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Marked Deuterium Isotope Effects on the Enantioselectivity in Rhodium-Catalyzed Asymmetric Hydrogenation of Enamides

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Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday

Abstract: Deuterium isotope effects on the enantioselectivity in the rhodium-catalyzed asymmetric hydrogenation of enamides and related substrates have been studied. Distinct deuterium isotope effects were observed in the hydrogenation of aryl-substituted enamides having an *ortho* substituent that is capable of forming a hydrogen bond. The observed isotope effects are interpreted in terms of the competitive reactions of two dihydride intermediates and dideuteride intermediates that exist in equilibrium in the catalytic cycle.

Keywords: asymmetric hydrogenation · deuterium · enamides · isotope effects · rhodium

Introduction

Hydrogen of different isotopic composition (H_2, HD, D_2) has been previously used in mechanistic studies of asymmetric hydrogenation. In 1978 Kagan et al. proved the *cis* addition of hydrogen in Rh-catalyzed asymmetric hydrogenation by using the reaction of (*Z*)-α-acetamidocinnamate with D_2.[1] Later Brown and Parker demonstrated the high potential of comparative hydrogenations with H_2, D_2, and HD for elucidating the subtle details of the catalytic cycle in Rh-catalyzed asymmetric hydrogenation.[2] Similarly, reduction with either H_2, D_2, or HD has been applied in mechanistic studies of Ru-catalyzed asymmetric hydrogenations.[3–5] The distribution of deuterium between the α- and β-positions of the resulting amino acid was applied in our own studies of the Rh-catalyzed asymmetric hydrogenation for drawing out conclusions on the preferred mechanistic pathway.[6] Especially fruitful was the use of HD hydrogenations for the explanation of the striking difference in the stereochemical outcome of Rh-BisP*-catalyzed hydrogenations of phenyl- and *tert*-butyl-substituted enamides.[7] The conclusions drawn from these studies have been supported by low-temperature NMR observation of crucial intermediates[7] and were consistent with the results of an independent computational study.[8]

Interestingly, so far there has been only a single observation of a notable change in the optical yield in asymmetric hydrogenation when the hydrogen of different isotopic composition is used for the catalytic reaction. Thus, we have reported that the enantiomeric excess of the product of the Rh-*t*Bu-BisP*-catalyzed hydrogenation of 1-acetylamino-1-(2-methoxyphenyl)ethene changed from 50% with H_2 to 24% with HD (in two independent runs), and dropped again with the use of D_2 (12% and 5% in two independent runs).[7b] In all other reactions reported so far no marked dependence of the optical yield on the isotopic composition of the hydrogen has been observed.

If the effect of the isotopic composition of hydrogen originates from first-order kinetic isotope effects at a crucial step in the catalytic cycle involving hydrogen transfer, one might expect more frequent observation of this effect. Hence, we report herein the scope of the marked deuterium isotope effects on optical yields and discuss the possible origins of the effects and their limitations.

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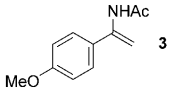
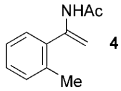
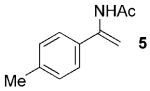
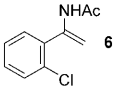
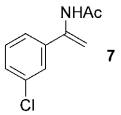
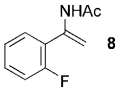
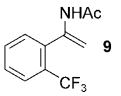
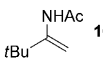
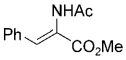
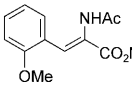
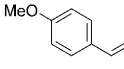
Results and Discussion

