Rationally designed improvement of the bis(phospholano)ethane ligand for asymmetric hydrogenation leads to a reappraisal of the factors governing the enantioselectivity of Duphos catalysts

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Enhancement of enantioselectivity in hydrogenations catalysed by δ vs. λ rhodium chelate complexes of *trans*-1,2-bis(phospholano)cyclopentanes cannot be rationalised using the current quadrant model for Duphos ligands and therefore a new consistent model is suggested.

Diphosphines containing the 2,5-dialkylphospholane moiety (*e.g.* *R,R*-Duphos, *R,R*-bpe) are currently the most efficient


R,R-Duphos   *R,R*-bpe
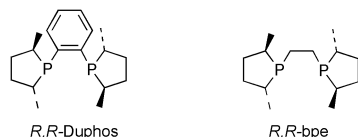
ancillary ligands for the asymmetric hydrogenation of many alkenes;[1–4] several of these catalytic processes are of commercial interest.[4] The enantioselectivity is a sensitive function of the ligand backbone.[1–7] For example, for the hydrogenations shown in eqns. (1) and (2), the enantioselectivity increases with

$$(1)$$

$$(2)$$
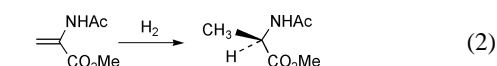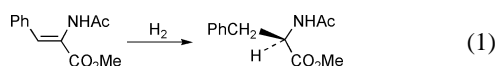
increasing rigidity of the ligand backbone. Here, we show an example of how the enantioselectivity for the bis(phospholane)-ethane complex **1** can be improved by rational design of the ligand backbone; our results challenge the currently accepted explanations for the selectivity of Duphos ligands.
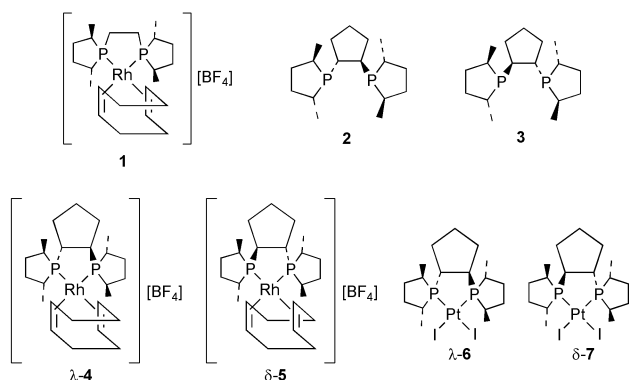

The chelate ring of the *R,R*-bpe complex **1** is flexible and an interconverting mixture of diastereomeric λ and δ chelate conformers would be anticipated [eqn. (3)]. It was predicted that

$$(3)$$
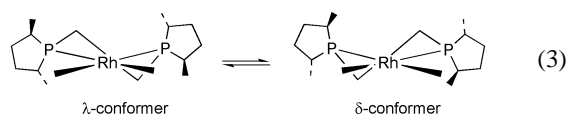
the λ conformer of **1** would give the higher enantioselectivity (see below)[3] and we reasoned that this hypothesis could be tested by comparing the optical yields obtained with **2** and **3**, the two diastereoisomers of *trans*-1,2-bis(*R,R*-phospholano)cyclopentane since **2** would give exclusively a λ-conformer chelate complex and **3** would give a δ-conformer.

The new ligands **2** and **3** were prepared from resolved *trans*-1,2-diphosphinocyclopentane[8] and the 1,4-diol cyclic sulfate[1] as shown in eqn. (4) for **2**. The rhodium(I) chelate complexes λ-

