Synthesis and Applications of HexaPHEMP, a Novel Biaryl Diphosphine Ligand

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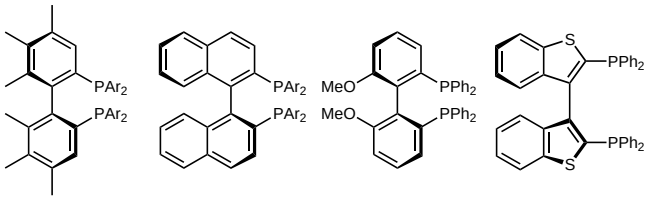
Abstract: The novel biaryldiphosphine ligand **1** (HexaPHEMP) has been prepared in five steps from commercially available 3,4,5-trimethylphenol using a concise synthetic route. This approach also allows fine tuning of the ligand's stereoelectronic properties through the variation of the aromatic groups on the ligating phosphorus atoms. In certain asymmetric hydrogenation processes, catalysts containing this ligand were found to have enhanced activity and selectivity over other biaryldiphosphine-containing catalysts.

Keywords: asymmetric catalysis; asymmetric hydrogenation; biaryldiphosphine; HexaPHEMP; P-ligands; ruthenium

Introduction

The development of chiral ligands required for the preparation of highly active and enantioselective transition metal catalysts remains of great interest and value. In particular, atropisomeric biaryldiphosphines have been utilised effectively in the asymmetric hydrogenation of a variety of functionalities including ketones, imines, α-keto esters, β-keto esters, β-diketones, α,β-unsaturated carboxylic acids, β-dehydroamino acids, itaconates, enamides and unsaturated alcohols.[1] Although a very large number of chiral biarylphosphine ligands have been prepared and investigated in small quantities for research, fewer have been developed commercially, and in such context the synthetic accessibility can often be a limiting factor. In fact, BINAP[2] (**2a**) and analogues, MeO-BIPHEP[3] (**3**) and BITIANP[4] (**4**) (Figure 1) are representative of the few chiral biaryldiphosphines that have been developed sufficiently for large-scale industrial use. In a quest to develop an accessible biaryldiphosphine ligand that forms catalytically active complexes with transition metals, having equal or improved activity and selectivity to equivalent complexes of known biaryldiphosphine ligands, we prepared a series of ligands based on the 4,4′,5,5′,6,6′-hexamethybiphenyl (HexaPHEMP) backbone **1**.[5] Herein, we outline the synthesis and preliminary catalytic results associated with these ligands.



1a (Ar = Ph)
1b (Ar = Xyl)
2a (Ar = Ph)
2b (Ar = *p*-Tol)
2c (Ar = Xyl)
3
4

Figure 1. Biaryldiphosphine ligands prepared at industrially useful scale.

Results and Discussion

Synthesis of HexaPHEMP Ligands

The route used to synthesise HexaPHEMP (**1a**) is shown in Scheme 1. We anticipated that symmetric 3,4,5-trisubstituted phenol **5** would provide straightforward access to biphenol derivatives through oxidative coupling. Indeed, oxidative coupling of 3,4,5-trimethylphenol (**5**) using 5 mol % $VO(acac)_2$[6] under a constant stream of air at r.t. for 48 h furnished the racemic biphenol **6** in 74% isolated yield. This was subsequently resolved by chiral HPLC (Chiral Technologies Europe). This reaction and separation were readily conducted on

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a 90 g scale. Each diol enantiomer was converted to the enantiomerically pure phosphine products separately and only the (*R*)-enantiomer is discussed below. Enantiomerically pure (*R*)-biphenol **6** was converted to the corresponding (*R*)-*bis*-triflate **7** using Tf_2O and pyridine in 95% yield following recrystallisation from methanol. Since our attempts to then introduce two phosphine groups simultaneously were unsuccessful, a stepwise approach was used. The first phosphine group was introduced *via* $Pd(OAc)_2$ (4 mol %)-catalysed cross-coupling of $Ph_2P(O)H$ and (*R*)-bis-triflate **7** in the presence of 1,4-bis(diphenylphosphino)butane (dppb) and Hünig's base in essentially quantitative yield.[7] This reaction was readily conducted on 75 g of starting material **7**. The phosphine oxide monotriflate **8a** was reduced using $HSiCl_3$ in the presence of Et_3N, giving phosphine monotriflate (*R*)-**9a** in 77% yield over two steps from bis-triflate **7**. The second phosphine group was introduced using a nickel-catalysed cross-coupling.[8] Thus, reaction of triflate **9a** with Ph_2PH in the presence of $NiCl_2$dppe (10 mol %) and DABCO gave enantiomerically pure HexaPHEMP (*R*)-**1a** in 74% yield. This reaction was conducted on a 60 g scale. The purified (*R*)-and (*S*)-HexaPHEMP ligands prepared using this procedure were white solids that showed single resonances in their $^{31}P\{^1H\}$ NMR spectra at -13.3 ppm.

