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Captured at last: a catalyst–substrate adduct and a Rh-dihydride solvate in the asymmetric hydrogenation by a Rh-monophosphine catalyst†

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The mechanism of asymmetric hydrogenation catalyzed by [Rh(NBD)((*R*)-PhenylBinepine)$_2$]SbF$_6$ 1 has been studied by NMR experiments and DFT computations. Either the low-temperature hydrogenation of the catalyst–substrate adduct 4 or the reaction of solvate dihydride 6 with MAC produced the hydrogenation product with over 99% ee (*S*).

Relatively cheap chiral monophosphines are widely used in Rh-catalyzed asymmetric hydrogenation.[1] They are considered to be synthetically more easily accessible and tunable[2] than the traditional chiral diphosphines and are more versatile, *e.g.* for use in combinatorial chemistry.[3]

However, the characterization of the intermediates in the catalytic cycle of the asymmetric hydrogenation catalyzed by the Rh complexes of chiral monophosphines proved to be a much more challenging task than it might have been expected from the extensively studied asymmetric hydrogenation catalyzed by various Rh complexes of chiral diphosphines.[4]

It is known from the mass-spectra that, unlike the case of configurationally stable Rh-diphosphine complexes, the reaction intermediates containing monophosphines are much more labile and that various species differing in the number of bound ligands can be simultaneously present in solution.[5] Most commonly it is accepted that the RhL_2S_2 species (S = solvent) must perform the flux of the catalysis, since the occurrence of non-linear effects excludes the possibility of the 1 : 1 complex being a catalyst,[6] whereas the RhL_4 or RhL_3S complexes lack enough coordination sites for the chelate binding of the prochiral substrates such as methyl *Z*-α-acetylaminocinnamate (MAC). However, this still remained a hypothesis until now.

Here we report the characterization of important intermediates in the asymmetric hydrogenation catalyzed by

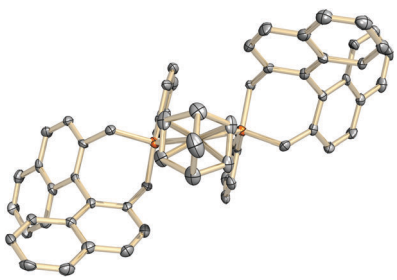

Fig. 1 Thermal ellipsoid plot of the catalytic precursor [Rh(NBD)((*R*)-PhenylBinepine)$_2$]SbF$_6$ **1** omitting the hydrogen atoms, anion and solvent.

$[RhL_2S_2]^+$ (L = (*R*)-phenylbinepine)[7] and their reactions resulting in perfect enantioselectivity. Either the low temperature hydrogenation of the catalyst–substrate complexes, or reactions of Rh-dihydride solvates with MAC yielded the hydrogenation product with optical purity over 99% ee.

Single crystal X-ray analysis of **1** exhibited the C_2-symmetric structure as evinced by NMR,[8] with a P–Rh–P angle of 97° (Fig. 1).‡

Upon treatment with hydrogen in CD_2Cl_2 at 1 atm of H_2 and ambient temperature the orange solution of **1** (0.025 M L^{-1}) yielded after 10 minutes (Scheme 1) a deep red solution of the dimer complex **3** (δ P^1 55.2 ppm, $^1J_{PRh}$ 195 Hz, $^2J_{PP}$ 41 Hz; δ P^2 59.3 ppm, $^1J_{PRh}$ 205 Hz, $^2J_{PP}$ 41 Hz) in equilibrium with the solvate **2** (δ P 57.4 ppm, $^1J_{PRh}$ 198 Hz).

Although a similar dimeric solvate $[RhL_2S_2]^+$ (L = ^{t}BuP(*R*-binaphthoxo, S = solvent) did not exhibit any appreciable binding to MAC,[9] chelate binding of MAC was recently detected for the case of L = MONOPHOS,[10] but the detailed analysis of the structure of adducts was not reported. In our case, addition of 2 equivalents of MAC to a solution of **3** in CD_2Cl_2 at ambient temperature resulted in immediate change of the color of solution to dark red, indicating the formation of catalyst–substrate adducts **4** (Scheme 2).

