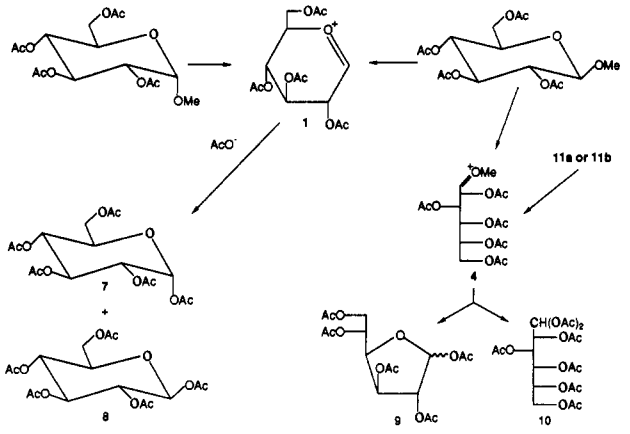
Scheme II



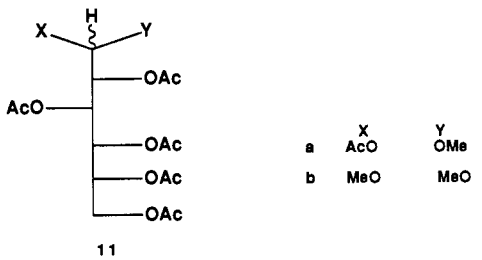
through an acyclic oxo-carbenium ion **4**, whereas an α-glycoside would be activated on *both* oxygens and, in the ideal case, react equally through cyclic and acyclic ions (**1** and **4**). In the case of hydrolysis, this difference is untestable since both ions, **1** and **4**, lead to the same product **2**. With a nucleophile other than water, however, it might be possible to trap each ion and therefore quantify the contribution of the acyclic species (e.g., **3**, Nu = OH).

Our experimental approach for examining these issues took advantage of the recent report of Dasgupta on the acetolysis of methyl α-D-glucopyranoside with anhydrous ferric chloride in acetic anhydride.[16] The products obtained were the peracetylated pyranose and furanose (isolated as a mixture) and the acyclic derivative. In this medium, the activator is the acetylium ion and the nucleophile is acetate (i.e., in Scheme I, A = CH_3CO^+, Nu = CH_3COO^-). Thus, use of this mild medium would allow us (a) to intercept the intermediates produced from α- or β-glycosides and (b) to determine their precise fates as they progress toward products.

First, we repeated the work of Dasgupta[16] on methyl α-D-glucopyranoside using a modified acetolysis medium (see Table I). Independent analysis by gas chromatography and ^1H NMR spectroscopy established that peracetylated α- and β-pyranoses **7** and **8** (Scheme II) accounted for 91% of the product mixture (entry i).

For the β-D-glucoside, the same four components were present but in very different amounts, with the major constituents (Table I, energy ii) being the furanosyl acetate **9** and the acyclic heptaacetate **10**. (Scheme II).

With respect to the acyclic oxo-carbenium ion **4**, trapping by acetate ion would lead to the acyl acetal **11a**, a type of derivative that has been isolated by Hudson from acetolysis of methyl arabinosides,[17] but never from a hexoside. A synthesis of **11a** was



	X	Y
a	AcO	OMe
b	MeO	MeO

11

therefore undertaken. Our approach was facilitated by the recent procedure described by Keith,[18] whereby dimethyl acetal **11b**[19] was converted into **11a** as a 1:1 mixture of diastereomers. Acetolysis of **11a** was complete in 0.75 h, and the product (Table I, entry iii) was comprised of furanose and acyclic peracetates. The 1(*R*) and 1(*S*) diastereomers of **11a** could be isolated by column chromatography, and acetolysis of each under similar conditions was found to give the same product mixture (Table I, entries iv and v).

The results in entries i and ii establish clearly that the α- and β-glucopyranosides react through different intermediates. Notably, the ratio of the α- and β-pyranosyl acetates is 4:1 in both entries, and thus it can be concluded that the cyclic oxo-carbenium ion **1** is produced from both anomers and is trapped by acetate ion to give **7** and **8**.

*The result in entry iii shows that the acyl acetal intermediate (and hence **4**) gives rise to furanose and acyclic products almost exclusively.* The differences in ratio of **9** and **10** in entries ii and iii suggest that **11a** may be reacting through additional intermediates. Nevertheless, the validity of ion **4** was further verified by exposing the *dimethyl acetal **11b** to the reaction conditions, whereupon **9** and **10** were produced in 2:1 ratio with no evidence of **7** and **8**.*

Contrary to what may be expected on the sole consideration of oxygen basicities (vida supra), it is the β, not the α, anomer that gives rise to both cyclic and acyclic ions. Clearly, therefore, there are factors other than oxygen basicities that are determining the course of glycoside hydrolysis. A search for these is underway and will be reported in due course.

