Structure and Dynamics of Intermediates in Asymmetric Hydrogenation by Rhodium Complexes of (2-Methoxyphenyl)-*P*-phenyl-*P*-(2′-diphenylphosphino)ethylphosphine

James A. Ramsden, Timothy D. W. Claridge and John M. Brown*

Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford, UK OX1 3QY

The four rhodium enamide complexes formed from the title ligand and methyl *Z*-acetamidocinnamate undergo rapid pair-specific intramolecular exchange and give rise to a single alkylhydride under hydrogen below −40 °C.

Much effort has been devoted to the mechanism of asymmetric hydrogenation of dehydroamino acids catalysed by rhodium complexes, with the purpose of understanding the origin of the high enantioselectivity observed.[1] It has already been established that the turnover-limiting step involves addition of hydrogen to the resting-state, which has two diastereoisomeric enamide complexes in rapid equilibrium with a solvate complex. Further, the configuration of the product correlates with the less favoured enamide complex, and reaction proceeds through an alkylhydride,[2] with a presumed but never observed dihydride intermediate *en route*.[3]

Our earlier work had been conducted with the rhodium complex of *R,R*-bis(*o*-methoxyphenylphenylphosphino)ethane **1a** for which diastereoisomeric enamide complexes are readily observed in around a 10 : 1 ratio; ^{31}P NMR studies indicate that they equilibrate at least in part by an intramolecular mechanism in which the η^2-alkene–rhodium bond dissociates and returns with an intervening rotation which causes C_α*Re*–C_α*Si* equilibration. This conclusion is reinforced by more recent EXSY studies on the related complexes derived from *S,S*-bis(2,3-diphenylphosphino)butane.[4] The existence of an intramolecular process had been disputed on the grounds that independently measured enamide association and dissociation rate constants are in excellent agreement with those derived from analysis of catalytic hydrogenation, leading to the conclusion that 'the contribution of intramolecular pathways to this conversion, if any, is small'.[5]

The synthesis of (2-methoxyphenyl)-*P*-phenyl-*P*-(2′-diphenylphosphino)ethylphosphine **2** in both enantiomeric forms[6] prompted us to examine related catalytic intermediates, since the additional complexity of the system (four diastereomeric enamide complexes) reveals further mechanistic information. Complex **1b** was prepared by previously described techniques,[7] and when activated by H_2 and treated with enamide **3a** gave rise to four distinct complexes in a ratio of 12 : 8 : 3 : 2. Each of the four Rh-coupled ^{31}P AB quartets can be assigned to a specific stereoisomer (Fig. 1) by analogy with previously reported ^{31}P chemical shifts,[7] and following the strong and universal precedent[8] that the α-*Si*-bound isomers will be thermodynamically favoured with the *R*-hand of a ligand where this forms a chelate ring of λ configuration.

The ambient ^{31}P EXSY spectrum[9] at short mixing times (30 ms) demonstrates a fast and stereospecific pairwise exchange between **4-*Re*** and **4-*Si***, and also between **5-*Re*** and **5-*Si***, which uniquely involves the interchange of high-field with high-field, or low-field with low-field phosphorus nuclei. At longer mixing times (150–300 ms) a slower non-specific exchange process was also evident, showing all possible cross-peaks. This further reinforces the idea that a fast intramolecular exchange competes successfully with a slower intermolecular process requiring dissociation–recombination, but does not constitute a formal proof.[10]

Using the 3-^{13}C-enriched dehydroamino ester **3b**,[11] ^{13}C NMR signals corresponding to the rhodium coordinated benzylidene carbon of the enamide were clearly seen in the region δ 75–95 [Fig. 2(*a*)].[2] Magnetisation transfer between different ^{13}C signals in the NMR spectrum of **4** ⇌ **5** containing an excess of **3b** differentiates between inter- and intramolecular exchange in a way that ^{31}P NMR cannot, because only the intermolecular process links the complexes to free substrate. ^{13}C EXSY was applied according to the protocols of Figs. 2(*b*) and (*c*). The result is unequivocal; at a delay time of 30 ms intramolecular exchange is dominant. Furthermore, this is limited to pairwise processes which link **4-*Re*** with **4-*Si***, and **5-*Re*** with **5-*Si***. At longer delay times (100–300 ms) there are additional cross-peaks between **4** and **5** and also cross-peaks