$$(4)$$
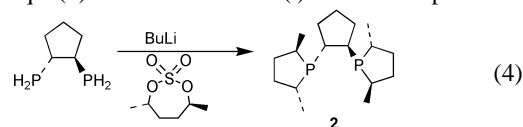
4 and δ-**5** have been synthesised and fully characterised but we have been unable to obtain crystals suitable for X-ray crystallography. However the crystal structures of the diiodo-platinum(II) complexes of **2** and **3**, λ-**6** and δ-**7** have been determined (Figs. 1 and 2).† These confirm the assignment of the chelate conformations. The bond lengths and angles around platinum in λ-**6** and δ-**7** are not substantially different (lengths differ by 0.01–0.02 Å and angles by 1–2°).[11] The principal effect of the change in backbone stereochemistry seems to be in the orientation of the phospholane rings. Changing the MP_2C_2 chelate conformation from λ to δ leads to a rotation about the M–P bond of *ca.* 30°, as measured by I–Pt–P–C torsions (see Figs. 1 and 2). As a consequence, the methyl groups are closer to the other ligands in the metal coordination plane (here iodine) in λ-**6** (I⋯CH_3 3.70 Å) than in δ-**7** (I⋯CH_3 4.11, 4.20 Å). Conversely the axial hydrogen atoms adjacent to the phosphorus are closer to the iodo ligands in δ-**7** (I⋯H 3.07, 3.00 Å) than
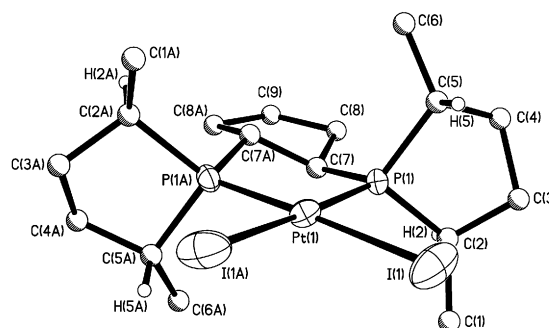

Fig. 1 Molecular structure and numbering scheme for λ-**6**. All but phospholane tertiary hydrogen atoms have been omitted for clarity. Important molecular dimensions: bond lengths (Å) Pt(1)–P(1) 2.237(2), Pt(1)–I(1) 2.6453(8); bond angle (°) P(1)–Pt(1)–P(1A) 88.25(10); torsion angles (°) I(1)–Pt(1)–P(1)–C(2) 46.5(2), I(1)–Pt(1)–P(1)–C(5) −69.2(2).
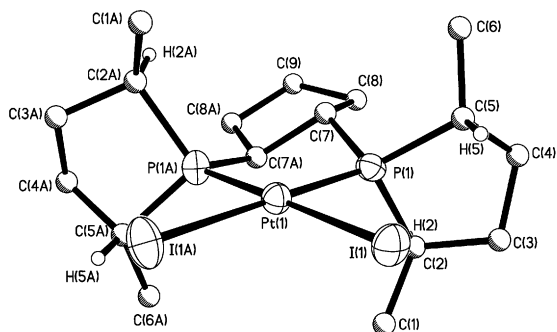
Fig. 2 Molecular structure and numbering scheme for δ-**7**. All but phospholane tertiary hydrogen atoms have been omitted for clarity. Important molecular dimensions include: bond lengths (Å) Pt(1)–P(1) 2.248(2), Pt(1)–P(1A) 2.258(2), Pt(1)–I(1) 2.6533(9), Pt(1)–I(1A) 2.6690(8); bond angle (°) P(1)–Pt(1)–P(1A) 86.44(9); torsion angles (°) I(1)–Pt(1)–P(1)–C(2) 78.4(2), I(1)–Pt(1)–P(1)–C(5) −38.3(2), I(1A)–Pt(1)–P(1A)–C(2A) 70.6(2), I(1A)–Pt(1)–P(1A)–C(5A) −47.5(2).

in λ-**6** (I···H 3.37 Å). The PC_4 rings in *R*-phospholanes have δ-conformations and so in δ-**7** the conformations are δδδ for the PC_4, PtP_2C_2 and PC_4 rings, respectively, while in λ-**6** these rings show δλδ conformations.

The results of the hydrogenations shown in eqns. (1) and (2) catalysed by the rhodium catalysts λ-**4**, δ-**5** and **1** are shown in Table 1. It is clear that the optical yields obtained with λ-**4** are inferior to **1** and those for δ-**5** are superior to **1**. The unequivocal conclusion is that the δ-chelate gives *higher* enantioselectivities than the λ-chelate, *i.e.* δ-**5** is the *matched* diastereomeric catalyst.[6] Since this is the opposite of what was predicted,[3] we decided to re-examine the basis of the current heuristic model for Duphos catalysts.[12]

Table 1 Optical yields for the hydrogenations of methyl-(*Z*)-2-acetamidocinnamate [eqn. (1)] and methyl-2-acetamidoacrylate [eqn. (2)][a]

Catalyst	Methyl-(*Z*)-2-acetamidocinnamate	Methyl-2-acetamidoacrylate
λ-**4**	77 (*R*)	73 (*R*)
1[b]	85 (*R*)	91 (*R*)
δ-**5**	98 (*R*)	95 (*R*)

[a] *Experimental conditions*: solvent MeOH, 2 atm H_2, 20–25 °C, 0.05–0.1% Rh catalyst, reaction time, 1–16 h. Conversions and enantiomeric excesses were determined by GC using a Hewlett-Packard 5800 A with a L-Chirasil-Val column. [b] Results from ref. 3.

