Xb, 80031-93-2; Xb cation, 80031-98-7; Xc, 81769-37-1; XIa, 80031-86-3; XIa cation, 81770-46-9; XIc, 81769-38-2; XIIb, 80031-94-3; XIIb cation, 80031-99-8; XIIc, 81769-39-3; XIIIa, 80031-87-4; XIIIa cation, 80043-73-8; XIIIb, 80043-66-9; XIIIb cation, 80032-05-9; XIIIc, 80031-89-6; XIIIc cation, 80032-06-0; XIVa, 12111-60-3; XIVa cation, 81770-41-4; XIVb, 33010-84-3; XIVb cation, 81770-42-5; XVa, 12094-63-2; XVa cation, 81770-43-6; XVb, 81770-44-7; XVb cation, 81770-45-8; $Cr(CO)_6$, 13007-92-6; $Cr(CO)_3(NH_3)_3$, 14974-11-9; 4-bromoanisole, 104-92-7; 4-chloro-3,5-dimethylanisole, 6267-34-1; 4-chloro-3,5-dimethylphenol, 88-04-0.

Supplementary Material Available: A listing of the structure factor amplitudes (25 pages). Ordering information is given on any current masthead page.

Mechanism of Asymmetric Homogeneous Hydrogenation. Rhodium-Catalyzed Reductions with Deuterium and Hydrogen Deuteride

John M. Brown* and David Parker

Dyson Perrins Laboratory, South Parks Road, Oxford, OX1 3QY, England

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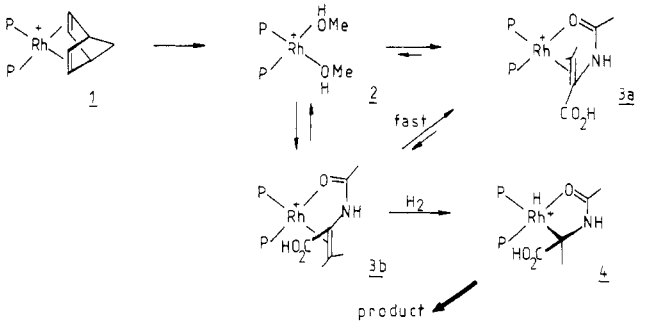
Propenoic acid, its tetramethylammonium salt, and *N*-vinylacetamide have been reduced with D_2 in methanol in the presence of a range of chiral rhodium bis(phosphine) ligands including (*RR*)-*trans*-4,5-bis((diphenylphosphino)methyl)-2,2-dimethyldioxolan ((*RR*)-diop), (*RR*)-1,2-bis((*o*-methoxyphenyl)-phenylphosphino)ethane ((*RR*)-dipamp), and (*SS*)-2,3-bis(diphenylphosphino)butane ((*SS*)-chiraphos). The optical purity of [2,3-$^2H_2$]propanoic acid was determined by ^2H NMR analysis of its (*S*)-methyl maldelate ester and that of *N*-[1,2-$^2H_2$]ethylacetamide by ^2H NMR analysis of *N*-ethylcamphanamide. In the former case, values of up to 60% were observed. Reduction of styrene with deuterium in the presence of ((*RR*)-diop)Rh complexes led to racemic product. Addition of HD to (*Z*)-acetamidocinnamic acid catalyzed by (diphos)-, (*RR*)-(dipamp)-, or (*RR*)-(diop)Rh complexes gave rise to a mixture of acetamido[2-^2H]- and acetamido[3-^2H]phenylalanine in which the former typically predominated by 1.35:1, whereas additions to octene, styrene, and *N*-vinylacetamide were not regioselective. The kinetic isotope effect (H_2 vs. D_2) for (diphos)Rh^+ catalyzed hydrogenation of (*Z*)-α-acetamidocinnamic acid is 1.22. Mechanistic implications are discussed.

Introduction

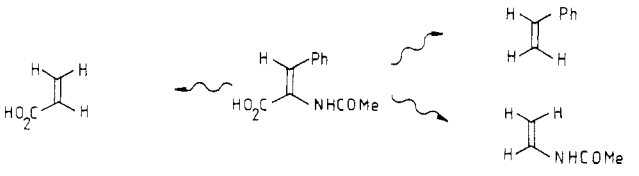
Recent research on asymmetric hydrogenation has been concerned with the preparation of new ligands,[1] reaction kinetics and X-ray identification of intermediates,[2] and the characterization of stable and transient species in solution by NMR.[3-5] The absolute configuration of intermediates may be inferred since the overall stereochemistry of hydrogenation is known,[6] and the mechanism shown in Scheme I is thus favored.

Speculations on the origin of stereoselectivity rely heavily on the numerous crystal structure determinations of chiral rhodium bis(phosphine) complexes[1c,e,2b,7] and the consistent conformational pattern first established by Knowles.[8] Opposed, C_2 related pairs of *P*-aryl rings are

Scheme I. Mechanism of Hydrogenation of Dehydroamino Acids by Chiral Rhodium Bis(phosphine) Complexes



Scheme II. "Dissection" of an Enamide into Component Monosubstituted Olefins



(1) Inter alia; (a) MacNeil, P. R.; Roberts, N. K.; Bosnich, B. *J. Am. Chem. Soc.* **1981**, *103*, 2273–80. (b) Meyer, D.; Poulin, J.-C.; Kagan, H. B.; Levine-Pinto, H.; Morgat, J. L.; Fromageot, P. *J. Org. Chem.* **1980**, *45*, 4680. (c) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932–4. (d) Samuel, O.; Couffingnal, R.; Laver, M.; Zhang, S. Y.; Kagan, H. B. *Nouv. J. Chim.* **1981**, *5*, 15–21. (e) Ojima, I.; Kogure, T.; Yoda, N. *J. Org. Chem.* **1981**, *45*, 4728–41. (f) Kashiwabara, K.; Hanoli, K.; Fujita, J. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2275–80. (g) Valentine, D., Jr.; Sun, R. C.; Toth, K. *J. Org. Chem.* **1980**, *45*, 3703–7; cf. preceding papers. (h) Koenig, K. E.; Bachman, G. L.; Vineyard, B. D. *Ibid.* **1980**, *45*, 2362–5.

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(3) (a) Brown, J. M.; Chaloner, P. A. *J. Am. Chem. Soc.* **1980**, *102*, 3040–8. (b) *J. Chem. Soc., Chem. Commun.* **1980**, 344–6. (c) Brown, J. M.; Chaloner, P. A.; Parker, D.; Descotes, G.; Lafont, D.; Sinou, D. *Nouv. J. Chim.* **1981**, *5*, 167–75.