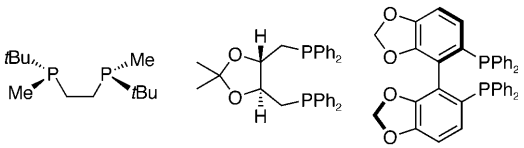
Our first experiment was conducted with the hydrogenation of 1-acetylamino-1-(*o*-methoxyphenyl)ethene using (*S*,*S*)-*t*Bu-BisP*, (*S*,*S*)-diop, and (*R*)-segphos as the chiral ligands in various solvents. Under the same reaction conditions, the asymmetric reduction was carried out using D_2 instead of H_2, and the *ee* values of the products were compared with those of the hydrogenation with H_2. In all cases significantly lower *ee* values of the products were observed, thus indicating marked deuterium isotope effects on the enantioselectivity (Table 1, entries 1–9). To clarify the scope and limitation of this kind of deuterium isotope effect, variously substituted enamides and dehydroamino acids were subjected to asymmetric hydrogenation using H_2 and D_2 in methanol at 25 °C. The results are summarized in Table 1.

Analyzing the data of Table 1, one can conclude that the scope of the effect is very narrow. It is strictly limited to the hydrogenation of enamides and is not observed in the asymmetric hydrogenation of dehydroamino acids, irrespective of the substrate structure (Table 1, entries 24–26). Moreover, it is almost exclusively observed for the hydrogenations yielding *ee* values that are not very high. Thus, the effect is marginal in the cases when R in the enamide is phenyl (Table 1, entry 10), *p*-tolyl (entry13), or *m*-chlorophenyl (entry 15). Entries 18–23 also demonstrate that no changes in *ee* value are observed for the systems yielding high *ee* values with H_2 when H_2 is replaced with deuterium (Table 1, entries 18 and 21). On the other hand, in the hydrogenations of the same substrate using poorly performing catalysts, a notable isotope effect on the *ee* value is observed (Table 1, entries 19 and

Table 1. Rhodium-catalyzed asymmetric hydrogenation of enamides with H_2 or D_2.

Entry[a]	Substrate	Ligand	Solvent	Product *ee* [%] (H_2)	Product *ee* [%] (D_2)
1		(*S*,*S*)-*t*Bu-BisP*	MeOH	57[b] (*R*)	5[c] (*S*)
2		(*S*,*S*)-*t*Bu-BisP*	THF	41 (*R*)	21[d] (*S*)
3		(*S*,*S*)-*t*Bu-BisP*	CH_2Cl_2	67 (*R*)	16 (*R*)
4		(*S*,*S*)-*t*Bu-BisP*	AcOEt	64 (*R*)	9 (*R*)
5		(*S*,*S*)-*t*Bu-BisP*	DMSO	54 (*R*)	21 (*R*)
6		(*S*,*S*)-diop	MeOH	89 (*R*)	80 (*R*)
7		(*S*,*S*)-diop	THF	75 (*R*)	57 (*R*)
8		(*R*)-segphos	MeOH	47 (*R*)	37 (*R*)
9		(*R*)-segphos	THF	68 (*R*)	47 (*R*)
10	 **2**	(*S*,*S*)-*t*Bu-BisP*	MeOH	99 (*R*)	95 (*R*)
11	 **3**	(*S*,*S*)-*t*Bu-BisP*	MeOH	98 (*R*)	75 (*R*)
12	 **4**	(*S*,*S*)-*t*Bu-BisP*	MeOH	61 (*R*)	79 (*R*)
13	 **5**	(*S*,*S*)-*t*Bu-BisP*	MeOH	99 (*R*)	96 (*R*)
14	 **6**	(*S*,*S*)-*t*Bu-BisP*	MeOH	48 (*R*)	70 (*R*)
15	 **7**	(*S*,*S*)-*t*Bu-BisP*	MeOH	99 (*R*)	98 (*R*)
16	 **8**	(*S*,*S*)-*t*Bu-BisP*	MeOH	94 (*R*)	82 (*R*)
17	 **9**	(*S*,*S*)-*t*Bu-BisP*	MeOH	55 (*R*)	45 (*R*)
18		(*S*,*S*)-*t*Bu-BisP*	MeOH	>99 (*S*)	>99 (*S*)
19	 **10**	(*S*,*S*)-diop	MeOH	0	18 (*R*)
20		(*R*)-segphos	MeOH	55 (*S*)	29 (*S*)
21		(*S*,*S*)-*t*Bu-BisP*	MeOH	>99 (*S*)	>99 (*S*)
22	 **11**	(*S*,*S*)-diop	MeOH	12 (*S*)	7 (*R*)
23		(*R*)-segphos	MeOH	64 (*S*)	64 (*S*)
24	 **12**	(*S*,*S*)-*t*Bu-BisP*	MeOH	99 (*R*)	99 (*R*)
25	 **13**	(*S*,*S*)-*t*Bu-BisP*	MeOH	99 (*R*)	99 (*R*)
26	 **14**	(*S*,*S*)-*t*Bu-BisP*	MeOH	99 (*R*)	99 (*R*)

