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ENANTIOSELECTIVE TWO-PHASE HYDROGENATION OF α-AMINO ACID PRECURSORS WITH WATER SOLUBLE RHODIUM COMPLEXES OF THE CATIONIC LIGAND (S,S)-2,4-bis[bis-(p-N,N,N-TRIMETHYLAMMONIUMPHENYL)PHOSPHINO]PENTANE, $[CH_3CH(P(p\text{-}C_6H_4NMe_3)_2CH_2CH(P(p\text{-}C_6H_4NMe_3)_2CH_3]^{4+}$

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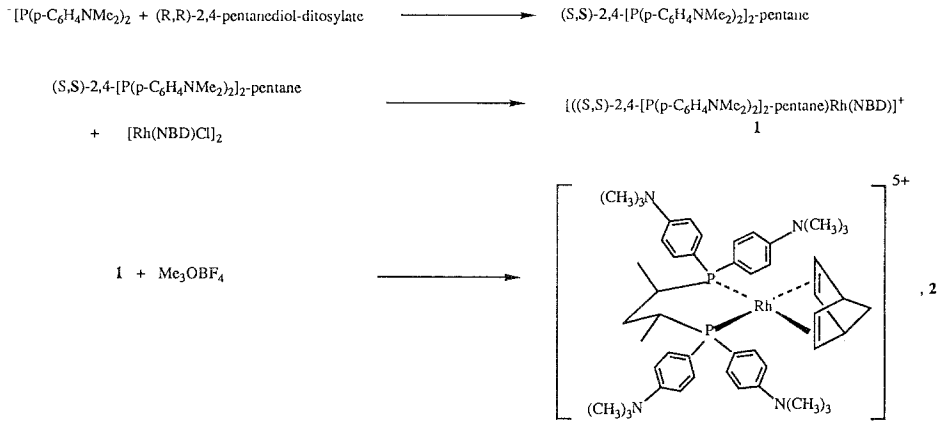
Enantioselective hydrogenation, rhodium complex, chiral cationic phosphine

Rhodium complexes of the chiral cationic phosphine, (S,S)-2,4-bis[bis-(p-N,N,N-trimethylammoniumphenyl)phosphino]pentane show excellent enantioselectivity for the hydrogenation of the DOPA precursor. (Z)-3-OMe,4-OAcC_6H_3CHC(COOH)(NHCOCH$_3$), and dehydrophenylalanineacetamide as slurries in water. The catalytic reactions may be done in either a two-phase system with the catalyst in the aqueous phase or as a slurry in water provided the substrates have some water solubility. Enantioselectivities of as high as 95% can be obtained.

The novel cationic rhodium complex [S,s-($CH_3CH(P(p\text{-}C_6H_4NMe_3)_2CH_2CH(P(p\text{-}C_6H_4NMe_3)_2CH_3)Rh(NBD)]^{5+}$, isolated as the tetrafluoroborate salt, shows excellent enantioselectivities in the two-phase hydrogenation of a variety of prochiral olefins. The enantioselectivities are nearly identical to those obtained



Scheme 1

with rhodium complexes of the sulfonated ligand, (S,S-$CH_3CH(P(m\text{-}C_6H_4SO_3Na)_2CH_2CH(P(m\text{-}C_6H_4SO_3Na)_2CH_3)$ [1]. Use of the water soluble catalyst with substrates and products of limited water solubility in the absence of a nonaqueous phase demonstrates that the catalysis occurs in the aqueous phase.