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(7) (a) Knowles, W. S.; Vineyard, B. D.; Sabacky, M. J.; Stults, B. R. "Fundamental Research in Homogeneous Catalysis"; Tsutsui, M., Ed.; Plenum Press: New York 1980; p 523. (b) Ball, R. G.; Payne, N. C. *Inorg. Chem.* **1977**, *16*, 1187. (c) Townsend, J. M.; Blount, J. F. *Ibid.* **1981**, *20*, 269–71. (d) Cullen, W. R.; Einstein, F. W. B.; Huang, C. H.; Willis, A. C.; Yeh, E. S. *J. Am. Chem. Soc.* **1980**, *102*, 988–93. (e) Ogha, Y.; Litaka, Y.; Achiwa, K. *Chem. Lett.* **1980**, 861–4.

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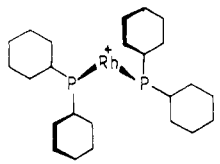
oriented so as to align the ring plane and the P–Rh bond parallel as in **5**, giving an alternating "face–edge" arrangement when viewed in the coordination plane. Steric interactions then control the energetics of complexation at different stages in the reaction cycle.



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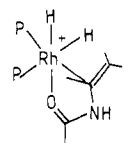

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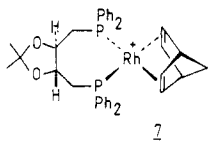
Since other factors, particularly the degree of rigidity of the chiral chelate ring, seem critical in determining the reactivity and stereoselectivity in asymmetric hydrogenation, we felt it worthwhile to carry out further experiments to elicit the detailed mechanism. This paper described addition of deuterium to monosubstituted prochiral olefins, "dissecting" the substituent effects obtained in an enamide (Scheme II). It was felt that steric effects would be unimportant in determining the optical yield, and other factors given prominence as a result. The reduction of (*Z*)-acetamidocinnamic acid with HD gives further insight into the reaction mechanism since the distribution of deuterium in the product shows considerable isotopic bias.

Discussion

Reduction of Styrene with Deuterium. Simple olefins lacking polar substituents are usually poor substrates in asymmetric hydrogenation, giving low optical yields.[9] The most favorable example is 2-phenylbut-1-ene, where optical yields of up to 60% in the reduced product 2-phenylbutane have been claimed.[10] The reaction of styrene with deuterium was carried out in methanol solution on a sufficient scale to measure the optical rotation of product, using complex **7** derived from (*RR*)-diop as procatalyst.



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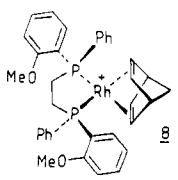

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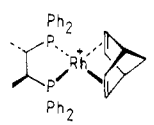

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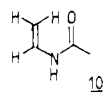

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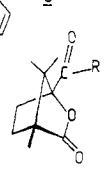

11 R=Cl

12 R=NHCHDCH$_2$D

No optical activity was observed under conditions where 2% could readily have been detected since [α-^{2}H]ethylbenzene has an appreciable specific rotation ([α] = 0.73°).[12] The phenyl group has no appreciable stereodirecting effect. In those cases where high selectivity is observed, it is known that the substrate binds to rhodium as a chelate.[2,3] Styrene forms 2:1 complexes with neutral rhodium(I) precursors such as bis(ethylene)rhodium(I) acetylacetonate,[13] and with cationic rhodium(I) complexes the arene may be bound preferentially.[14] Whatever the structure of complexes that are formed in hydrogenation, they are not conducive to stereoselectivity.

Table I. Deuterium Addition to *N*-Vinylacetamide[a]

entry	phosphine	conversn,[c] %	enantiomer excess (±3%)[d]
A	(*RR*)-diop	100	25*R*
B	(*SS*)-chiraphos	100	31*S*
C	(*RR*)-dipamp	100	11*S*
D	(*RR*)-diop[b]	85	24*R*

[a] In methanol solution using a cationic norbornadiene bis(phosphine) procatalyst ($p(D_2) = 1$ atm; 20 °C; catalyst: substrate = 1:100). Runs have been reproduced. [b] Et_3N was added–3 equiv per Rh. [c] Estimated by ^{1}H NMR analysis on the crude product (300 MHz, $CDCl_3$). No exchange at the α position was observed. [d] Configuration by comparison with a standard sample prepared by Schmidt reaction of authentic [α-^{2}H]propanoic acid.[16]

Reduction of *N*-Vinylacetamide with Deuterium. *N*-vinylacetamide (**10**) was prepared according to the published procedure requiring thermolysis of 1,1-diacetamidoethane at 200 °C and 15 mm[15] and purified by chromatography on Florosil. Its reduction was effected in methanol solution using **7**, **8**, or **9** as procatalyst and deuterium at 760 mmHg. The absolute configuration was established by comparison with the camphanamide of a standard sample prepared by Schmidt reaction of authentic [α-^{2}H]propanoic acid[16] (Table I). Optical purities were determined in each case by reaction with camphanoyl chloride (**11**),[17] giving *N*-[1,2-$^2H_2$]ethylcamphanamide (**12**). The *N*-α-methylene group in the parent amide exhibits a 16-line multiplet in its ^{1}H NMR spectrum at 300 MHz with H_S and H_R just separated. In the case of **12**, the optical purity may be determined by estimating the H_R/H_S ratio, most conveniently when the $-CH_2D$ group is concurrently irradiated. At the decoupling power levels necessary for accurate intensity measurement some residual coupling remained, and a more convenient and effective method was to measure the ^{2}H NMR spectrum, with proton decoupling. Two separate singlets at 2.90 and 3.05 ppm were then observed, corresponding respectively to D_S and D_R (by comparison with the proton NMR result). In all three cases product was completely deuterated, proton exchange with solvent[6] being absent. The optical yields obtained (Table I) are appreciable but do not approach values observed for conventional enamide substrates.

By concurrent investigation of reaction intermediates by ^{31}P NMR in the manner previously described,[3] it was shown that the methanol solvates derived from **8** and **9** did not complex strongly with *N*-vinylacetamide, although appreciable line broadening of the original signal was observed. The methanol solvate derived from **7** reacted with *N*-vinylacetamide to give a single species, **13** (or a rapidly equilibrating diastereomeric mixture)[5] although the spectrum is exchange broadened down to 225 K (Table II).

Reduction of Tetramethylammonium 2-Propenoate with Deuterium. Addition of deuterium to the tetramethylammonium salt of propenoic acid in methanol

(8) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946–52.
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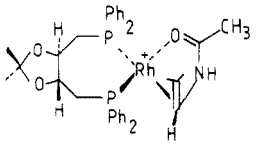

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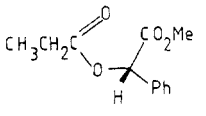

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catalyzed by 7 proceeded rapidly at room temperature. The product was examined by ^1H NMR in CD_3OD and irradiation at the CH_2D site showed two signals arising from the site adjacent to the carboxylate due to CHD and CH_2, respectively. The latter was shifted 0.05 ppm downfield[18] and demonstrated that 6% of isotopic exchange accompanied reduction. The crude product was converted into free acid by ion-exchange which was purified by distillation, and shown to have (+)-(*S*) configuration (Table III).