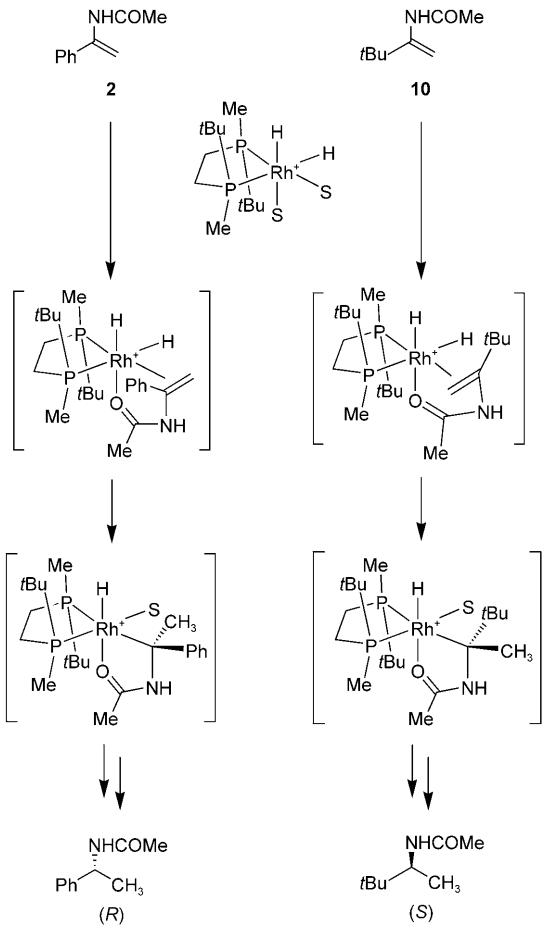
[a] All reactions were carried out at 25 °C. [b] Mean value of three independent runs (56 % *ee* (*R*), 66 % *ee* (*R*), and 49 % *ee* (*R*)). [c] Mean value of three independent runs (7 % *ee* (*S*), 0 % *ee*, and 7 % *ee* (*S*)). [d] Mean value of two independent runs (21 % *ee* (*S*) and 21 % *ee* (*S*)).



(*S*,*S*)-*t*Bu-BisP* (*S*,*S*)-diop (*R*)-segphos

20), although not in every case (entry 23). In the majority of the observed cases of the marked isotopic effect, the absolute *ee* value decreased when D_2 was used instead of H_2, though this is also not a uniform trend (e.g., Table 1, entry 14).

The narrow scope of the observed isotopic effects suggests that its origin is unlikely a kinetic isotope effect at some stage of the catalytic cycle. More likely is a proposal that the change of the isotopic composition of the catalyst species affects the competition between the two alternative pathways, which has been observed only in the case when enamides are the substrates. Thus, it has been shown by experiment[7] and computational analysis[9] that the asymmetric hydrogenation can occur either through α- or β-monohydride intermediates, depending on the properties of the substituent R of the enamide, and these two pathways result in opposite senses of enantioselection (Scheme 1). Therefore, it is reasonable to consider that when only moderate enantioselectivity can be achieved in a case such as with *o*-methoxyphenyl-substituted enamide, the competition of two pathways leading to the opposite sense of enantioselection might be involved in determining the final optical purity of the product.