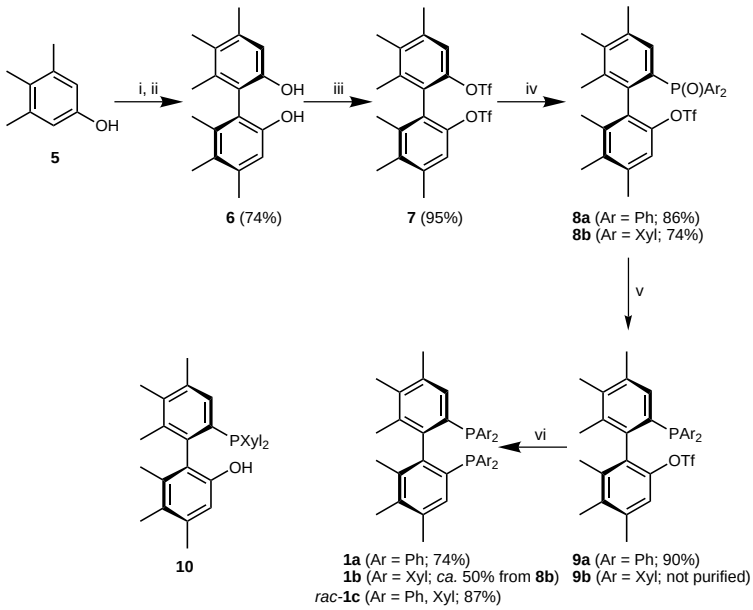
The Xyl-HexaPHEMP analogue **1b** (Xyl = 3,5-dimethylphenyl) was prepared as for HexaPHEMP (**1a**) by substituting $Ph_2P(O)H$ and Ph_2PH in the palladium and nickel coupling steps with $(Xyl)_2P(O)H$ and Xyl_2PH, respectively. Although the palladium-catalysed coupling proceeded well, the nickel-catalysed step appeared more difficult and afforded a mixture of (*S*)-Xyl-HexaPHEMP (**1b**) and the Xyl-phosphine monotriflate starting material **9b**. The mixture was treated with TBAF providing a chromatographically separable mixture of (*S*)-Xyl-HexaPHEMP (**1b**) and phenol **10**. The purified (*S*)-ligand **1b** was a white solid that showed a single resonance in the ^{31}P NMR spectrum at -13.0 ppm. We have also confirmed that the non-C_2-symmetric mixed phosphine ligand **1c** can be prepared using a $NiCl_2$dppe-catalysed coupling of Xyl_2PH with racemic monotriflate **9a**.

Asymmetric Hydrogenations using HexaPHEMP-Based Catalysts

With the requisite ligands in hand we prepared a series of precatalysts for evaluation of the HexaPHEMP backbone with several hydrogenation substrates.

β-Enamides

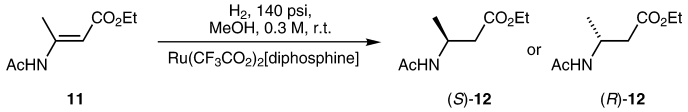
Few examples of β-amino acid syntheses *via* asymmetric hydrogenation of β-acetamidocrotonates have been reported,[9,10,11] and only Noyori[9] has used ruthenium-based catalysts for this purpose. We sought to investigate the efficiency of the ruthenium precatalyst system $Ru(CF_3CO_2)_2$[(*S*)-HexaPHEMP], prepared using anal-



For **1a**: (i) $V(O)(acac)_2$ (5 mol %), DCM, air, 48 h, r.t.; (ii) Chiral HPLC; (iii) Tf_2O (2.3 equiv.), pyridine (2.5 equiv.), DCM, 18 h, r.t.; (iv) $Ph_2P(O)H$ (1.15 equiv.), $Pd(OAc)_2$ (4 mol %), dppb (4 mol %), *i*-Pr_2NEt (2.0 equiv.), DMSO, 110 °C, 16 h; (v) $HSiCl_3$ (5 equiv.), Et_3N (10 equiv.), toluene, reflux, 4 h; (vi) Ph_2PH (1.5 equiv.), Ni(dppe)Cl_2 (10 mol %), DABCO (2.0 equiv.), DMF, 110 °C, 16 h.

Scheme 1. Synthesis of HexaPHEMP ligands.

Table 1. Asymmetric hydrogenation of (*E*)-ethyl β-acetamidocrotonate (**11**).[a]

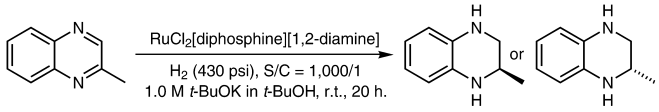


11 (*S*)-**12** (*R*)-**12**

Entry	Diphosphine	S/C	Time	Conversion [%]	ee [%]
1	(*R*,*R*)-*i*-Pr-DuPHOS	100	30 min	>99	39 (*R*)
2	(*R*)-BINAP	100	<2 min	>99	93 (*S*)
3	(*R*)-BINAP	10,000	16 h	>99	95 (*S*)
4	(*S*)-HexaPHEMP	100	<1 min	>99	95 (*R*)
5	(*S*)-HexaPHEMP	1,000	<1 min	>99	95 (*R*)
6	(*S*)-HexaPHEMP	10,000	16 h	75	95 (*R*)

[a] Reactions were conducted at 140 psi H_2, r.t. in MeOH. Conversion and ees were determined by GC analysis (Chirasil DEX-CB column). Absolute configuration is in parentheses.