NMR spectra of the catalyst–substrate complexes are temperature dependent. At ambient temperature two diastereomers *re*-**4** and *si*-**4** in a 4 : 1 ratio are observed interconverting with **2** and with each other. When the temperature is lowered down to −90 °C, the signals of each diastereomer are split into two sets due to the presence of conformers caused by hindered rotation around Rh–P bonds.[11]

Chelate binding of the substrate occurs in the major species as confirmed by the characteristic signals of the coordinated double bond (δ (CH═) 80.1 ppm, $^2J_{CP}$ 15 Hz; δ (C═) 79.9 ppm,

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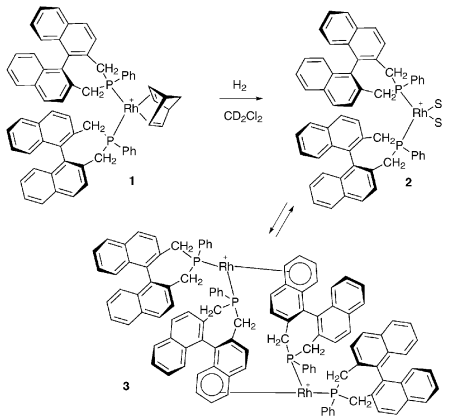
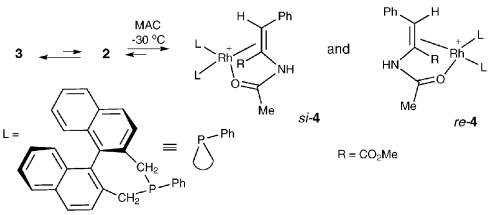
† Electronic supplementary information (ESI) available: Experimental details, NMR charts, HPLC charts, Cartesian coordinates of the optimized structures, DFT computational analysis. CCDC 846908. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc17335b



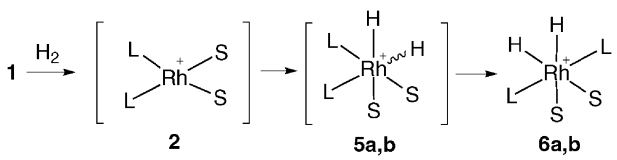
Scheme 1 Hydrogenation of the coordinated diene in the catalytic precursor **1** in CD_2Cl_2. (S = solvent).



Scheme 2 Formation of the catalyst–substrate complexes **4**.

$^2J_{CP}$ 22 Hz, $^1J_{CRh}$ 5 Hz) and of the amido carbonyl (δ 184.8, ppm $^3J_{CP}$ 5 Hz) in the ^{13}C NMR spectrum taken at −50 °C.

We argued further that the dimerization of **2** could be avoided in the presence of more donating solvents. Indeed, reaction with hydrogen of a suspension of **1** in a mixture of CD_2Cl_2 and CD_3OD or of a solution of **1** in a mixture of CD_2Cl_2 and THF-d_8 at ambient temperature gave clear pale yellow solutions. NMR analysis showed quantitative formation of the corresponding solvate dihydride **6a** or **6b**, respectively (Scheme 3; Fig. 2). The pattern of the NMR spectra, the chemical shifts of the hydride signals of **6a**,**b** (δ −22.6 ppm and −22.3 ppm, respectively), as well as the diagnostic *trans*-P–P coupling in the ^{31}P NMR spectrum of **6b** ($^2J_{PP}$ 393 Hz) unequivocally pointed to the *cis*(H)–*trans*(P) structure of **6a**,**b**. Apparently, initially formed *via* oxidative addition *cis*(H)–*cis*(P) dihydrides **5a**,**b** rearranged immediately into the more stable compounds **6a**,**b** (Scheme 3).



Scheme 3 Formation of solvate dihydride complexes **6a**,**b**.