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A General, Catalytic, and Enantioselective Synthesis of α-Amino Acids

E. J. Corey* and John O. Link

Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138

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In recent years, much research has been directed toward the development of enantioselective syntheses of α-amino acids[1] and the use of α-amino acids as key starting materials for the synthesis of complex chiral molecules.[2] Interest in synthetic, unnatural α-amino acids has also increased sharply because of emerging therapeutic and biological possibilities. This communication reports a new, practical, and very general approach to α-amino acids which is based on the use of a robotlike catalyst for enantioselective reduction of ketones.[3]

Many types of trichloromethyl ketones are available by synthesis either from the reaction of aldehydes with nucleophilic trichloromethide reagents followed by oxidation[4] or from the reaction of nucleophilic carbon reagents with trichloroacetyl chloride. Most trichloromethyl ketones can be reduced by catecholborane[3f] (1.5 equiv) in the presence of the (*S*)-oxazaborolidine catalyst **1** (0.1 equiv) in toluene or CH_2Cl_2 to form (*R*) secondary alcohols (**2**) with greater than 97:3 enantioselectivity, as indicated in Table

(1) For an excellent recent monograph on this subject, see: Williams, R. M. *Synthesis of Optically Active Amino Acids*; Pergamon Press: Oxford, 1989.
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(4) Gallina, C.; Giordano, C. *Synthesis* **1989**, 466-468. In our laboratory, both $Na_2Cr_2O_7$-H_2SO_4-HOAc and Swern oxidations have been effective oxidants.

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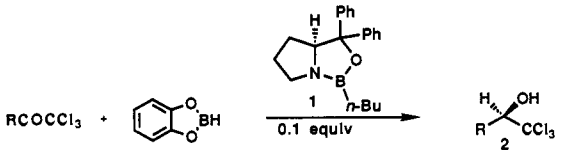
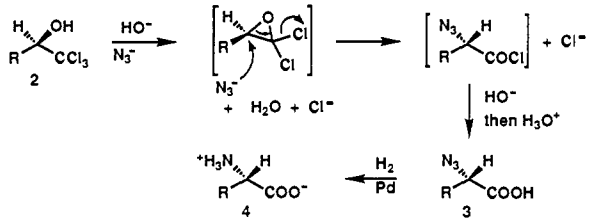
Table I. Enantioselective Reduction of Trichloromethyl Ketones



R in $RCOCCl_3$	solvent	temp, °C (time, h)	2, % ee[b]
n-C_5H_{11}	toluene	−60[a] (12)	95[c]
$C_6H_5(CH_2)_2$	toluene	−78 (12)	95[c]
4-$C_6H_5C_6H_4CH_2$	CH_2Cl_2	−44 (10)	96[d]
2-naphthylmethyl	CH_2Cl_2	−23 (1.7)	93[c]
c-C_6H_{11}	CH_2Cl_2	−20[a] (48)	92[e]
t-C_4H_9	toluene	−20[a] (56)	98[f]
t-C_4H_9	toluene	+23 (12)	95

[a] These reactions were initiated at −78 °C and brought to the indicated temperature after 1 h. [b] Alcohol ee % determined by Chiracel (Diacel Co.) HPLC analysis with the following columns. [c] Chiracel AD. [d] Chiracel OD. [e] Chiracel OJ. [f] Chiracel OD analysis on the benzoate ester.

Scheme I. Conversion of (*R*)-(Trichloromethyl)carbinols **2** to (*S*)-α-Azido Acids **3** and (*S*)-α-Amino Acids **4**



I. The pathway for the conversion of the (trichloromethyl)-carbinols **2** to (*S*)-α-amino acids is outlined in Scheme I. In general, treatment of the (*R*)-(trichloromethyl)carbinols **2** with NaOH (4 equiv) and NaN_3 (2 equiv) in homogeneous solution in aqueous 1,2-dimethoxyethane at 23 °C for 12 h effected smooth conversion to (*S*)-α-azido acids **3** with clean inversion of configuration. The reaction is considered to proceed via the *gem*-dichlorooxirane intermediate shown in Scheme I on the basis of much precedent.[5] Table II summarizes the results for the synthesis of six widely-different α-amino acids. The mildness of the reaction conditions is indicative of a high degree of reactivity of the *gem*-dichlorooxirane intermediate in S_N2 displacement by aqueous azide, a consequence of concerted ring opening to form the α-azido carbonyl moiety. Such reactivity accounts for the effectiveness of the synthesis of *tert*-butylglycine via the azido acid **3** (R = *tert*-butyl), which requires S_N2 displacement by N_3^- at a neopentyl carbon. This example testifies to the generality of the amino acid synthesis outlined in Scheme I, since the bulk of the *tert*-butyl group has no adverse effect on either the enantioselective reduction to form carbinol **2** (R = *tert*-butyl)[6] or the conversion of **2** (R = *tert*-butyl) to the α-azido acid **3** (R = *tert*-butyl).[7] The reduction of α-azido acid **3** to α-amino acid **4** occurred smoothly under unexceptional conditions (H_2, 1 atm, Pd–C). Finally, recrystallization of the various amino acids **4** led to pure (*S*)-α-amino acid with ca. 85% recovery.[8]

Table II. Conversion of (*R*)-(Trichloromethyl)carbinols **2** to (*S*)-α-Azido Acids **3** and (*S*)-α-Amino Acids **4** (Scheme I)