Scheme 1. Two pathways of the hydrogenation of enamides.[7]

To get further insight into the origin of the isotopic effects on the *ee* values we have approached this problem computationally. Taking into account the large number of possible pathways and the relative insignificance of substituting hydrogen for deuterium from the energetic point of view, we did not try to get quantitative justification of the observed effects, but rather looked for the specific structural features in the crucial intermediates that might be responsible for the observed effects. From this point of view, the dihydride intermediates seemed to be the most promising targets, since it is generally accepted that these species are of major importance for the stereoselection in Rh-catalyzed asymmetric hydrogenation.

We optimized the structures of two dihydride intermediates of hydrogenation of the *o*-methoxyphenyl-substituted enamide **1**, ***Rα*** and ***Sβ*** (Figure 1). The stabilities of these intermediates are practically equal: ***Sβ*** is only 0.6 kcal mol^{-1} less stable than ***Rα***. It is noteworthy that in the case of *t*Bu-substituted enamide **10** the corresponding ***Rα*** dihydride intermediate is 10.1 kcal mol^{-1} less stable than the ***Sβ*** dihydride intermediate. Of interest is the different conformation of the *o*-methoxyphenyl cycle (Figure 1). In ***Rα***, as expected, the stable conformation is determined by the intramolecular hydrogen bond between the OMe substituent and the NH group of the enamide. On the other hand, in the most stable conformation of ***Sβ*** this hydrogen bond is broken to make

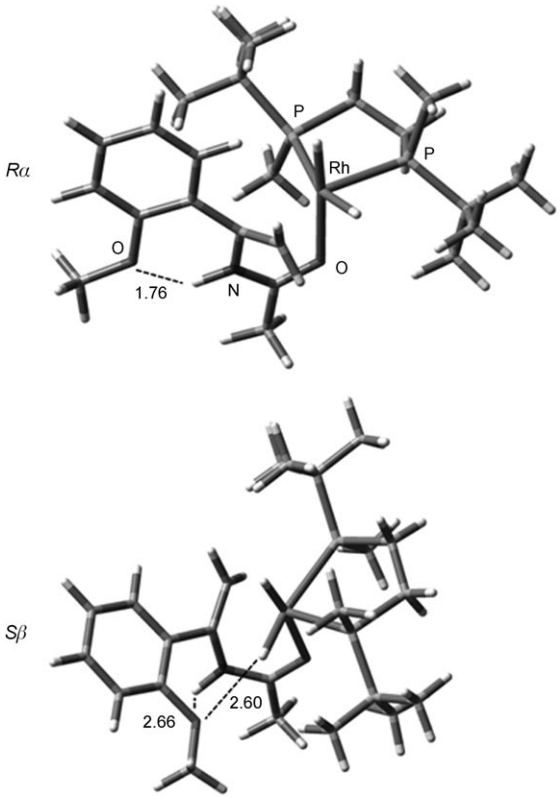
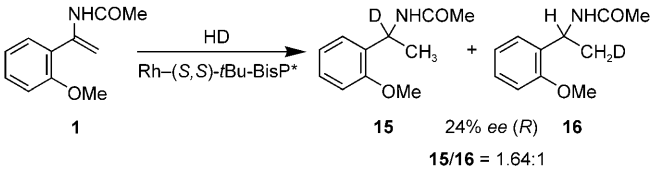


Figure 1. Structures of the dihydride intermediates ***Rα*** and ***Sβ*** optimized at the B3LYP/SDD level of theory.

possible the approach of the methoxy group to the equatorial hydride, yielding a Rh–H···OMe hydrogen bond.