Phosphines can be modified to include cationic functional groups by the quaternization of the amine functionality of amine substituted phosphines [2,3]. To date examples of ligands with cationic functional moieties are limited to one such group per ligand. We have recently shown that tertiary phosphines containing the p-N,N-dimethylaminophenyl group are readily synthesized via the potassium phosphide $KP(p\text{-}C_6H_4NMe_2)_2$ [4]. Through the substitution of a ditosylate with $KP(p\text{-}C_6H_4NMe_2)_2$ four dimethylamino groups can be incorporated directly into a chelating phosphine. Reaction with R,R-2,4-pentanediol-ditosylate yields S,S-$(CH_3CH(P(p\text{-}C_6H_4NMe_2)_2\text{-}CH_2CH(P(p\text{-}C_6H_4NMe_2)_2CH_3)$*. These ligands were designed to have the polar functional group para to the phosphorus atom in contrast the sulfonated phenylphosphines which necessarily have the functional group in the meta position [1,5]. Since the orientation of the phenyl rings appears to be a necessary [6], although not sufficient condition [7], for good enantioselection it was thought that the introduction of substituents to the para position may be preferable for the modification of ligands which have been shown to provide good selectivity.

The quaternization of the ligand cannot be achieved directly due to the possibility of addition to phosphorus as well. Phosphorus may be protected however by coordination to rhodium [3]. Thus [S,S-$(CH_3CH(P(p\text{-}C_6H_4NMe_2)_2CH_2CH(P(p\text{-}C_6H_4NMe_2)_2CH_3)Rh(NBD)]BF_4$, **1**, ** is quaternized by the addition of Me_3OBF_4 to dry acetone solutions of the rhodium complex. The synthetic reactions are summarized in scheme 1. The extent of quaternization is readily monitored by NMR spectroscopy. The N-methyl region of the ^{13}C NMR spectra of [S,S-$(CH_3CH(P(p\text{-}C_6H_4NMe_3)_2CH_2CH(P(p\text{-}C_6H_4NMe_3)_2CH_3)Rh$

* Analytical data for S,S-$(CH_3CH(P(p\text{-}C_6H_4NMe_2)_2CH_2CH(P(p\text{-}C_6H_4NMe_2)_2CH_3)$. Mp 168° C; $[\alpha]_D^{20} = -90.2$ (*c* 1.839 in $CHCl_3$); Anal. calcd for $C_{37}H_{50}N_4P_2$; C, 72.55; H, 8.16; N, 9.15; P, 10.13; found C, 73.07; H, 8.16; N, 9.27; P, 10.22; $^{31}P\{^1H\}$ NMR (81.01 MHz, $CDCl_3$): −5.23 ppm (s); $^{13}C\{^1H\}$ NMR (50.3 MHz, $CDCl_3$) 150.6 s, 150.5 s, 134.63 d ($J_{PCC} = 21.0$ Hz), 134.56 d ($J_{PCC} = 20.0$ Hz), 123.7, 122.9 d,d ($J_{PC} = -8.5$ Hz), 112.6, 112.0 d,d ($J_{PCCC} = 6.2$ Hz), 40.2 s, 36.5 t ($J_{PCC} = 19.0$ Hz), 27.9 d,d ($J_{PC} = -12.1$ Hz) ($J_{PCCC} = 7.7$ Hz), 15.8 d ($J_{PCC} = 18.1$ Hz).

** Analytical data for **1**, [S,S-$(CH_3CH(P(p\text{-}C_6H_4NMe_2)_2CH_2CH(P(p\text{-}C_6H_4NMe_2)_2CH_3)Rh(NBD)]BF_4$. Anal. calcd. for $C_{44}H_{58}BF_4N_4P_2Rh\cdot CH_2Cl_2$: C, 55.1; H, 6.13; N, 5.72; P, 6.33; Rh, 10.51; found; C, 53.48; H, 6.34; N, 5.64; P, 6.25; Rh, 10.48. $^{31}P\{^1H\}$ NMR (81.01 MHz, d_6-acetone): 24.55 ppm (d, $J_{RhP} = 152.1$ Hz); $^{13}C\{^1H\}$ NMR (67.9 MHz, d_6-acetone) 153.2 s, 152.4 s, 137.4 t ($J_{PCC} = 7.0$ Hz), 133.8 t ($J_{PCC} = 4.8$ Hz), 114.8 t ($J_{PC} = 25.5$ Hz), 112.4 t ($J_{PC} = 23.1$ Hz), 113.1 d ($J_{PCCC} = 4.6$ Hz), 112.5 t ($J_{PCCC} = 6.5$ Hz), 87.6 q ($J_{RhC} = J_{PRhC} = 6.1$ Hz) 86.7 q ($J_{RhC} = J_{PRhC} = 5.8$ Hz), 70.0 br s, 54.2 s, 40.0 s, 39.9 s, 37.3 br s ($J_{PCC} < 3$ Hz) 27.2 t ($J_{PC} = 17.3$ Hz) 17.9 br s.