Table 2. Precatalyst screening against neat 2-methylquinoxaline (**13**).[a]



13 (*R*)-**14** (*S*)-**14**

Entry	Diphosphine	Diamine	Conversion [%]	ee [%]
1	(*R*,*R*)-Et-DuPHOS	(*R*,*R*)-DACH	98	40 (*S*)
2	(*R*)-BINAP	(*R*)-DAIPEN	94	62 (*S*)
3	(*R*)-BINAP	(*R*,*R*)-DPEN	99	66 (*S*)
4	(*S*)-HexaPHEMP	(*S*,*S*)-DPEN	>99	69 (*R*)
5	(*S*)-Xyl-HexaPHEMP	(*S*,*S*)-DPEN	>99	72 (*R*)
6	(*S*)-BINAP	(*S*,*S*)-DACH	>99	61 (*S*)
7	(*S*)-HexaPHEMP	(*S*,*S*)-DACH	>99	65 (*R*)
8	(*S*)-Xyl-HexaPHEMP	(*S*,*S*)-DACH	99	73 (*R*)

[a] Reactions were conducted with neat **15** (5.6 M), at 430 psi H_2, 50 °C, S/C/B 1000/1/50, 20 h, 0.05 equiv. 1.0 M *t*-BuOK in *t*-BuOH. Conversion and ees were determined by GC analysis (Chirasil DEX-CB column). Absolute configuration is in parentheses.

ogous literature methods,[12] for reduction of (*E*)-ethyl β-acetamidocrotonate (**11**) in comparison to catalysts prepared from other diphosphines (Table 1). The (*S*)-HexaPHEMP-based catalyst was highly active at molar substrate-to-catalyst (S/C) ratios of 100, 1,000 and 10,000/1, and was found to give similar performance to the (*R*)-BINAP catalyst (entries 2 and 3) but was significantly better than our (*R*,*R*)-*i*-Pr-DuPHOS[13] catalyst (entry 1).

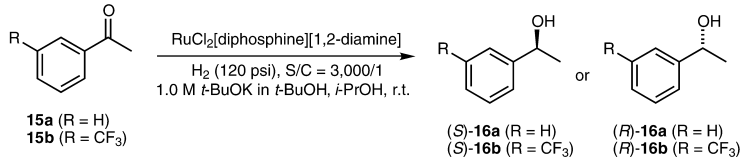
Imines

Noyori's $RuCl_2$[diphosphine][1,2-diamine] complexes[14] are excellent precatalysts for the asymmetric homogeneous hydrogenation of simple ketones, not requiring the presence of secondary binding functionality.[15] These precatalysts are converted into active catalysts by treatment with excess base (e.g., *t*-BuOK) *in situ*. These ruthenium complexes can also be used for the asymmetric hydrogenation of imines[16,17] which are a challenging class of substrates.[5,16,17] We examined the asymmetric hydrogenation of the heteroaromatic diimine **13** and found that the HexaPHEMP-based catalysts (Table 2; entries 4, 5, 7 and 8) provided slightly improved selectivity over BINAP-based systems (entries 2, 3 and 6). Interestingly, our Et-DuPHOS-based catalyst (entry 1), which was found to be very selective for another imine substrate,[16] performed poorly for the asymmetric hydrogenation of diimine **15**. A small improvement in the selectivity was achieved by use of the more electron-rich Xyl-HexaPHEMP-based catalysts (entry 5 and 8). It is worth noting that an iridium-based catalyst reported by Bianchini et al.[18] provided a 73% ee with 97% yield for this particularly challenging substrate.

Ketones

Among the various diphosphines that have been examined with $RuCl_2$[diphosphine][1,2-diamine] complexes,

Table 3. Asymmetric hydrogenation of acetophenone (**15**).[a]



Entry	R	Diphosphine	Diamine	Time	Conversion [%]	ee [%]
1	H	(*S*)-BINAP	(*S*,*S*)-DPEN	17 h	>99	85 (*R*)
2	H	(*S*)-BINAP	(*S*,*S*)-DACH	3 h	85	82 (*R*)
3	H	(*R*)-BINAP	(*R*)-DAIPEN	1 h	>99	86 (*S*)[b]
4	H	(*R*)-MeO-BIPHEP	(*R*,*R*)-DPEN	12 h	>99	84 (*S*)
5	H	(*R*)-HexaPHEMP	(*R*,*R*)-DPEN	1 h	>99	86 (*S*)
6	H	(*R*)-HexaPHEMP	(*R*,*R*)-DACH	20 min	>99	86 (*S*)
7	H	(*R*)-HexaPHEMP	(*R*)-DAIPEN	30 min	>99	90 (*S*)
8	H	(*S*)-Xyl-HexaPHEMP	(*S*,*S*)-DPEN	61 min	>99	99 (*R*)
9	H	(*S*)-Xyl-HexaPHEMP	(*S*,*S*)-DACH	24 min	>99	96 (*R*)
10	H	(*S*)-Xyl-HexaPHEMP	(*S*)-DAIPEN	28 min	>99	99 (*R*)[c]
11	3′-CF_3	(*S*)-Xyl-HexaPHEMP	(*S*,*S*)-DPEN	56 min	>99	99 (*R*)
12	3′-CF_3	(*S*)-Xyl-HexaPHEMP	(*S*,*S*)-DACH	49 min	>99	95 (*R*)
13	3′-CF_3	(*S*)-Xyl-HexaPHEMP	(*S*)-DAIPEN	41 min	>99	99 (*R*)[c]