Although hydrogen bonds in which transition-metal hydrides serve as hydrogen-bond donors are considered to be uncommon, and though the nature of this bond is still unclear,[9] there are several definite observations of such interactions for cationic[10] and even neutral[11] metal hydrides. We conclude that this kind of interaction may be a crucial factor in the observation of the significant isotopic effects on the *ee* value in the asymmetric hydrogenation of enamides. This conclusion is in accord with the strongest effects observed for *o*-methoxyphenyl- (**1**), *o*-chlorophenyl- (**6**), and *o*-fluorophenyl-substituted (**8**) enamides and the absence of the isotopic effect on the *ee* value in the case of *m*-chlorophenyl-substituted enamide **7**. On the other hand, the notable effects observed for *p*-methoxyphenyl- and *o*-tolyl-substituted enamides **3** and **4** demonstrate that other factors may also contribute to the isotopic effects on the *ee* value.

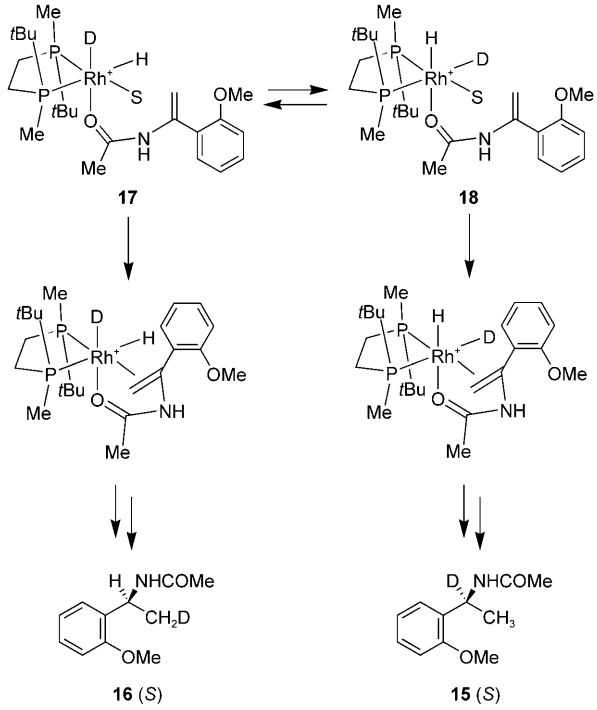
Another interesting experimental fact relevant to this discussion is the anomalously high ratio of the product deuterated in the α-position to the product deuterated in the β-position that was observed in the hydrogenation of **1** with HD (Scheme 2).[7b] Usually values from 1.15 to 1.35 are observed



Scheme 2. Hydrogenation of enamide **1** using HD.[7b]

for the hydrogenations proceeding through the formation of α-monohydrides,[7b,12] whereas predominance of the β-deuterated product is characteristic for the reactions involving formation of β-monohydrides.[7b] These values are nicely correlated with the distribution of deuterium between the axial and equatorial positions in the monodeuterated solvate dihydride (1.3:1).[12] Hence, the significant deviation from the value 1.3, which is observed exclusively for substrate **1**, means the occurrence of H/D scrambling at some reaction stages and can be mechanistically connected to the strongest isotope effect on *ee* value observed for this enamide. A good point supporting this suggestion is the fact that the decrease of the *ee* value when using HD instead of H_2 was approximately half of that observed when using D_2 instead of H_2 (Scheme 2, Table 1).

Thus, let us assume that Rh–H···OMe hydrogen bonding makes the pathway through the β-monohydride more favorable, which results in a decrease in *ee* value for the catalytic hydrogenation of **1** compared to **2**. Since exchanging H_2 for HD and D_2 in the hydrogenation of **1** leads to a further increase of the relative amount of the *S* product, one can conclude that the Rh–D···OMe hydrogen bonding makes the pathway through the β-monohydride still more favorable. Hence, when HD was used for the hydrogenation of **1**, the transfer of equatorial deuterium occurred preferentially, which led to the abnormal distribution of deuterium between the α- and β-positions (Scheme 3). The fast exchange of hydrogen and deuterium between the axial and equatorial positions most probably occurs through pseudorotation in the semidissociated complexes **17** and **18**. This process is considered to be pivotal for successful enantioselection in Rh-catalyzed asymmetric hydrogenations.[13,14] Another possibility is the exchange through a molecular hydrogen complex.[12]



Scheme 3. Plausible mechanism for the preferential formation of **15** (*S*) and **16** (*S*).

