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Investigation into an asymmetric hydrogenation promoted by rhodium–phosphetane complexes

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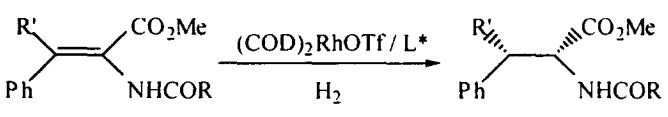
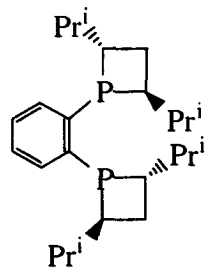
Abstract

The bis-phosphetanes **1** and **2** have been used as chiral ligands in the rhodium-catalysed hydrogenations of dehydroamino acid derivatives. An unusual increase of the optical yields at high hydrogen pressures has been noticed. Mechanistic implications are discussed.

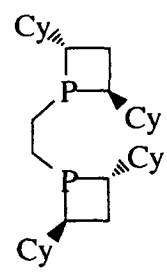
Since the initial works of H.B. Kagan and W.S. Knowles in the early seventies,[1] the rhodium-catalysed hydrogenation of (*Z*)-dehydrophenylalanine derivatives has become the model reaction most commonly used to evaluate the efficiency of new chiral phosphines. This reaction has been considered in this work as well, for a preliminary evaluation of the catalytic potential of the recently reported (*S,S*)-1,2-bis(2,4-diisopropylphosphetano)benzene **1**[2] ((*S,S*)-*i*Pr-CnrPHOS) and of the new diphosphine **2** in rhodium promoted hydrogenations.



R = Me. R' = H
R = Ph. R' = Me



(*S,S*)-**1**



(*S,S*)-**2**

Only a moderate enantioselectivity (74% ee, (*R*)(−)-enantiomer)[3] was afforded by (*S,S*)-**1** when the dehydro-*N*-acetyl-phenylalanine methyl ester was hydrogenated in the usual reaction conditions (1% $(COD)_2RhOTf$, (*S,S*)-**1**, MeOH, room temperature, 5 bars H_2). Surprisingly, a significant effect of

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the hydrogen pressure on the enantioselectivity has been noticed: as shown in Fig. 1, increased H_2 pressures give higher optical yields (82% ee at 10 bars versus 90% ee at 100 bars), at variance with the normal trend.[4] An analogous and even more pronounced effect has been observed by using the new bis(phosphetano)ethane ligand (*S,S*)-**2**:[5] the enantiomeric excess increases from 15 to 70% by increasing the H_2 pressure from 10 to 100 bars, at room temperature.

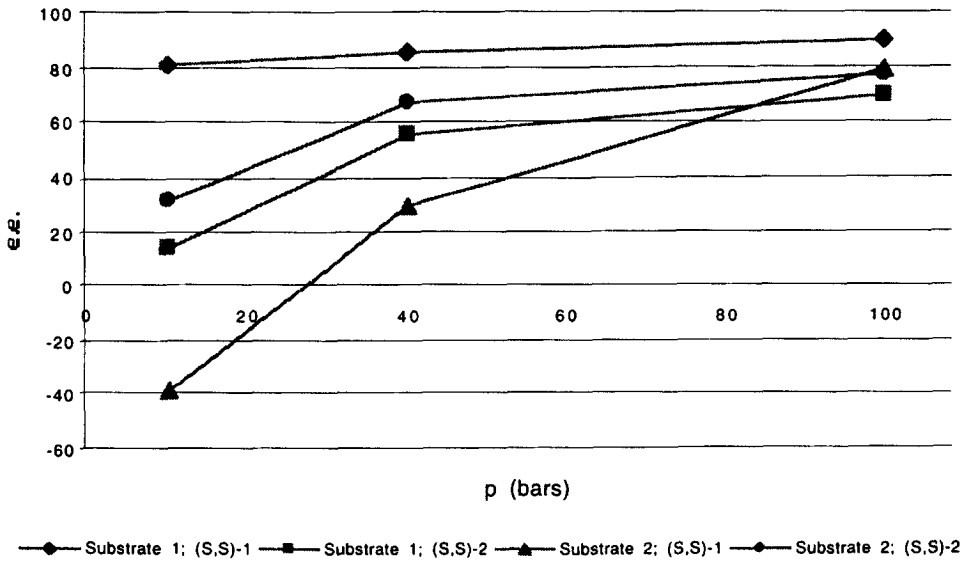

Figure 1. Rhodium-catalysed hydrogenations: effect of H_2 pressure on enantioselectivity (ee versus H_2 pressure). Substrate 1: (*Z*)-PhCH=C(NHAc)CO_2Me; substrate 2: (*Z*)-PhC(Me)=C(NHCOPh)CO_2Me. Reaction conditions: 1% catalyst, room temperature, 20 h, CH_2Cl_2/benzene

