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Novel Heterobidentate Ligands for Asymmetric Catalysis: Synthesis and Rhodium-catalysed Reactions of S-Alkyl (R)-2-Diphenylphosphino-1,1'-binaphthyl-2'-thiol

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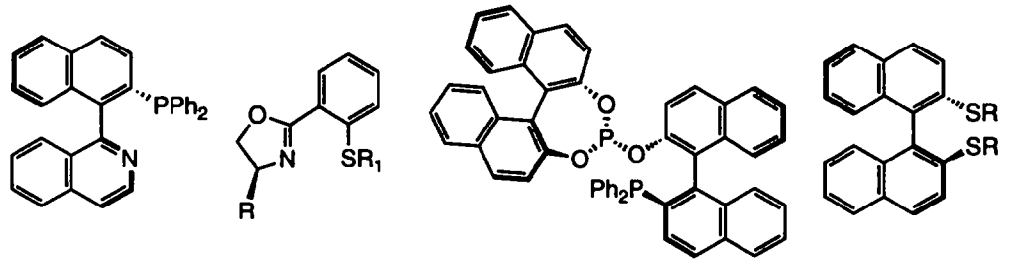
Abstract: Atropisomerically pure S-alkyl (R)-2-diphenylphosphino-1,1'-binaphthyl-2'-thiol derivatives have been synthesized through a multistep reaction sequence starting from (R)-binaphthol. Pd(II) and Rh(I) complexes containing the S-methyl derivative **14** as a chelate ligand have been prepared and characterized. Rh(I) complexes containing **14** or the S-*iso*-propyl derivative **15** effectively catalyse the asymmetric hydroformylation of styrene and the hydrogen transfer reduction of acetophenone.

Chiral heterobidentate ligands in which one donor atom is phosphorus and the second is different (nitrogen, oxygen or sulfur) have been relatively neglected with respect to their homobidentate counterparts for several years. A notable exception is the case of P-N chelate ligands derived from aminoacids or from 1,2-disubstituted ferrocenes which were introduced since early in Ni- and Pd-catalysed cross-coupling reactions with remarkable success.[1] In the last two years, however, an upsurge of interest in heterobidentate ligands has been observed and their number is increasing rapidly. The list of the new entries in the P-N ligand family includes a novel ferrocenylaminophosphine,[2] pyridylphosphines either with axial[3] or central chirality[4] and phosphinoaryldihydrooxazoles, independently prepared by several different groups.[5] While most of these ligands have been introduced with remarkable success in the Pd-catalysed allylic substitution,[2,5] a rhodium complex with the atropisomeric phosphinonaphthyl isoquinoline **1** efficiently catalysed the asymmetric hydroboration of vinylarenes in high enantioselectivity.[6] This expands the potential of this kind of heterochelate ligands in asymmetric catalysis.

Although the main research efforts in this field have been focussed on novel P-N chelates, N-S ligands have attracted attention as well. The effectiveness of chiral oxazolines with an additional sulfur donor like **2** as chiral modifiers in asymmetric palladium catalysed allylic substitution has been quite recently pointed out.[7,8] Enantioselectivities up to 98% e.e.have been obtained.[9]



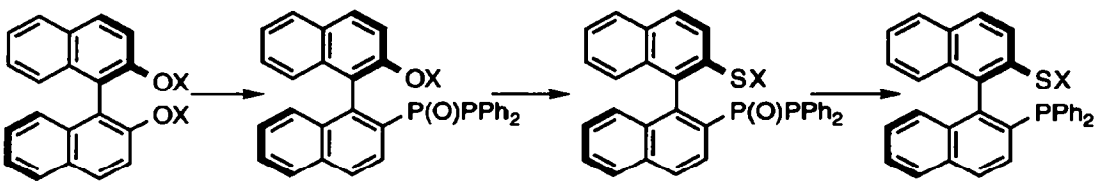
1 **2** **3** **4**

A major breakthrough in the rhodium-catalysed asymmetric hydroformylation of terminal[10] as well as internal[11] olefines has been recorded upon introduction of the binaphthyl-core phosphine-phosphite P-P ligand **3** as the chiral inducer. There is little doubt that the excellent enantioselectivities obtained are the consequence of the distinct donor properties of the two phosphorus centers present in the atropisomeric ligand.

