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A concise synthesis of a new xylyl-biaryl diphosphine ligand for asymmetric hydrogenation of ketones

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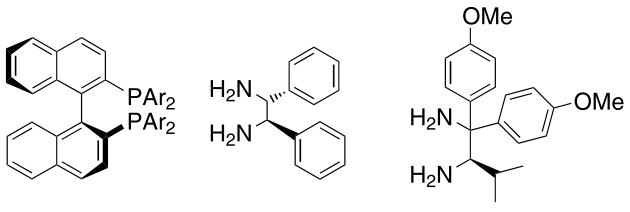
Abstract—A concise synthesis of a symmetrical biaryl diphosphine ligand bearing 3,5-dimethylphenyl substituents at phosphorus is described. The ruthenium catalysts [diphosphine $RuCl_2$ diamine] containing the new ligand Xyl-TetraPHEMP were found to be as active and as selective as the state-of-the-art catalysts for homogeneous asymmetric ketone hydrogenation.

In 1995 Noyori reported that ketones with no secondary binding functionality could be effectively hydrogenated in the presence of ruthenium catalysts.[1] The chiral variant contains an axially chiral diphosphine and a diamine ligand. This seminal discovery has in the last few years led to the development of the first highly practical and selective methodology for homogeneous asymmetric ketone hydrogenation.

Ruthenium precatalysts [diphosphine $RuCl_2$ diamine] formed by the diphosphines BINAP **1a** and Tol-BINAP **1b** (Fig. 1) and the diamine DPEN **2** displayed exceptional reactivity[2] even at very low catalyst loadings (expressed as substrate to catalyst ratio, S/C = [mol of substrate]/[mol of catalyst]) for the asymmetric hydrogenation of acetophenone. However, it was only with the introduction of the diphosphine ligand Xyl-BINAP **1c** and the diamine DAIPEN **3** (Fig. 1) that consistently high enantioselectivities were obtained across a wide range of aromatic,[3,4] heteroaromatic[5] and α,β-unsaturated ketones[3] as well as aminoketones.[6]



Ar = Ph, (*S*)-BINAP (*S*)-**1a**
Ar = 4-Tolyl, (*S*)-Tol-BINAP (*S*)-**1b**
Ar = 3,5-Xylyl, (*S*)-Xyl-BINAP (I)-**1c**

(*R*,*R*)-DPEN-**2**

(*R*)-DAIPEN-**3**

Figure 1. Ligands used for ketone hydrogenation catalysts.

The search for alternative, efficient catalytic systems for the hydrogenation of ketones led us to the discovery that [diphosphine $RuCl_2$ diamine] catalysts incorporating the diphosphine ligand PhanePhos **4a** (Fig. 2), or its derivative Xyl-PhanePhos **4b**, are as effective as the best BINAP catalysts and have broad industrial applicability.[7] In addition, we have recently developed a new class of biaryl diphosphine ligands, the HexaPHEMP series (Fig. 2).[8] We have verified that [diphosphine $RuCl_2$ diamine] catalysts based on HexaPHEMP **5a** and Xyl-HexaPHEMP **5b** perform as well as the corresponding catalysts based on the BINAP analogues and, in some cases, they display improved activity and selectivity. As in the case of the BINAP based catalysts the xylyl-substituted ligand **5b** provides the optimum enantioselectivities and reactivities. This trend is confirmed in a recent report by Chan demonstrating that Xyl P-Phos **6b** (Fig. 2) is the ligand of choice in the P-Phos ligand series.[9] Pregosin and co-workers have described this as the 3,5-dialkyl *meta*-effect.[10] It has been shown that substitution in the 3 and 5 positions of a pendant phenyl ring hinders rotation around the P–C(*ipso*)

Keywords: asymmetric hydrogenation; ketone hydrogenation; biaryl phosphines; chiral ligands.