According to the mechanistic work of Halpern et al.,[6] which led to the generally accepted catalytic cycle shown in Fig. 2, a negative pressure effect is expected as far as the major hydrogenation product arises from the minor, less stable olefin–rhodium complex. This is indeed the case with most of the known chiral diphosphines and especially with DIOP,[4] DIPAMP[6b] and BINAP[7] ligands.

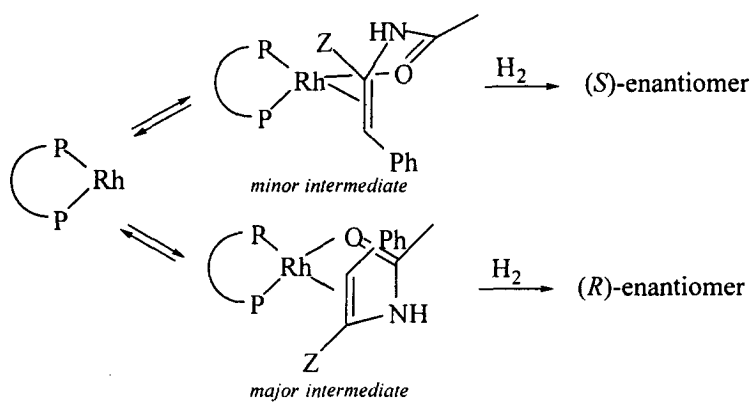

Figure 2. Catalytic intermediates of the Rh/diphosphine catalysed hydrogenations. Diphosphine=(*R*)-BINAP or (*S,S*)-DIOP or (*S,S*)-CHIRAPHOS

However, a positive pressure effect should be observed when the major enantiomer is produced from the preferentially formed catalyst–substrate complex. In other words, the isoinversion principle[8] applies to pressure effects in rhodium-catalysed hydrogenations where a reversible interconversion of diastereomeric intermediates competes with the hydrogenation step.

The positive pressure effect observed in this work can be easily explained if the major hydrogenation product is issued from the more stable intermediate. This seems to be the case here, if we consider the generally accepted model for the substrate–catalyst complex, as shown in Fig. 3. The (*S,S*)-diphosphines **1** and **2** hinder the upper-left and bottom-right space quadrants around the rhodium atom; the preferred coordination mode of the olefin should avoid the sterical interactions between the ester group (*Z*) and the phosphorus ligand, thus complexation of the *Si* face of the olefin should be favored.

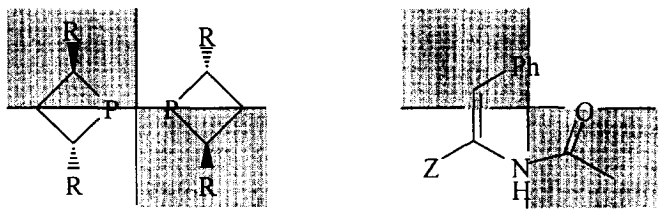

Figure 3. Assumed preferred coordination mode in the intermediate [(*Z*)-PhCH=C(NHAc)CO_2Me]Rh[(*S,S*)-**1**]$^+$ complex

Hydrogenation of this intermediate should lead to the (*R*)-amino acid derivative, which is indeed the observed major product. (*S,S*)-DIOP, (*R*)-BINAP or (*R,R*)-CHIRAPHOS, which define the same chiral array in their rhodium complexes,[9] afford the (*S*)-enantiomer of the hydrogenation product: the chiral sense of enantioselection (as well as the pressure effect) with ligands **1** and **2** is thus opposite to that obtained with these phosphines. However, it appears from literature data that DuPHOS-promoted hydrogenations follow the same stereochemical course as those promoted by phosphetane ligands **1** and **2**: (*S,S*)-*i*Pr-DuPHOS and (*R,R*)-Me-DuPHOS, which present the same chiral array as **1**, afford the (*R*)-configurated amino acid derivative in very high enantiomeric excess.[10]

