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The Stereochemistry of Enamide Intermediates in DuPHOS-Rh(I) Catalysed Asymmetric Hydrogenation

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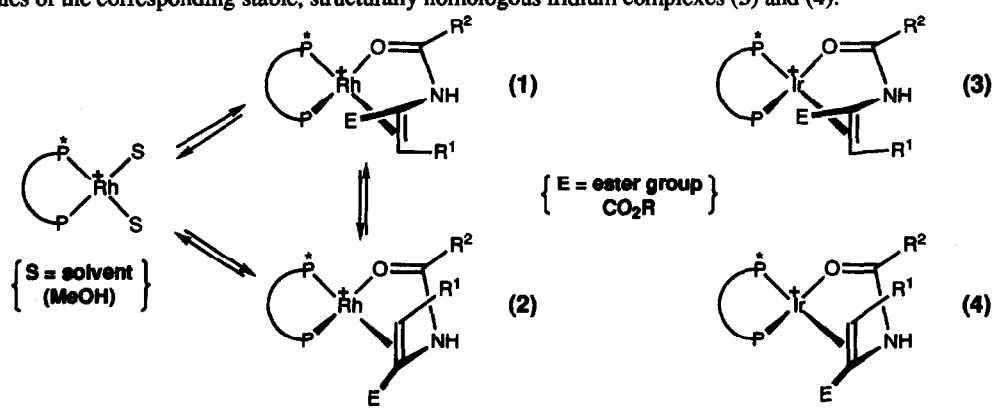
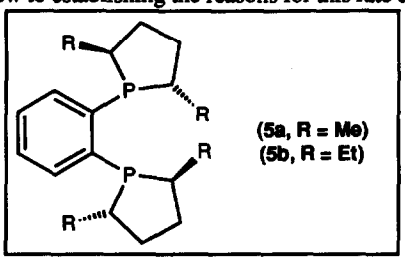
Abstract: *Stereochemical aspects of the title reaction were investigated for the (S,S)-Me-DuPHOS ligand* ***5a****, largely by NMR examination of Ir complexes. They were found to behave in an analogous fashion to that established for P-aryl diphosphine-rhodium(I) complexes.*

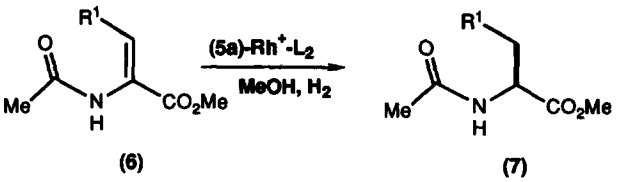
The mechanism of the homogeneous asymmetric hydrogenation of dehydroamino acids to give α-amino acids in high enantiomeric excess, using diphosphinerhodium(I) complexes as catalyst, has been investigated by several workers using a variety of techniques.[1-3] It has been established that the resting state of catalysis involves a rapid equilibrium between two diastereoisomeric catalyst-substrate complexes (**1**) and (**2**), in which the rhodium atom is bound to opposite enantiotopic faces of the C=C double bond of the alkene. The very high selectivity of the reaction is consistent with strongly differentiated reactivity of these two species towards hydrogen. For all ligands so far studied it has been demonstrated that the favoured diastereoisomer (**1**), often present at equilibrium to the extent of >95%, has the opposite formal configuration to the product of hydrogenation. Thus the disfavoured diastereoisomer (**2**), although often undetectable by NMR at equilibrium, has been assumed to carry the flux of catalysis. This is in accord with structural and kinetic analyses,[1,3] and also more generally with NMR studies of the corresponding stable, structurally homologous iridium complexes (**3**) and (**4**).[2]



A new class of ligands based on the *trans*-2,5-dialkylphospholane moiety has been developed at the du Pont laboratories.[4] These are exemplified by Me- and Et-DuPHOS (**5a** and **5b** respectively), and have proved to be very efficient asymmetric catalysts for the hydrogenation of dehydroamino acids (**6**) to S-α-amino acids (**7**), and also for the hydrogenation of enol esters and N-acylhydrazones. By comparison with asymmetric hydrogenation catalysed by rhodium complexes of enantiomerically pure *bis*-(diphenylphosphino)alkanes, the catalytic turnover is unusually rapid, being about fifty times that for the corresponding CHIRAPHOS complex,