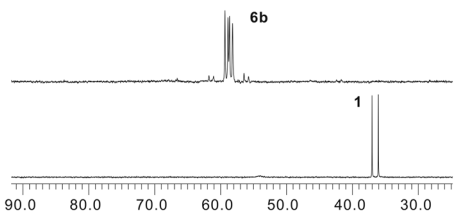
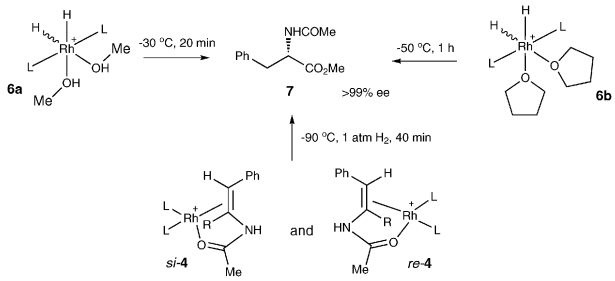


Fig. 2 ^{31}P NMR spectra (162 MHz, CD_2Cl_2–THF-d_8 1 : 1, 0 °C) of the catalytic precursor **1** (bottom) and of the solvate dihydride **6b** (up).

Our computations confirmed that **5a** is 6–8 kcal mol^{-1} less stable than **6a** (depending on the conformation), hence the former cannot be detected in the NMR spectra, but is nevertheless kinetically accessible. On the other hand, unlike the Rh-diphosphine case[12] the *trans*(H)–*trans*(P) dihydrides were computed to be strongly destabilized for about 30 kcal mol^{-1}.

We conducted three independent stoichiometric experiments: hydrogenation of **4** at −90 °C and reactions of **6a** and **6b** with MAC at low temperatures. Much to our delight, despite the difference in the experimental set-ups and in the temperature regimes of hydrogenation, the product **7** obtained in these experiments was always of >99% ee (*S*) (Scheme 4). The spectral changes in the course of hydrogenation of **4** at −90 °C are shown in Fig. 3. It was possible to detect in the spectra a monohydride intermediate **8** (δ P^1 42.7 ppm, $^1J_{PRh}$ 96 Hz; δ P^2 52.6 ppm, $^1J_{PRh}$ 148 Hz; P–P coupling not measured because of broad signals; δ H −19.8, broad), but it was rather



Scheme 4 Different experimental set-ups resulting in perfect enantioselection.

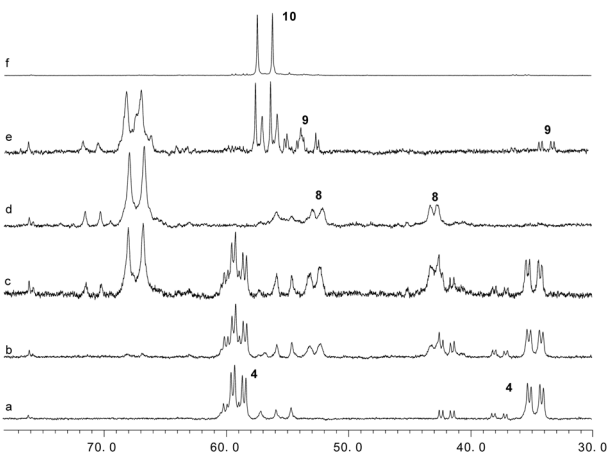
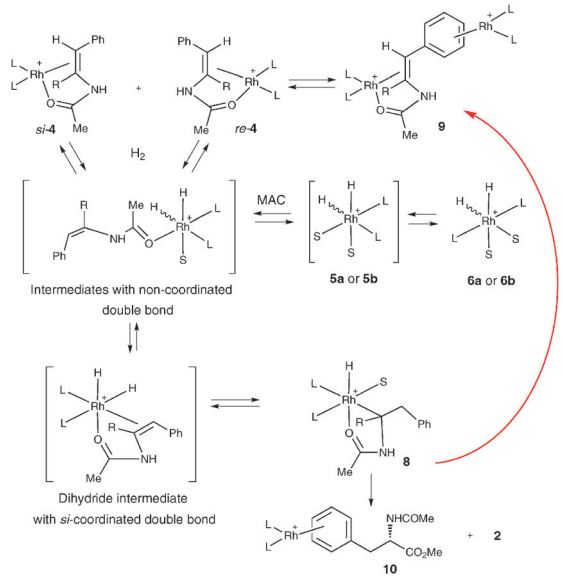


