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1,2-Bis(2,5-diphenylphospholano)methane, a new ligand for asymmetric hydrogenation

Mark Jackson* and Ian C. Lennon

Dowpharma, Chirotech Technology Ltd, a subsidiary of The Dow Chemical Company, Unit 162 Cambridge Science Park, Milton Road, Cambridge CB4 0GH, UK

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Abstract—1,2-Bis(2,5-diphenylphospholano)methane (Ph-BPM) has been prepared in good yield from 2,5-*trans*-diphenylphospholane–borane adduct. Rhodium and ruthenium complexes of this ligand have been prepared and their usefulness in asymmetric hydrogenation has been investigated. [Ph-BPM Rh(COD)]BF_4 showed high activity and selectivity for itaconate and dehydroamino acid hydrogenation. Ph-BPM $RuCl_2$(DPEN) was effective for imine hydrogenation.

Asymmetric hydrogenation has been readily adopted as a method of choice to provide single enantiomer products by both industry and academia. Many ligands and catalysts are now commercially available and numerous applications have been reported.[1] There is still a need to develop new catalytic systems with improved activity and selectivity.

Recently, a series of 1,2-bis(alkylmethylphosphino)-methanes **1** (abbreviated as MiniPHOS, alkyl = *tert*-butyl, cyclohexyl, isopropyl, phenyl) were prepared and their use was demonstrated in the Rh(I)-catalysed asymmetric hydrogenation of dehydroamino acids and itaconate derivatives.[2] Rh(I) complexes of these ligands have also been used in the enantioselective hydrogenation of enamides[3] and (*E*)-β-(acylamino)acrylates.[4] In addition, Pfizer has reported a novel methylene bridged ligand **2**, which has three hindered quadrants (one of the methyl groups of MiniPHOS has been replaced with *tert*-butyl).[5] This ligand is also highly effective for the Rh(I)-catalysed asymmetric hydrogenation of dehydroamino acids. In general, these methylene bridged ligands show good activity for asymmetric hydrogenation.

We demonstrated that the ligand, 1,2-bis(2,5-diphenylphospholano)ethane (Ph-BPE) **3**, exhibited enhanced activity and selectivity over the existing members of the BPE ligand family in rhodium-catalysed asymmetric hydrogenation.[6] As a result of this we have investigated the synthesis and applications of the methylene bridged analogue, 1,2-bis(2,5-diphenylphospholano)methane (Ph-BPM) **4** (Fig. 1).

A single enantiomer of 1-hydroxy-1-oxo-2,5-*trans*-diphenylphospholane **5** was prepared using the literature procedure.[7] The phosphinic acid was reduced using phenylsilane in toluene to give (*R*,*R*)-2,5-*trans*-diphenylphospholane–borane adduct **6** (Scheme 1). There are a variety of potential methods for converting compound **6** into (*R*,*R*)-Ph-BPM. Unfortunately, direct reaction with dibromomethane was unsuccessful. The reaction

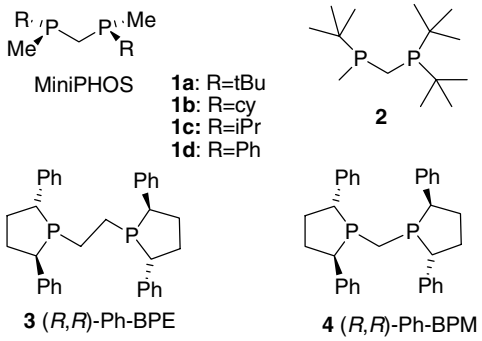

Figure 1.