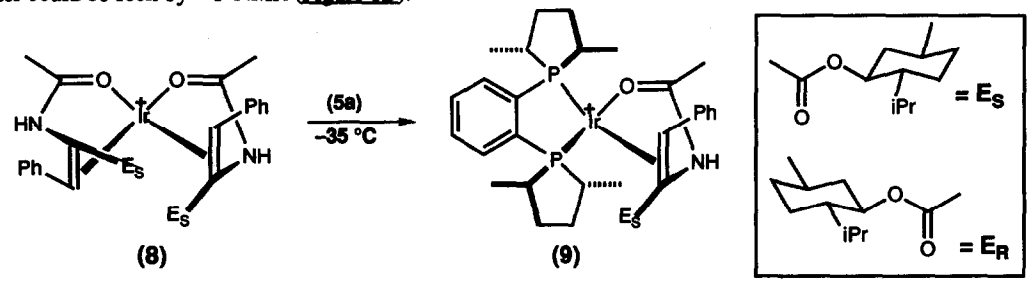
for example.[5] It was therefore of interest to study the details of catalysis by complexes of ligand (**5a**), with a view to establishing the reasons for this rate enhancement.



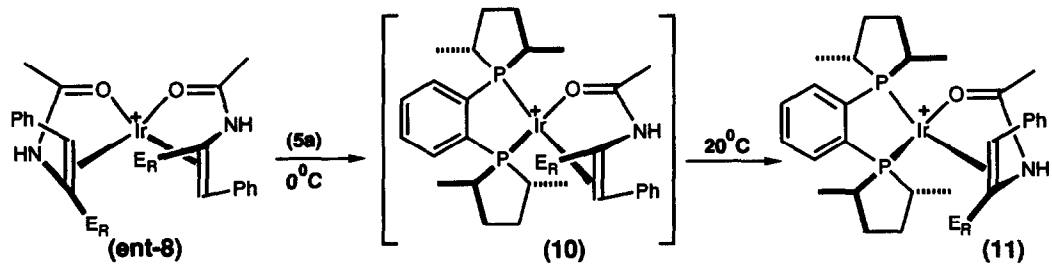


(6) (7)

The iridium chemistry of menthyl esters of dehydroamino acids was developed earlier to permit determination of the configuration of complexed enamides without recourse to X-ray analysis.[2] Thus the enantiomerically pure iridium *bis*-enamide complexes (**8**) and (**ent-8**) (respectively derived from 1S- and 1R-menthol) were treated separately at low temperatures under argon with one equivalent of (S,S)-Me-DuPHOS (**5a**). Complex (**8**) reacted rapidly at –35 °C to give a single *bis*-phosphine iridium enamide complex (**9**) of the type previously reported,[3] observed by ^{31}P NMR. This species remained unchanged on warming to and maintaining at room temperature (Figure 1A). By contrast, complex (**ent-8**) did not react with ligand (**5a**) below 0 °C. The first formed complex (**10**) was metastable, and converted slowly at or above 0 °C into the stable diastereomer (**11**). After standing for 1 hour at room temperature, this conversion was complete and only the latter could be seen by ^{31}P NMR (Figure 1B).



(8) (9)



(ent-8) (10) (11)

Earlier work had clearly established that the configuration of the stable iridium complexes is the same as that of the stable rhodium diastereomer in asymmetric hydrogenation.[2] Thus the favoured rhodium complex has the metal bound to the α-*si*-face of the double bond, corresponding to complexes (**9**) and (**11**), while the disfavoured rhodium complex has the opposite configuration, as in complex (**10**). Since hydrogenation of dehydroamino acids with the [(S,S)-Me-DuPHOS]-Rh catalyst has been shown to give (S)-amino acid derivatives, hydrogenation must occur *via* the complex which has rhodium bound to the α-*re*-face of the double bond, i.e. the energetically disfavoured form. The stereochemical relationships for Me-DuPHOS must therefore be the same as for the conventional *bis*-(diarylphosphino)alkane complexes.[2,3]

