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Origin of the Minor Enantiomeric Product in a Noyori Asymmetric Hydrogenation: Evidence for Pathways Different to the Major Mechanism**

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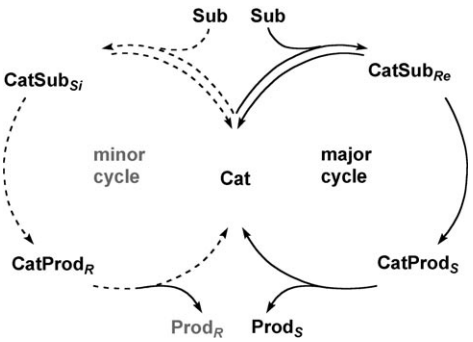
In a typical asymmetric catalytic process, a prochiral substrate (Sub) is converted into a major ($Prod_S$) and a minor ($Prod_R$) enantiomeric product via diastereomeric catalyst–substrate (CatSub) and catalyst–product (CatProd) complexes (Scheme 1). The two cycles are diastereomorphic to each



Scheme 1. Competition between diastereomorphic catalytic cycles.

other, but they take place through a single mechanism. As such, the Arrhenius equation can be applied confidently to correlate the $Prod_S/Prod_R$ ratio to the relative stabilities of the diastereomeric transition states at the first irreversible step from CatSub to CatProd.[1] The energy profile thus obtained can be utilized to estimate the structural difference between the two transition states. In most cases, however, this premise of a single mechanism has not been confirmed.[2] We have long suspected that in some cases $Prod_S$ and $Prod_R$ may be

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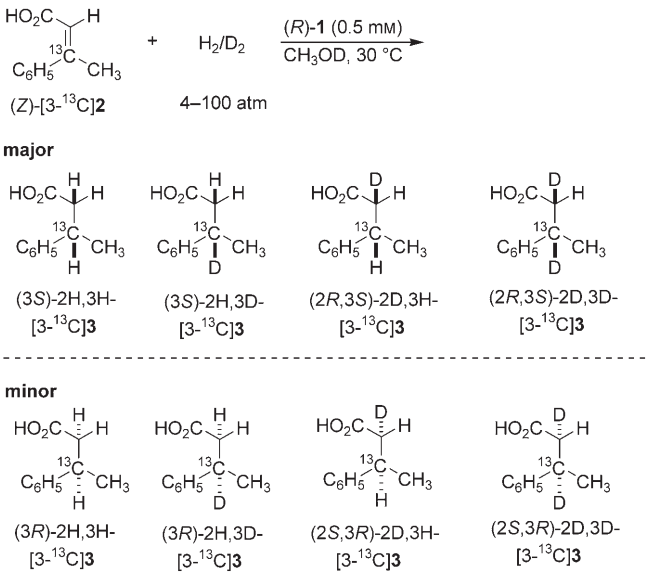
Supporting information for this article (asymmetric hydrogenation and isotope-labeling experiments) is available on the WWW under http://www.angewandte.org or from the author.

generated through entirely different catalytic cycles in which several chain carriers produced in a given reaction system convert the same substrate but with different reactivities and enantioselectivities. In such a catalytic process, various reaction parameters dynamically link the species, and therefore the observed enantioselectivity becomes the average contribution of the mechanistically different cycles.[3] Herein, we report for the first time a clear example of asymmetric catalysis that yields $Prod_S$ and $Prod_R$ from the same substrate but through different mechanisms.