This nonconventional stereochemical issue, can probably be related to the electron-rich nature of the DuPHOS and phosphetane ligands which should favor the oxidative addition of H_2 during the catalytic cycle. Thus, at sufficiently high H_2 pressure — fast hydrogenation step — the stereochemistry should become determined by the initial preferred binding of the prochiral olefinic substrate. Such conditions seem to be attained already at low pressure in the case of DuPHOS ligands, and at higher H_2 pressures with the phosphetane-based ligands **1** and **2**.

An alternative hypothesis accounting for the observed pressure effect could be the competition between the classical 'olefin' mechanism and the 'hydride' mechanism,[11] the last being promoted by the electron-rich nature of the ligands.

The same effect of H_2 pressure on the optical yields has also been noticed in the hydrogenation of the tetrasubstituted enamide (*Z*)-PhC(Me)=C(NHCOPh)CO_2Me: ligand (*S,S*)-**1** affords ee values of 38% (2*S*,3*R*-isomer) at 10 bars, 30% (2*R*,3*S*-isomer) at 40 bars and 80% at 100 bars. Ligand (*S,S*)-**2** gives ee values of 32% (2*R*,3*S*-isomer) at 10 bars (25% conversion), 68% at 40 bars, 78% at 100 bars (75% conversion). High pressures favor the (2*R*,3*S*)-enantiomer[12] and a reversal of chirality is observed at low hydrogen pressure by using ligand (*S,S*)-**1**.

Detailed mechanistic studies are in progress to support the experimental data above, which already offer new perspectives for understanding and optimisation of these fundamental catalytic processes.

References

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3. Enantiomeric excesses were measured by HPLC (Daicel Chiralcel OD-H, hexane:*i*-PrOH, 90:10). The absolute configuration was assigned from $[\alpha]_D$ values [Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Winkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946: (*S*)-enantiomer: $[\alpha]_D$ +16 (*c* 2, MeOH)] and HPLC retention times, by comparison with known compounds.
4. Nogradi, M. In *Stereoselective Synthesis*; VCH: Weinheim, 1995; p. 46, and references cited therein.
5. Compound (*S,S*)-**2**: colorless solid; ^{31}P NMR (C_6D_6) δ: 23 ppm; ^{13}C NMR (62.9 MHz, C_6D_6, selected data) δ: 20.8 (J_{C-P}=11.0 Hz, CH_2), 34.4 (t, J_{C-P}=3.3 Hz, CH), 36.5 (t, J_{C-P}=3.1 Hz, CH), 40.1 (CH), 40.9 (t, J_{C-P}=7.5 Hz, CH) ppm. Mass spectrum (E.I.): 502 (M, 10%), 474 (15%), 237 (25%), 81 (100%). $[\alpha]_D$ +266 (*c* 0.5, CH_2Cl_2). Compound (*S,S*)-**2** has been prepared from 1,2-bis(phosphino)ethane and the cyclic sulfate of (*R,R*)-1,3-dicyclohexylpropanediol. The detailed procedure will be reported later.
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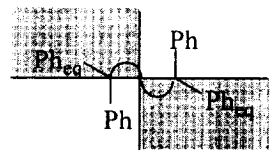
9. For instance, the equatorial phenyl groups of (*R*)-Binap in the λ conformation induce sterical hindrance in the upper-left and bottom-right space quadrants (P-chirality).



In the rhodium catalysed hydrogenations, (*R*)-Binap affords (*S*)-*N*-acetylphenylalanine derivatives. Noyori, R. *Chem. Soc. Rev.* **1989**, *18*, 187. See, also: Sakuraba, S.; Morimoto, T.; Achiwa, K. *Tetrahedron: Asymmetry* **1991**, *2*, 597.
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12. Enantiomeric excesses were measured by ^1H NMR analysis with $Eu(tfc)_3$ as the chiral resolving agent. The (–)-enantiomer (*c* 1, $CHCl_3$) was obtained at high pressure. The absolute stereochemistry of the major isomer is assumed to be (2*R*,3*S*) by analogy to the stereochemical issue of the reported DuPHOS catalysed hydrogenation of the *N*-acetyl derivative: Burk, M. J.; Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 9375.