[a] Reactions were conducted at 120 psi H_2, r.t., S/C/B 3000/1/50, 20 h, with 0.05 equiv. 1.0 M *t*-BuOK in *t*-BuOH. Conversion and ees were determined by GC analysis (Chirasil DEX-CB column). Absolute configuration is in parentheses.
[b] Noyori et al. reported 87% ee using $RuCl_2$[(*S*)-BINAP][(*S*,*S*)-DAIPEN] precatalyst.[15]
[c] Noyori et al. reported 99% ee using $RuCl_2$[(*S*)-Xyl-BINAP][(*S*,*S*)-DAIPEN] precatalyst.[15]

Noyori's BINAP-based catalysts consistently allow the hydrogenation of prochiral ketones with impressive chemo- and stereoselectivity, very high activity and catalyst efficiency. We have also developed catalysts based on the PhanePhos[19] ligand that have proven, when used in combination with DPEN (1,2-diphenylethylenediamine), to be as effective.[20]

In order to make direct comparisons between our results and those achieved with BINAP-ruthenium catalysts, we performed parallel experiments with both catalyst systems under identical conditions with the same substrates. Thus, we prepared ruthenium dichloride complexes of BINAP (**2a**), HexaPHEMP (**1a**) and Xyl-HexaPHEMP (**1b**) with DPEN, DACH (*trans*-1,2-diaminocyclohexane) and DAIPEN (1,1-dianisyl-2-isopropyl-1,2-ethylenediamine) for testing in the asymmetric hydrogenation of acetophenone **15a** and 3′-trifluoromethylacetophenone **15b** (Xyl-HexaPHEMP only). As is evident from Table 3, the HexaPHEMP-based catalysts performed consistently better than BINAP catalysts, particularly in terms of activity under identical reaction conditions (*cf.* entries 1–3 and 5–7). Given that the DACH ligand is a much cheaper diamine than DAIPEN[21] it was pleasing to observe that the (*R*)-HexaPHEMP/(*R*,*R*)-DACH system (entry 6) was as selective as the (*R*)-BINAP/(*R*)-DAIPEN system (entry 3) but was about three times more active. In another comparative experiment, a MeO-BIPHEP-based catalyst (entry 4) gave a similar enantiomeric excess and was markedly less active. Xyl-HexaPHEMP (**1b**)-based catalysts (entries 8–13) showed similar activity but much higher selectivity. The selectivities obtained using $RuCl_2$[(*S*)-Xyl-HexaPHEMP][diamine] (entries 8 to 13) precatalyst were comparable to those achieved using our Xyl-PhanePhos-ruthenium catalysts.[20] Although the preferred diamine with PhanePhos was DPEN, DAIPEN was preferred for Xyl-HexaPHEMP-based catalysts.

Conclusion

In conclusion, we have synthesised a novel ligand system that is useful for producing highly active and enantioselective hydrogenation catalysts. In all cases studied, HexaPHEMP or Xyl-HexaPHEMP performed as well as or better than the corresponding BINAP ligands. The oxidative phenolic coupling is greatly facilitated by the symmetry of 3,4,5-trimethylphenol, which affords a single clean product. The synthetic approach allows the incorporation of different phosphorus-containing moieties into the backbone to produce a family of ligands, which we are currently investigating.

Experimental Section

General Information

The commercially available diamines DPEN (Fluka) and DAIPEN (Strem) were used as received. DACH[22] and bis(3,5-dimethylphenyl)phosphine oxide[23] were prepared according

to literature procedures. BINAP (Strem) and MeO-BIPHEP (Fluka) were purchased and used as received. Et-DuPHOS and *i*-Pr-DuPHOS were prepared as previously described.[13] 2-Methylquinoxaline (Aldrich) was distilled before use. The following reagents were used as received: 3,4,5-trimethylphenol (Lancaster), CH_2Cl_2 (Fisher; HPLC grade), $V(O)(acac)_2$ (Aldrich), pyridine (Acros; 99% +), MTBE (Fisher; HPLC grade), conc. HCl (37%: Fisher), MeOH (Fisher; HPLC grade), $HP(O)Ph_2$ (Acros; 97%), $Pd(OAc)_2$ (Acros), dppb (Acros), $NEt(i\text{-}Pr)_2$ (Acros; 98% +), DMSO (Acros; 99.9%; spectroscopic grade), trichlorosilane (Acros), NEt_3 (Aldrich), PhMe (Fisher; HPLC grade), $HPPh_2$ (Fluka 95%), $Ni(dppe)Cl_2$ (Aldrich), DABCO (Acros 97%), DMF (Acros +99%), and cyclohexanone (Acros 99.8%), silica gel (Matrex* Silica 60, Fisher), Biotage Cartridge (KP Sil 32–63 μm 60 Å silica).

