (25 cm×4.6 mm) from Daicel. (−)-ABAC was provided by ChiroTech Technology Limited (Cambridge, UK). The bromide precursors for the chlorophosphine syntheses, cycloocta-1,5-diene (COD), lead(IV) acetate, palladium(II) acetate, *N*-bromosuccinimide, trifluoroacetic acid, α-acetamidocinnamic acid, methyl 2-acetamidoacrylate and dimethyl itaconate, were purchased from Aldrich. *n*-Tributyltin hydride was purchased from Avocado. Fluoroboric acid diethyl ether complex (54% in diethyl ether) and sodium borohydride were purchased from Fluka.

4.2. (1S,5R)-(−)-Bicyclo[3.2.0]hept-2-en-6-one **1**

(−)-ABAC (100 g, 321 mmol, 1 equiv.) was dissolved in aqueous hydrochloric acid (592 g, 20% w/w, 10 equiv.) and stirred for 1 h at room temperature. The product (−)-(**1**) was extracted with diethyl ether (3×600 mL) and concentrated carefully under reduced pressure at 10°C to yield (−)-(**1**) (32 g) as a clear oil (296 mmol, 92%). Bp 57°C, 18 mbar. R_f (EtOAc:PE, 1:2)=0.74; ^{1}H NMR ($CDCl_3$, 300 MHz) 2.47 (ddddd, J=17.1, J=9.6, J=2.1, J=1.8, J=1.8, 1H), 2.63–2.67 (m, 1H), 2.69–2.73 (m, 1H), 3.32 (dddd, J=17.4, J=8.7, J=3.0, J=0.6, 1H), 3.43–3.52 (m, 1H), 3.83–3.91 (m, 1H), 5.77–5.81 (m, 1H), 5.83–5.87 (m, 1H); ^{13}C NMR (75 MHz) 34.83 (CH_2), 36.85 (CH), 54.23 (CH_2), 61.92 (CH), 132.21, 132.95 (C_2 and C_3), 211.5 (C_6); IR (Nujol) 1790 cm^{-1} (CO stretch), 2800 cm^{-1} (CH stretch).

4.3. (1R,2S,3S,5R)-(−)-2-Bromo-3-hydroxy-bicyclo[3.2.0]heptan-6-one **2**

To a solution of (−)-**1** (20.01 g, 185.0 mmol) in acetone (371 mL) and water (106 mL) was added *N*-bromosuccinimide (42.87 g, 241.0 mmol) in portions. The reaction mixture was stirred at room temperature for 20 h. Aqueous sodium metabisulfite (80 mL; 10% w/w) was added to the solution until the initial yellow colour had faded. The acetone was removed under reduced pressure. The residue (white precipitate in water) was redissolved in EtOAc (500 mL), and washed twice with water (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), concentrated under reduced pressure and the residue (pale yellow solid) purified by crystallisation in EtOAc (53 mL) and PE (100 mL) to give (−)-(**2**) (34.51 g; 91%) as white crystals. R_f (EtOAc:PE, 1:2)=0.44; mp 86°C; ^{1}H NMR ($CDCl_3$, 300 MHz) 2.20 (d, ^3J=2.4, 1H, OH, H/D exch.), 2.24 (d, ^2J=14.1, 1H, H_{4endo}), 2.53 (ddd, ^2J=14.1, ^3J=9.6, ^3J=3.9, 1H, H_{4exo}), 3.19–3.23 (m, 2H, H_{7endo} and H_{7exo}), 3.56 (ddd, ^3J=14.1, ^3J=7.5, ^3J=7.5, 1H, H_1), 3.78–3.85 (m, 1H, H_5), 4.32 (s, 1H, H_2), 4.65 (br s, 1H, H_3); ^{13}C NMR ($CDCl_3$, 75 MHz) 37.39 (C_4), 39.08 (C_1), 53.23 (C_7), 57.43 (C_5), 63.44 (C_2), 81.99 (C_3), 211.50 (C_6); MS (CI/NH_3) *m/z* 224.0 (35%, $[M^{81}Br+NH_4]^+$), 222.0 (37, $[M^{79}Br+NH_4]^+$), 142.0 (100, $[M+NH_4-HBr]^+$), 126.0 (70, $[M+NH_4-BrNH_3]^+$); HRMS (CI/NH_3) calcd for $C_7H_{13}BrO_2N$ $[M+NH_4]^+$: 222.01297; found: 222.01263; $[\alpha]_D^{20}$ −45 ($CHCl_3$, *c* 20.2); anal. found: C, 41.08; H, 4.43; calcd for $C_7H_9BrO_2$: C, 41.00; H, 4.42.