Determination of the optical purity of α-deuterated carboxylic acids is not readily effected, and chiroptical methods have generally been employed.[19] We converted deuterated carboxylic acid into its (*S*)-methyl mandelate ester using dicyclohexylcarbodiimide and 4-(dimethylamino)pyridine in dichloromethane at −10 °C. The product was purified by distillation or preparative TLC. A sample of undeuterated ester **14** was prepared similarly and its proton NMR spectrum recorded in C_6D_6. The CH_2 group α to the carboxylic acid appeared as a 16-line multiplet at 2.47 ppm with H_R and H_S almost completely separated. The spectrum of material from reduction with deuterium showed two broadened multiplets around 2.5 ppm, the clarity being considerably improved by concurrent irradiation of the CH_2D site (Figure 1a). Solvent-exchanged material was apparent as a part obscured AB quartet. The deuterium NMR spectrum of the same sample showed clear separation of D_S and D_R (Figure 1b), and since the complication of isotopic exchange was avoided, it was utilized to estimate the optical purity of product. In this manner the enantiomeric excess, and extent of isotope exchange, was determined for a series of deuterium reductions employing **7**, **8**, and **9** as procatalysts.

The mechanism of this isotopic exchange process was further investigated by reducing tetramethylammonium propenoate with H_2 in CD_3OD, employing complex **7**. Under these conditions the extent of exchange was much lower, presumably because a primary kinetic isotope effect disfavors deuteron transfer from solvent. It was nevertheless possible to record the ^2H NMR spectrum of the reduction product (Figure 1c) and to demonstrate that the chirality of the portion which is exchanged at C2 is *opposite* to that of the product formed on reducing the substrate with D_2 in CH_3OH with the same catalyst. Reversal of the chirality of the product was also observed for reduction of tetramethylammonium propenoate catalyzed by complex **8** and employing H_2 in CD_3OD. No isotopic exchange was observed when reductions were carried out with D_2 in CD_3OD nor was any deuterium detected in the starting material after partial reduction by D_2 in CH_3OH and analysis of the recovered material by both ^1H and ^2H NMR. Furthermore, tetramethylammonium propenoate did not undergo any detectable deuterium incorporation after 2 days at room temperature in CD_3OD under a deuterium atmosphere in the presence of the solvate complex derived by in situ reduction of

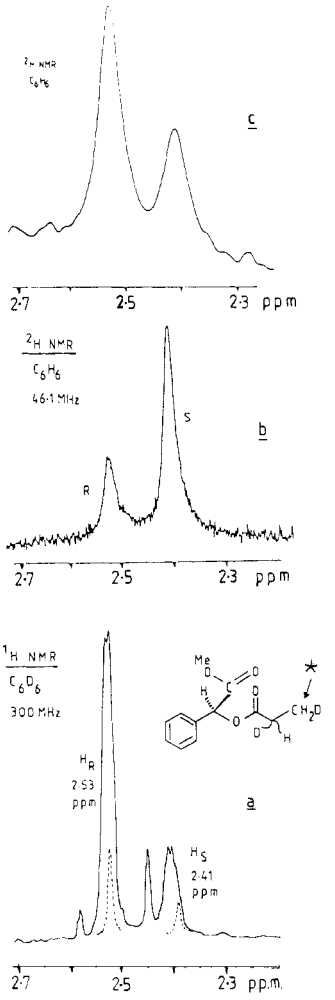
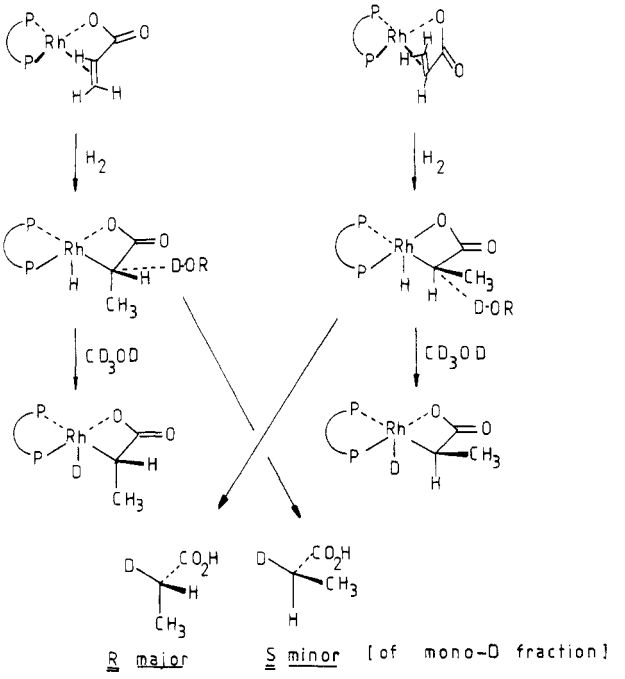


Figure 1. Proton and deuterium NMR spectra of the (*S*)-methyl mandelate ester derived by addition of D_2 to tetramethylammonium propenoate catalyzed by complex **7**: (a) ^1H NMR in C_6D_6 with concurrent irradiation of the methyl group; (b) ^2H NMR of the same chemical shift region in C_6H_6, (c) ^2H NMR of the reduction product from H_2 in CD_3OD; see text.

Scheme III. Suggested Mechanism for Isotope Exchange with Solvent during Addition of Hydrogen to Propenoate Catalyzed by 7



(18) Halliday, J. D.; Bindner, P. E. *Can. J. Chem.* **1976**, *54*, 3775–82.
(19) Eliel, E. L.; Arigoni, D. *Top. Stereochem.* **1969**, *4*, 127–245. Retey, J.; Unoni-Ronchi, A.; Arigoni, D. *Experientia* **1966**, *22*, 72. Ringdahl, B.; Cymerman-Craig, J.; Keck, R.; Retey, J. *Tetrahedron Lett.* **1980**, 3965–9. For a preliminary report of the ^2H NMR method see: Brown, J. M.; Parker, D. *Tetrahedron Lett.* **1981**, 2815–8, 4994.

Table II. ^{31}P NMR Spectra of Intermediates in (*RR*)-(diop)Rh Catalyzed Reductions[a]

substrate	temp, K	diastereomer ratio	$\delta(P_1)$	$\delta(P_2)$	J_{RhP_1}	J_{RhP_2}	$J_{P_1P_2}$
N-vinylacetamide	225	*b*	43.3	2.0	150	135	50
propenoic acid	228	6:1[c]	31.5	18.3	140	134	41
			30.5	30.5	141	141	
triethylammonium propenoate	228	*a*[d]	44.5	9.6	170	168	53
2-methylpropenoic acid	252	5:1[c]	30.7	29.7	141	137	39
			31.4	17.6	140	134	41
tetramethylammonium 2-methylpropenoate	252	1:1[d]	39.3	13.2	171	172	52
			34.7	14.2	170	172	53

[a] Chemical shifts are quoted in ppm downfield from H_3PO_4; [Rh] = 0.03 M; substrate:Rh = 6:1; solutions were orange for 1:1 complexes and pale yellow for 2:1 complexes. [b] Only one species observed; this implies a rapid diastereomer interversion at 225 K[5] or high stereoselectivity in complexation; chemical shifts and coupling constants (Hz) are consistent with enamide complex A. [c] Complexes of 2:1 stoichiometry for which a putative structure is B.[20] [d] Complexes of 1:1 stoichiometry, structure C (cf. ref 20 for these structures).