Ligand Synthesis

4,4′,5,5′,6,6′-Hexamethyl-2,2′-biphenyldiol (6): 3,4,5-Trimethylphenol (76.4 g, 561 mmol) was dissolved in CH_2Cl_2 (140 mL), vanadyl acetylacetonate (7.44 g, 26.1 mmol) was added and the reaction was stirred under a constant stream of air for 48 h. The solvent was removed under reduced pressure and the residue was refluxed in Et_2O (300 mL) for 30 min. The mixture was allowed to cool to −20 °C for 2 h, before filtering off the product. The product was further purified by refluxing in ethanol (100 mL), for 1 h. The solution was again cooled to −20 °C for 2 h before filtering. The product (56.1 g, 74%) was obtained as a white crystalline solid. This was resolved into constituent enantiomers by preparative chiral HPLC (in collaboration with Chiral Technologies Europe). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.90 (s, 6H), 2.15 (s, 6H), 2.30 (s, 6H), 4.50 (s, 2H), 6.75 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 15.4 (CH_3), 16.9 (CH_3), 20.9 (CH_3), 114.4 (CH), 118.0 (C), 127.7 (C), 136.8 (C), 138.4 (C), 151.2 (C).

The following experiments were conducted with enantiomerically pure material.

4,4′,5,5′,6,6′-Hexamethyl-2,2′-bis(trifluoromethanesulfonyloxy)-biphenyl (7): To a cooled suspension of 4,4′,5,5′,6,6′-hexamethyl-2,2′-biphenyldiol (39.8 g, 0.147 mol) and pyridine (30.0mL, 0.368 mol) in CH_2Cl_2 (550 mL) was added a solution of trifluoromethanesulfonic anhydride (59.0 mL, 0.349 mol) in CH_2Cl_2 (50 mL) at such a rate to maintain the temperature in the range between 5–10 °C. After the addition was complete the reaction mixture was allowed to warm slowly to room temperature and it was stirred for 18 h. The reaction mixture was diluted with MTBE (2000 mL) and washed twice with 5% HCl (800 mL) with saturated aqueous $NaHCO_3$ solution (800mL) and brine (800 mL). It was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. After recrystallisation from MeOH (300 mL) 4,4′,5,5′,6,6′-hexamethyl-2,2′-bis(trifluoromethanesulfonyloxy)-biphenyl was obtained as a colourless solid; yielöd: (4.8 g (95%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.00 (s, 6H), 2.24 (s, 6H), 2.38 (s, 6H), 7.04 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.0 (CH_3), 17.6 (CH_3), 21.0 (CH_3), 118.3 (CF_3), 119.7 (CH), 125.9 (C), 136.1 (C), 138.8 (C), 138.9 (C), 145.0 (C); ^{19}F NMR ($CDCl_3$, 376 MHz): d = −75.2.

4,4′,5,5′,6,6′-Hexamethyl-2-diphenylphosphinoyl-2′-trifluoromethanesulfonyloxy-biphenyl (8a): 4,4′,5,5′,6,6′-Hexamethyl-2,2′-bis(trifluoromethanesulfonyloxy)-biphenyl (74.1 g, 0.138 mol), diphenylphosphine oxide (35.2 g, 0.174 mol), palladium acetate (1.56 g, 0.007 mol), 1,4-bis(diphenylphosphino)butane (2.97 g, 0.007 mol) and *i*-Pr_2NEt (67.6 mL, 0.386 mol) were dissolved in DMSO (490 mL) and heated under nitrogen at 110 °C for 16 h. The reaction mixture was diluted with EtOAc (3400 mL) and washed twice with 5% HCl (1000 mL) and brine (1000 mL). The combined aqueous layers were extracted with EtOAc (800 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to yield the crude product as a red oil (87.0 g). The title compound was obtained as a yellow foam after purification by column chromatography (Biotage 75, eluent EtOAc); yield. 69.9 g (86%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.75 (s, 3H), 1.89 (s, 3H), 2.07 (s, 3H), 2.23 (s, 3H), 2.25 (s, 3H), 2.26 (s, 3H), 6.55 (s, 1H), 7.13 (d, 1H, $J_{P,H}$ =14.5 Hz), 7.24–7.48 (m, 6H), 7.57 (m, 2H), 7.72 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 15.7 (CH_3), 16.5 (CH_3), 17.0 (CH_3), 17.9 (CH_3), 20.8 (CH_3), 21.0 (CH_3), 118.2 (CF_3), 118.7 (CH), 127.7 (CH), 128.1 (CH), 128.3 (CH), 128.8 (C), 129.8 (C), 130.9 (CH), 131.2 (2 × CH), 131.3 (CH), 131.6 (2 × CH), 132.1 (CH), 133.0 (CH), 133.2 (C), 134.0 (C), 134.9 (C), 135.7 (C), 136.4 (C), 137.6 (C), 137.9 (C), 138.8 (C), 140.5 (C), 145.1 (C); ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −75.6; ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz): δ = 29.2.