4.4. (1R,3R,5R)-(−)-3-Hydroxy-bicyclo[3.2.0]heptan-6-one **3**

To a solution of (−)-**2** (2.01 g; 9.80 mmol) in dry toluene (15 mL) was added under nitrogen *n*-tributyltin hydride (4.28 g, 15 mmol) and AIBN (15 mg, 0.1 mmol). The reaction mixture was heated to 80°C for 1 h, allowed to cool to room temperature and concentrated under reduced pressure providing a yellow liquid. The tin residues were removed by partitioning between acetonitrile (50 mL) and hexane (35 mL) and extracting the acetonitrile layer with hexane (4×35 mL). The combined hexane layers were then back-extracted with acetonitrile (3×30 mL). The combined acetonitrile layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the crude product was purified by chromatography on silica gel with PE:EtOAc (2:1, v/v). The product was crystallised from hexane to yield the title compound (938 mg; 76%) as white crystals. R_f (EtOAc:PE, 1:2)=0.21; mp 62°C; ^{1}H NMR ($CDCl_3$, 300 MHz) 1.74 (s, 1H, OH, H/D exch.), 1.88 (ddd, ^2J=14.1, ^3J=9.3, ^3J=3.6, 1H, H_{4exo}), 1.98 (m, 2H, $2H_2$), 2.20 (d, ^2J=14.1, 1H, H_{4endo}), 2.93 (m, 1H, H_1), 3.05 (ddd, ^2J=18.0, ^3J=3.7, ^3J=3.6, 1H, H_{7endo}), 3.22 (ddd, ^2J=18.0, ^3J=3.7, ^3J=9.6, 1H, H_{7exo}), 3.62 (m, 1H, H_5), 4.56 (br s, 1H, H_3); ^{13}C NMR (75 MHz) 28.54 (C_1), 40.38, 41.16 (C_2, C_4), 53.47 (C_7), 63.39 (C_5), 75.75 (C_3), 214.50 (C_6); MS (EI) *m/z* 126 (4%, $[M]^+$), 108 (76, $[M-H_2O]^+$), 83 (100); HRMS (EI) calcd for $C_7H_{10}O_2$ $[M]^+$: 126.06808; found: 126.06785; $[\alpha]_D^{20}$ −124 ($CHCl_3$, *c* 20.3).

