# Synthesis of Chiraphos *via* asymmetric hydrogenation of 2,3-bis(diphenylphosphinoyl)-buta-1,3-diene

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**(*S*,*S*)-2,3-Bis(diphenylphosphinoyl)butane, an immediate precursor of (*S*,*S*)-CHIRAPHOS, can be obtained with 70% de and 71% op *via* double asymmetric hydrogenation of 2,3-bis(diphenylphosphinoyl)buta-1,3-diene in the presence of Ru–(*S*)-BINAP catalysts.**

Recently, we have described a new strategy for the synthesis of Chiraphos,[1]† a well-known bidentate chiral ligand for asymmetric catalysis. The key step of the synthesis is the diastereoselective hydrogenation of 2,3-bis(diphenylphosphinoyl)-buta-1,3-diene **1** which affords a pair of enantiomers (*R*,*R*)- and (*S*,*S*)-**2** and the *meso* species (*R*,*S*)-**2**. This latter isomer is useless, therefore its formation must be avoided in order to remove the need for a difficult purification step. In the previously reported synthesis,[1] a racemic mixture of (*R*,*R*)- and (*S*,*S*)-**2** was obtained in *ca*. 70% yield by reacting **1** with $NaBH_4$. Using this reducing agent, *ca*. 30% of *meso*-**2** was also produced, but was promptly separated and discarded since it forms an insoluble adduct with one molecule of NaOH and one molecule of $NaBH_4$.[1]

The recent improvements achieved in asymmetric hydrogenation[2] by means of homogeneous chiral transition metal catalysts prompted us to investigate the direct synthesis of enantiopure (*R*,*R*)-**2** or (*S*,*S*)-**2** by hydrogenation of **1** in the presence of an asymmetric catalyst (Scheme 1).

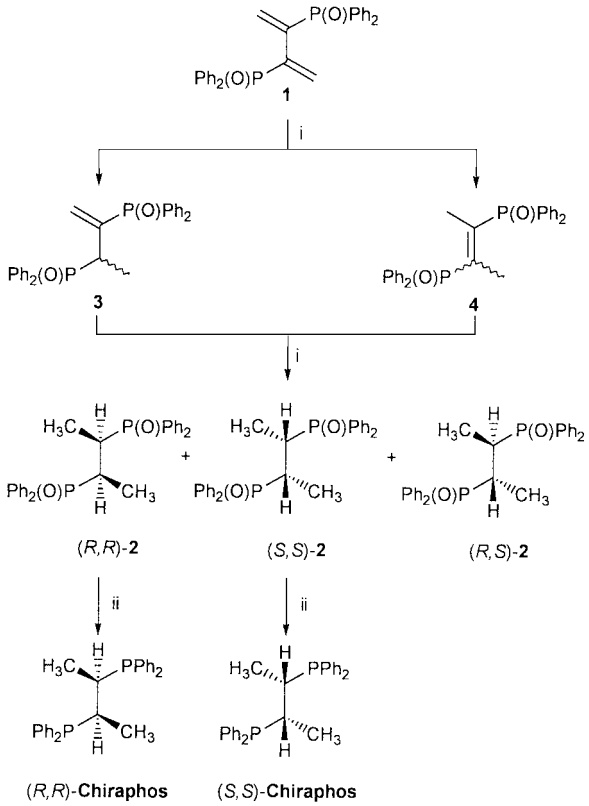
Interest in this subject goes beyond the synthetic application envisaged here since, although a large number of reports concerned with asymmetric reduction of monoenes have been published, only a few examples of asymmetric reduction of dienes have appeared so far.[3] Further interest is added by the peculiar nature of **1**.

Two different Ru-BINAP complexes, *i.e.* [RuCl(*p*-cymene){(*S*)-BINAP}]Cl[4] and $[Ru(OAc)_2\{(S)\text{-BINAP}\}]$,[5] were tested as catalysts. The relevant data, together with the reaction conditions, are reported in Table 1.

The reactions were carried out in a magnetically stirred stainless steel autoclave. The product's composition was determined by NMR spectroscopy, since in previous studies we found that all the species which may form during the reaction (see Scheme 1) give well-separate signals in the $^{31}P$ NMR spectrum.[1]

When only the stereoisomers of **2** were present into the crude reaction mixture, the enantioselectivity of the reaction was determined by polarimetry on samples recrystallized from benzene/n–hexane to remove the catalyst.[6] In the case of runs 1 and 4, owing to the presence of the chiral intermediate **3**, a catalyst-free sample of the crude reaction mixture was treated with (1*S*)-(+)-camphorsulfonic acid to form *inter alia* the corresponding (*S*,*S*)-**2**–(1*S*)-(+)-camphorsulfonic and (*R*,*R*)-**2**–(1*S*)-(+)-camphorsulfonic adducts. The enantioselectivity of the reaction was then calculated by integration of their relevant resonances in the $^{31}P$ NMR spectrum.[7]