Table III. Deuterium Addition to Propenoic Acid[a]

tetramethylammonium salt			free acid		
procatalyst	exchange[b]	enantiomer excess[c]	procatalyst	exchange	enantiomer excess
(*RR*)-diop	6	51*S*	(*RR*)-diop	16	14*R*
(*RR*)-dipamp	2.5	15*S*	(*RR*)-dipamp	7	35*R*
(*SS*)-chiraphos	5	16*R*	(*SS*)-chiraphos	13	58*R*
diphos	5	0	(*SS*)-chiraphos	4[d]	49*R*

[a] Duplicate or triplicate determinations, values of enantiomer excess are quoted ±2% and values of isotopic exchange quoted ±1%. Reductions were effected in methanol with the appropriate rhodium bis(phosphine) norbornadiene complex, $p(D_2)$ = 1 atm, 20 °C; catalyst:substrate = 1:100. [b] Exchange refers to the α position of product. [c] Determined by ^1H NMR and ^2H NMR analysis of derived mandelate ester. [d] Reduction effected in CD_3OD.

complex **7**. Taken together, these experiments show that isotopic exchange occurs during the catalytic cycle. Either a small proportion of reduction occurs by external protonation of the rhodium alkyl intermediate or there is an isotopic exchange (Rh–H → Rh–D) which occurs more readily for the disfavored diastereomer. These possibilities are represented in Scheme III.

The complexation of α,β-unsaturated carboxylic acids and carboxylates to bis(phosphine)rhodium cations has been discussed elsewhere,[20] and seven-ring chelates bind the substrate more strongly than five-ring chelates. Presumably coordination is favored by a bis(phosphine) which exhibits a large bite angle (typically 96° for seven-ring chelates and 82° for five-ring chelates). Propenoic acid forms a pair of diastereomeric 1:1 complexes in ratio 5:1 on complexation to (diop)Rh^+ in the presence of NEt_3 (Table II), but stable adducts were not observed from dipamp or chiraphos precursors.

Reduction of Propenoic Acid with Deuterium. It is usually the case that carboxylic acids reduce with lower optical efficiency in the absence of base.[21] Reductions of propenoic acid with deuterium were slower than those of its tetramethylammoium salt but proceeded to completion. The optical purity and extent of isotopic exchange are recorded in Table IIIb. Surprisingly, five-ring chelate complexes **8** and **9** effect much higher optical yields of product than the seven-ring chelate **7**. In all cases the extent of α exchange was much greater than for carboxylates. The exchanged product was shown to have opposite stereochemistry, by carrying out reduction with H_2 in CD_3OD as described earlier with **7** as procatalyst. The derived mandelate ester had an optical purity of 12% by ^2H NMR and was of *S* configuration. Complex **9**, which gives the highest optical yield, shows a marked reduction in product optical purity measured by ^2H NMR when addition of deuterium is carried out in CD_3OD. This is again consistent with an reductive exchange mechanism proceeding in the opposite stereochemical sense to the major reaction. The small amount of exchange observed here (entry 4) may arise from the carboxylic acid entity. There is no participation of ortho hydrogen from the aryl rings of the phosphine ligand, despite good precedent.[22] Deuteration of propenoic acid was carried out with **9** in an experiment with catalyst:reactant ratio of 1:10. On completion of reduction **9** was reformed by addition of norbornadiene and isolated. Examination by ^1H and ^2H NMR showed that no deuterium had been incorporated.

The stable complexes formed by carboxylic acids with rhodium bis(phosphine) chelates possess 2:1 stoichiometry.[20] Both propenoic acid and 2-methylpropenoic acid (vide infra) complex in this way, two diastereomeric species being formed on reaction with **7** in methanol following hydrogenation (Table II). No characterizable complexes were formed from either dipamp or chiraphos.

Reduction of Tetramethylammonium 2-Methylpropenoate with Deuterium. Reduction of enamides by homogeneous rhodium catalysts proceeds through a transient alkylrhodium hydride.[23] Its formation follows the rate-determining step so that the stereochemistry is already fixed. It is not known whether the reduction of α,β-unsaturated carboxyates proceeds by a similar mechanism or whether breakdown of the alkylrhodium hydride is rate determining in this case. The reduction of 2-methylpropenoate by D_2 is informative. At the bound olefin state **15** two distinct diastereomeric complexes are formed if the bis(phosphine) counterligand is optically active. If the rate-determining step involves deuterium addition to **15**, this distinction should lead to enantioselectivity in product formation. If breakdown of the alkylrhodium hydride **16** is rate determining, then the product is likely to be optically inactive since the two

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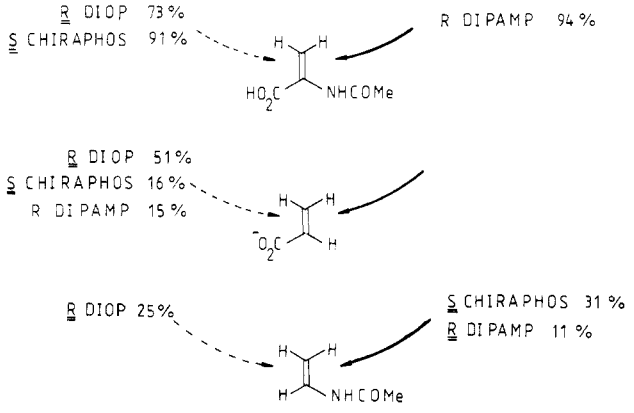
(21) See: Dang, T. P.; Kagan, H. B. *J. Chem. Soc., Chem. Commun.* 1971, 481–2. Achiwa, K. *Chem. Lett.* 1978, 561–5.
(22) Parshall, G. W. *Acc. Chem. Res.* 1975, *4*, 113–9.
(23) Kagan, H. B.; Sinou, D. *J. Organomet. Chem.* 1976, *114*, 325.