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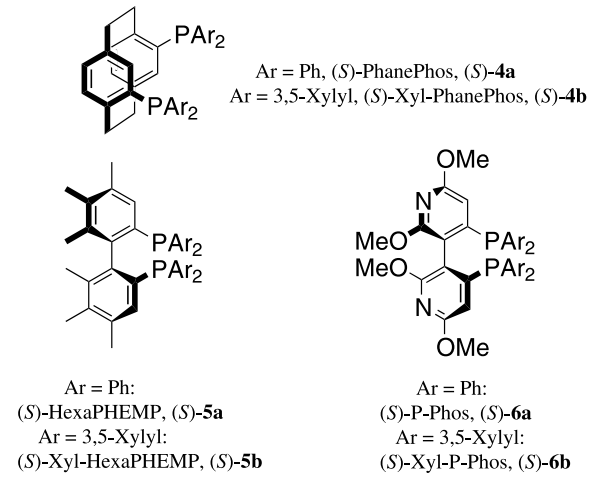
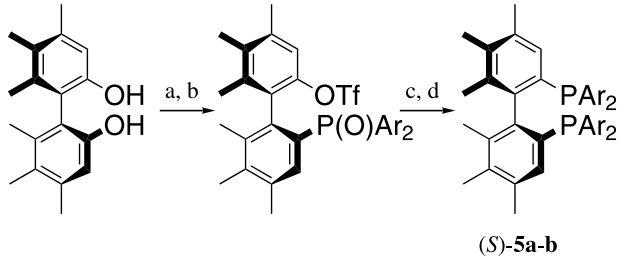
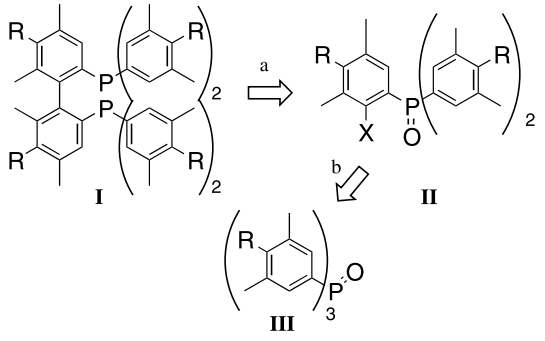


Figure 2. Alternative diphosphine ligands for ketone hydrogenation.



Scheme 1. *Reagents*: (a) Tf_2O, pyridine; (b) 4% $Pd(OAc)_2$, 4% dppb, $Ar_2P(O)H$, *i*-Pr_2NEt; (c) $HSiCl_3$, Et_3N; (d) 10% $NiCl_2$(dppe), Ar_2PH, DABCO.



Scheme 2. Synthetic strategy: (a) Ullmann coupling; (b) P=O directed *ortho*-lithiation.

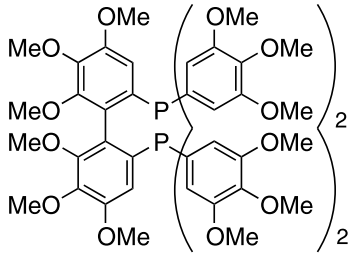
bond giving a more rigid chiral environment around the central metal atom, therefore, exerting a greater directing effect on the substrate. However, the nature of the enhanced reactivity in this system remains to be clarified. To date, xylyl-substituted biaryl diphosphines, along with PhanePhos, remain the ligands of choice for ruthenium-catalyzed ketone hydrogenation.

The industrial synthesis of BINAP is very short as the ligand can be synthesized from the corresponding diol, via the ditriflate, in two steps.[11] In the case of HexaPHEMP **5a** and Xyl-HexaPHEMP **5b**[8] there is no simple method of introducing two phosphine or phosphine oxide moieties directly from the ditriflate. As a consequence the ligand must be formed by the stepwise introduction of phosphine units via metal-catalyzed coupling reactions (Scheme 1). The coupling of the electron-rich backbone and electron-rich phosphines can be capricious and, especially in the case of **5b**, the handling of very air-sensitive reagents can pose problems.[12]

In order to circumvent such complications we sought to develop an alternative synthetic strategy to the target xylyl-substituted biaryl diphosphines. The disconnection approach chosen for a ligand of general formula **I** (Scheme 2) is based on the coupling of two symmetrical phosphine units **II**. The methyl substituents in positions 3 and 5 of the phosphine oxide **III** make the atropoisomers of the derived structure **I** configurationally stable and produce the desired 3,5-substitution pattern on the phosphorus substituents (optimal for ketone hydrogenation catalysis). The nature of the group R depends on the availability of the starting materials and on the desired electronic fine-tuning of the ligand.