This new case was identified in the hydrogenation of (*Z*)-3-phenyl-2-butenoic acid ((*Z*)-**2**) in the presence of [Ru-$(CH_3CO_2)_2$\{(*R*)-binap\}] ((*R*)-**1**).[4] Under standard conditions ((*R*)-**1** (0.5 mM), (*Z*)-**2** (100 mM), Sub/Cat = 200:1, methanol, 30 °C, 1–4 atm), (*S*)-3-phenylbutanoic acid ((*S*)-**3**) was obtained with 94 % ee when a pressure of 1–4 atm was applied. The value decreased to 92 % *ee* at 50 atm and to 88 % *ee* at 100 atm,[5] whereas the reaction rate was enhanced when the pressure of the hydrogen was increased.[6] The substrate (*Z*)-**2** is stable and undergoes neither *Z*/*E* geometrical nor α,β/β,γ (C2–C3/C3–C4) positional isomerization during the course of the hydrogenation.[5,7] To improve the accuracy of the isotope-labeling experiments, the ^{13}C-labeled substrate (*Z*)-[3-^{13}C]**2** was used, and the (*R*)-**1**-catalyzed hydrogenations were carried out in CH_3OD by changing the hydrogen pressure and the ratio of H_2 and D_2. All the reactions were stopped at low conversions to minimize complications caused by gas–solvent and gas–gas isotope exchange.[2,5] The enantiomeric products, (*S*)-**3** (major) and (*R*)-**3** (minor), were separated by chiral HPLC (CHIRALCEL OD (20 mm × 25 cm); eluent: hexane/2-PrOH/AcOH 1000:1:3),[5] and the ratio of the eight isotopomers (3*S*)-2H,3H-[3-^{13}C]**3**, (3*S*)-2H,3D-[3-^{13}C]**3**, (2*R*,3*S*)-2D,3H-[3-^{13}C]**3**,[9] (2*R*,3*S*)-2D,3D-[3-^{13}C]**3**,[9] (3*R*)-2H,3H-[3-^{13}C]**3**, (3*R*)-2H,3D-[3-^{13}C]**3**, (2*S*,3*R*)-2D,3H-[3-^{13}C]**3**,[9] and (2*S*,3*R*)-2D,3D-[3-^{13}C]**3**[9] was determined by $^{13}C\{^1H,^2H\}$ NMR spectroscopic analysis of the *S* and *R* products (Scheme 2).[5,10]

Figure 1 represents the change in the distribution pattern of the major and minor enantiomeric products in going from the H_2 to H_2/D_2 conditions. When the reaction was carried out in CH_3OD under a pressure of 4 atm of H_2, a mixture of (*S*)-**3** and (*R*)-**3** was obtained in a ratio of 97:3. The major *S* product consisted of 2H,3H, 2H,3D, 2D,3H, and 2D,3D isotopomers (10:89:0:1). Under an atmosphere of H_2/D_2 (1:1) in CH_3OD, the ratio shifted to 3:46:3:48. This change in distribution can be understood simply in terms of the Ru monohydride mechanism proposed in the Ru–binap-catalyzed hydrogenation of tiglic acid[11,12] or α-(acylamino)acrylic esters.[2,13] In short, a RuH species, generated from (*R*)-**1** and H_2, delivers hydride to the *Si* face at C2 of (*Z*)-**2** to form the (3*R*)-C3–Ru intermediate. Cleavage of the C–Ru bond utilizes both H_2 gas (the RuH/C3–Ru/H_2 route) and CH_3OD (the RuH/C3–Ru/H^+ route), and leads to a mixture of (3*S*)-2H,3H and (3*S*)-2H,3D (10:89).[14,15] Under a 1:1 mixture of H_2/D_2 gas, the RuH/C3–Ru/H_2 route should produce the four isotopomers in a 1:1:1:1 ratio (blue line) and the RuH/C3–Ru/H^+ route should produce 2H,3D and 2D,3D in a 1:1 ratio (green line); therefore, a relative proportion of ≈3 each for the (3*S*)-2H,3H, (3*S*)-2H,3D, (3*S*)-2D,3H, and (3*S*)-2D,3D isotopomers will be derived from the 10 part, and ≈44 for the (3*S*)-2H,3D and (3*S*)-2D,3D isotopomers from the 89 part. Simple calculation estimates the ratio to be 3:47:3:47, which is consistent with the observed ratio.



Scheme 2. Structures of the eight possible isotopomers from the reduction of (*Z*)-[3-^{13}C]**2** in CH_3OD under H_2/D_2 mixtures at different pressures.