Both catalysts require rather severe reaction conditions to carry out the hydrogenation. With [RuCl(*p*-cymene){(*S*)-BINAP}]Cl the hydrogenation of **1** proceeds with complete




**Scheme 1** *Reagents and conditions*: i, $H_2$, catalyst; ii, $HSiCl_3$, $NEt_3$.

**Table 1** Hydrogenation of 2,3-bis(diphenylphosphinoyl)buta-1,3-diene **1** with Ru–BINAP catalysts[a]

| | | | | Yield (%) | | | |
|---|---|---|---|---|---|---|---|
| Run | Catalyst | *T*/°C | *t*/h | **3** | (*R*,*S*)-**2** | (*S*,*S*)-**2** + (*R*,*R*)-**2** | Op **2** (%)[b] |
| 1 | [RuCl(*p*-cymene){(*S*)-BINAP}]Cl[c] | 50 | 216 | 53 | 0 | 47 | 0 |
| 2 | [RuCl(*p*-cymene){(*S*)-BINAP}]Cl[c] | 100 | 120 | 0 | 0 | 100 | 8 |
| 3 | $[Ru(OAc)_2\{(S)\text{-BINAP}\}]$[d] | 100 | 67 | 45 | 10 | 45 | ND[e] |
| 4 | $[Ru(OAc)_2\{(S)\text{-BINAP}\}]$[d] | 100 | 163 | 18 | 13 | 69 | 68 |
| 5 | $[Ru(OAc)_2\{(S)\text{-BINAP}\}]$[d] | 100 | 310 | — | 15 | 85 | 71 |

[a] MeOH (15 ml), substrate (2.0 mmol), $P(H_2)$ = 100 atm. [b] In all cases the prevailing configuration is (*S*,*S*)-**2**. [c] Substrate/Ru = 120. [d] Substrate/Ru = 10. [e] Not determined.

diastereoselectivity since no *meso*-**2** is formed. Surprisingly, operating at 50 °C in the presence of this catalyst, a racemic mixture of **2** is obtained, while working at 100 °C a modest induction is observed (run 2). This rather unusual enhancement of the enantioselectivity on increasing the reaction temperature suggests that different catalytic species are actually at work; an example of such behaviour has been previously reported in the literature.[8]

With [Ru(OCOCH$_3$)$_2$\{(*S*)-BINAP\}] lower reaction rates are obtained. Thus, even at 100 °C and using a substrate/catalyst ratio of 10, long reaction times are necessary to achieve complete hydrogenation of diene **1** (run 5). Most significant is that the reaction proceeds with good diastereo- (de = 70%) and enantio-selectivity [the op of the prevailing (*S*,*S*)-**2** isomer is 71%]. Presumably the P=O bond is acting as a co-ordinating group in the reaction, rather as an amide does in the hydrogenation of acylamino acrylates.[9,10]

Concerning the reaction mechanism, there are two possible pathways for the hydrogenation of the diene **1** (Scheme 1): (i) two consecutive 1,2-hydrogen additions; (ii) an initial 1,4-hydrogen addition to give (*cis* or *trans*) **4** followed by hydrogenation of the remaining double bond.

At shorter reaction times (runs 3 and 4) only **2** and **3** are detected in the reaction mixture, suggesting that the reaction proceeds *via* two consecutive 1,2-hydrogen additions; moreover it appears that the first double bond hydrogenation is faster than the second one. On the other hand, an independent experiment showed that a pure sample of **4**[11] is not hydrogenated in the presence of [Ru(OCOCH$_3$)$_2$\{(*S*)-BINAP\}] under the conditions in Table 1.

In conclusion, even if the process is not yet ready for practical application owing to the incomplete stereoselectivity this work demonstrates the possibility of employing the asymmetric catalysis in the synthesis of a chiral diphosphine. According to this strategy a chiral ligand could be synthesised using another chiral phosphine ligand, thus giving a new example of chiral amplification.

## Notes and references

† Chiraphos: 2,3-bis(diphenylphosphino)butane.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2 *Catalytic Asymmetric Synthesis*, ed. I. Ojima, VCH, New York, 1993.

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4 K. Mashima, K. Kusano, T. Ohta, R. Noyori and H. Takaya, *J. Chem. Soc., Chem. Commun.*, 1989, 1208.

5 M. Kitamura, M. Tokunaga and R. Noyori, *J. Org. Chem.*, 1992, **57**, 4053.

6 Polarimetry measurements on different recrystallised samples of **2** have shown that there is no variation in the op due to recrystallisation from benzene–*n*-hexane.