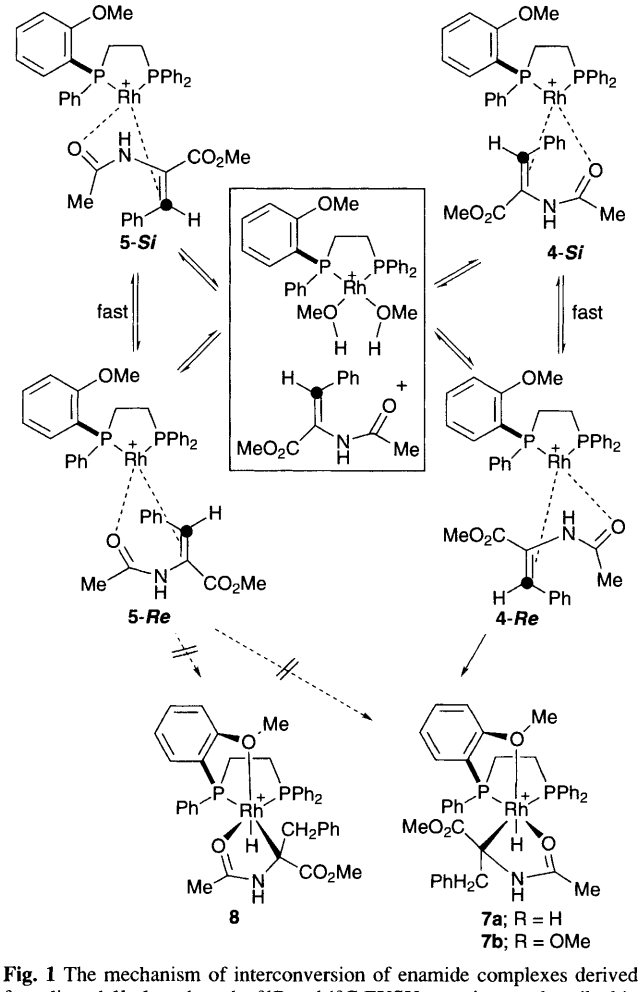
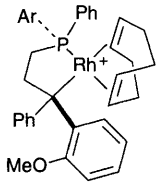
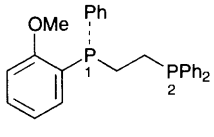


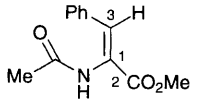
Fig. 1 The mechanism of interconversion of enamide complexes derived from ligand **1b**, based on the ^{31}P and ^{13}C EXSY experiments described in the text. ^{31}P chemical shifts (202 MHz, MeOH, ambient): **4-*Si*** [32%] δ 74.9, 59.9; **4-*Re*** [12%] δ 71.9, 60.9; **5-*Si*** [48%] δ 75.5, 52.4; **5-*Re*** [8%] δ 76.1, 62.7; J_{P-Rh} = 148–162, J_{P-P} = 34–40 Hz.



1a Ar = *o*-MeOC$_6$H$_4$
1b Ar = Ph



2



3a
3b; ^{13}C-3

between the uncomplexed ester **3b** and the enamide complexes **4** and **5** which are all of comparable intensity. These observations are uniquely consistent with a rapid intramolecular process in which the coordinated alkene dissociates and rotates about the enamide C–N bond before recomplexation. This reaction is stereospecific, and generates a formal 14-electron intermediate such that the amide always remains *trans* to the same phosphorus nucleus. This result reinforces and extends our earlier work with complex **1**; intramolecular exchange is now unquestionably the fastest process accessible to complexed enamides. Concurrent **4–5** interconversion requires dissociation of the enamide complex and recombination from the pool.

When the mixture of enamide complexes was prepared *in situ* at low temperatures, such that the disfavoured diastereomers ***4-Re*** and ***5-Re*** were present in higher than equilibrium concentration, reaction with H_2 below −40 °C gave rise to a *single* alkylhydride by ^{1}H NMR (Fig. 3). If the addition of dihydrogen were to occur with equal facility to both ***4-Re*** and ***5-Re***, then two alkylhydrides would be expected. On H_2 addition to the stereoisomerically pure iridium enamide precursor, a single stable alkylhydride **6** was observed in which one of the methoxy groups is coordinated *trans* to the Ir–H bond;[12]