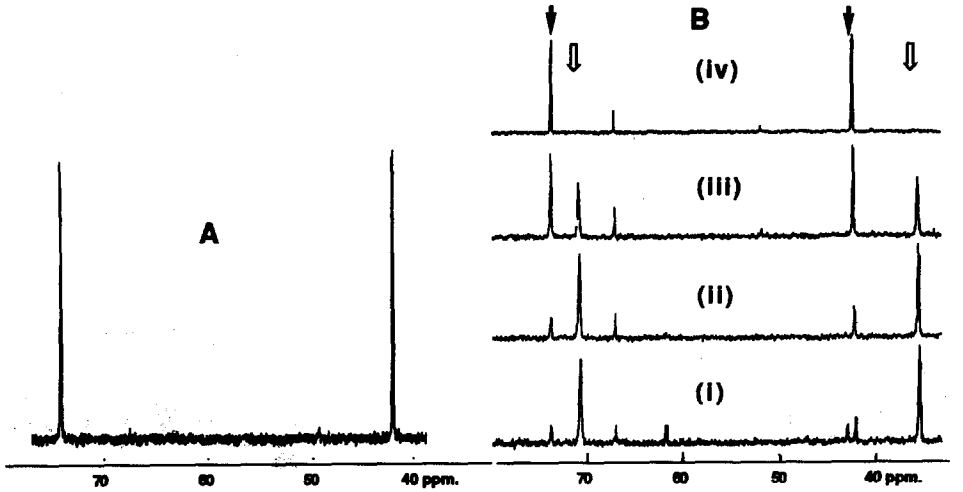
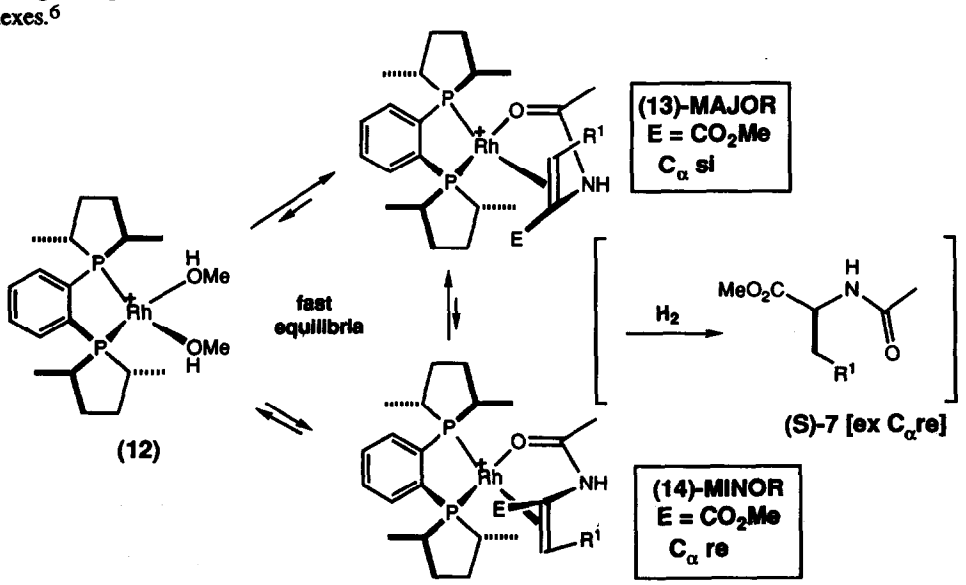


Figure 1A : (8) → (9) at -35 °C [stable form]

Fig. 1B: (ent-8) → (10) [metastable, peaks ь] → (11) [stable, peaks -]; (i) 0 °C, (ii) 10 °C, (iii) 20 °C, (iv) ambient, 1h.

