On the Origin of Opposite Stereoselection in the Asymmetric Hydrogenation of Phenyl- and *tert*-Butyl-Substituted Enamides

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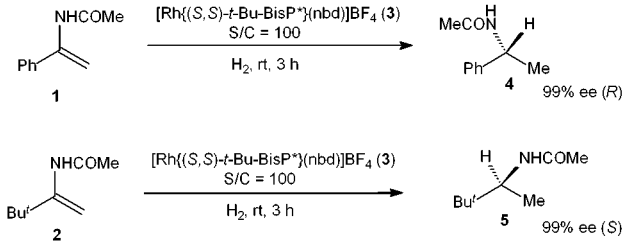
The mechanistic studies of the asymmetric hydrogenation were actively carried out by many groups during the last three decades.[1] However, most of these works used dehydroamino acids as substrates. We are unaware of any data relevant to the mechanism of asymmetric hydrogenation of enamides. Usually the explanations of the mechanism of stereoselection in the asymmetric hydrogenation of dehydroamino acids regard the carboxy group as an important stereoregulating factor.[1,2] In the structure of an enamide the carboxy group is replaced by aryl or alkyl substituent, and the steric demand of this substituent may be different in various substrates. In this respect the striking difference in the stereochemical outcome of asymmetric hydrogenations of 1-acetamido-1-phenylethene (**1**) and 2-acetamido-3,3-dimethyl-1-butene (**2**) reported recently by Burk et al.[3] has drawn our attention. Thus, whereas enamide **1** was hydrogenated in the presence of (*S,S*)-Me-DuPHOS−Rh catalyst to give *S*-hydrogenation product with >95% ee,[4] the hydrogenation of **2** with the same catalyst rendered corresponding *R*-product with >99% ee.[3] Being interested in the mechanism of stereoselection in asymmetric hydrogenations catalyzed by BisP*-Rh catalysts,[5] we have chosen to explore the hydrogenation of **1** and **2** in the presence of (*S,S*)-bis(*tert*-butylmethylphosphino)ethane−Rh complex (**3**).

Similarly to the above cited results of Burk et al., we have found that in the presence of **3** both **1** and **2** gave quantitative yields of almost enantiomerically pure amides **4** and **5** (ee in both cases was 99%), but the sense of stereoselection was opposite: (*R*)-**4** and (*S*)-**5** were obtained (Scheme 1). To rationalize this striking difference, we have studied the structure of detectable intermediates and carried out the isotope-labeling experiments in both cases.

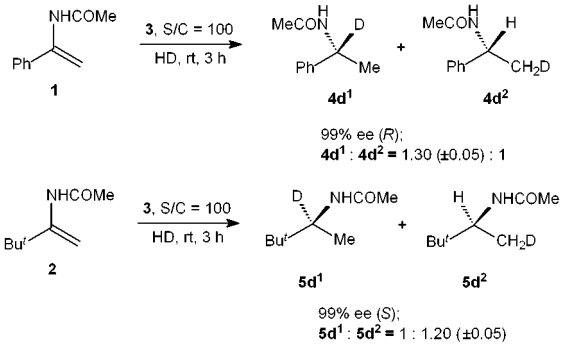
When **1** and **2** were hydrogenated with deuterium hydride in the presence of **3**, the distribution of deuterium between the α- and *β*-positions of the hydrogenation product was in both cases unequal and opposite (Scheme 2). The ratio of the products **4d^1** and **4d^2,** with deuterium in α- and *β*-positions respectively, obtained in hydrogenation of **1** with HD was 1.30 (±0.05):1. On the other hand, hydrogenation of **2** with HD gave the products **5d^1** and **5d^2** in the ratio 1:1.20 (±0.05). Thus, the isotope partitioning in asymmetric hydrogenations with HD evidently correlated with the difference in stereochemical outcome of the hydrogenations.

To check the reversibility of the migratory insertion step,[6,7] we carried out catalytic hydrogenations of **1** and **2** with D_2. In both cases the complete absence of deuterium scrambling was

Scheme 1. Hydrogenation of **1** and **2** with H_2



Scheme 2. Hydrogenation of **1** and **2** with HD



demonstrated by ^{1}H, ^{2}H, and ^{13}C NMR data. Therefore, the migratory insertion step in the catalytic cycles of asymmetric hydrogenation of **1** and **2** is irreversible.