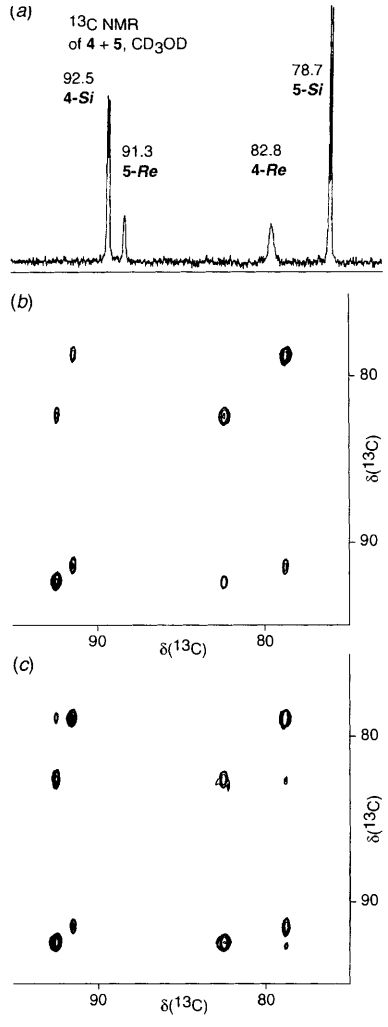


Fig. 2 (*a*) ^{13}C spectrum of 3-^{13}C-enriched enamide complex in the region δ 75–95, CD_3OD; (*b*) EXSY spectrum of the same sample, 30 ms mixing time, 305 K, demonstrating exchange only between ***4-Re*** and ***4-Si*** and between ***5-Re*** and ***5-Si***; (*c*) EXSY spectrum of the same sample, 300 ms mixing time, in which cross-peaks between **4** and **5** are visible. Under the conditions of spectrum (*b*), the intermolecular exchange cross-peaks involving **3b** at δ 134 are extremely weak, but for conditions (*c*) the same cross-peaks are strong.

in that case the configuration was fully established by intracomplex NOE mapping. The present case is analogous in that the observed hydride has structure **7a** where the methoxyaryl phosphine is *trans* to the amide group, rather than **8**. Support for this structure comes from a comparison of ^{31}P chemical shifts with the corresponding diphos and dipamp alkylhydrides.†‡ In a parallel sequence starting with the 2,4-dimethoxyphenyl analogue of ligand **1b**, a corresponding species **7b** was the only transient observed. The simplest pathway between enamide and alkylhydride involves exclusive H_2 addition to ***4-Re***. At this stage we cannot rule out the intervention of competitive addition to ***5-Re*** but note that after long contact of the sample with H_2 at −50 °C, then **7a** together with ***5-Si*** rather than ***4-Si*** are the main species present, suggesting that formation of the alkylhydride from **5** requires prior isomerisation to **4**.

There is still a gap between our level of mechanistic understanding of rhodium asymmetric hydrogenation and our insights into the origin of enantioselection. The present experiments demonstrate the dominance of intramolecular enamide exchange in the catalytic resting state, which must occur through alkene dissociation. The best molecular mechanics analysis of the hydrogen addition step failed to find a low-energy dihydride intermediate, with the models derived from both major and minor enamide complexes experiencing serious steric compression.[3] But the reaction pathway cannot proceed through addition of reactant to a transient solvate dihydrogen complex, averting the dihydrogen complex, since this would require unreasonable rate constants in some specific cases.[13] With additional information now available for reactive intermediates on the pathway, the H_2 addition process needs to be better defined, as does the critical role of the methoxy group in influencing the stereochemical course of hydrogenation.

We thank the Core Programme of LINK Asymmetric Synthesis (SERC, DTI, Glaxo, Pfizer, Roche, SKB, Zeneca) for support of this work and Johnson-Matthey for the loan of

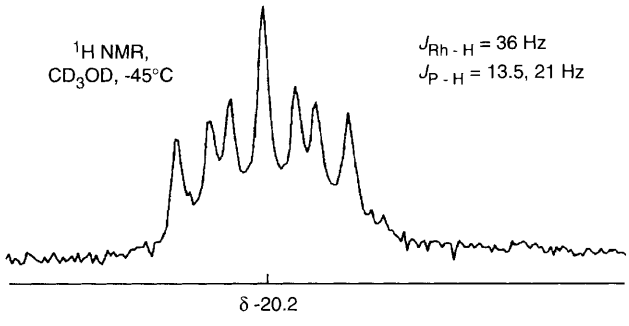
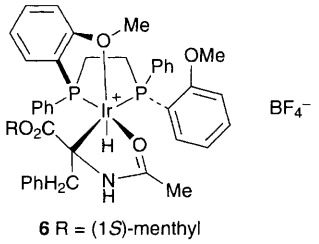