In the stereochemical model of refs. 3, 6 and 12, it is assumed that the alkyl substituents of the phospholanes block the diagonal of quadrants shown in Fig. 3(a) for bis(*R*-phospholane) chelates. In turn this implies that the favoured, major, adduct diastereoisomer is that in which the enamide substrate is bound through its *si* face (see ref. 12 for explicit confirmation of this view).

Seminal mechanistic work[9] revealed that the major enantiomer formed in asymmetric hydrogenation by rhodium complexes of 'traditional' chiral diphosphines such as chiraphos was derived from the minor diastereoisomer of the prochiral alkene complex. Burk and coworkers showed[10] that, when the hydrogenation shown in eqn. (1) is catalysed by [Rh(*S*,*S*-Duphos)(cod)]⁺, the major product enantiomer (having *S*-configuration) is derived, in Halpern-like manner, from the minor diastereoisomer of the substrate complex (which there-
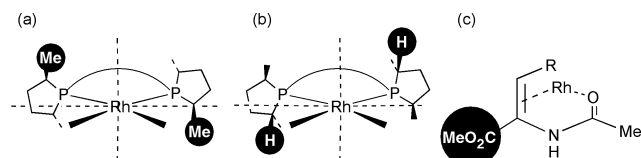
fore must be *re*-face bound). Indeed they were able to confirm this assignment of adduct stereochemistry by NMR experiments and by analogy with iridium chemistry. By implication, for *R*,*R*-phospholanes, as here, the minor adduct is *si*-face bound (and the *R*-configuration product results from its Halpern-type hydrogenation). This directly contradicts the standard quadrant model prediction noted above.

In λ-**6** the phospholane methyl groups are closer to the metal coordination plane than in δ-**7** and therefore would be expected to present more steric interaction at the sites where the alkene substrates would bind. However in δ-**7** (whose analogue δ-**5** is the more stereoselective catalyst) the axial hydrogen atoms are closer to the substrate binding site. This leads us to suggest an alternative stereochemical model for these phospholane ligands: it is the *axial* hydrogens rather than the equatorial methyls that offer the critical, diastereofacially-discriminating steric interactions with a prochiral substrate. The corollary of this suggestion is that the diagonal of blocked quadrants [Fig. 3(b)] is orthogonal to that currently accepted. The new quadrant diagram predicts (in accord with ref. 10) that the *less* stable (minor) diastereoisomer is formed when the substrate is *si*-face bound, Fig. 3c. A Halpern-type hydrogenation mechanism would then lead to the observed *R*-configuration of the product, again in accord with the results reported in ref. 10.

Hydrogenation of very bulky enamides (*e.g.* $H_2C=CBu^tN$-HAc) catalysed by *R*,*R*-Duphos complexes leads to a product of *S*-configuration. While this inversion of stereochemistry poses problems for any quadrant model, we note that it is possible that extreme bulk of the α-substituent may render the concentration of the minor adduct diastereoisomer effectively zero, thereby leading to no product from that pathway regardless of the rate of hydrogenation of the major (only) species.

Note added in proof: The quadrant models discussed in this paper implicitly assume that crowding in the plane of the metal–diphosphine moiety is important in enantioselection. A recent report (I. D. Gridnev, N. Higashi, K. Asakura and T. Imamoto, *J. Am. Chem. Soc.*, 2000, **122**, 7183) suggests that octahedral *cis*-dihydride species are critical.

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Fig. 3 (a) Quadrants that are reportedly[3,6,12] blocked by the methyl substituents in Rh(*R*,*R*-bpe) chelate; (b) quadrants that are proposed to be blocked by the axial hydrogens in a Rh(*R*,*R*-bpe) chelate; (c) *si*-face binding of substrate alkenes.