Addition of 2-fold excess of enamide **1** to the deuteriomethanol solution of solvate complex **6** at −20 °C resulted in immediate formation of two diastereomers of catalyst−substrate complex **7** in ratio changing from 4:1 at −90 °C to 2:1 at 0 °C. No detectable amounts of the solvate complex **6** could be detected in equilibrium with **7** within the temperature interval from −90 to +30 °C,[8] and therefore the tightness of the substrate binding is comparable to that in the catalyst−substrate complex of **6** and methyl (*Z*)-α-acetamidocinnamate.[5]

The catalyst−substrate complex **8** prepared from **6** and enamide **2** was notably less stable compared to **7**; significant equilibrium amounts of **6** were found in the whole temperature interval from −100 to +30 °C.[9] Only one isomer of **8** was observed.

We failed to detect a monohydride intermediate in the case of enamide **1**; hydrogenation of **7** at −100 °C gave directly the product **4**.[10] On the other hand, hydrogenation of the equilibrium mixture of **2**, **6**, and **8** for 5 min at −100 °C followed by immediate placement of the sample in the probe of NMR spectrometer precooled to −100 °C led to the obsevation of a monohydride intermediate **10** (Scheme 3). A second diastereomer of **10** was observed in ^{1}H- and ^{31}P NMR (the ratio of diastereomers is 100:7).[11] Monohydride **10** is stable below −85 °C; at higher temperatures it decomposes rapidly affording **6** and the hydrogenation product **5**. The optical yields and the sense of stereoselection of the hydrogenation products obtained in the NMR experiments were always the same as in the catalytic hydrogenations of either **1** or **2**.

(1) (a) Brown, J. M. *Hydrogenation of Functionalized Carbon−Carbon Double Bonds*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, pp 119−182 and references therin. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994. (c) Ojima, I. *Catalytic Asymmetric Synthesis*; VCH: Weinheim, 1993.

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(6) Brown, J. M.; Parker, D. *Organometallics* **1982**, *1*, 950−956.

(7) Brauch, T. W.; Landis, C. R. *Inorg. Chim. Acta* **1998**, *270*, 285−297.

(8) The NMR data suggest that the major isomer of **7** contains *re*-coordinated **1**, both intra- and intermolecular pathways of interconversion of **7a** and **7b** were detected by 2D EXSY spectra; the former pathway is notably faster than the latter.

(9) The ratio **8**:**6** changes from 5:1 at −100 °C to 1:1 at 0 °C.; the chemical shift of the α-C in the ^{13}C NMR spectrum is only high-field shifted by 10 ppm, compared to the same signal of free **2** that suggests only weak binding.

(10) In these conditions **4** equilibrates with a catalyst-product complex (see ref 5).

(11) The minor diasteromer of **10** also gives (*S*)-**5**, since the ee is higher than the diastereomeric ratio of **10**.

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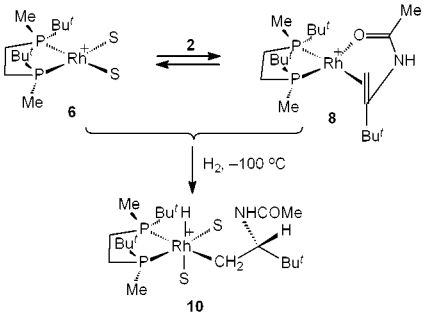
Scheme 3. Formation of Monohydride Intermediate **10**



In the hydride region of the ^{1}H NMR spectrum **10** gives a multiplet at −21.2 ppm. It correlates with two doublets at 53.2 and 86.7 ppm in the ^{31}P NMR spectrum ($^2J_{PP}$ is less than 5 Hz). The chemical shift of the low-field signal in the ^{31}P NMR is considerably different from those of the known monohydride intermediates,[5,12,13] and is consistent with the presence of a weakly bound solvent molecule in the *trans*-site. This fact suggests that the amide carbonyl is not chelated in **10**. In accord with this conclusion, the carbonyl signal in the ^{13}C NMR spectrum of **10** is not split and is only slightly low-field shifted with respect to the carbonyl signals of **2** and **5** ($\delta = 176$; compare with $\delta = 185$ of the chelated carbonyl in **8**, which is split in double doublet). The signal of the carbon bound to acetamido group in **10** resonates as a broadened singlet at $\delta = 61.7$. This signal becomes a doublet in the gated-decoupled spectrum, indicating that it belongs to a methyne carbon.[14]