4,4′,5,5′,6,6′-Hexamethyl-2-diphenylphosphino-2′-trifluoromethanesulfonyloxy-biphenyl (9a): 4,4′,5,5′,6,6′-Hexamethyl-2-diphenylphosphinoyl-2′-trifluoromethanesulfonyloxy-biphenyl (69.9 g, 0.119 mol) was dissolved in PhMe (1600 mL) and Et_3N (189 mL, 1.35 mol) was added. The reaction mixture was cooled to 0 °C and trichlorosilane (68.2 mL, 6.78 mol.) was added at such a rate as to maintain the reaction temperature below 7°C. The reaction mixture was heated at reflux for 16 h. The reaction mixture was allowed to cool to room temperature and excess trichlorosilane was evaporated under vacuum. The residue was diluted with PhMe (1200 mL) and then washed sequentially with saturated aqueous $NaHCO_3$ solution (500 mL) and 5% HCl (1000 mL). The combined aqueous washings were extracted twice with PhMe (1000 mL). The combined organic layers were washed with brine (1000 mL). The organic layer was stirred on Carbon (Darco 12–20 mesh, 600 g) and $MgSO_4$. It was filtered through a pad of Celite (500 mL) and sand and the solvent was evaporated under reduced pressure to give 4,4′,5,5′,6,6′-hexamethyl-2-diphenylphosphino-2′-trifluoromethanesulfonyloxy-biphenyl as a pale yellow foam; yield: 60.5 g (90%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.48 (s, 3H), 1.91 (s, 3H), 2.08 (s, 3H), 2.21 (s, 3H), 2.22 (s, 3H), 2.36 (s, 3H), 6.83 (d, 1H), 6.98 (s, 1H), 7.12 (m, 2H), 7.15–7.27 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.8 (CH_3), 15.0 (CH_3), 16.0 (CH_3), 16.3 (CH_3), 16.3 (CH_3), 19.9 (CH_3), 117.1 (CF_3), 118.4 (CH), 126.9 (CH), 127.0 (CH), 127.1 (CH), 127.1 (CH), 127.5 (CH), 131.0 (C), 131.79 (CH), 131.8 (CH), 132.0 (CH), 132.2 (CH), 133.0 (C), 133.2 (CH), 133.4 (CH), 134.3 (C), 134.9 (C), 135.2 (C), 135.9 (C), 136.0 (C), 136.5 (C), 136.5 (C), 137.3 (C), 137.6 (C), 143.8 (C); ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −75.4; ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz): δ = −11.9.

HexaPHEMP (1a): [1,2-Bis(diphenylphosphino)ethane]dichloronickel(II) (5.5 g, 0.0104 mol) was dissolved in degassed DMF (400 mL). Diphenylphosphine (29.4 g, 0.158 mol) was added and the reaction mixture was heated at 110 °C for 30 min. In a second flask, 4,4′,5,5′,6,6′-hexamethyl-2-diphenylphosphino-2′-trifluoromethanesulfonyloxy-biphenyl (60.0 g, 0.105 mol) was dissolved in degassed DMF (400 mL) and 1,4-

diazabicyclo[2.2.2]octane (23.5 g, 0.209 mol) was added. The hot catalyst solution was transferred via teflon tubing to the reaction mixture in the second flask, stirred at room temperature. After the addition was complete the reaction mixture was stirred at 110 °C for 16 h, then allowed to cool to room temperature and degassed cyclohexanone (200 mL) was added. The solvents were evaporated under reduced pressure. EtOAc was added and a solid was filtered off and washed with EtOAc. The solvent was evaporated under reduced pressure. HexaPHEMP was obtained as a colourless solid after purification by column chromatography (Biotage 75, eluent EtOAc-heptane1:3); yield: 46.5 g (74%). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.21$ (s, 6H), 2.00 (s, 6H), 2.22 (s, 6H), 6.85 (s, 2H), 7.20 – 7.26 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 16.3$ (CH_3), 17.2 (CH_3), 21.4 (CH_3), 127.7 (CH), 128.3 – 128.4 (6 CH), 128.9 (CH), 133.2 – 133.4 (2 CH, C), 134.6 (C), 135.5 (C), 135.6 (CH), 136.4 (C), 137.7 (C), 139.8 (C), 144.7 (C); ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz): $\delta = -13.3$.

4,4′,5,5′,6,6′-Hexamethyl-2-bis(3,5-dimethylphenyl)phosphinoyl-2′-trifluoromethylsulfonyloxy-biphenyl (8b): 4,4′,5,5′,6,6′-Hexamethyl-2,2′-bis(trifluoromethanesulfonyloxy)-biphenyl (4.00 g, 7.48 mmol), bis(3,5-dimethylphenyl)-phosphine oxide (2.42 g, 9.35 mmol), palladium acetate (168 mg, 0.75 mmol), 1,4-bis(diphenylphosphino)butane (319 mg, 0.75 mmol) and *i*-Pr_2NEt (3.26 mL, 18.71 mmol) were dissolved in DMSO (40 mL) and the solution was heated under nitrogen at 110 °C for 23 h. A mixture of bis(3,5-dimethylphenyl)phosphine oxide (1.93 g, 7.48 mmol), palladium acetate (84 mg, 0.37 mmol), 1,4-bis(diphenylphosphino)butane (160 mg, 0.37 mmol) and *i*-Pr_2NEt (1.30 mL, 7.48 mmol) were dissolved in DMSO (5 mL) and heated under nitrogen at 110 °C until the mixture became homogenous. This solution was added to the original reaction mixture, which was then heated under nitrogen at 110 °C for 22 h. The solvent was evaporated under high vacuum providing a brown syrup which was chromatographed over silica gel (60% MTBE/heptane) giving the title compound as a white foam; yield: 3.57 g (5.56 mmol, 74%). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.83$ (s, 3H), 1.88 (s, 3H), 2.08 (s, 3H), 2.21 (s, 6H), 2.23 (s, 3H), 2.24 (s, 3H), 2.27 (s, 6H), 6.57 (s, 1H), 7.00 (s, 1H), 7.06 (s, 2H), 7.09 (s, 1H), 7.23 (m, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz): $\delta = -75.6$; ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz): $\delta = 28.9$.