Table IV. Rhodium Complex Catalyzed Additions of Hydrogen Deuteride[a]

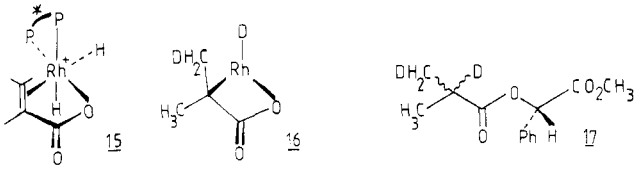
phosphine	substrate	analytical method[d]	selectivity[b]
diphos	oct-1-ene	^{2}H NMR (0.71 vs. 1.12 ppm)	1.03:1[c]
diop	oct-1-ene	^{2}H NMR	1.00:1
diop	styrene	^{2}H NMR (1.20 vs. 2.35 ppm)	1.01:1
diop	vinylacetamide	^{2}H NMR (1.11 vs. 3.21 ppm)	1.02:1
diphos	(*Z*)-PhCH=C(CO_2H) NHAc	^{1}H NMR	1.37:1
diop	(*Z*)-PhCH=C(CO_2H) NHAc	^{1}H NMR	1.36:1
dipamp	(*Z*)-PhCH=C(CO_2H) NHAc	^{1}H NMR	1.33:1

[a] Duplicate or triplicate determinations; p(HD) = 600 mm, 292 ± 2 K; catalyst:substrate = 1:50. [b] The isomer with deuterium at the more heavily substituted site is given first. [c] Corrected for the consequences of olefin isomerization competitive with catalyzed reduction. [d] ^{2}H NMR spectra were recorded in C_6H_6, and ^{1}H NMR spectra were recorded in Me_2SO-d_6.

Scheme IV. Summary of Optical Yields in Deuterium Addition to Monosubstituted Olefins



diastereomers are only differentiated by the configuration at the CH_3CCH_2D center.



In practice, only **7** is an efficient catalyst for reduction of tetramethylammonium 2-methylpropenoate. The optical purity of the product was determined by its conversion into (*S*)-methyl mandelate ester (**17**). This exhibited signals in its ^{2}H NMR spectrum at 1.21 and 1.33 ppm (CH_2D in *SS* and *RS* diastereomers) and at 2.55 ppm (*D*CC=O). On this basis the enantiomeric excess was determined to be 14%, of unknown absolute configuration. This is substantial enough to suggest that the stereochemistry is fixed prior to formation of the metal alkyl.

Summary. Data are summarized in Scheme IV, which compares literature values for optical yields obtained in the reduction of α-acetamidoacrylic acid with those acquired here for monosubstituted olefins. The lack of detailed correlation suggests a possible divergence of mechanism between the two cases, and it is significant that the five-ring chelates derived from **8** and **9** do not form characterizable complexes with any of the monosubstituted olefins, implying that their metal-binding constants are much lower than those of dehydroamino acids. Reductions catalyzed by diop complexes do show stereochemical correlation with those of dehydroamino acids, but there is less similarity to α-phenyl olefins.[23]

Reductions with Deuterium Hydride. Addition of HD to olefins has been used previously in homogeneous systems as a mechanistic probe. Neither $(PPh_3)RhCl$[24] nor

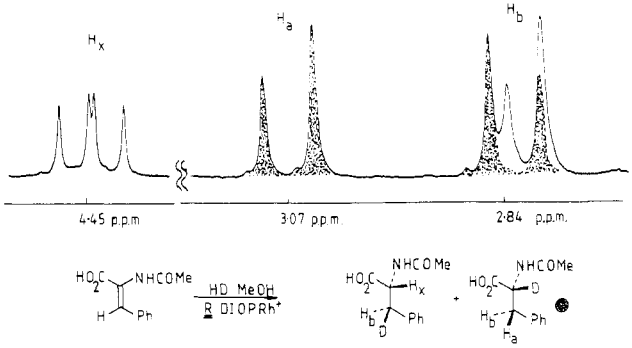


Figure 2. Proton NMR of the reduction product from (*Z*)-α-acetamidocinnamic acid and HD in CH_3OH catalyzed by complex **7**, in Me_2SO-d_6.

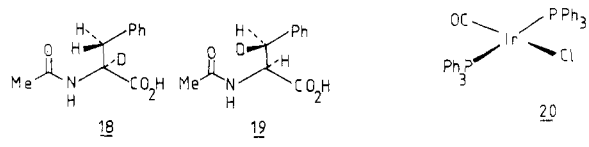
Table V. Kinetic Isotope Effect in Reduction of (*Z*)-Acetamidocinnamic Acid[a]

run (H_2)	correlatn coeff	k_2[b]	run (D_2)	correlatn coeff	k_2[b]
H1	0.9999	15.11	D1	0.9996	11.61
H2	0.9989	14.71	D2	0.9992	11.99
H3	0.9996	14.12	D3	0.9999	11.94
H4	0.9998	14.37	D4	0.9994	11.70

[a] Reactions were carried out in methanol solution (4 mL) containing bicyclo[2.2.1]heptadiene)(1,2-bis(diphenylphosphino)ethane)rhodium(I) tetrafluoroborate (7×10^{-3} M) and substrate (0.33 M) at 292 ± 1 K. [b] Rate constants are calculated from the expression[2a] $dp/dt = k_2[Rh][H_2]$ in mol L^{-1} s^{-1}, corrected to NTP and using the solubility values of H_2 and D_2 quoted in the text.

7[6] was reported to show any directional specificity. With the availability of high-field NMR and methods for direct analysis of both proton and deuteron content, a more detailed analysis was instigated.

The course of addition of HD to a series of olefins is recorded in Table IV. The reaction product from (*Z*)-α-acetamidocinnamic acid was analyzed by ^{1}H NMR, the appropriate region of the spectrum from one such reduction being shown in Figure 2. Since the addition is stereospecifically cis the two possible products (shown in a single enantiomeric form) are **18** and **19**. Careful analysis of the product suggests that the deuterium is unequally distributed, **18** predominanting over **19** by 1.36 ± 0.03:1 in all cases. This bias is not seen in other reductions examined by ^{2}H NMR. Styrene, 1-octene, and *N*-vinylacetamide all give equal proportions of the two possible reduction products, within experimental error.



(24) Jardine, F. H.; Osborn, J. A.; Wilkinson, G. *J. Chem. Soc. A* **1967**, 1574–8.

Further information on asymmetric hydrogenation of enamides was obtained by measuring the kinetic isotope effect in (diphos)Rh^+ reduction of (*Z*)-α-acetamidocinnamic acid (Table V). Runs were carried out alternately with H_2 and D_2 to minimize systematic error, and in all cases the reaction showed zero-order dependence on substrate concentration up to 95% reaction. At 292 K (750 mm) the solubility of hydrogen in methanol is 3.71×10^{-3} mol L^{-1}.[25] The solubility of deuterium in methanol is unknown, but it is always more soluble in organic solvents than is hydrogen and in water, the only hydroxylic solvent for which accurate data is recorded, its solubility at 292 K is 1.07 times greater,[26] the highest differentiation reported. With this value, an estimate for the solubility of deuterium in methanol of 3.97×10^{-3} mol L^{-1} may be derived. On this basis the corrected kinetic isotope effect is 1.23 ± 0.05, to be compared with a value of k_{H_2}/k_{D_2} of 1.22 for the cis addition of hydrogen to Vaska's complex **20** which is essentially irreversible at 298 K (700 mm).[27]