On the basis of presented evidence we conclude that **10** has the structure shown in Scheme 3. This conclusion corresponds to the results of HD hydrogenation. We have shown recently that upon hydrogenation of solvate complex **6** with HD, the isotopomer **9d^1** with apical disposition of deuterium forms predominantly with the factor 1.3 (±0.1): 1.[5] Therefore, if the consequence of substrate coordination and migratory insertion is faster than the interconversion of isotopomers,[15] the partitioning of deuterium in the products indicates the fashion of the substrate coordination during the migratory insertion step. Predominance of the α-deuterated product corresponds to coordination of type **A** and transfer of the equatorial hydride to the CH_2-group of enamide yielding monohydride intermediate **C** with Rh bound to C_{tert} (Scheme 4). The coordination of type **B** provokes transfer of equatorial hydride to C_{tert}, yielding monohydride intrmediate **D**, that results in predominance of β-deuterated product (Scheme 4).[16]

The mode of the binding of the substrate in **7**, the sense of stereoselection, as well as the sense and the order of deuterium distribution in hydrogenation with HD observed for the phenyl-substituted enamide **1** are exactly the same as those determined previously for methyl (*Z*)-α-acetamidocinnamate.[5] Therefore, the mechanism of stereoselection in the case of **1** is apparently the same, and the main stereoregulating factor is minimization of the repulsion between the chelate ring made by the substrate and the alkyl groups of the catalyst in the transition state of the migratory insertion step.[5]

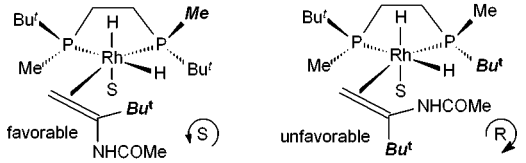
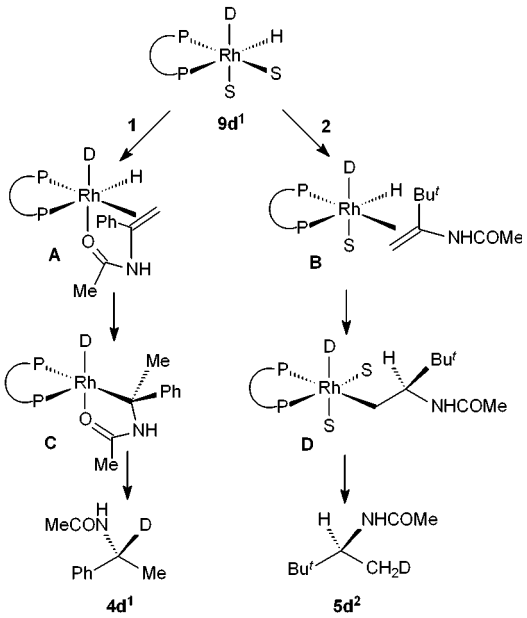


Figure 1. Mechanism of stereoselection in the catalytic hydrogenation of **2**.

Scheme 4. Proposed Mechanism of the Reactions of **1** and **2** with Major Isomer of Solvate Dihydride **9d**[1]



Apparently, much more pronounced steric demand of enamide **2** makes the formation of a similar chelate cycle extremely unfavorable, and it chooses an alternative mode of coordination with the dihydride, in which its *t*-Bu group is much further distanced from the alkyl groups of the catalyst. Figure 1 shows that the minimization of the repulsion between the *t*-Bu group from the enamide and the alykyl group from the catalyst results in formation of (*S*)-**5**.

In conclusion, our isotope labeling and NMR data suggest that the striking difference in the stereochemical outcome of the asymmetric hydrogenations of **1** and **2** can be explained by the different mode of the coordination of the substrate at the migratory insertion step of the catalytic cycle.

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Supporting Information Available: Experimental details and full characterization data for all new compounds; NMR charts of **4**, **5**, **4d**, **5d**, **7**, **8**, **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) We failed to find in the ^{13}C NMR spectrum the multiplet of the CH_2 group due to its low intensity, possible overlap with other signals, and gradual decomposition of **10** even at −90 °C, preventing correlation experiments. In the ^{1}H NMR spectrum the relatively sharp multiplet at $\delta = 2.95$ was assigned to the signal of the CH_2 group bound to rhodium since it is coupled to *trans*-phosphorus according to selective decoupling experiments.

(15) There are reasons to suppose this since the reaction is very fast even at −100 °C.

(16) Experimental data give no indication as to whether the substrate is chelated in the intermediate **B**.