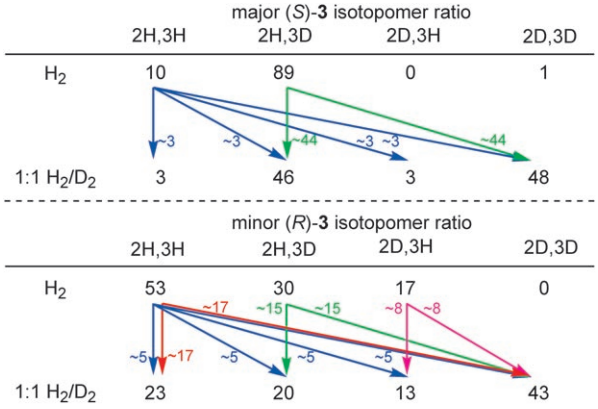


Figure 1. Change of the isotopomer ratios in the (*R*)-binap–Ru-catalyzed hydrogenation of (*Z*)-[3-^{13}C]**2** in CH_3OD under 4 atm of H_2 or H_2/D_2 (1:1). Top: (*S*)-[3-^{13}C]**3** obtained as the major product (97 %). Bottom: (*R*)-[3-^{13}C]**3** obtained as the minor product (3 %). The colored arrows indicate the reaction pathways and the estimated distribution of the isotopomers when the conditions are switched from H_2 to H_2/D_2 (1:1). → RuH/C3–Ru/H_2 and/or RuH/C2–Ru/H_2 (RuH/H_2); → RuH/C3–Ru/H^+; → RuH_2; → RuH/C2–Ru/H^+.

In contrast, the minor *R* enantiomer contained largely the (3*R*)-2H,3H (53 %) together with the (3*R*)-2H,3D (30 %) and (3*R*)-2D,3H (17 %) isotopomers. More gaseous hydrogen appears to be consumed in the formation of the minor product than in that of the major *S* enantiomer, and formation of the 2D,3H isotopomer is characteristic of the minor product. The reaction carried out in CH_3OD under a mixture of H_2/D_2 (1:1) generated a 23:20:13:43 mixture of the four 3*R* isotopomers. The ambiguous isotope-labeling patterns, which

are totally different from those of the major enantiomer, can be explained by assuming that the RuH_2 route[5] (red line) and the RuH/C2–Ru/H^+ route (purple line) are involved as well as the above two reaction pathways (blue and green lines) (Figure 1, minor). The two hydrides on RuH_2 are delivered from the same *Re*,*Si* face of (*Z*)-**2** to C2 and C3 in a pairwise manner.[16] In the RuH/C2–Ru route, a conjugate-type addition of the hydride of a RuH species onto the *Si* face of C3 generates a (2*R*,3*S*)-C2–Ru intermediate,[17] which then undergoes hydrogenolysis (RuH/C2–Ru/H_2) or protonolysis (RuH/C2–Ru/H^+). Thus, the 2H,3H, the 2H,3D, and the 2D,3H isotopomers in the H_2/CH_3OD reaction are produced through the pathways RuH_2 and RuH/H_2,[18] the RuH/C3–Ru/H^+ route, and the RuH/C2–Ru/H^+ route, respectively. In light of the 2H,3H:2H,3D:2D,3H:2D,3D distribution coefficients (1:1:1:1 for RuH/C3–Ru/H_2 and RuH/C2–Ru/H_2 (blue line), 0:1:0:1 for RuH/C3–Ru/H^+ (green line), 1:0:0:1 for RuH_2 (red line), and 0:0:1:1 for RuH/C2–Ru/H^+ (purple line)), the isotopomer ratio obtained by the replacement of H_2 with a 1:1 mixture of H_2/D_2 gas is calculated to be 22:20:13:45. Figure 2a shows the good agreement between the values estimated from the H_2/CH_3OD results (colored bars) and the experimental values (gray bars). The colors correspond to those of the reaction pathways shown in Figure 1.

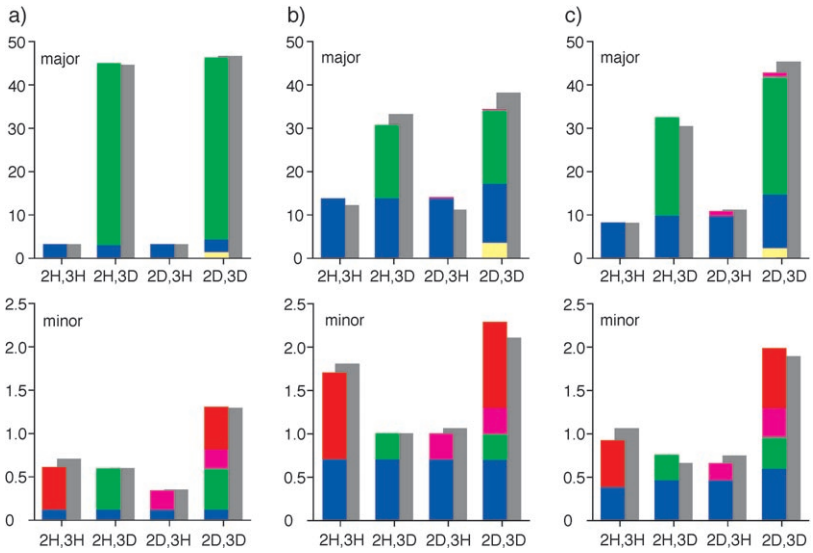
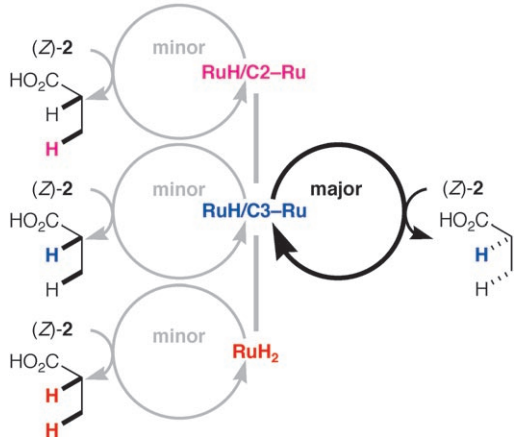