As a corollary to these experiments, the rhodium catalyst-substrate complexes were examined directly by ^{31}P NMR, in the absence of hydrogen. A solution of the solvate complex (**12**) (ca. 0.03M in MeOH) was prepared by hydrogenation of the precursor cycloocta-1,5-diene complex, and (**5a**) added under argon (5-molar excess). The resulting mixture showed two sets of signals in the ^{31}P NMR, corresponding to one form of the enamide complex, now presumed to be (**13**) [δ 88.0 ($J_{P\text{-}Rh}$ 164, $J_{P\text{-}P}$ 33 Hz), 83.1 ($J_{P\text{-}Rh}$ 158 Hz)], and to methanol complex (**12**) [δ 96.7 ($J_{P\text{-}Rh}$ 201 Hz)]. At ambient temperature the signals corresponding to complex (**12**) were sharp, whereas those due to complex (**13**) showed significant exchange broadening. These observations indicate that the binding constant K for enamide association is only in the c. 10^2 M^{-1} range, contrasting with previous values of 5 x 10^3 - 10^5 M^{-1} previously seen for related 5-ring chelate diphosphine complexes.[6]



It therefore seems that the mechanism and stereochemical course of hydrogenation of dehydroamino acids with DuPHOS-rhodium(I) catalysts is similar to that delineated for other diphosphinerhodium catalysts. The enhanced reactivity in this case appears to be due to the low binding constant for the enamide complex, effectively lowering the energy difference between the resting state and the turnover-limiting transition-state. Correlations have previously been made between the sense of twist of the diolefin in catalytic precursor complexes and the stereochemical course of hydrogenation.[7] It is of interest to note that DuPHOS complexes fit into the previously observed pattern (Figure 2). In summary, the stereochemical rule for chiral phospholanes accords with that developed for arylphosphines.

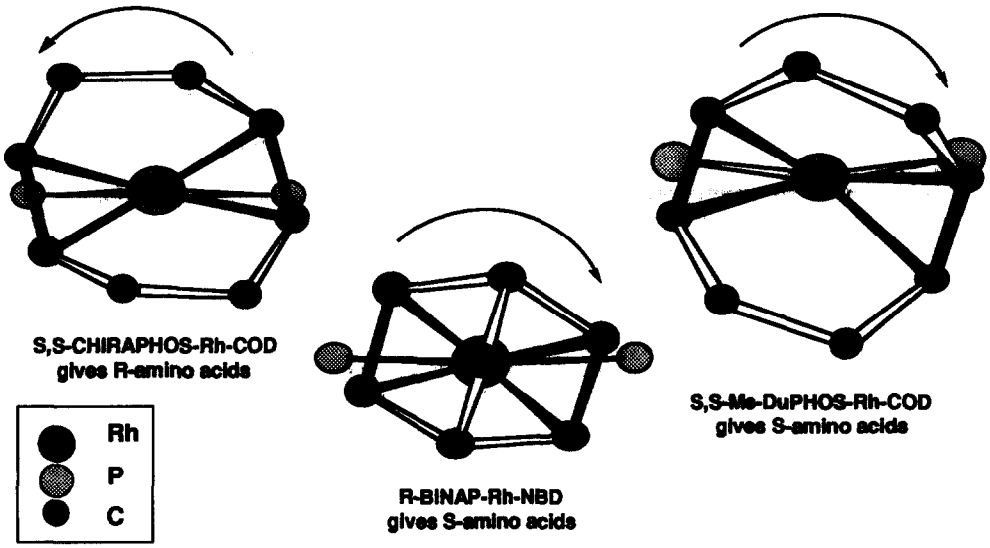


Figure 2. Elevation views of the X-ray crystal structures of the diolefinRhP_2 fragment of diphosphine complexes viewing into the RhP_2 plane, and showing the correlation between ligand twist and the sense of dehydroamino acid asymmetric hydrogenation; clockwise twist correlates with S-amino-acid, anticlockwise with R-amino acid. The olefinic bonds (vertical in an undistorted structure) and their connections to rhodium are highlighted. COD = cycloocta-1,5-diene; NBD = norbornadiene, bicyclo[2.2.1]hepta-2,5-diene.

Acknowledgements

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