A disconnection approach where the construction of the phosphine (or phosphine oxide) units precedes the assembly of the biaryl backbone has been previously described[13] but, with one exception, these routes do not use a symmetrical starting material. The exception is ligand **7**[14] (Fig. 3) that, however, does not meet our requirements for a 3,5-dimethyl substitution at the phosphorus units and, in fact, does not produce a useful ruthenium catalyst for ketone hydrogenation.[15]

Additionally, an important difference between our synthetic approach and more traditional approaches to the synthesis of biaryl diphosphines is that the metalation and subsequent functionalization of the symmetrical



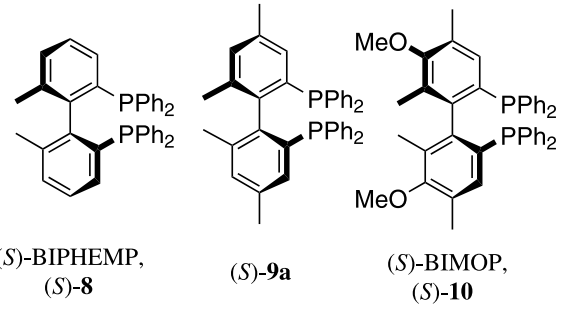
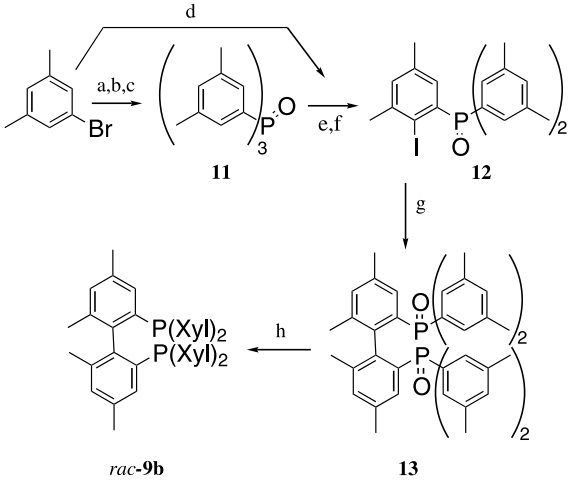


Figure 3. Biaryl diphosphine ligands.

phosphine oxide rely solely on the assistance of the P=O bond and not on the presence of neighbouring methoxy or alkoxy substituents for directed metalation. Ligands such as **8** (BIPHEMP),[16] **9a**[16] and **10** (BIMOP)[17] possess methyl substituents as the groups responsible for the conformational rigidity of the biaryl backbone (Fig. 3) but their syntheses involve a complex series of transformations.

We chose to exemplify our synthetic route by examining the case where, in structure **I**, R = H (Scheme 3). The new ligand **9b** was named Xyl-TetraPHEMP by analogy with HexaPHEMP **5**. The starting material tris(3,5-dimethylphenyl)phosphine oxide **11** was readily prepared by addition of 3,5-dimethylmagnesium bromide to PCl_3 followed by oxidation of the crude material. Compound **11** was then transformed into the *ortho*-iodo derivative **12** by treatment with an excess of 1-lithio-3,5-dimethylbenzene and subsequent quenching with iodine. The use of a lithium reagent bearing the same residue as the phosphine oxide was necessary in order to avoid the formation of by-products derived from the nucleophilic attack of the lithium species on the phosphorus. Schlosser has previously demonstrated the utility of this strategy for the derivatization of triphenylphosphine oxide via *ortho*-lithiation with phenyllithium as a degenerate base.[18]

The high-yielding coupling of compound **12** in the presence of activated copper powder produced the racemic biaryl backbone. The reduction of diphosphine oxide **13**[19] under standard conditions produced *rac*-Xyl-TetraPHEMP **9b**.[20] The resolution of the ligand was performed via the formation of diastereoisomeric palladium salts **14**, chromatographic separation and decomplexation by treatment with concentrated HCl followed by neutralization of the organic phase and treatment with KCN (CAUTION) (Scheme 4).[13b,21] This procedure allowed quick access to the enantiomerically pure material[22,23] necessary to study the catalytic applications. Resolution methods more amenable to scaling up are currently under evaluation.