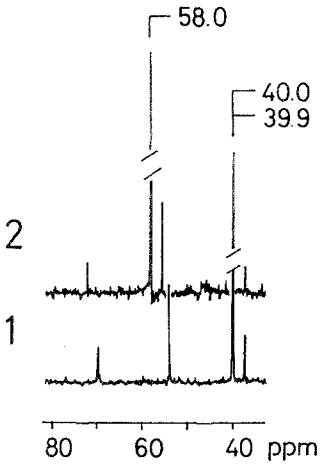


Fig. 1. The ^{13}C NMR spectra of **1** and **2** in the N-methyl region. Two signals are observed for the NMe_2 groups in **1** and only a single resonance is detected for these groups in **2**. The other signals, at 70, 54 and 37 ppm for **1** and 74, 56, and 38 for **2** are assigned to the saturated carbons in norbornadiene and the methylene carbon in the chelate ring respectively.

(NBD)][BF_4]$_5$, **2**, * and complex **1** are shown in fig. 1. From the absence of peaks due to -NMe_2 in the spectrum **2** it is estimated that the degree of quaternization is > 95%.

Table 1 summarizes the catalytic results for complexes **1** and **2** under a variety of conditions for several substrates. In homogeneous methanol solution **1** behaves similarly to its unmodified analog [(skewphos)Rh(NBD)]$^+$ [6b,8]. Thus, the para dimethylamino group has little effect on the enantioselectivity for a given substrate; it appears that enantioselection is not very sensitive to the position of

Table 1a
Hydrogenation of prochiral α-amino acid precursors [a]; results with **1** as the catalyst at 20 °C and 1 bar H_2.

Solvent	Substrate	e.e. (%)	Reaction time (m)
MeOH	**3**	95	20
MeOH	**4**	92	5.1
MeOH	**5**	76	3.2
MeOH	**6**	56	3.4
EtAc-benzene	**5**	65	5.1
EtAc-benzene [b]	**5**	26	

* Analytical data for **2**, [S,S-(CH_3CH(P(p-$C_6H_4NMe_3$)$_2CH_2CH$(P(p-$C_6H_4NMe_3$)$_2CH_3$)Rh (NBD)][BF_4]$_5$. Anal. calcd. for $C_{48}H_{70}B_5F_{20}N_4P_2Rh$: C, 44.2; H, 5.38; N, 4.30; Rh, 7.90; found; C, 43.70; H, 5.37; N, 4.25; Rh, 7.96; $^{31}P\{^1H\}$ NMR (81.01 MHz, D_2O): 28.9 ppm (d, J_{RhP} = 152.3 Hz); $^{13}C\{^1H\}$ NMR (50.3 MHz, D_2O), 151.2 s, 150.2 s, 139.5 t (J_{PCC} = 9.0 Hz), 135.76 t (J_{PCC} = 6.3 Hz), 122.7 t (J_{PCCC} = 7.9 Hz), 122.5 t (J_{PCCC} = 6.6 Hz), 94.9 q (J_{RhC} = J_{PRhC} = 6.0 Hz), 89.5 m (not resolved), 73.9 br s, 58.8 br s, 56.3 s, 37.7 br s, 27.4 t (J_{PC} = 18 Hz), 18.8 br s; the phenyl carbon bonded to phosphorus was not observed.

Table 1b
Results with **2** as the catalyst at 20 °C and 14 bar H_2.