It is intriguing that the regioselectivity in HD addition [α:β = 1.36:1] is greater than the overall kinetic isotope effect [H_2:D_2 = 1.23:1]. It may reflect a degree of fluxionality at the rhodium dihydride stage, similar to *cis*-$RuH_2(PEt_3)_4$,[28] but the difference is to small to warrant detailed speculation. The results support on irreversible hydride step, in accord with the lack of para ⇌ ortho hydrogen equilibration during the course of asymmetric hydrogenation of enamides.[29]

Experimental Section

^1H nuclear magnetic resonance spectra were obtained on a Bruker WH 300 (300.13-MHz) instrument. Chemical shifts are expressed in parts per million (ppm) from tetramethylsilane. ^{31}P NMR spectra were recorded on a Bruker WH 90 (36.43 MHz), and chemical shifts are quoted relative to external phosphoric acid (85%). ^2H NMR spectra were recorded on the Bruker WH 300 (46.07 MHz); spectra were recorded unlocked, and chemical shifts are quoted relative to benzene-d_6 (7.27 ppm). Typical accumulations were taken with 50 transients, with quadrature detection, collected in 8K data points, with a pulse angle of 75°, a sweep width of 500 Hz, and an offset of 22 500 Hz.

Infrared spectra were recorded either as thin films, on potassium bromide disks, or in the stated solvent, by using a Perkin-Elmer 257-spectrometer or a Unicam SP 1000. The following abbreviations are used: vs = very sharp, s = strong, m = medium, and w = weak. Ultraviolet spectra were recorded on a Unicam SP 800A spectrophotometer in 1-cm cells as solutions in the solvents indicated. Extinction coefficients (dm^3 mol^{-1} cm^{-1}) are given in parentheses after the absorption. Mass spectra were either determined on a V. G. Micromass 16F spectrometer by the direct insertion technique or on a Varian CH7. All mass peaks are normalized to the largest peak. Melting points were determined on a Reichert-Kofler block and are uncorrected. Microanalyses were performed by Dr. F. B. Strauss and his staff, Oxford. Analytical samples were obtained by either evaporative short-bath distillation in vacuo or by recrystallization from the indicated solvent and drying in vacuo at 0.05 mmHg for several hours. Optical rotations were recorded on a Perkin-Elmer 141 polarimeter and were recorded three times (mean value given). Silica gel for column chromatography was BDH 60-120 mesh. Thin-layer chromatography (TLC) was performed on 0.2-mm thick E. Méck silica plates 60F-254; preparative thin-layer chromatography was performed on plates (20 cm × 20 cm × 1 mm) coated with E. Mêrck silica gel (60 $PF_{254+366}$).

All reactions were conducted under an argon atmosphere using standard vacuum-line techniques and Schlenk glassware. All transfers of liquids and solutions of air-sensitive materials were carried out with dried, inert-gas purged syringes fitted with stainless-steel needles or with thin steel tubing. Argon was prepurified by passage through liquid paraffin, concentrated sulfuric acid, potassium hydroxide pellets, and glass wool. Commerical solvents were distilled prior to use from an appropriate drying agent and otherwise purified according to standard procedures.

Catalytic additions of H_2, D_2, or HD were performed on a simple hydrogenation apparatus attached to the vacuum line. Hydrogen deuteride was generated in situ by addition of cold methanol by syringe to an evacuated, cold (−70 °C) Schlenk tube containing lithium aluminum deuteride (>99%) (*Caution!*). Kinetic studies were carried out in a Schlenk tube (100 cm^3) with a rubber septum cap, connected to a gas burette (50 cm^3). Methanol (4.00 cm^3) was placed in the flask and this was stirred by a 1-cm "Teflon" coated magnet driven by an external motor so that it operated at the gas–liquid interface. The rhodium bis(phosphine) procatalyst (2.80×10^{-5} mol) and reactant (1.33×10^{-3} mol) were added, and the solution was degassed by three freeze–thaw cycles. Hydrogen or deuterium (>99%, Matheson) was admitted and the system equilibrated at 292 K (±1) for 5 min. The volume of hydrogen in the burette was measured at 30-s intervals by leveling the water level in the burette with that in an external reservoir.

Catalytic Deuteration of Tetramethylammonium Propenoate. To a solution of tetramethylammonium propenoate (290 mg, 2.0 mmol) in dry methanol (5 mL) was (bicyclo[2.2.1]heptadiene)(*trans*-4,5-bis((diphenylphosphino)methyl)-2,2-dimethyldioxolan)rhodium(I) tetrafluoroborate (15.6 mg, 20 μmol) in a Schlenk tube. The solution was degassed by three freeze–thaw cycles, and deuterium was admitted at −75 °C. The system was allowed to equilibrate at room temperature ($p(D_2)$ = 1 atm), and the solution was stirred at room temperature until the yellow color of the olefin–carboxylate complex was discharged (3 h). Solvent was removed in vacuo and the crude product analyzed for conversion and H/D exchange (^1H NMR, 300 MHz, CH_2D irradiation). The residue was taken up in water (10 mL) and filtered and cationic ion-exchange resin added (1.75 equiv, Dowex 50W, purified by Soxhlet extraction with methanol). When the pH of the solution was 5 (pH paper, Merck), the acid was extracted with ether (3 × 5 mL), separated, dried over sodium sulfate, and filtered and solvent removed under reduced pressure (15 °C (15 mm)). The [2,3-$^2H_2$]propanoic acid (100 mg, 70%) was analyzed by ^1H NMR (300 MHz, $CDCl_3$, CH_2D irradiated) to check that no further exchange had occurred during isolation.

Methyl *O*-[2,3-$^2H_2$]Propanoylmandelate. To a solution of [2,3-$^2H_2$]propanoic acid (74 mg, 1 mmol) in dry dichloromethane (5 mL) at −10 °C was added methyl mandelate (166 mg, 1.0 mmol) and 4-(dimethylamino)pyridine (5 mg), followed by dicyclohexylcarbodiimide (206 mg, 1.0 mmol). The solution was stirred for 1 h at −10 °C and then allowed to come to room temperature over 2 h. The precipitated urea was removed by filtration and solvent removed under reduced pressure. The residue was taken up in dichloromethane (5 mL) and filtered again, before solvent was removed in vacuo to give the crude ester, 190 mg (80%). The ester was purified by preparative thin-layer chromatography (silica, 20 cm × 20 cm × 1 mm, ethyl acetate–hexane (1:2)). The ester band (R_f 0.05) was removed and extracted with dichloromethane–methanol (10:1, Soxhlet); solvent was removed under reduced pressure to give the pure ester: NMR (^1H, C_6D_6) δ 1.22 (2 H, br d, CH_2D), 2.41 (H_S, br t, 24% of CHD), 2.53 (H_R, br t, 76% of CHD), 6.09 (1 H, s, CHD), 7.2–7.5 (5 H, m, Ar); (^2H, C_6H_6) δ 1.22 (1 ^2H, s), 2.41 (s, 76% of ^2H CH_2D), 2.53 (s, 24% of CH_2D). The [2,3-$^2H_2$]propanoic acid is then 52*S* (±2%).