4.5. (1R,3R,5R,6S)-(−)-Bicyclo[3.2.0]heptan-3,6-diol **4**

To a solution of (−)-**3** (19.33 g, 153.0 mmol) in dry methanol (560 mL) at −78°C was added sodium borohydride (7.52 g; 199.0 mmol) in portions over 5 min. The reaction mixture was stirred for 2 h and then quenched with saturated aqueous ammonium chloride (20 mL). The mixture was concentrated under reduced pressure and the yellow liquid obtained was diluted with EtOAc (600 mL) and washed with water (100 mL) and twice with brine (100 mL). The organic layers were dried ($MgSO_4$) and the solvent concentrated under reduced pressure. The product was purified by silica gel chromatography with PE:EtOAc (2:3, v/v) and crystallised from hexane to yield diol (−)-**4** (13.70 g, 70%) as white crystals. R_f (EtOAc:PE, 1:2)=0.21; mp 111°C; ^{1}H NMR (C_6D_6:CS_2, 1:2, v/v, 400 MHz) 1.59 (ddd, ^2J=14.2, ^3J=8.8, ^3J=5.0, 1H, H_{4exo}), 1.63 (m, 2H, H_{2endo} and H_{2exo}), 1.75 (dddd, ^2J=13.4, ^3J=4.8, ^3J=4.8, ^4J=1.3, 1H, H_{7endo}), 2.03 (d, ^2J=14.2, 1H, H_{4endo}), 2.35–2.41 (m, 1H, H_1), 2.55 (dddd, ^2J=13.4, ^3J=9.2, ^3J=8.8, ^4J=1.6, 1H, H_{7exo}), 2.98 (ddd, ^3J=8, ^3J=8, ^3J=8, 1H, H_5), 4.13 (m, 1H, H_6), 4.31 (ddd, ^3J=3.2, ^3J=3.2, ^3J=3.2, 1H, H_3), 5.02 (d, ^3J=3.6, 1H, OH_3, H/D exch.), 5.14 (d, ^3J=10.4, 1H, OH_6, H/D exch.); ^{13}C NMR (C_6D_6:CS_2, 1:2, v/v, 100 MHz) 32.68 (C_1), 35.48 (C_4), 38.27 (C_7), 43.12 (C_2), 45.57 (C_5), 65.26 (C_6), 76.08 (C_3); MS (CI/NH_3) *m/z* 146.1 (75%, $[M+NH_4]^+$), 129.1 (100, $[M+H]^+$), 128.1 (43, $[M]^+$), 111.0 (40, $[M+H-H_2O]^+$), 93.0 (17, $[M+H-2H_2O]^+$); HRMS (CI/NH_3) calcd for $C_7H_{13}O_2$ $[M+H]^+$: 129.09156; found: 129.09144; $[\alpha]_D^{20}$ −52.4 ($CHCl_3$, *c* 20.0); anal. found: C, 65.28; H, 9.45; calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Ee >99% by chiral GC (Lipodex® E).

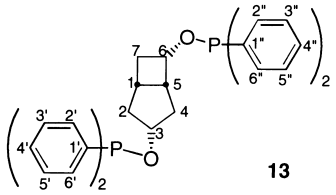
4.6. Synthesis of diarylchlorophosphines. General method A

4.6.1. Bis(2-thienyl)chlorophosphine **11**

A 3 l three-neck flask fitted under nitrogen with a condenser and a dropping-funnel was charged with magnesium turnings (42 g, 1.72 mol) in THF (150 mL). To this suspension was added, in portions, a few drops of a solution of 2-bromothiophene (250 g, 1.53 mol) in THF (200 mL). When the Grignard reaction had started, the rest of the halide solution was added slowly to maintain a gentle reflux. After the addition was complete, the reaction was stirred for another 2 h at room temperature. The reaction flask was cooled to 0°C in an ice bath and **5** (120 g) in THF (100 mL) was added via the dropping-funnel. The reaction was stirred for 2 h at 0°C and then for 1 h at 40–50°C. After cooling down to room temperature, pentane (1.2 L) was added to precipitate the magnesium salts. The salts were filtered off, and the solvent was removed under reduced pressure. To remove the salts completely, the residue was redissolved in pentane and filtered once more through a Celite® pad. After removal of the solvent, the solid residue was dissolved in a Schlenk flask under nitrogen in pentane (600 mL) and the resulting orange solution cooled to 0°C with an ice bath. Dry HCl gas (excess) was passed through concentrated sulfuric acid and then bubbled through the reaction solution for 1 h. The salts was filtered off under nitrogen, and the filter cake was washed with pentane (5×100 mL). After removal of the solvent the crude yellow oil was distilled to give **11** (100 g, 56%) as a pale yellow solid. Bp 144°C, 0.1 mbar; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.19 (ddd, *J*=5.1, *J*=3.4, *J*=1.8, 1H), 7.63 (ddd, *J*=6.4, *J*=3.4, *J*=1.0, 1H), 7.78 (dd, *J*=5.1, *J*=1.0, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 127.67 (d, $^3J_{PC}$=8.7, C_4), 133.82 (s, C_5), 135.97 (d, $^2J_{PC}$=35.9, C_3), 140.19 (d, $^1J_{PC}$=46.8, C_2); ^{31}P NMR ($CDCl_3$, 162 MHz) 51.1 (s); MS (EI) *m/z* 234 (16%, $[M^{37}Cl]^+$), 232 (40, $[M^{35}Cl]^+$), 197 (36, $[M-Cl]^+$), 166 (100, $[M-Cl-P]^+$ rearr.); HRMS (EI) calcd for $C_8H_6ClPS_2$ $[M]^+$: 231.93372; found: 231.93406.