Conclusions

In summary, we have studied the scope of a rare phenomenon: dependence of the *ee* value of the product in asymmetric hydrogenations on the isotopic composition of dihydrogen. The strongest effects are observed for the hydrogenation of aryl-substituted enamides having an *ortho* substituent that is capable of forming a hydrogen bond. This effect may be connected with the possibility of formation of a Rh–H···OMe hydrogen bond in the dihydride intermediate (or similar related species).

Experimental Section

General

Unless otherwise noted, all anaerobic and moisture-sensitive manipulations were carried out with standard Schlenk techniques under predried nitrogen or with glovebox techniques under prepurified argon. NMR

spectra were recorded on a JEOL JNM LA-500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C) and an LA-400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C). Chemical sifts are reported in δ (ppm) referenced to an internal $SiMe_4$ standard for ^{1}H NMR and [D]chloroform (δ = 77.00 ppm) for ^{13}C NMR. HPLC analyses were performed using a Shimadzu LC-10AD VP pump, a SPD-10 A VP UV detector, and a Shimadzu CTO-10AC VP column oven with appropriate chiral columns. GC analyses were performed with a Shimadzu GC-17A Ver.3.

Materials

1-Aryl-1-acetylaminoethenes were prepared from aryl methyl ketone oximes according to the procedure described in the literature.[15] Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen prior to use. Toluene was distilled from sodium benzophenone ketyl under nitrogen and stored in a glass flask with a teflon stopcock under nitrogen. MeOH was distilled from magnesium under nitrogen and stored in a glass flask with a teflon stopcock under nitrogen. Hydrogen gas of 99.9999% purity (Nippon Sanso) and deuterium gas of 99.6% purity (Nippon Sanso) were used.

Synthesis/Characterization

General procedure for the asymmetric hydrogenation using Rh-*t*Bu-BisP* complex: A 50 mL thick-wall glass bottle was charged with substrate (0.5 mmol) and [Rh((*S*,*S*)-*t*Bu-BisP*)(nbd)]BF_4 (0.005 mmol; nbd = 2,5-norbornadiene) and the bottle was connected to the hydrogen tank by stainless steel tubing. The vessel was evacuated and filled with hydrogen gas to a pressure of 2 atm. This operation was repeated and the bottle was immersed in a dry-ice/acetone bath. The upper cock of the bottle was opened and anhydrous, degassed solvent was added quickly using a syringe. After four vacuum/H_2 cycles, the bottle was pressurized to 3 atm and was immersed in a constant-temperature bath (25 °C). The solution was magnetically stirred for 12–24 h to complete the reaction, and the resulting mixture was passed through silica gel using EtOAc as an eluent. The filtrate was concentrated and was submitted to direct analysis of the *ee* value of the product by HPLC or GC.

In the same manner, asymmetric deuteration was carried out using D_2 in place of H_2.

(*R*)-1-Acetylamino-1,2-dideuterio-1-phenylethane: ^{1}H NMR ($CDCl_3$): δ = 2.14 (s, 2H), 3.00 (s, 3H), 5.76 (br s, 1H), 7.17–7.29 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): δ = 21.27 (t, J = 20.6 Hz), 23.43, 26.17, 127.35, 128.64, 143.05, 169.04 ppm. Enantiomeric excess determination: HPLC, Daicel Chiralpak AD-H, hexanes/2-propanol 9:1, flow rate 1.0 mL min^{-1}, t_R = 6.89 (*R*), 8.23 (*S*) min.