Keywords: Rhodium; Asymmetric catalysis; Hydrogenation; Phospholane.
* Corresponding author. Tel.: +44 1223 728065; fax: +44 1223 506701; e-mail: pjackson@dow.com

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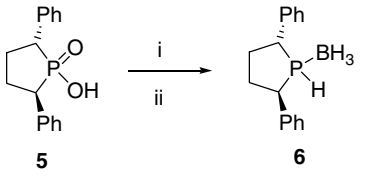
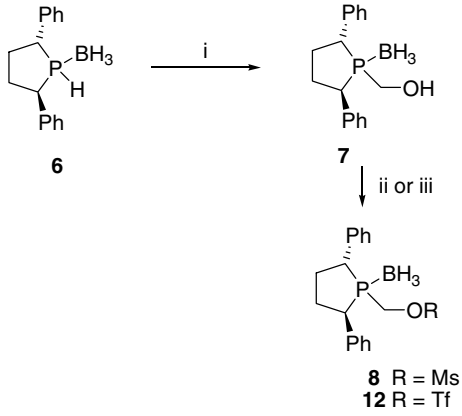
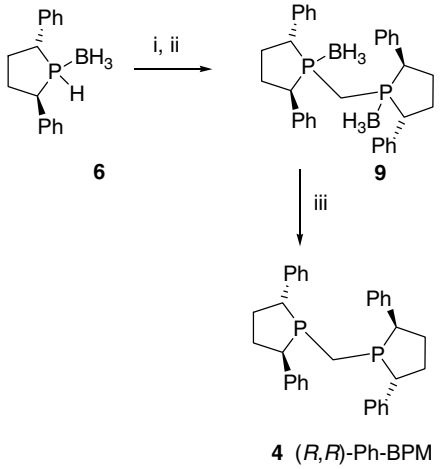


Scheme 1. Reagents and conditions: (i) $PhSiH_3$, PhMe; (ii) $BH_3{\cdot}Me_2S$ (83%).



Scheme 2. Reagents and conditions: (i) $(CH_2O)_n$, KOH, MeOH (86%); (ii) MsCl, DIPEA, THF (90%); (iii) Tf_2O, Et_3N, DCM (90%).



Scheme 3. Reagents and conditions: (i) *n*-BuLi, THF; (ii) **8** (12%) or **12** (61%); (iii) DABCO, PhMe (99%).

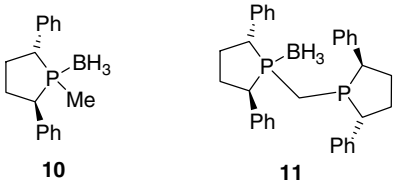


Figure 2.

Table 1. Hydrogenation using [(*R*,*R*)-Ph-BPM Rh(COD)]BF_4

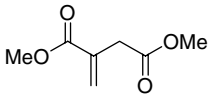
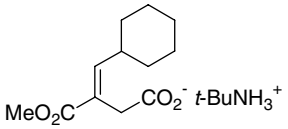
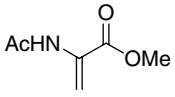
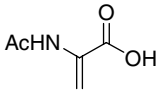
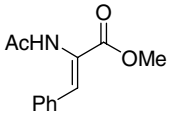
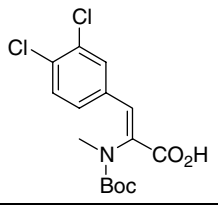
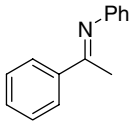
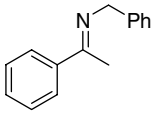
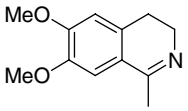
Entry	Substrate	S/C	Conditions	Conv. (%)	ee (%)
1		10,000	MeOH, 30 °C, 10 bar H_2, 15 min	100	99.5 (*R*)
2		1000	MeOH, 30 °C, 10 bar H_2, 6 h	100	91 (*R*)
3		5000	MeOH, 30 °C, 6 bar H_2, 1 h	>99	>99 (*S*)
4		5000	MeOH, 30 °C, 6 bar H_2, 75 min	>99	>99 (*S*)
5		3000	MeOH, 30 °C, 10 bar H_2, 18 h	>99	99 (*S*)
6		200	MeOH, 30 °C, 10 bar H_2, 18 h	96%	95 (*R*)