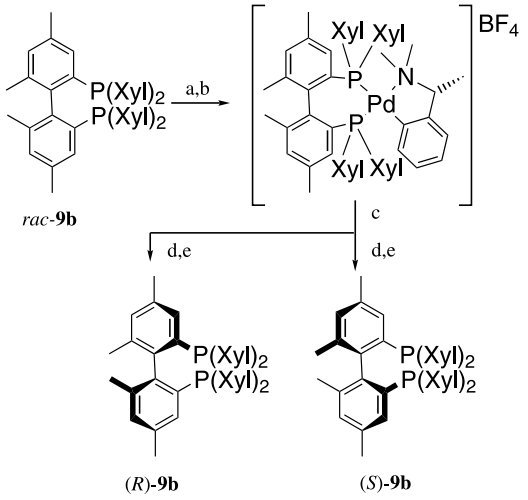


Scheme 3. *Reagents and conditions*: (a) Mg excess, THF, reflux 1 h, then rt for 1 h; (b) PCl_3 in Et_2O (0.22 equiv.), rt, 20 h; (c) H_2O_2, DCM, 77% yield based on PCl_3; (d) *t*-BuLi (2 equiv.), THF, −78°C, 40 min, then used in step; (e) 1-lithio-3,5-dimethylbenzene (3.3 equiv.) added to **11** in THF, −78°C, then −20°C for 2.5 h; (f) I_2 (3.6 equiv.), THF, −78°C, then rt 18 h, 74% yield based on **11**; (g) Cu powder (3 equiv.), DMF, 150°C, 5.5 h, 94% yield; (h) $HSiCl_3$ (21 equiv.), Et_3N (22 equiv.), toluene, reflux, 22 h, 76% yield.

The ruthenium precatalysts of general structure [Xyl-TetraPHEMP $RuCl_2$ diamine] **15**[24] were prepared according to literature methods[2] and tested in the hydrogenation of acetophenone (Table 1).

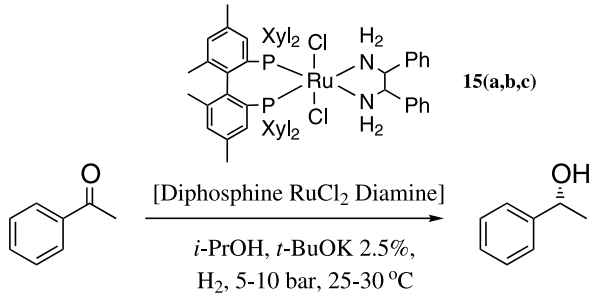
Initial experiments allowed us to identify the 'matching' and 'mismatching' pairs of Xyl-TetraPHEMP **9b** and DPEN **2** ligands (entries 1 and 2). Both enantiomeric pairs of 'matching' precatalyst [(*R*)-Xyl-TetraPHEMP $RuCl_2$ (*R*,*R*)-DPEN] **15a** and [(*S*)-Xyl-TetraPHEMP $RuCl_2$ (*S*,*S*)-DPEN] **15c** were then tested under slightly improved conditions and they produced a fast and highly selective hydrogenation (99% ee, entries 3 and 4). Although the early reports in the literature[3–6] indicated that the best results are usually obtained when diamine DAIPEN **3** is used in conjunction with xylyl biaryl diphosphines, more recently it has been found that excellent selectivity can also be obtained with the more readily available DPEN.[7–9] In the case under examination the precatalyst [(*R*)-Xyl-TetraPHEMP $RuCl_2$ (*R*)-DAIPEN] **15d** surprisingly gave a slightly lower selectivity (98% ee, entry 5) in the hydrogenation of acetophenone than the DPEN containing catalyst (99% ee). However, the reaction rate was faster and the reaction was readily demonstrated at low catalyst loading (S/C = 15,000, entry 6).

In conclusion, we have reported an example of a new synthetic approach to xylyl-substituted biaryl diphos-



Scheme 4. *Reagents and conditions*: (a) di-μ-chloro-bis[(*R*)-dimethyl(1-methyl)benzylaminato-C2,N]dipalladium(II) (0.95 equiv.), MeOH, 45°C, 6 h; (b) $NaBF_4$ (4.7 equiv.), MeOH, 45°C, 2 h, 92% yield based on *rac*-**9b**; (c) chromatographic resolution MTBE/toluene 4/1; 84% yield of (*S*,*R*)-**14**, 88% yield of (*R*,*R*)-**14**; (d) HCl 37%, DCM, rt, 2.5 h; (e) KCN, DCM/H_2O, rt, 5 h, 60% yield of (*S*)-**9b**, 35% yield of (*R*)-**9b**.