(*R*)-1-Acetylamino-1,2-dideuterio-1-(2′-methoxyphenyl)ethane: ^{1}H NMR ($CDCl_3$): δ = 1.42 (s, 2H), 1.96 (s, 3H), 3.88 (s, 3H), 6.42 (br, 1H), 6.89–6.93 (m, 2H), 7.20–7.26 ppm (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 21.00 (t, J = 18.9 Hz), 23.60, 46.97 (t, J = 22.2 Hz), 55.29, 111.03, 120.87, 128.02, 128.40, 130.76, 157.02, 168.72 ppm. Enantiomeric excess determination: HPLC, Daicel Chiralpak AD-H, hexanes/2-propanol 9:1, flow rate 1.0 mL min^{-1}, t_R = 6.49 (*R*), 8.37 (*S*) min.

(*R*)-1-Acetylamino-1,2-dideuterio-1-(4′-methoxyphenyl)ethane: ^{1}H NMR ($CDCl_3$): δ = 1.41 (s, 2H), 1.93 (s, 3H), 3.77 (s, 3H), 6.26 (br, 1H), 6.83–6.86 (m, 2H), 7.21–7.24 ppm (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 21.15 (t, J = 19.0 Hz), 23.21, 47.69 (t, J = 21.4 Hz), 55.15, 113.83, 127.27, 135.29, 158.65, 169.08 ppm. Enantiomeric excess determination; HPLC, Daicel Chiralpak AD-H, hexanes/2-propanol 9:1, flow rate 0.5 mL min^{-1}, t_R = 15.46 (*R*), 19.04 (*S*) min.

(*R*)-1-Acetylamino-1,2-dideuterio-1-(2′-methylphenyl)ethane: ^{1}H NMR ($CDCl_3$): δ = 1.44 (s, 2H), 1.95 (s, 3H), 2.37 (s, 3H), 5.69 (br, 1H), 7.17–7.29 ppm (m, 4H); ^{13}C NMR ($CDCl_3$): δ = 19.06, 20.59 (t, J = 19.0 Hz), 23.18, 44.88 (t, J = 21.0 Hz), 124.64, 126.19, 127.21, 130.62, 135.81, 141.04, 168.90 ppm. Enantiomeric excess determination: HPLC, Daicel Chiralpak AD-H, hexanes/2-propanol 9:1, flow rate 1.0 mL min^{-1}, t_R = 4.74 (*S*), 5.64 (*R*) min.

(*R*)-1-Acetylamino-1,2-dideuterio-1-(4′-methylphenyl)ethane: ^{1}H NMR ($CDCl_3$): δ = 1.45 (s, 2H), 1.97 (s, 3H), 2.33 (s, 3H), 5.62 (br, 1H), 7.14–7.16 (m, 2H), 7.20–7.22 ppm (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 21.00, 21.22 (t, J = 20.0 Hz), 23.42, 126.11, 129.29, 137.02, 140.12, 168.98 ppm. Enantiomeric excess determination: HPLC, Daicel Chiralpak AD-H, hexanes/2-propanol 9:1, flow rate 1.0 mL min^{-1}, t_R = 5.49 (*R*), 6.80 (*S*) min.

(*R*)-1-Acetylamino-1,2-dideuterio-1-(2′-chlorophenyl)ethane: ^{1}H NMR ($CDCl_3$): δ = 1.41 (s, 2H), 1.96 (s, 3H), 6.54 (br, 1H), 7.15–7.24 (m, 2H), 7.31–7.34 ppm (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 20.44 (t, J = 19.8 Hz), 23.08, 46.57 (t, J = 21.5 Hz), 126.95, 127.00, 128.24, 129.88, 132.62, 140.66, 169.23 ppm. Enantiomeric excess determination: HPLC, Daicel Chiralpak AD-H, hexanes/2-propanol 9:1, flow rate 1.0 mL min^{-1}, t_R = 5.11 (*S*), 5.94 (*R*) min.