Very recently we reported that rhodium complexes containing the atropisomeric sulfur ligands **4** hydroformylate styrene with 24:1 branched selectivity and 15% e.e.[12] A notable feature of sulfide ligands is that upon coordination to the metal, the sulfur becomes a stereogenic centre. This may positively affect the transfer of the chiral information to the metal centre and hence to the substrate. In the search for new chiral ligands for asymmetric catalysis based on the atropisomeric binaphthyl backbone, we have addressed our efforts towards the synthesis of heterobidentate P-S derivatives that could act as chelate ligands. Although the ligating properties of the sulfur centre in sulfides is well known and a few chelate P-S complexes of late transition metals have been prepared and characterized,[13] the use of chiral chelating P-S ligands in asymmetric catalysis has no precedent.[14]

In principle, the synthesis of 2,2'-unsymmetrically substituted 1,1'-binaphthalene derivatives can be dealt with according to two distinct strategies involving either dissymetrization of a suitable binaphthyl precursor or heterocoupling of two different β-substituted naphthyl derivatives. For our target we found more advantageous the first strategy and relied on commercially available binaphthol **5** as the starting product (Scheme 1).

Scheme 1



5 X=H
6 X= CF_3SO_2

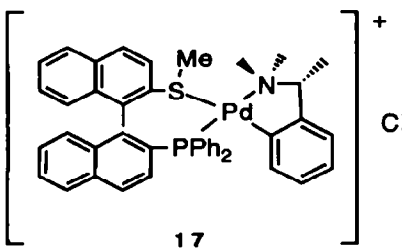
7 X=H
8 X= $C(S)NMe_2$

9 X= $C(O)NMe_2$ **10** X=H
11 X=Me **12** X= *iso*-Pr
13 X= CH_2Ph

14 X=Me
15 X= *iso*-Pr
16 X=H

Reaction of ditriflate **6** with diphenylphosphine oxide in DMSO in the presence of palladium acetate/1,4-*bis*-diphenylphosphinobutane as catalyst according to a reported procedure[15] afforded the hydroxy phosphinoxide **7**[7] in 70-5% yield.[16] This was converted into the N,N-dimethylthiocarbamate **8** (1.2 eq of NaH in DMF, 0°C, 1h; then dimethylthiocarbamoyl chloride, 85°C, 1h, 90%) which was subjected to Newmann-Kwart thermorearrangement[17] (neat; 275°C, 20') to produce the transposed phosphine oxide thiolcarbamate **9** (70-5%). Treatment with $LiAlH_4$ (THF, rt, 90%) afforded the thiol **10** which was easily alkylated at sulfur with the suitable alkyl halide (Et_3N, MeOH, rt, 3h, 90-7%) to give the phosphine oxide sulfides **11-13**. These were deoxygenated with trichlorosilane/triethylamine[18] (xylene, 120°C, 5h, 85-95%) to complete the synthesis. Following this set of reactions, ligands **14** and **15** were obtained in 30-5% overall yield from either racemic or enantiopure binaphthol.

Reaction of racemic **14** with the enantiopure chloride-bridged C,N-cyclopalladated complex of N,N-dimethyl (R)-α-methylbenzylamine[19] gave an equimolar mixture of only two diastereomeric cationic complexes which showed well separated signals in the ^1H and ^{31}P NMR. As it has been observed that in these Pd complexes the softest donor takes up the position *trans* to the NMe_2 group,[20] this compound could be confidently assigned the structure **17**.[21] When the same complex was prepared from a sample of **14** obtained from enantiopure (R)-binaphthol, only one set of signals was detectable. This allowed to confirm that the e.e. of this sample of **14** was higher than 95%, as determined indipendently by HPLC, and to prove that the overall synthetic sequence used for its preparation is completely stereoconservative.



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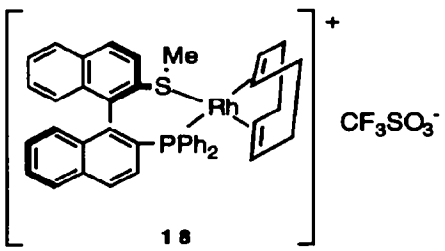

18

Reaction of (R)-**14** with one equivalent of $[Rh(cod)(\mu\text{-}OMe)]_2/CF_3SO_3SiMe_3$ (CH_2Cl_2, rt, 2h, 91%) gave a cationic complex which has been formulated as the chelate mononuclear derivative **18**.[22] In addition to elemental analysis, this attribution is supported by multinuclear NMR data which show the presence of Rh couplings with P (^1J = 145.8 Hz) as well as with SMe (^2J = 10.2 Hz). To the best of our knowledge this is the first chiral rhodium complex containing a P-S chelate ligand.