Table 1. Hydrogenation of acetophenone



Entry	Phosphine	Amine	S/C	Time (h)	Conv.[d] (%)	Ee[d] (%)
1[a]	(*R*)-**9b**	(*R*,*R*)-**2**	5,000	5	>99	99 (*S*)
2[a]	(*R*)-**9b**	(*S*,*S*)-**2**	5,000	5	89	54 (*S*)
3[b]	(*R*)-**9b**	(*R*,*R*)-**2**	5,000	3	>99	99 (*S*)
4[b]	(*S*)-**9b**	(*S*,*S*)-**2**	5,000	3	>99	99 (*R*)
5[c]	(*R*)-**9b**	(*R*)-**3**	5,000	1	>99	98 (*S*)
6[c]	(*R*)-**9b**	(*R*)-**3**	15,000	2	>99	98 (*S*)

[a] Reactions were run at room temperature under 5 bar H_2 in 50 mL magnetically stirred Parr pressure vessels.
[b] Reactions run at 30°C under 10 bar H_2 in an overhead stirred Argonaut Endeavour multi-well pressure vessel.
[c] Reactions at 30°C under 10 bar H_2 in 50 mL magnetically stirred Parr pressure vessels.
[d] Determined by chiral GC analysis (column: Chirasil DEX-CB).

phines. Such ligands play a fundamental role in what is, at present, the most efficient and cost-effective technology for the asymmetric reduction of a wide variety of ketones. The ruthenium catalysts containing the new ligand Xyl-TetraPHEMP perform in this catalysis protocol according to our best expectations. The development of a new family of ligands based on the synthetic strategy outlined herein will contribute to expanding the array of tools available for asymmetric catalysis.

Acknowledgements

We are grateful to Dr. Christophe Malan for preliminary discussions and Natasha Cheeseman for the initial development of analytical assays.

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19. *rac*-4,4′,6,6′-Tetramethyl-2,2′-bis[bis(3,5-dimethylphenyl)-phosphinoyl]biphenyl, *rac*-**13**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.68 (s, 6H, CH_3), 2.03 (s, 12H, CH_3), 2.21 (s, 6H, CH_3), 2.29 (s, 12H, CH_3), 6.85 (s, 2H, ArH), 6.93 (s, 4H, ArH), 7.09 (s, 4H, ArH), 7.12 (s, 2H, ArH), 7.34 (s, 2H, ArH), 7.37 (s, 2H, ArH). ^{31}P NMR (162 MHz, $CDCl_3$): δ 31.1 ppm (s). LCMS (APCI: CH_3CN/H_2O): 723 (100%, $M+H^+$), 724 (53%).
20. *rac*-4,4′,6,6′-Tetramethyl-2,2′-bis[bis(3,5-dimethylphenyl)-phosphino]biphenyl, *rac*-**9b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51 (s, 6H, CH_3), 2.12 (s, 12H, CH_3), 2.22 (s, 12H, CH_3), 2.26 (s, 6H, CH_3), 6.77 (s, 2H, ArH), 6.80 (m, 4H, ArH), 6.86 (m, 4H, ArH), 6.89 (s, 2H, ArH), 6.92 (s, 2H, ArH), 6.95 (s, 2H, ArH). ^{31}P NMR (162 MHz, $CDCl_3$): δ −13.4 ppm (s). LCMS (APCI: CH_3CN/H_2O): 691 (100%, $M+H^+$), 692 (58%).
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22. Samples of (*R*)-**9b** and (*S*)-**9b** were oxidized to the corresponding diphosphine oxides **13** by treatment with H_2O_2. HPLC analysis: column: Regis DACH-DNB (25 cm×4.6 mm); heptane:ethanol 90:10; 0.5 mL/min; room temperature; detection: ELSD, neb. temp: 50°C, evap. temp: 80°C, gas flow: 1 SLM; retention times: (*R*)-**9b**: 26 min, >98% ee; (*S*)-**9b**: 32 min, >98% ee.
23. (*R*)-4,4′,6,6′-Tetramethyl-2,2′-bis[bis(3,5-dimethylphenyl)-phosphino]biphenyl, (*R*)-**9b**: HRMS calcd for $[M-1]^+$ $C_{48}H_{51}P_2$ 689.3466 amu, found 689.3446 amu.
24. ^{31}P NMR (162 MHz, $CDCl_3$); **15a** δ [(*R*)-Xyl-TetraPHEMP]$RuCl_2$[(*R*,*R*)-DPEN] 45.1 (s) ppm; **15b** δ [(*R*)-Xyl-TetraPHEMP]$RuCl_2$[(*S*,*S*)-DPEN] 43.7 (s) ppm; **15d** δ [(*R*)-Xyl-TetraPHEMP]$RuCl_2$[(*R*)-DAIPEN] 43.3 (d, $J_{P,P}=38.4$ Hz), 46.5 3 (d, $J_{P,P}=38.4$ Hz) ppm.