(*R*)-1-Acetylamino-1,2-dideuterio-1-(3′-chlorophenyl)ethane: ^{1}H NMR ($CDCl_3$): δ = 1.40 (s, 2H), 1.96 (s, 3H), 6.34 (br, 1H), 7.16–7.28 ppm (m, 4H); ^{13}C NMR ($CDCl_3$): δ = 21.33 (t, J = 19.8 Hz), 23.16, 47.97 (t, J = 21.4 Hz), 124.42, 126.15, 127.29, 129.82, 134.33, 145.44, 169.36 ppm. Enantiomeric excess determination: HPLC, Daicel Chiralpak AD-H, hexanes/2-propanol 9:1, flow rate 0.5 mL min^{-1}, t_R = 9.86 (*R*), 11.49 (*S*) min.

(*R*)-1-Acetylamino-1,2-dideuterio-1-(2′-fluorophenyl)ethane: ^{1}H NMR ($CDCl_3$): δ = 1.46 (s, 2H), 1.98 (s, 3H), 6.10 (br, 1H), 7.01–7.11 (m, 2H), 7.21–7.30 ppm (m, 2H). ^{13}C NMR ($CDCl_3$): δ = 21.08 (t, J = 19.7 Hz), 23.33, 115.84 (d, J = 22.3 Hz), 124.27 (d, J = 3.3 Hz), 128.18 (d, J = 4.9 Hz), 128.86 (d, J = 9.1 Hz), 130.08 (d, J = 13.2 Hz), 160.72 (d, J = 246.4 Hz), 168.00 ppm. Enantiomeric excess determination: HPLC, Daicel Chiralpak AD-H, hexanes/2-propanol 9:1, flow rate 0.5 mL min^{-1}, t_R = 10.32 (*R*), 11.82 (*S*) min.

(*R*)-1-Acetylamino-1,2-dideuterio-1-(2′-trifluoromethylphenyl)ethane: ^{1}H NMR ($CDCl_3$): δ = 2.10 (s, 2H), 3.00 (s, 3H), 6.32 (br s, 1H), 7.27–7.37 (m, 1H), 7.525.53 (m, 2H), 7.63 ppm (d, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$): δ = 21.38 (t, J = 19.8 Hz), 23.23, 48.10 (t, J = 23.9 Hz), 122.59, 122.63, 124.09, 125.42, 129.06, 129.77, 144.38, 169.33 ppm. Enantiomeric excess determination: HPLC, Daicel Chiralpak AD-H, hexanes/2-propanol 9:1, flow rate 1.0 mL min^{-1}, t_R = 4.66 (*R*), 5.62 (*S*) min.

(*S*)-2-Acetylamino-1,2-dideuterio-3,3-dimethylbutane: ^{1}H NMR ($CDCl_3$): δ = 0.90 (s, 9H), 1.03 (s, 2H), 1.99 (s, 3H), 5.38 ppm (br, 1H); ^{13}C NMR ($CDCl_3$): δ = 15.70 (t, J = 18.9 Hz), 23.57, 26.08, 33.91, 52.24 (t, J = 21.4 Hz), 169.24 ppm. Enantiomeric excess determination: capillary GC, VARIAN Chirasil-DEX CB column (25 m), 110 °C, isothermal, carrier gas N_2, flow rate 24 cm s^{-1}, t_R = 21.16 (*S*), 22.28 (*R*) min.

(*S*)-1-Acetylamino-1-adamantyl-1,2-dideuterioethane: ^{1}H NMR ($CDCl_3$): δ = 0.99 (s, 2H), 1.45–1.99 (m, 18H), 5.27 ppm (br, 1H); ^{13}C NMR ($CDCl_3$): δ = 14.12 (t, J = 19.8 Hz), 23.60, 28.22, 35.53, 36.99, 38.28, 52.50 (t, J = 21.4 Hz), 169.39 ppm. Enantiomeric excess determination: HPLC, Daicel Chiralpak AD-H, hexanes/2-propanol 9:1, flow rate 1.0 mL min^{-1}, UV 210 nm, t_R = 8.29 (*R*), 12.79 (*S*) min.

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