Figure 2. Observed (gray) and estimated (colored) isotopomer ratios of the major *S* and minor *R* products in the (*R*)-binap–Ru-catalyzed hydrogenation of (*Z*)-[3-^{13}C]**2** in CH_3OD under: a) 4 atm of H_2/D_2 (1:1), b) 100 atm of H_2/D_2 (1:1), and c) 50 atm of H_2/D_2 (44:56). Colored values are estimated from the experimental results of 4, 50, and 100 atm H_2/CH_3OD conditions. ■ RuH/C3–Ru/H^+; ■ RuH/C3–Ru/H_2 and/or RuH/C2–Ru/H_2; ■ RuH_2; ■ RuH/C2–Ru/H^+; ■ unknown mechanisms; *x* axis: isotopomers of **3**; *y* axis: yield [%].

This tendency is also seen with changes in the pressure of the hydrogen gas and the H_2/D_2 ratio (Figure 2b,c).[19] An increase in hydrogen pressure from 4 to 100 atm in CH_3OD approximately tripled the formation of the minor enantiomer (Figure 2a, minor vs. Figure 2b, minor), and enhanced the contribution of gaseous hydrogen to both the major and minor product pathways. The amount of major product formed by the RuH/H_2 pathway (blue bars) increased approximately five times and was coupled with a significant decrease in the involvement of the RuH/C3–Ru/H^+ route (green bars), whereas the contribution of the RuH_2 pathway (red bars) to the formation of the minor product doubled. In the case of the reaction carried out in CH_3OD under H_2/D_2 gas (44:56) at 50 atm, the *S* and *R* products (96:4) consisted of the eight isotopomers in a 9:31:11:45:1.0:0.6:0.7:1.7 ratio, as indicated by the gray bars in Figure 2c. A reasonable agreement with the estimation from the results obtained from the reaction in CH_3OD under 50 atm of H_2 was observed after a 0.44/0.56 correction to the above distribution coefficients.

Each asymmetric catalytic cycle proceeding through the RuH/C3–Ru/H_2, RuH/C3–Ru/H^+, RuH/C2–Ru/H_2, RuH/C2–Ru/H^+, or RuH_2 routes, or other possible reaction pathways, has its own energy diagram, according to which the overall rate as well as the stereochemistry is determined.[20] Neither the details of the kinetics nor the structures of the intermediates are known at present, but a series of isotope-labeling experiments indicated that this Ru–binap-catalyzed asymmetric hydrogenation of an α,β-unsaturated carboxylic acid involves several catalytic species and that a significant amount of the minor *R* enantiomer is formed through the RuH/C2–Ru/H^+ and RuH_2 pathways, which are hardly involved in the formation of the major product (Scheme 3). Asymmetric catalytic reactions convert a prochiral substrate



Scheme 3. Possible catalytic cycles producing the major *S* and minor *R* enantiomers from the same (*Z*)-**2** substrate through different chain carriers. C3 substituents of (*Z*)-**2** and products have been omitted for clarity.

into an enantiomer-enriched chiral product. The observed enantioselectivity has generally been interpreted to result from competing diastereomorphic catalytic cycles caused by a single chiral catalyst. However, this supposition has not been substantiated. Together with earlier examples,[2,11,12] our study calls into question such a generalized treatment.

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[10] The authentic (2*R**,3*S**)-2D,3H-**3** and (2*S**,3*S**)-2D,3H-**3** were prepared by diimide reduction of (*Z*)-2D-**2** and (*E*)-2D-**2**, respectively.[9] The isotope stability of the product was confirmed.[5]

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