The diarylchlorophosphines **7**–**12** were synthesised using the same general method A as for **11**.

4.7. Synthesis of the bisphosphinite ligands (B[3.2.0]DPO) **13**–**19**. General method B



13

To a solution of (−)-**4** (300 mg, 2.34 mmol) in dry THF (15 mL) under nitrogen was added triethylamine (0.50 g, 4.91 mmol). This solution was cooled to 0°C in an ice bath and the chlorophosphine (4.91 mmol) was added dropwise. When the addition was complete, the ice bath was removed and stirring was continued at ambient temperature for 15 h. The triethylammonium salt was filtered off through a Celite® pad under nitrogen, and the solvent was removed under reduced pressure to give the crude product, used at this stage for in situ catalyst preparations. For analytical purposes further purification was carried out. To remove the remaining salts, chlorophosphine and impurities from this crude, a mixture of dry diethyl ether:pentane (2:1, v/v) was added to the crude ligand, and this solution was filtered under nitrogen through a neutral alumina pad. Removal of the solvent gave the bisphosphinite ligand as an oil; most of the products became solid after a few days. The purity was checked by ^{31}P NMR.

4.7.1. (*1*R,*3*R,*5*R,*6*S)-*3,6-Bis[diphenylphosphinooxy]-bicyclo[3.2.0]heptane* **13**

This bisphosphinite was synthesised using general method B, and obtained as a white solid (98% yield, 40% ^{31}P NMR purity). ^{13}C NMR ($CDCl_3$, 100 MHz) 30.01 (C_1), 33.88 (C_4), 37.47 (C_7), 40.98 (C_2), 45.52 (C_5), 70.26 (C_6), 85.11 (C_3), 128.17, 128.23, 128.85, 128.89, 128.98, 129.01, 129.12, 130.13, 130.25, 130.34, 130.49, 130.51, 130.68, 130.71, 130.73 (20 CH, Ph), 142.06, 142.25, 142.49 (4 C^{IV}, Ph); ^{31}P NMR ($CDCl_3$, 162 MHz) 107.98 (s, 1P), 109.83 (s, 1P); HRMS (EI) calcd for $C_{31}H_{26}F_4O_2P_2$ $[M]^+$: 496.17210; found: 496.17177.

4.7.2. (*1*R,*3*R,*5*R,*6*S)-*3,6-Bis[di(4′-fluorophenyl)phosphinooxy]-bicyclo[3.2.0]heptane* **14**