Xyl-HexaPHEMP (1b): A mixture of 3,3′,4,4′,5,5′-hexamethyl-6-bis(3,5-dimethylphenyl)phosphinyl-6′-trifluoromethylsulfonyloxybiphenyl (2.2 g, 3.3 mmol) and trichlorosilane (6.7 mL, 66.4 mmol) in PhMe (15 mL) was heated at reflux for 16h. The solvent was evaporated to dryness under high vacuum with gentle heating. The resulting residue of 4,4′,5,5′,6,6′-hexamethyl-2-bis(3,5-dimethylphenyl)phosphino-2′-trifluoromethylsulfonyloxy-biphenyl was dissolved in degassed DMF (15 mL) and 1,4-diazabicyclo[2.2.2]octane (560 mg, 5.0 mmol) was added. In a second flask, [1,2-bis(diphenylphosphino)ethane]dichloronickel(II) (105 mg, 0.2 mmol) was dissolved in degassed DMF (8 mL). Bis(3,5-dimethylphenyl)phosphine (1.2 g, 4.8 mmol) was added and the reaction mixture was heated at 110 °C for 30 min. The resulting solution was transferred via teflon tubing to the first flask. After the addition was complete the reaction mixture was stirred at 110 °C for 3 days and then evaporated to dryness under high vacuum at 110 – 150 °C. The residue was dissolved in PhMe (10 mL) and heated at 70 °C with trichlorosilane (20 mL, 198 mmol) for 4 h. Following evaporation to dryness under high vacuum with gentle heating, the product was dissolved in EtOAc (300 mL) and washed with distilled water (200 mL) and brine (200 mL), dried over $MgSO_4$, filtered and evaporated to give a white foam. ^{31}P{^{1}H}-NMR analysis indicated that this was a mixture of the desired product **1b** and Xyl-phosphine monotriflate **9b**. A portion of the product mixture (3.0 g) in THF (60 mL) was treated with 1 M TBAF in THF (5 mol % water) (4.8 mL, 5.8 mmol) under reflux for 12.5 h. After 3 h another portion of 1 M TBAF in THF (4.8 mL, 5.8 mmol) was added to the reaction mixture, followed by a third portion (2.4 mL, 2.9 mmol) after 7.5 h. The mixture was diluted with CH_2Cl_2 (300 mL) and washed twice with distilled water (200 mL), then with brine (200 mL), dried over $MgSO_4$, filtered and evaporated to give a yellow foam (2.75 g). This material was chromatographed over silica gel (eluting with 1% MTBE/heptane) providing the title product as a white foam; yield: 898 mg (1.25 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.32$ (s, 6H), 2.04 (s, 6H), 2.14 (s, 6H), 2.21 (s, 12H), 2.24 (s, 6H), 6.79 (s, 2H), 6.83 – 6.89 (m, 10H), 6.95 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 15.9$ (CH_3), 17.1 (CH_3), 21.0 (CH_3), 21.2 (CH_3), 21.3 (CH_3), 128.9, 130.0, 130.8, 130.9, 132.8, 132.9, 134.9, 135.7, 137.0 (aromatic C and CH); ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz): $\delta = -13.0$.

Catalyst Preparation

$Ru(CF_3CO_2)_2$(diphosphine): $[RuCOD(CF_3CO_2)_2]_2$ (14.4 mg, 0.033 mmol) and the respective diphosphine **1** (0.066 mmol) were placed in a 50 mL Schlenk flask. The entire apparatus was evacuated and back filled with N_2 three times to establish an inert atmosphere. THF (anhydrous, deoxygenated, 10 mL) was added and the reaction mixture stirred at 40 °C for 5 h. The reaction mixture was then reduced to dryness under vacuum and the resulting tan coloured solid washed with hexane (10 mL). After drying under vacuum for 3 h, ^{31}P{^{1}H}-NMR spectroscopy (sample prepared under nitrogen using $CDCl_3$) showed the tan coloured powder to be the desired complex (assumed to be the H_2O-included complex formed *in situ* whilst preparing the NMR sample; see ref.[12]).

For (*S*)-HexaPHEMP based catalyst: ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz): $\delta = 55.6$ (d, $J = 35.2$ Hz), 49.5 (d, $J = 35.2$ Hz).

$RuCl_2$(diphosphine)(diamine): The precatalysts were prepared according to the procedure described by Noyori et al.;[24] diphosphines were generally allowed to react with the ruthenium dimer for *ca.* 30-60 min. Diamines were then reacted with the ruthenium-diphosphine intermediates at room temperature overnight. The DMF was removed under high vacuum at *ca.* 70 °C giving tan-coloured solids. These were dissolved in CH_2Cl_2 (anhydrous, degassed) and the CH_2Cl_2 was evaporated under reduced pressure. This process was repeated, and then again once with Et_2O (anhydrous, degassed).

For $RuCl_2$[(*S*)-HexaPHEMP][(*S,S*)-DPEN]: ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz): $\delta = 45.9$.

For $RuCl_2$[(*S*)-HexaPHEMP][(*S,S*)-DACH]: ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz): $\delta = 45.5$.

For $RuCl_2$[(*S*)-Xyl-HexaPHEMP][(*S,S*)-DPEN]: ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz): $\delta = 44.7$.