Fig. 3 ^{1}H NMR spectrum of the Rh–H region of complex **7a** in CD_3OD at 228 K, showing the region δ −20.0 to −20.5. No other high-field peaks are visible. The ^{31}P spectrum at −50 °C showed two doublets at δ 71 (J_{P-Rh} 138 Hz) and δ 52 (J_{P-Rh} 95 Hz), with the P–P coupling obscured by line-broadening.



6 R = (1*S*)-menthyl

rhodium salts. We acknowledge a useful exchange of information with Dr R. Selke (Max Planck Group, Rostock).

Received, 27th July 1995; Com. 5/04998I

Footnote

† The phosphorus *trans* to amide at δ 71 is P^1 (predicted, δ 73) rather than P^2 (predicted, δ 57).[2,5]

‡ diphos = 1,2-bis(diphenylphosphino)ethane, dipamp = (*R,R*)-1,2-bis[(2-methoxyphenyl)phenylphosphino]ethane.

References

1 B. R.Bender, M. Koller, D. Nanz and W. Von Philipsborn, *J. Am. Chem. Soc.*, 1993, **115**, 5889 and references therein; B. McCulloch, J. Halpern, M. R. Thompson and C. R. Landis, *Organometallics*, 1990, **9**, 1392; *Asymmetric Catalysis in Organic Synthesis*, ed. R. Noyori, Wiley-Interscience, New York, 1994, ch. 1.

2 A. S. C. Chan and J. Halpern, *J. Am. Chem. Soc.*, 1980, **102**, 838; J. M. Brown and P. A. Chaloner, *J. Chem. Soc., Chem. Commun.*, 1980, 344.

3 J. S. Giovannetti, C. M. Kelly and C. R. Landis, *J. Am. Chem. Soc.*, 1993, **115**, 4040.

4 H. Bircher, B. R. Bender and W. Von Philipsborn, *Magn. Reson. Chem.*, 1993, **31**, 293; further evidence from dynamic ^{31}P NMR is on hand; R. Kadyrov, T. Freier, D. Heller, M. Michalik and R. Selke, *J. Chem. Soc., Chem. Commun.*, 1995, 1745.

5 J. Halpern and C. R. Landis, *J. Am. Chem. Soc.*, 1987, **109**, 1746.

6 J. A. Ramsden, J. M. Brown, M.B. Hursthouse and A. I. Karaulov, *Tetrahedron Asymmetry*, 1994, **5**, 2033.

7 J. M. Brown, P. L. Evans and A. P. James, *Org. Synth.*, 1989, **68**, 64.

8 E.g. S. K. Armstrong, J. M. Brown and M. J. Burk, *Tetrahedron Lett.*, 1993, **34**, 689, and references therein; in the present case the disfavoured *Re*-isomers correlate with the favoured *S* enantiomer of product, and e.e.s. of 80–85% are obtained.

9 For recent applications of EXSY to organometallic structure, see: M. T. Ashby, G. N. Govindan and A. K. Grafton, *J. Am. Chem. Soc.*, 1994, **116**, 4801; A. Gogoll, J. Oernebro, H. Grennberg and J. E. Backvall, *J. Am. Chem. Soc.*, 1994, **116**, 3631; E. W. Abel, E. S. Blackwall, K. G. Orrell and V. Sik, *J. Organomet. Chem.*, 1994, **464**, 163.

10 J. M. Brown and P. A. Chaloner, *J. Chem. Soc. Chem. Commun.*, 1983, 646; J. M. Brown, P. A. Chaloner and G. A. Morris, *J. Chem. Soc. Perkin Trans. 2*, 1987, 1597.

11 Prepared as before (ref. 2) but with an improved procedure for the synthesis of ^{13}C-benzaldehyde as oxazolone precursor; *cf.* H. C. Brown, C. Gundu Rao and S. U. Kulkarni, *Synthesis*, 1979, 704.

12 J. M. Brown and P. J. Maddox, *J. Chem. Soc., Chem. Commun.*, 1987, 1276.

13 U. Sharma, P. J. Guiry and J. M. Brown, in preparation.