Fig. 3 ^{31}P NMR spectra (162 MHz, CD_2Cl_2) illustrating the low temperature hydrogenation of **4**: (a) initial spectrum; (b) after 17 min hydrogenation at −90 °C; the signals of a monohydride intermediate **8** are clearly seen. It partially decomposes releasing **2** that is immediately bound to **4** by the excess of free MAC; (c) after additional 10 min hydrogenation at −90 °C; only the coordinated substrate was left in the reaction mixture and the releasing catalyst is bound to some catalyst–product complexes (δ 67–72 ppm), where probably the Rh coordinates to the aromatic rings; (d) after additional 10 min hydrogenation at −90 °C; all substrate is hydrogenated (e) after raising the temperature to −50 °C; all monohydride is decomposed, some substrate is seen again in a 1 : 2 complex **9**; several catalyst–product complexes are observed together with **10**; (f) after raising the temperature to 25 °C; single catalyst–product complex **10** is observed.



Scheme 5 Catalytic cycle of asymmetric hydrogenation catalyzed by **2** in the low temperature hydrogenation of **4** and reactions of **6a**,**b** with MAC.

unstable and involved in some exchange even at −90 °C that prevented accurate structure elucidation. Other characterized intermediates are the 2 : 1 catalyst–substrate complex **9**[13] and the final catalyst–product complex **10** (Scheme 5).

The most remarkable changes in the ^{31}P and ^{1}H NMR spectra are observed when, after the substrate is completely hydrogenated (Fig. 3d, confirmed by the ^{1}H NMR spectrum), the temperature is raised to −50 °C and the substrate reappeared again—in the form of complex **9**. This observation suggests that the reversibility of the process persists until the late steps of the catalytic cycle (Scheme 5).[4b] It is also in accord with the perfect ee of the product obtained in this experiment. Since *re*-**4** and *si*-**4** do not interconvert at −90 °C, complete absence of the second enantiomer of the product requires the intermediacy of species with non-coordinated double bonds.

Previously with PHANEPHOS-Rh it had been established that the hydrogenation process is reversible until the formation of an agostic intermediate that is the immediate precursor of the monohydride species.[14] In the present case, the reversibility seems to be pushed further ahead until the stage of the monohydride and only reductive elimination is then left as the irreversible step of the catalytic cycle. It is known since long that the reductive elimination step can occur slowly enough for observable accumulation of a monohydride intermediate[15] but to our knowledge this is the first example of an apparently reversible migratory insertion step.

It should be noted that the highest ee achieved so far in the hydrogenation of MAC catalyzed by **1** was 90% (toluene, 25 °C, S/C 100)[8b] that is significantly lower than the >99% observed in our stoichiometric experiments. Since the low-temperature hydrogenation of MAC using catalytic amounts of **2** gave the product with 89% ee, the lower ee in catalytic reactions may be consequent to the presence of a large excess of the substrate that affects the equilibria of the catalytic cycle.

In conclusion, we have characterized for the first time several intermediates of the catalytic cycle of monophosphine-Rh catalyzed asymmetric hydrogenation. All of them are L_2Rh species, hence the *modus operandi* of the monophosphine catalysts is reliably established.

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Notes and references

‡ Single crystals of complex **1** were grown from a saturated CH_2Cl_2 solution.

Crystal data for **1**: $C_{66}H_{53}Cl_9F_6P_2RhSb$, M = 1565.82, orthorhombic, a = 11.1730(13) Å, b = 22.609(3) Å, c = 25.378(3) Å, V = 6410.7(13) Å^3, T = 93 K, space group $P2_12_12_1$, Z = 4, μ(Mo-Kα) = 11.608 mm^{-1}, 47 975 reflections measured, 14 633 unique reflections (R_{int} = 0.0444). The final R_1 [$I > 2\sigma(I)$] was 0.0510 and the final w$R(F_2)$ was 0.1278 (all data). The goodness of fit on F^2 was 1.000. The Flack parameter was −0.03 (3). CCDC 846908.

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