Complex **18** is an active catalyst for the hydroformylation of styrene as well as for the hydrogen transfer reduction of acetophenone by 2-propanol. In the first process, at 60°C under standard conditions (benzene; substrate:Rh: = 500:1; $CO:H_2$ = 1; 60 bars) the reaction was completely chemoselective towards aldehydes and a quantitative conversion was attained in 4 h (14 h at 40°C). The branched isomer accounted for 88% of the product, but the e.e.was negligible (2.5%). The same result was obtained using $Rh(acac)(CO)_2$ in the presence of a four fold excess of ligand as *in situ* catalyst. Using the S-*iso*-propyl derivative (R)-**15** as *in situ* ligand, a higher amount of branched aldehyde (94%) was obtained under standard conditions. Operating at lower temperatures (40°C) and higher pressures (120 bars), slights improvements of the regioselectivity (96%) as well as of the e.e. (14%) were observed with the latter ligand.

The high catalytic activity displayed by rhodium(I) complexes with bidentate nitrogen ligands in promoting the hydrogen transfer reduction of ketones in high enantioselectivity is well documented.[23] According to an established experimental methodology,[24] we have tested the new ligands also in this catalysis. Preliminary runs have pointed out that the catalytic system prepared *in situ* by addition of one equivalent of ligand (R)-**14** or (R)-**15** to $[Rh(cod)(\mu\text{-}OMe)]_2$ is able to promote, in the presence of KOH, the hydrogen transfer from 2-propanol to acetophenone at 82°C, with *ca.* 100 turnovers in the first 30 min. After this time, however, a steady decrease of the reaction rate was observed and conversions not higher than 55-75% could be recorded in 14 h. A similar pattern was observed for the enantioselectivity: the phenyl methyl carbinol formed in the initial stages of the reaction had *ca.* 20% e.e., but this value decreased steadily as the reaction proceeded and, after 14 h, the e.e. was lower than 5%. As racemization of the product on prolonged reaction times is expected in this reaction, the initial value compares favourably with the results obtained using chiral bidentate diphosphines in this process.[23]

These preliminary results are illustrative of the role that chiral P-S chelate ligands may play in asymmetric catalysis. Further applications of these ligands can be easily foreseen and some of them are currently under investigation in our laboratory.

Acknowledgements

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14 Asymmetric cross-coupling of Grignard reagents has been accomplished in 70-80% e.e. by means of Ni and Pd catalysts containing chiral P-N-S ligands. P-S-Chelate coordination seems not involved. G.

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16 All new compounds gave satisfactory elemental analyses. Selected data are as follows:

(R)-(-)-8: Yield 90%; mp 128-9°C (dichloromethane/petroleum ether); $[\alpha]^{25}_D$ -149.3 (c=1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 2.98 (s, 3H), 3.05 (s, 3H), 6.80-8.00 (series of m, Ar, 22H); ^{31}P-NMR ($CDCl_3$) δ 27.25; *m/z* 557.2 (M^+), 453.0 (100%), 283.9 (48%), 200.9 (27%), 87.9 (53%).

(R)-(+)-9: Yield 70%; mp 118-9°C (dichloromethane/petroleum ether); $[\alpha]^{25}_D$ +5.7 (c=1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 2.73 (bs, 6H), 6.80-8.10 (series of m, Ar, 22H); ^{31}P-NMR ($CDCl_3$) δ 28.99; *m/z* 557.2 (M+), 453.1 (100%), 284.0 (58%), 201.0 (36%), 72.1 (50%).

(R)-(+)-10: Yield 90%; mp 100-2°C (benzene); $[\alpha]^{25}_D$ +42.3 (c=1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 3.48 (s, 1H), 6.80-8.10 (series of m, Ar, 22H); ^{31}P-NMR ($CDCl_3$) δ 28.73; *m/z* 486.0 (M^+), 284.0 (100%), 201.0 (15%), 77.1 (11%).

(R)-(+)-11: Yield 94%; mp 154-5°C; $[\alpha]^{25}_D$ +126.2 (c=0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 2.27 (s, 3H), 6.88-8.00 (series of m, Ar, 22H); ^{31}P-NMR ($CDCl_3$) δ 28.89; *m/z* 500.2 (M^+), 453.1 (100%), 282.0 (12%), 226.1 (9%), 77.1 (8%).