For $RuCl_2$[(*S*)-Xyl-HexaPHEMP][(*S,S*)-DACH]: ^{31}P{^{1}H NMR ($CDCl_3$, 162 MHz): $\delta = 44.2$.

For $RuCl_2$[(*S*)-Xyl-HexaPHEMP][(*S*)-DAIPEN]: ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz): $\delta = 42.7$ (d), 46.0 (d, $J = 38.6$ Hz).

Asymmetric Hydrogenation

All hydrogenations were carried out in 50 mL Parr hydrogenation vessels or in a Baskerville multiwelled hydrogenation vessel equipped with injection ports with a rubber septum for the addition of the solvent *via* syringe, a pressure gauge, a tightly fitting removable internal glass liner, and a magnetic stirring bar. Commercially available anhydrous *i*-PrOH (Fluka) was degassed prior to use by sparging with nitrogen for at least 30 minutes. A commercially available 1.0 M solution of *t*-BuOK in *t*-BuOH (Aldrich) was used following degassing.

Asymmetric Hydrogenation of (*E*)-Ethyl β-Acetamidocrotonate (11): A glass liner was charged with (*E*)-ethyl β-acetamidocinnamate (1 equiv.; conducted on a 1.0 mmol scale at S/C 100/1), the respective catalyst (as indicated in Table 1; 0.01, 0.001 or 0.0001 equiv.) and a magnetic stirrer bar. The liner was placed in the base of a 50 mL Parr pressure vessel and the reactor assembled, flushed with nitrogen (5 pressurisation/release cycles, 140 psi). MeOH (to make a 0.3 M solution) was added through the septum of the reactor *via* syringe. The reactor was purged once more with nitrogen (8 pressure/release cycles, 140 psi). The reactor was finally pressurised to 140 psi with hydrogen and stirred at room temperature until the theoretical amount of hydrogen gas had been consumed. The remaining hydrogen was then released and the solution in the glass liner transferred to a vial. A sample was diluted with EtOAc and the conversion and ees were determined by GC analysis [Chirasil DEX-CB; 60 °C for 5 min, then 5 °C/min to 160 °C then 15 °C/min to 200 °C: 21.2 min (first eluting enantiomer) and 21.8 min (second eluting enantiomer).

Asymmetric Hydrogenation of 2-methylquinoxaline (13): The catalyst (as indicated in Table 2; 0.008 mmol) was placed in a glass liner and the vessel assembled. This was purged with nitrogen at least three times, by pressurising to 5 bar and releasing the pressure. 2-Methylquinoxaline (**13**) (1.15 g, 8.0 mmol) was added and the reaction was purged three times with nitrogen. A solution of *t*-BuOK in *t*-BuOH (1.0 M, 0.40 mL, 0.40 mmol) was added and the reaction was purged a further three times with nitrogen. Finally, the vessel was pressurised to 30 bar of hydrogen and stirred at 50 °C (oil bath) for 20 h. A sample of the product was diluted with acetone and treated with trifluoroacetic anhydride and pyridine for several minutes. This was then analysed by GC [Chirasil DEX CB; 130 °C for 20 min, then 10 °C/min to 200 °C, hold for 5 min: 18.2 min (*S*), 18.9 min (*R*)] for determination of conversion and ee. The absolute configurations of the enantiomeric products were determined by optical rotation measurements of upgraded (crystallised from *i*-PrOH) product samples prepared by hydrogenation of 2-methylquinoxaline (**13**) using $RuCl_2$[(*S*)-HexaPHEMP][(*S*,*S*)-DACH] ($[\alpha]_D^{24}$: +23.1° (c 1.0, EtOH)) and $RuCl_2$[(*R*)-BINAP][(*R*)-DAIPEN] ($[\alpha]_D^{24}$: −23.1° (c 1.0, EtOH)) (lit.[25] $[\alpha]_D^{24}$: −35.8° (c 1.0, EtOH) for (*S*)-2-methyl-1,2,3,4-tetrahydroquinoxaline).

Asymmetric Hydrogenation of acetophenones 15a and 15b: Standard procedure at S/C 3000/1: the catalyst (as indicated in Table 3; 0.002 mmol) was placed in a 50 mL Parr hydrogenation vessel. The vessel was evacuated and refilled with nitrogen three times. A solution of the ketone (6 mmol) in anhydrous *i*-PrOH (3 mL) was introduced with a syringe via the vessel injection port and the vessel was purged with nitrogen. A 1 M solution of *t*-BuOK in *t*-BuOH (0.1 mL, 0.1 mmol) was added through the injection port, the vessel was purged with hydrogen and pressurised to 120 psi. The reaction was stirred at room temperature until the theoretical amount of hydrogen was consumed. A reaction sample was diluted with acetone and analysed by chiral GC [For acetophenone: Chirasil DEX CB, 100 °C for 7 min, then 30 °C/min to 200 °C: 9.3 min (*R*), 9.5 min (*S*). The stereochemistry of 1-phenylethanol was assigned by comparison with commercially available (*R*)-1-phenylethanol (Aldrich). For 3′-trifluoromethylacetophenone: Chirasil DEX CB, 100 °C for 7 min, then 15 °C/min to 200 °C: 10.6 min (*R*), 10.9 min (*S*)].

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