Catalytic Deuteration of Tetramethylammonium 2-Methylpropenoate. To a solution of tetramethylammonium 2-methylpropenoate (304 mg, 2.0 mmol) in dry methanol (5 mL) was added (bicyclo[2.2.1]heptadiene)(2*S*,3*S*)-2,3-bis(diphenylphosphino)butane)rhodium(I) tetrafluoroborate (13.9 mg, 0.02 mmol) in a Schlenk tube. The procedure followed was as described

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(26) Muccitelli, J.; Yen, W.-Y. *J. Soln. Chem.* **1978**, *7*, 257.
(27) Chock, P. B.; Halpern, J. *J. Am. Chem. Soc.* **1966**, *88*, 3511. Hyde, E. M.; Shaw, B. L. *J. Chem. Soc., Dalton Trans.* **1975**, 765.
(28) Meakin, P.; Muetterties, E. L.; Tebbe, F. N.; Jesson, J. P. *J. Am. Chem. Soc.* **1971**, *93*, 4701–10. Meakin, P.; Muetterties, E. L.; Jesson, J. P. *Ibid.* **1973**, *95*, 75–86.
(29) Brown, J. M.; Canning, L. R.; Downs, A. J.; Forster, A., to be submitted for publication.

above for the propenoate; analysis of the product acid (^{1}H NMR, $CDCl_3$, 300 MHz) indicated 50% conversion to 2-methyl[2,3-$^2H_2$]propanoic acid with 0% (±0.1) H/D exchange.

Methyl *O*-(2-Methyl[2,3-$^2H_2$]propanoyl)mandelate. To a solution of 2-methyl[2,3-$^2H_2$]propanoic acid (50%, 87 mg, 1 mmol) in dry dichloromethane (5 mL) at −10 °C was added methyl mandelate (166 mg, 1.0 mmol), 4-(dimethylamino)pyridine (5.0 mg), and dicyclohexylcarbodiimide (232 mg, 1.1 mmol). After 3 h at 0 °C, the precipitated urea was filtered, the solvent removed in vacuo, and the residue redissolved in dichloromethane (5 mL) and filtered again before solvent was removed in vacuo to give a colorless oil (165 mg, 70%). The ester was purified by preparative thin-layer chromatography (silica, ethyl acetate–30:40 petroleum ether (1:2)), and the ester band (R_f 0.34) was extracted with dichloromethane–methanol (10:1, Soxhlet). Solvent was then removed under reduced pressure to give the ester: NMR (^{1}H, C_6D_6) δ 1.21, 1.33 (br, s, CH_2D, CH_3), 3.21 (3 H, s, OMe), 6.05 (1 H, s, CHO), 7.1–7.4 (5 H, m, Ar); (^{2}H, C_6H_6) δ 1.21 (s, 57% of CD), 1.33 (s, 43% of CD) 2.55 (1 ^{2}H, *DC*(Me)(CH_2D)). The 2-methyl[2,3-$^2H_2$]propanoic acid is then 14% optically pure (±2%).

Catalytic Deuteration of *N*-Vinylacetamide. To a solution of *N*-vinylacetamide (170 mg, 2.0 mmol) in dry methanol (5 mL) was added (bicyclo[2.2.1]heptadiene)-((2*S*,3*S*)-2,3-bis(diphenylphosphino)butane)rhodium(I) tetrafluoroborate (13.9 mg, 0.02 mmol) in a Schlenck tube. The deuterium was admitted at −70 °C; the system was equilibrated to room temperature ($p(D_2)$ = 1 atm) and then stirred until the pale color of the complex had been discharged, and the the solution was orange-yellow (solvent complex, 3 h). Solvent was removed in vacuo and the crude product analyzed by ^{1}H NMR (300 MHz, $CDCl_3$; 100% conversion, 0% isotope exchange). The crude product was distilled (bath temperature 60 °C (0.07 mm) II and suspended in water (10 mL). Hydrobromic acid was added (40%, 1.5 mL) and the solution refluxed (18 h). Removal of solvent, in vacuo, afforded [1,2-$^2H_2$]ethylamine hydrobromide as a white solid (177 mg, 70%) which was converted directly into the camphanamide as described below.

[1,2-$^2H_2$]Ethylcamphanamide. To a suspension of [1,2-$^2H_2$]ethylamine hydrobromide (126 mg, 1.0 mmol) in dry dichloromethane (7.5 mL) was added triethylamine (150 mg, 1.5 mmol) and (−)-camphanoyl chloride (238 mg, 1.1 mmol). The solution was stirred for 3 h at −10 °C and then poured into dilute aqueous sodium hydroxide solution (0.5 M, 25 mL), the mixture extracted with dichloromethane (2 × 10 mL), washed with saturated aqueous sodium chloride solution (2 × 5 mL) and water (2 × 10 mL), and dried (anhydrous potassium carbonate), and solvent removed under reduced pressure to give a colorless solid (170 mg, 75%), which was sublimed (70–75 °C (0.07 mm)) to give colorless needles: mp 92–94 °C; NMR (^{1}H, C_6D_6) δ 0.71 (3 H, s, CCCH.3), 0.84, 0.85 (3 H + 3 H, s + s, $C(CH_3)_2$), 0.70 (3 H, br d, CHDCH_2D, J_{HH} = 7.15 Hz), 2.89 (dq, H*S*, J_{HD} = 2.8 Hz, J_{NHCH} = 6 Hz), 3.04 (dq, H_R), 6.15 (1 H, br s, NH); integration of H_S:H_R indicated 31*S* (±2) enantiomer excess; (^{2}H, C_6H_6) δ 0.70 (1 ^{2}H, s, CH_2D), 2.89 (s, CHD), 3.04 (s, CHD); integration of signals at δ 2.89 and 3.04 indicated 31*S* (±2) enantiomer excess; this result was repeated three times.