Table 2. Hydrogenation using [(*R*,*R*)-Ph-BPM $RuCl_2$(*S*,*S*)-DPEN

Entry	Substrate	S/C/B	Conditions	Conv. (%)	ee (%)
1		200:1:10	^{i}PrOH, 60 °C, 10 bar H_2, 5 mol % KO^{t}Bu in ^{t}BuOH, overnight	>99	71
2		100:1:5	^{i}PrOH, 60 °C, 10 bar H_2, 5 mol % KO^{t}Bu in ^{t}BuOH, overnight	>99	82
3		100:1:10	^{i}PrOH, 70 °C, 10 bar H_2, 10 mol % KO^{t}Bu in ^{t}BuOH, overnight	100	89

was attempted using both borane adduct **6** and the corresponding free phosphine.

The methylene bridge was introduced via hydroxymethylation of compound **6** using formaldehyde (Scheme 2).[8] In our first approach to produce Ph-BPM, the hydroxy group of compound **7** was converted into mesylate **8** which was then reacted with compound **6** to give Ph-BPM borane adduct **9** (Scheme 3). Yields were low and the reaction gave a complex mixture of products with the only identifiable impurity being the methylated compound **10** (Fig. 2).

The addition of TMEDA to the lithiated diphenylphospholane–borane adduct, prior to addition of the mesylate, resulted in an improved yield. The initial product **11** contained only one BH_3. This was removed by treatment with DABCO to give (*R*,*R*)-Ph-BPM **4** in 26% overall yield for the two steps. Whilst being far from ideal this enabled the preparation of synthetically useful quantities of the ligand. Use of triflate **12** instead of mesylate **8** resulted in a vastly improved yield of borane adduct **9**. Deprotection using DABCO in toluene gave (*R*,*R*)-Ph-BPM **4** in near quantitative yield. This improved method is now suitable for preparation of multigram quantities of the ligand.[9]

[(*R*,*R*)-Ph-BPM Rh(COD)]BF_4 was prepared by reaction of the ligand with [$Rh(COD)_2$]BF_4 in dichloromethane.[10] Good activity and selectivity was shown for a number of common substrates, including dimethyl itaconate, methyl acetamidoacrylate, acetamidoacrylic acid and methyl acetamidocinnamate (Table 1).[11] The precatalyst (*R*,*R*)-Ph-BPM $RuCl_2$(*S*,*S*)-DPEN was prepared for use in imine hydrogenation (Table 2).[12] (*R*,*R*)-Ph-BPM $RuCl_2$(*R*,*R*)-DPEN was also prepared but showed inferior selectivity. *N*-(1-Phenylethylidene)aniline was hydrogenated with moderate selectivity, alternative catalysts for this substrate have been reported.[13] *N*-(1-Phenylethylidene)benzylamine was hydrogenated with good selectivity, comparable with the best literature results.[14] 1-Methyl-6,7-dimethoxy-3,4-dihydroisoquinoline was hydrogenated with good selectivity. This substrate has also been hydrogenated successfully under transfer hydrogenation conditions[14] and using iridium catalysis.[15]

1,2-Bis(2,5-diphenylphospholano)methane (Ph-BPM) has been prepared in good yield from 2,5-*trans*-diphenylphospholane–borane adduct. The route developed is suitable for the large scale synthesis of this ligand. [Ph-BPM Rh(COD)]BF_4 demonstrated excellent activity and selectivity for itaconate and dehydroamino acid hydrogenation substrates. Work is in progress to identify new applications for this ligand and to further extend the phenyl phospholane ligand family.