This bisphosphinite was synthesised using general method B, and obtained as a white solid (88% yield, 99% ^{31}P NMR purity). ^{13}C NMR ($CDCl_3$, 100 MHz) 30.41 (s, C_1), 34.02 (d, $^3J_{PC}$=5.6, C_4), 37.18 (d, $^3J_{PC}$=6.6, C_7), 41.07 (d, $^3J_{PC}$=4.8, C_2), 45.65 (d, $^3J_{PC}$=4.9, C_5), 70.17 (d, $^2J_{PC}$=16.4, C_6), 84.99 (d, $^2J_{PC}$=17.9, C_3), 115.56, 115.59, 115.61 (3 dd, intensity: 1:2:1, $^2J_{FC}$=20.8, $^3J_{PC}$=7.2, 7.4, 7.6, $C_{3'}$, $C_{5'}$, $C_{3''}$ and $C_{5''}$), 132.29, 132.37, 132.81, 132.91 (4 dd, $^3J_{FC}$=22.9, 22.9, 23.5, 23.5, $^2J_{PC}$=8.1, $C_{2'}$, $C_{6'}$, $C_{2''}$ and $C_{6''}$), 137.58–138.23 (m, 13 signals, $C_{1'}$ and $C_{1''}$), 163.61, 163.70, 163.77, 163.80 (4 d, $^1J_{FC}$=247.7, $C_{4'}$ and $C_{4''}$); ^{31}P NMR ($CDCl_3$, 101 MHz) 105.63 (s, 1P), 107.26 (s, 1P); MS (EI) *m/z* 568 (0.3%, $[M]^+$), 458 (13), 316 (16), 239 (37), 238 (43), 237 (100), 219 (33); HRMS (EI) calcd for $C_{31}H_{26}F_4O_2P_2$ $[M]^+$: 568.13446; found: 568.13466.

4.7.3. (*1*R,*3*R,*5*R,*6*S)-*3,6-Bis[di(4′-trifluoromethylphenyl)phosphinooxy]-bicyclo[3.2.0]heptane* **15**

This bisphosphinite was synthesised using general method B, and obtained as a white solid (84% yield, 98% ^{31}P NMR purity). ^{13}C NMR ($CDCl_3$, 100 MHz) 30.77 (s, C_1), 34.19 (d, $^3J_{PC}$=5.8, C_4), 37.01 (d, $^3J_{PC}$=6.5, C_7), 41.25 (d, $^3J_{PC}$=4.9, C_2), 45.81 (d, $^3J_{PC}$=5.0, C_5), 70.87 (d, $^2J_{PC}$=16.8, C_6), 85.75 (d, $^2J_{PC}$=17.9, C_3), 124.07, 124.08, 124.10, 124.12 (4 q, $^1J_{FC}$=270.6, 4 CF_3), 125.41 (m, $C_{3'}$, $C_{5'}$, $C_{3''}$ and $C_{5''}$), 130.10, 130.24, 130.76, 130.80 (4 d, $^2J_{PC}$=21.6, 21.6, 22.4, 22.2, $C_{2'}$, $C_{6'}$, $C_{2''}$ and $C_{6''}$), 131.17–132.00 (m, $C_{4'}$ and $C_{4''}$), 146.20, 146.43, 146.66, 146.68 (4 d, $^1J_{PC}$=23.1, 22.9, 23.0, 19.0, $C_{1'}$ and $C_{1''}$); ^{31}P NMR ($CDCl_3$, 101 MHz) 103.21 (s, 1P), 104.59 (s, 1P); MS (EI) *m/z* 768 (0.3%, $[M]^+$),

447 (15, $[M-P(Aryl)_2]^+$), 431 (9, $[M-OP(Aryl)_2]^+$), 339 (84), 337 (60), 321 (54), 93 (100); HRMS (EI) calcd for $C_{35}H_{26}F_{12}O_2P_2$ $[M]^+$: 768.12164; found: 768.12020.

*4.7.4. (1*R,*3*R,*5*R,*6*S*)-3,6-Bis[di(3′,5′-dimethyl-4′-methoxyphenyl)phosphinooxy]-bicyclo[3.2.0]-heptane* ***16***