Solvent	Substrate	e.e. (%).	Reaction time (h)
H_2O/EtAc-benzene [c]	**4**	67	6
H_2O/EtAc-benzene [c]	**5**	44 [d]	6
		43	6
		41	10
		42	10
H_2O/EtAc-benzene [c]	**6**	54	9
H_2O-slurry	**3**	78	6
		93 [e]	
H_2O-slurry	**4**	67	6
		95 [f]	
H_2O-slurry	**5**	40	2
H_2O-slurry	**7**	– [g]	24

[a] Catalyst concentration 0.025 mmol in 10 mL solvent, substrate/Rh = 100. All products are of the R configuration. Conversion: 100%. Products from mixtures with **1** as the catalyst were extracted with diethylether (3×50 ml) after addition of 5 ml 5% HCl. Products from aqueous solutions of 2 were extracted with diethylether or ethylacetate-benzene. Chemical yield > 90%. Typical Rh-contamination determined by atomic absorption spectroscopy is 2.5–3 ppm for both work-up procedures. Enantioselectivities were determined by polarimetry by comparision with literature values for the hydrogenated products [10–12]

[b] 14 bar H_2.

[c] Ratio: 2:1:1.

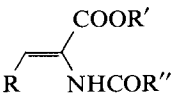
[d] First of four cycles.

[e] Product was filtered off and washed with 5 ml water. Chemical yield: 75%.

[f] Product was filtered off and washed with 5 ml water. Chemical yield: 55%.

[g] No conversion was observed.

Substrates



	R	R'	R''
3	3-OMe, 4-OAc C_6H_4	H	CH_3
4	C_6H_5	H	CH_3
5	C_6H_5	CH_3	CH_3
6	C_6H_5	CH_3	C_6H_5
7	C_6H_5	H	C_6H_5

monosubstitution on the phenyl ring. A loss in enantioselectivity is observed in the hydrogenation of **5** in ethylacetate/benzene compared to methanol; a further loss in enantioselectivity is observed when the pressure is increased from 1 atm to 14 atm.

The enantioselectivities observed for **2** as a hydrogenation catalyst under two-phase conditions (water/ethylacetate-benzene) at 14 atm are the same or slightly lower than for **1** in homogeneous solution at 1 atm for substrates **5** and **6**. Thus, under two-phase conditions the enantioselectivity obtainable with **2** as catalyst is more resistant to increases in pressure than with **1** in homogeneous ethylacetate-benzene. This may reflect, in part, the fact that hydrogen is not very soluble in water.

Substrates **3**, **4** and **5** have limited solubility in water (1.1, 3.8 and 5.0 mg/ml respectively). When **4** is slurried in the two-phase mixture water/ethylacetate-benzene with **2** as the catalyst in the aqueous phase hydrogenation proceeds with good enantioselectivity. The nonaqueous phase is superfluous in this case since the substrate will partition between the two phases. When either **3** or **4** is slurried directly in aqueous solutions of **2** complete conversion to products is obtained after 6 hours at 20 °C and 14 atm pressure H_2. Isolated yields of 75% of hydrogenated **3** are obtained from the slurry reaction simply by filtration. Clearly these results satisfy the conditions of ease of separation of catalyst and product normally associated with a heterogeneous catalyst. Since the racemates have greater solubility than the optically pure material crystallization results in isolation of a product that has greater optical purity than the obtained in the catalytic reaction [9]. The homogeneous catalyst used commercially by Monsanto also depends on the precipitation of the product solution [9]. However in this case the rhodium complex is monocationic and not water soluble; the solvent used commercially is aqueous ethanol.

Given the slight water solubility of **3**, **4**, and **5** it is likely that the slurry reactions take place homogeneously in the aqueous phase; substrate **7**, which shows no measurable water solubility, is not hydrogenated when slurried with **2** for 24 h at 14 atm H_2. The similarity of the results for **4** and **5** under two-phase and slurry conditions and the low enantioselectivity observed with **5** in EtAc-benzene at 14 bar H_2 demonstrates that the catalysis occurs in the aqueous phase when a nonaqueous phase is present.

The aqueous solutions of **2** can be recycled without loss of enantioselectivity when care is taken to rigorously exclude oxygen from the system.

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