References and notes

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9. *Borane adduct* **6** (3.44 g, 13.54 mmol) was dissolved in dry THF (30 ml) under nitrogen. The solution was cooled to −65 °C and a solution of *n*-BuLi (2.5 M in hexanes, 0.34 ml, 0.86 mmol) was added dropwise. After 1 h a solution of **12** (6.20 g, 14.90 mmol) in dry THF (15 ml) was added. The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with 1 M aqueous HCl (30 ml). The THF phase was separated and concentrated under reduced pressure. The aqueous phase was extracted with DCM (2 × 30 ml). The DCM extracts were combined with the THF concentrate and washed with water (20 ml), dried ($MgSO_4$) and filtered

through silica (25 g) eluting with DCM (50 ml). The solution was concentrated under reduced pressure and the residue crystallised from ethyl acetate/heptane (1:3, 16 ml) to give **9** (4.33 g, 61%). Borane adduct **9** (986 mg, 1.90 mmol) and DABCO (639 mg, 5.69 mmol) were charged to a 50 ml Schlenk flask. The flask was deoxygenated by evacuation and filling with nitrogen (×5). Toluene (10 ml) was added and the solution was heated at 60 °C for 2 h. The solution was allowed to cool to room temperature with stirring overnight. The reaction mixture was filtered through a pad of silica (6 g) under nitrogen, eluting with toluene (20 ml). The solvent was evaporated under reduced pressure to give (*R*,*R*)-Ph-BPM **4** (929 mg, 99%), ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.25–6.90 (20H, m), 3.60–3.50 (2H, m), 3.27–3.18 (2H, m), 2.36–2.24 (2H, m), 2.16–2.06 (2H, m), 1.94–1.70 (4H, m) and 0.68 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 144.4 (t, *J* 8 Hz), 139.1, 128.7, 128.6, 128.3 (t, *J* 5 Hz), 128.1, 126.2, 125.8, 49.3 (t, *J* 5 Hz), 47.3 (t, *J* 5 Hz), 36.9, 31.8 and 22.0 (t, *J* 34 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ ppm 4.5. Found HRMS *m*/*z* $[M+H]^+$, 493.220, $C_{33}H_{35}P_2$ requires 493.2214.

10. *Data for [(R,R)-Ph-BPM Rh(COD)]BF$_4$*: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.62–7.55 (8H, m), 7.47–7.40 (2H, m), 7.20–7.15 (6H, m), 6.81 (4H, d, *J* 8 Hz), 5.30 (2H, m), 3.70–3.60 (4H, m), 3.32–3.26 (2H, m), 3.15–2.98 (2H, m), 2.52–2.38 (6H, m), 2.25–2.15 (2H, m), 2.08–1.96 (4H, m), 1.70–1.60 (2H, m) and 1.38–1.28 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 140.4, 135.3, 129.9, 129.4, 129.1, 128.3, 127.8, 127.4, 100.2, 99.7, 49.5, 47.3, 39.8 (t, *J* 20 Hz), 31.2, 30.6, 30.1 and 28.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ ppm −6.9 (d, *J* 136 Hz).
11. *Representative procedure*: The reaction was carried out in an Argonaut Endeavor hydrogenation vessel. The glass liner was charged with dimethyl itaconate (1.58 g, 10.0 mmol) and [(*R*,*R*)-Ph-BPM Rh(COD)]BF_4 (0.8 mg, 0.001 mmol, S/C 10,000). The vessel was charged to 10 bar nitrogen and vented (×5). Degassed methanol (4 ml) was added. The vessel was charged to 10 bar nitrogen and vented (×2). The reaction was stirred at 1000 rpm and heated to 30 °C. The vessel was charged to 10 bar hydrogen. Hydrogen uptake was complete after 15 min. The mixture was cooled to room temperature, vented and evaporated to give (*R*)-2-methylsuccinic acid dimethyl ester, conversion 100%, ee 99.5% (Chiraldex GTA, 30 m × 0.25 mm, injector/detector 180 °C, helium 14 psi, 90 °C for 6 min, then ramp at 1 °C/min to 105 °C, retention times *S* 9.81 min, *R* 10.03 min).
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