This bisphosphinite was synthesised using general method B, and obtained as a white solid (90% yield, 99% ^{31}P NMR purity). ^{13}C NMR ($CDCl_3$, 100 MHz) 16.19, 16.21, 16.23 (3 s, intensity: 1:2:1, 8 CH_3), 29.25 (s, C_1), 33.66 (d, $^3J_{PC}$=5.7, C_4), 38.30 (d, $^3J_{PC}$=6.8, C_7), 40.91 (d, $^3J_{PC}$=4.5, C_2), 45.13 (d, $^3J_{PC}$=4.5, C_5), 59.58 (bs, 4 OCH_3), 69.58 (d, $^2J_{PC}$=15.7, C_6), 84.23 (d, $^2J_{PC}$=16.9, C_3), 130.64 (bd, $^3J_{PC}$=7.4, $C_{3'}$, $C_{5'}$, $C_{3''}$ and $C_{5''}$), 130.86, 131.03, 131.25, 131.31 (4 d, $^2J_{PC}$=22.2, 22.0, 22.1, 23.0, $C_{2'}$, $C_{6'}$, $C_{2''}$ and $C_{6''}$), 136.91–137.41 (m, $C_{1'}$ and $C_{1''}$), 157.89, 157.99, 158.04, 158.05 (4 s, $C_{4'}$ and $C_{4''}$); ^{31}P NMR ($CDCl_3$, 162 MHz) 105.44 (s, 1P), 107.66 (s, 1P); MS (EI) *m/z* 728 (6%, $[M]^+$), 453 (38), 427 (6, $[M-P(Aryl)_2]^+$), 317 (100), 301 (58), 276 (3, $[M-Ar-OP(Aryl)_2]^+$); HRMS (EI) calcd for $C_{43}H_{54}O_6P_2$ $[M]^+$: 728.33954; found: 728.33997.

*4.7.5. (1*R,*3*R,*5*R,*6*S*)-3,6-Bis[di(4′-methoxyphenyl)phosphinooxy]-bicyclo[3.2.0]heptane* ***17***

This bisphosphinite was synthesised using general method B, and obtained as a white solid (84% yield, 99% ^{31}P NMR purity). ^{13}C NMR ($CDCl_3$, 100 MHz) 30.24 (s, C_1), 34.07 (d, $^3J_{PC}$=4.7, C_4), 37.69 (d, $^3J_{PC}$=5.8, C_7), 41.15 (d, $^3J_{PC}$=3.3, C_2), 45.72 (d, $^3J_{PC}$=3.7, C_5), 55.34 (s, 4 OCH_3), 69.87 (d, $^2J_{PC}$=15.4, C_6), 84.73 (d, $^2J_{PC}$=17.4, C_3), 114.05 (″d″, *J*=7.0, $C_{3'}$, $C_{5'}$, $C_{3''}$ and $C_{5''}$), 132.10–132.83 (m, $C_{2'}$, $C_{6'}$, $C_{2''}$ and $C_{6''}$), 133.77–134.32 (m, $C_{1'}$ and $C_{1''}$), 160.59, 160.70, 160.78, 160.79 (4 s, $C_{4'}$ and $C_{4''}$); ^{31}P NMR ($CDCl_3$, 101 MHz) 107.45 (s, 1P), 109.68 (s, 1P); MS (EI) *m/z* 616 (3%, $[M]^+$), 369 (14), 262 (34), 261 (100), 245 (45); HRMS (EI) calcd for $C_{35}H_{38}O_6P_2$ $[M]^+$: 616.21436; found: 616.21316.

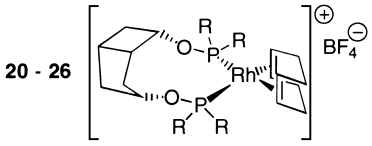
*4.7.6. (1*R,*3*R,*5*R,*6*S*)-3,6-Bis[di(2′-thienyl)phosphinooxy]-bicyclo[3.2.0]heptane* ***18***