(R)-(+)-12: Yield 90%; mp 88-9°C; $[\alpha]^{25}_D$ +117.8 (c=0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.08 (d, *J*= 6.6 Hz, 3H), 1.16 (d, *J*= 6.6 Hz, 3H), 3.43 (sept, *J*= 6.6 Hz, 1H), 6.85 (d, *J*= 8.7 Hz, Ar, 1H), 7.05 (m, Ar, 4H), 7.15-7.48 (series of m, Ar, 13H), 7.60 (t, *J*= 6.9 Hz, Ar, 1H), 7.87 (dd, *J*= 8.7, 11.4 Hz, Ar, 1H), 7.93 (d, *J*= 9.6 Hz, Ar, 1H), 8.00 (dd, *J*= 1.2, 8.4 Hz, Ar, 1H); ^{31}P-NMR ($CDCl_3$) δ 29.27 (s); *m/z* 528.2 (M+), 453.1 (100%), 282.0 (18%).

(R)-(+)-14: Yield 96%; mp 95-6°C; $[\alpha]^{25}_D$ +52.6 (c=0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 2.32 (s, 3H), 6.70-8.00 (series of m, Ar, 22H); ^{31}P-NMR ($CDCl_3$) δ 13.56 (s); *m/z* 484.2 (M^+), 469.2 (9%), 437.1 (100%), 281.0 (32%), 218.1 (19%), 77.1 (5%).

(R)-(+)-15: Yield 95%; mp 90-3°C; $[\alpha]^{25}_D$ +81.2 (c=0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.18 (d, *J*= 6.6 Hz, 3H), 1.22 (d, *J*= 6.6 Hz, 3H), 3.67 (sept, *J*= 6.6 Hz, 1H), 6.80 (d, *J*= 8.4 Hz, Ar, 1H), 7.10 (t, *J*= 7.2 Hz, Ar, 1H), 7.10 (d, *J*= 7.2 Hz, Ar, 1H), 7.15-7.45 (series of m, Ar, 12H), 7.53 (dt, *J*= 1.5, 8.1 Hz, Ar, 1H), 7.60 (dd, *J*= 3.0, 8.7 Hz, Ar, 1H), 7.74 (d, *J*= 8.7 Hz, Ar, 1H), 7.90 (d, *J*= 8.1 Hz, Ar, 1H), 7.99 (m, Ar, 3H); ^{31}P-NMR ($CDCl_3$) δ 13.82 (s); *m/z* 528.6.(M^+), 437.1 (100%), 281.0 (22%), 218.1 (45%).

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21 *Selected data for* **(R,R)-(+)-17:** Yield 89%; mp 155-8°C; $[\alpha]^{25}_D$ +171.4 (c=0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.61 (d, *J*= 5.4 Hz, 3H, $-CH_3$), 2.15 (s, 3H, $-SCH_3$), 2.68 (bs, 3H, $-N(CH_3)_2$), 2.95 (bs, 3H, $-N(CH_3)_2$), 3.96, (m, 1H), 5.95 (m, Ar, 1H), 6.15 (m, Ar, 1H), 6.70-7.98 (series of m, Ar, 24H); ^{13}C-NMR ($CDCl_3$) (alifatic carbons only) δ 15.69, 17.28, 44.60, 49.55, 73.87; ^{31}P-NMR ($CDCl_3$) δ 48.91 (s). Anal. Calcd. for $C_{43}H_{39}ClNPPdS$: C, 66.67; H, 5.07; N, 1.80. Found: C, 67.01; H, 5.20; N, 1.73.

22 *Selected data for* **(R)-(+)-18:** Yield 91%; mp 208-9°C; $[\alpha]^{25}_D$ +118.9 (c=0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.90 (bs, 2H), 2.35 (bs, 4H,),2.51 (m, 2H) 2.54 (s, 3H, $-SCH_3$), 4.50 (bs, COD, 2H), 6.10 (d, *J*= 9.9 Hz, Ar, 1H), 6.65 (bs, COD, 2H), 6.85 (m, Ar, 3H), 7.24 (m, Ar, 5H), 7.55 (m, Ar, 6H), 7.69 (m, Ar, 2H), 7.95-8.10 (series of m, Ar, 5H); ^{31}P-NMR ($CDCl_3$) δ 23.03 (d, $^1J_{P\text{-}Rh}$= 145.8 Hz); ^{13}C-NMR ($CDCl_3$) (alifatic carbons only) δ 16.20 (d, $^2J_{C\text{-}Rh}$= 10.2 Hz, $-CH_3$), 29.4 (s, COD), 32.8 (s, COD); Anal. Calcd. for $C_{42}H_{37}F_3O_3PRhS_2$: C, 59.72; H, 4.41 Found: C, 60.02; H, 4.54.

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