Catalytic Hydrodeuterations (All Runs Were Carried Out in Duplicate). 1. (*Z*)-α-Acetamidocinnamic Acid. To a solution of (*Z*)-α-acetamidocinnamic acid (241 mg, 1.0 mmol) in methanol (5 mL) was added (bicyclo[2.2.1]heptadiene)-(*trans*-4,5-bis(diphenylphosphino)methyl)-2,2-dimethyldioxolan)rhodium(I) tetrafluoroborate (15.6 mg, 20 μmol) in a Schlenk tube, and the solution was degassed by three freeze–thaw cycles. Hydrogen deuteride (generated by addition of cold methanol (0.8 mL) to 2.0 mmol of lithium aluminum deuteride at −78 °C) was then admitted and the system allowed to equilibrate (p(HD) = 1 atm, 20 °C). The solution was stirred until the colour of the methanol complex was regenerated (30 min), when solvent was removed in vacuo: NMR (^{1}H, 300 MHz, $(CD_3)_2SO$) δ 1.83 (3 H, s, NHCOCH_3), 2.82 (d + d, H_S, 1 H), 3.07 (d, J_{gem} = 17.5 Hz, H_R, 0.58 H) 4.51 (0.42 H, CH(CO_2H)), 7.25 (5 H, m, Ar) 8.20 (1 H, br d, NH), 12.80 (1 H, br s, CO_2H). The sole products were therefore (2*R*,3*R*)-*N*-acetyl[3-^{2}H]phenylalanine (42%) and (2*R*)-*N*-acetyl[2-^{2}H]phenylalanine (58%); 89% plus 11% (2*S*,3*S*) + (2*S*). The same ratio of products (58:42) was obtained by using (bicyclo[2.2.1]heptadiene)-1,2-bis(diphenylphosphino)ethane)-rhodium(I) tetrafluoroborate as catalyst and with (bicyclo [2.2.1]heptadiene)((*R*,*R*)-1,2-bis((*o*-methoxyphenyl)phenylphosphino)ethane)rhodium(I) tetrafluoroborate.

2. *N*-Ethenylethanamide. The procedure described above was reported by using *N*-ethenylethanamide (127 mg, 1.5 mmol) and (bicyclo[2.2.1]heptadiene)(*trans*-4,5-bis((diphenylphosphino)methyl)-2,2-dimethyldioxolan)rhodium tetrafluoroborate (10.5 mg, 12.7 μmol). After being stirred for 2 h at room temperature, solvent was removed under reduced pressure and the product was distilled (bath temperature 40 °C (0.1 mmHg)), to give *N*-[^{2}H]Ethylethanamide (119 mg, 90%): NMR (^{1}H, 300 MHz, $CDCl_3$) δ 1.11 (2.50 H, br d, CH_3 and CH_2D), 1.92 (3 H, s, COMe), 3.21 (1.50 H, br q and br dt, CH_2N and CHDN), 5.95 (1 H, br s, NH); (^{2}H, 46.1 MHz, $CHCl_3$) δ 1.11 (0.50 ^{2}H, CH_2D), 3.21 (0.50 ^{2}H, CH*D*).

3. 1-Octene. The procedure described above was repeated by using 1-octene (215 mg, 2.0 mmol) and (bicyclo[2.2.1]heptadiene)(1,2-bis(diphenylphosphino)ethane)rhodium(I) tetrafluoroborate (13.6 mg, 40 μmol). After the solution was stirred for 1 h at room temperature, distilled water (1.5 mL) was added and the solution transferred to a Craig tube and centrifuged. The product, [^{2}H]octane, was removed as the upper layer by pipette: NMR (^{2}H, 46.1 MHz, C_6H_6) δ 0.71 (0.5 ^{2}H, CH_2D) 1.12 (0.5 ^{2}H, CH*D*). An identical result was obtained by using (bicyclo-[2.2.1]heptadiene)(*trans*-4,5-bis((diphenylphosphino)methyl)-2,2-dimethyldioxolan)rhodium(I) tetrafluoroborate as catalyst.

4. Styrene. The procedure described above was repeated by using styrene (184 mg, 2.0 mmol) and (bicyclo[2.2.1]heptadiene)(*trans*-4,5-bis((diphenylphosphino)methyl)-2,2-dimethyldioxolan)rhodium(I) tetrafluoroborate (31.2 mg, 40 μmol). After the solution was stirred at room temperature for 6 h, distilled water (2.5 mL) was added and the product which separated as the upper layer was removed by pipette: NMR (^{2}H, 46.1 MHz, C_6H_6) δ 1.20 (0.50 ^{2}H, CH_2D), 2.35 (0.50 ^{2}H, CH*D*).

(+)-(*S*)-Methyl Mandelate. (+)-(*S*)-Mandelic acid (15 g, 106 mmol) and concentrated sulfuric acid (0.5 mL) in dry methanol (50 mL) were refluxed for 3 h. Potassium carbonate (1.0 g) was added and the solvent removed in vacuo. The resulting oil was dissolved in ether (100 mL), washed with saturated aqueous sodium bicarbonate (50 mL), water (50 mL), and saturated aqueous sodium chloride (50 mL), and then dried (anhydrous magnesium sulfate), and the solvent was removed in vacuo. Recrystallization from ether/hexane gave methyl mandelate as colorless needles: 13.3 g (76%); mp 54–55 °C (lit.[18] mp 53.5–56 °C), $[\alpha]^{20}_D$ + 143° (*c* 1.66, MeOH) (lit.[18] $[\alpha]^{20}_D$ +143.5° (*c* 1, MeOH).

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Registry No. 7, 60584-05-6; 8, 75085-38-0; 9, 79790-89-9; 10, 5202-78-8; 11, 39637-74-6; 12 isomer 1, 81623-54-3; 12 isomer 2, 81623-55-4; 17 isomer 1, 81583-88-2; 17 isomer 2, 81583-89-3; 18, 81583-90-6; 19, 75671-37-3; diphos, 60430-43-5; tetramethylammonium propenoate, 16431-85-9; (±)-[2,3-$^2H_2$]propanoic acid, 81583-91-7; (*S*,*S*)-methyl *O*-[2,3-$^2H_2$]propanoylmandelate, 81583-92-8; (*R*,*S*)-methyl *O*-[2,3-$^2H_2$]propanoylmandelate, 81583-93-9; (+)-(*S*)-methyl mandelate, 21210-43-5; (*S*)-[2,3-$^2H_2$]propanoic acid, 81623-56-5; tetramethylammonium 2-methylpropenoate, 16431-84-8; (±)-2-methyl[2,3-$^2H_2$]propanoic acid, 81583-94-0; (*R*)-2-methyl[2,3-$^2H_2$]propanoic acid, 81654-75-3; (*S*)-2-methyl[2,3-$^2H_2$]propanoic acid, 81623-57-6; (*R*)-[1,2-$^2H_2$]ethylamine HBr, 81583-95-1; (*Z*)-α-acetamidocinnamic acid, 55065-02-6; (2*R*,3*R*)-*N*-acetyl[3-^{2}H]phenlalanine, 81623-58-7; (2*R*)-*N*-acetyl[2-^{2}H]phenylalanine, 81583-96-2; 1-octene, 111-66-0; 1-[^{2}H]octane, 3050-61-1; 2-[^{2}H]octane, 3050-62-2; styrene, 100-42-5; (±)-[α-^{2}H]ethylbenzene, 65805-35-8; [[2-^{2}H]-ethyl]benzene, 1861-04-7; (+)-(*S*)-mandelic acid, 17199-29-0; (*R*)-*N*-acetyl[1,2-$^2H_2$]ethylamine, 81583-97-3; (*S*)-*N*-acetyl[1,2-$^2H_2$]ethylamine, 81583-98-4; 2-methylpropenoic acid, 79-41-4; propenoic acid, 79-10-7; (*R*)-[2,3-$^2H_2$]propanoic acid, 81623-59-8.