This bisphosphinite was synthesised using general method B, and obtained as a pale yellow paste (92% yield, 98% ^{31}P NMR purity). ^{13}C NMR ($CDCl_3$, 100 MHz) 30.19 (s, C_1), 33.64 (d, $^3J_{PC}$=5.5, C_4), 37.51 (d, $^3J_{PC}$=6.7, C_7), 41.03 (d, $^3J_{PC}$=4.7, C_2), 45.54 (d, $^3J_{PC}$=4.9, C_5), 69.59 (d, $^2J_{PC}$=11.9, C_6), 84.40 (d, $^2J_{PC}$=14.7, C_3), 127.66, 127.68 (2 d, $^3J_{PC}$=7.8, $C_{4'}$ and $C_{4''}$), 131.72, 131.87, 132.02, 132.04 (4 s, $C_{5'}$ and $C_{5''}$), 133.84, 134.17, 134.25, 134.43 (4 d, $^2J_{PC}$=29.5, 30.1, 31.0, 30.7, $C_{3'}$ and $C_{3''}$), 146.26, 143.41, 143.70, 144.00 (4 d, $^1J_{PC}$=33.9, 35.2, 31.7, 35.2, $C_{2'}$ and $C_{2''}$); ^{31}P NMR ($CDCl_3$, 101 MHz) 85.16 (s, 1P), 88.08 (s, 1P); MS (EI) *m/z* 520 (0.7%, $[M]^+$), 323 (3.5, $[M-P(thienyl)_2]^+$), 297 (61), 280 (15), 215 (45), 213 (76), 197 (100); HRMS (EI) calcd for $C_{23}H_{22}O_2P_2S_4$ $[M]^+$: 519.99780; found: 519.99753.

*4.7.7. (1*R,*3*R,*5*R,*6*S*)-3,6-Bis[di(cyclohexyl)phosphinooxy]-bicyclo[3.2.0]heptane* ***19***

This bisphosphinite was synthesised using general method B, and obtained as a white solid (56% yield, 43% ^{31}P NMR purity). ^{13}C NMR ($CDCl_3$, 100 MHz) 24.94–27.00 (m), 27.81–28.37 (m), 30.19 (s), 36.56 (s), 37.24–37.96 (m), 44.01 (s), 59.90 (s), 72.22 (d, $^2J_{PC}$=17.8, C_6), 86.72 (d, $^2J_{PC}$=18.3, C_3); ^{31}P NMR ($CDCl_3$, 162 MHz) 147.36 (s, 1P), 150.51 (s, 1P); MS (FAB) *m/z* 437.2 (6%, $[M-C_6H_{11}]^+$), 307.2 (13, $[M-OP(C_6H_{11})_2]^+$), 231.1 (44), 215.1 (100).

*4.8. Preparation of the rhodium complexes **21**–**26**. General method C*



To the bisphosphinites **13**–**19** (2.2 mmol) in a Schlenk flask under nitrogen was added degassed methanol (20 mL) and $[(COD)_2Rh]BF_4$ (4.8 mmol) at room temperature. The mixture was stirred for 2 h and the solvent was carefully removed under reduced pressure. The residue was then used promptly for NMR characterisation.

4.8.1. [((1R,3R,5R,6S)-3,6-Bis[diphenylphosphinooxy]-bicyclo[3.2.0]heptane)Rh(COD)]$^+$ BF_4^- ***20***

^{31}P NMR ($CDCl_3$, 162 MHz) 109.50 (d, J_{RhP}=178, 1P), 114.80 (d, J_{RhP}=178, 1P).

4.8.2. [((1R,3R,5R,6S)-3,6-Bis[di(4′-fluorophenyl)phosphinooxy]-bicyclo[3.2.0]heptane)Rh(COD)]$^+$ BF_4^- ***21***

^{31}P NMR ($CDCl_3$, 162 MHz) 105.53 (dd, J_{RhP}=182, J_{PP}=10.8, 1P), 109.22 (dd, J_{RhP}=182, J_{PP}=10.8, 1P).

4.8.3. [((1R,3R,5R,6S)-3,6-Bis[di(4′-trifluoromethylphenyl)phosphinooxy]-bicyclo[3.2.0]heptane)-Rh(COD)]$^+$ BF_4^- ***22***

^{31}P NMR ($CDCl_3$, 162 MHz) 96.29 (dd, J_{RhP}=176, J_{PP}=20.6, 1P), 113.07 (dd, J_{RhP}=176, J_{PP}=20.6, 1P).