7 The adducts between **2** and (1*S*)-(+)-camphorsulfonic acid were prepared as follows: an 80:20 mixture of **2**:**3** (~500 mg recovered by recrystallisation of a sample of run 4) was dissolved in 10 ml of $CHCl_3$ and the mixture was heated to reflux temperature (mixture A). Separately, 220 mg (0.88 mmol) of (1*S*)-(+)-camphorsulfonic acid were dissolved in 15 ml of EtOAc (mixture B). The hot mixture B was added to mixture A and the system was further heated for 2 min. The crude solid recovered after evaporation of the solvents was characterised by $^{31}$P NMR ($CDCl_3$): $\delta$ 40.7 (s), 40.4 (s). Signals due to the adducts between **3** and (1*S*)-(+)-camphorsulfonic acid were also present: $\delta$ 38.23 (d, $J_{P,P}$ 20.0), 38.21 (d, $J_{P,P}$ 21.0 ), 35.06 (d, $J_{P,P}$ 21.0 ), 35.00 (d, $J_{P,P}$ = 20.0). Pure samples of (*S*,*S*)-(−)-**2**–(1*S*)-(+)-camphorsulfonict and (*R*,*R*)-(+)-**2**–(1*S*)-(+)-camphorsulfonic adducts were synthesised as described above starting from pure samples of (*S*,*S*)-(−)-**2** or (*R*,*R*)-(+)-**2** and (1*S*)-(+)-camphorsulfonic acid to identify the two species present in the $^{31}$P NMR spectrum. *Selected data* for (*S*,*S*)-(−)-**2**–(1*S*)-(+)-camphorsulfonic adduct: $\delta_P$($CDCl_3$, 85% $H_3PO_4$) 40.7 (s); $\delta_H$($CDCl_3$) 0.83 (3H, s, C*H*$_3$C), 1.07 (3H, s, C*H*$_3$C), 1.25 (6H, m, C*H*$_3$) 1.50–2.70 (7H, m, C*H*$_2$C*H*$_2$C*H*C*H*$_2$), 3.00 (2H, m, C*H*$_3$CH), 3.00 (1H, d, C*H*$_2$SO$_3$H, $J_{H,H}$ 15.0), 3.50 (1H, d, C*H*$_2$SO$_3$H, $J_{H,H}$ 15.0), 7.30–-7.80 (20H, m, arom), 8.20 (1H, s, CH$_2$SO$_3$*H*); $\nu_{max}$(KBr)/cm$^{-1}$ 3400 (OH, br), 3000–2900 (aliphatic and aromatic C–H, w), 1700 (C=O, s); $[\alpha]_D^{23}$ −14.0 (*c* 2.0 in $CH_2Cl_2$). For (*R*,*R*)-(+)-**2**–(1*S*)-(+)-camphorsulfonic adduct: $\delta_P$ ($CDCl_3$, 85% $H_3PO_4$) 40.4 (s); $\delta_H$($CDCl_3$) 0.91 (3H, s, C*H*$_3$C), 1.08 (3H, s, C*H*$_3$C), 1.30 (6H, m, C*H*$_3$) 1.54–2.60 (7H, m, C*H*$_2$C*H*$_2$C*H*C*H*$_2$), 2.95 (2H, m, C*H*$_3$CH), 3.05 (1H, d, C*H*$_2$SO$_3$H, $J_{H,H}$ 15.2), 3.54 (1H, d, C*H*$_2$SO$_3$H, $J_{H,H}$ 15.2), 7.30–7.80 (20H, m, arom), 8.20 (1H, s, CH$_2$SO$_3$*H*); $\nu_{max}$(KBr)/cm$^{-1}$ 3400 (OH, br), 3000–2900 (aliphatic and aromatic C–H, w), 1700 (C=O, s); $[\alpha]_D^{23}$+25.0 (*c* 2.0 in $CH_2Cl_2$). Slight differences in the $^{31}$P NMR ($CDCl_3$) chemical shifts of the mixture containing the two diastereoisomers may be observed due to variations in sample concentration.

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9 A. S. Chan, J. J. Pluth and J. Halpern, *J. Am. Chem. Soc.*, 1980, **102**, 5952; H. Kawano, T. Ikariya, Y. Ishii, S. Yoshikawa, Y. Uchida and H. Kumobayashi, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1571.

10 We are indebted to a referee for this suggestion.

11 A sample of pure monoene **4** was obtained by hydrogenation of **1** in the presence of Pd on carbon (10% Pd) at 80 °C and $P(H_2)$ = 100 bar followed by recrystallisation from benzene. $\delta_P$ ($CDCl_3$, 85% $H_3PO_4$) 31.88 (s); $\delta_H$($CDCl_3$) 1.99 (6 H, m, C*H*$_3$), 7.4–7.8 (20H, m, arom); $\delta_C$($CDCl_3$) 22.2 [*C*H$_3$, appt t, X part of an AA′X (A and A′ are the P atoms) spin system], 128.6 (*C*, arom, appt t), 131.4 (*C*, arom, appt t), 131.9 (*C*, s, arom.), 133.3 (*C*, s, arom.), 145.3 (C=, quin, AA′X spin system). Owing to the high symmetry of the molecule, the NMR data do not allow determination of the stereochemistry of the molecule.


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