4.8.4. [((1R,3R,5R,6S)-3,6-Bis[di(3′,5′-dimethyl-4′-methoxyphenyl)phosphinooxy]-bicyclo[3.2.0]-heptane)Rh(COD)]$^+$ BF_4^- ***23***

^{31}P NMR ($CDCl_3$, 162 MHz) 105.53 (dd, J_{RhP}=182, J_{PP}=10.8, 1P), 109.22 (dd, J_{RhP}=182, J_{PP}=10.8, 1P).

4.8.5. [((1R,3R,5R,6S)-3,6-Bis[di(4′-methoxyphenyl)phosphinooxy]-bicyclo[3.2.0]heptane) Rh(COD)]$^+$ BF_4^- ***24***

^{31}P NMR ($CDCl_3$, 162 MHz) 105.94 (dd, J_{RhP}=182, J_{PP}=9.7, 1P), 110.61 (dd, J_{RhP}=182, J_{PP}=9.7, 1P).

4.8.6. [((1R,3R,5R,6S)-3,6-Bis[di(2′-thienyl)phosphinooxy]-bicyclo[3.2.0]heptane)Rh(COD)]$^+$ BF_4^- ***25***

^{31}P NMR ($CDCl_3$, 162 MHz) 79.77 (dd, J_{RhP}=175.9, J_{PP}=39.2, 1P), 93.3 (dd, J_{RhP}=175.9, J_{PP}=39.2, 1P).

4.8.7. [((1R,3R,5R,6S)-3,6-Bis[di(cyclohexyl)phosphinooxy]-bicyclo[3.2.0]heptane)Rh(COD)]$^+$ BF_4^- ***26***

^{31}P NMR ($CDCl_3$, 162 MHz) 210.11 (d, J_{RhP}=175.5, 1P), 218.78 (d, J_{RhP}=179.1, 1P).

4.9. Asymmetric hydrogenation reactions. General method D

To the B[3.2.0]DPO ligand **13**–**19** (0.01 mmol) was added in a Schlenk flask under nitrogen degassed methanol (5 mL) and $[(COD)_2Rh]BF_4$ (11 μmol). The reaction mixture was stirred at room temperature until everything was dissolved. A 50 mL hydrogenation autoclave was charged with 1.0 mmol of the substrate **27**–**29** and a magnetic stirrer bar. The autoclave was assembled, flushed five times with hydrogen (to 200 psi), and the solution of the catalyst formed in situ was added through the solvent port. Hydrogenation was effected at room temperature (200 psi hydrogen pressure), and was complete after 3 h in all cases (reaction monitored either by GC/MS, ^{1}H NMR or TLC). The enantiomeric excesses (ees) of the hydrogenated products **30**–**32** were determined either by chiral HPLC or by chiral GC and are reported in Tables 1 and 2.

4.9.1. Hydrogenation of α-acetamidocinnamic acid **27**

The α-acetamidocinnamic acid was hydrogenated following general method D. The ee was determined by chiral HPLC (Chiralpak AD). Mobile phase: heptane:*i*-PrOH:trifluoroacetic acid, 90:10:1, v/v/v. Flow rate: 1 mL/min, 20 μL injected in IPA. t_R (min): 10 (*R*)-enantiomer, 12.5 (*S*)-enantiomer.

4.9.2. Hydrogenation of methyl 2-acetamidoacrylate **28**

The methyl 2-acetamidoacrylate was hydrogenated following general method D. The ee was determined by chiral GC (Chirasil Dex CB column). Injection: 200°C, program: 60°C for 5 min, then 10°C/min, to 200°C and left for 10 min. Detection: FID 200°C, split 1/100, 1 μL injected in methanol. t_R: 12.80 (*S*)-enantiomer, 12.95 (*R*)-enantiomer.

4.9.3. Hydrogenation of dimethyl itaconate **29**

The dimethyl itaconate was hydrogenated following general method D. The ee was determined by chiral GC (Chiraldex G-TA column). Injection: 200°C, program: 80°C for 25 min, split 1/100, 1 μL injected in methanol. t_R: 18.80 (*S*)-enantiomer, 20.10 (*R*)-enantiomer.

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