R in **2**	% yield of **3**	% yield of **4**	$[\alpha]^{24}_D$ of **4** (solv)[a]
n-C_5H_{11}	89	94	+23.6° (6 N HCl)[b]
$C_6H_5(CH_2)_2$	91	92	+46.8° (1 N HCl)[c]
4-$C_6H_5C_6H_4CH_2$	82	98[h]	+12.4° (MeOH)[d]
2-naphthylmethyl	84	88	−29.6° (HOAc)[e]
c-C_6H_{11}	89	92	+30.2° (5 N HCl)[f]
t-C_4H_9	ca. 80	94	−10.8° (H_2O)[g]

[a] Concentration of ca. 1.0. [b] Lit. $[\alpha]^{27}_D$ +23.9° (c = 4, 6 N HCl) (Baker, C. G.; Meister, A. *J. Am. Chem. Soc.* **1951**, *73*, 1336–1338). [c] Lit. $[\alpha]^{20}_D$ +48° (c = 1, 1 N HCl) (Bradshaw, C. W.; Wong, C.-H.; Hummel, W.; Kula, M.-K. *Bioorg. Chem.* **1991**, *19*, 29–39). [d] Rotation taken on the methyl ester hydrochloride salt: $[\alpha]^{20}_D$ +11.8° (c = 1, MeOH) (Shieh, W.-C.; Carlson, J. Private communication). [e] Lit. $[\alpha]^{23}_D$ −27° (c = 0.51, HOAc) (Prasad, K. U.; Roeske, R. W.; Weitl, F. L. *J. Med. Chem.* **1976**, *19*, 492–5). [f] Lit. $[\alpha]^{25}_D$ −34.5° (c = 0.51, 5 N HCl, *R* config) (Tamura, M.; Harada, K. *Synth. Commun.* **1978**, *8*, 345–51). [g] Lit. $[\alpha]^{21}_D$ −10.9° (c = 1.0, H_2O) (Miyazawa, T.; Takashima, K.; Mitsuda, Y.; Yamada, T.; Kuwata, S.; Watanabe, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1539–40). [h] Yield for the hydrogenation of the α-azido methyl ester (from the acid **3** and CH_2N_2).

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(6) Each instance of reduction of trichloromethyl ketone to an (*R*) alcohol **2**, which is recorded in Table I, conforms to the predicted[3a,b] absolute stereochemical course of the reaction with the trichloromethyl group being effectively larger than the other carbonyl appendage. It should be noted also that coordination of the chiral reducing complex[3a,b] to the carbonyl lone pair which is syn to the CCl_3 group of the trichloromethyl ketones entails some degree of electrostatic repulsion between the chlorines of CCl_3 and the syn-coordinated boronate moiety. In addition, the electron-withdrawing power of the CCl_3 group also serves to activate the carbonyl group for reduction.

(7) As expected, very bulky trichloromethyl ketones such as neopentyl and benzhydryl trichloromethyl ketones undergo reduction at a much slower rate and with lower enantioselectivity than the cases reported in Table I.

(8) The following procedure for the synthesis of (*S*)-*tert*-butylglycine is illustrative. **A. (*R*)-3,3-Dimethyl-1,1,1-trichloro-2-butanol**: (*S*)-α,α-Diphenylprolinol (835 mg, 3.3 mmol, Aldrich), *n*-butylboronic acid (404 mg, 4.0 mmol), and 20 mL of toluene were heated at reflux with a Dean–Stark apparatus containing 3-Å molecular sieves in the side arm under N_2 for 12 h. Concentration to ca. 3 mL at 1 atm, removal of the remaining toluene in vacuo, and addition of 15 mL of dry, air-free toluene afforded a 0.2 M solution of (*S*)-oxazaborolidine catalyst **1**. Addition of 3,3-dimethyl-1,1,1-trichloro-2-butanone (6.75 g, 33 mmol), cooling to −78 °C, and dropwise addition of freshly distilled catecholborane (15 mL, 49.5 mmol, 3 M in toluene) over 10 min with vigorous stirring afforded a white precipitate. The mixture was warmed to −20 °C to effect solution, and after 56 h at −20 °C, the reaction was quenched with methanolic HCl (744 μL, 0.5 M) and concentrated at 20 Torr. Addition of 40 mL of 2:1 low-boiling petroleum ether–ether afforded (*S*)-α,α-diphenylprolinol·HCl (875 mg, 92%), which was recovered by filtration. The filtrate was diluted with 90 mL of ether, washed with saturated aqueous Na_2CO_3 until colorless (7 × 30 mL) and then brine (3 × 30 mL), dried ($MgSO_4$), and concentrated to afford (*R*)-3,3-dimethyl-1,1,1-trichloro-2-butanol as a volatile colorless solid (7.63 g, containing 15 mass % toluene by ^1H NMR, 96% corrected yield, 97% ee); a similar reduction of 633 mg of ketone afforded the alcohol in 96% yield and >99% ee. An analytical sample was prepared by chromatography on silica gel with 15:1 low-boiling petroleum ether–ether: mp 45–47 °C; $[\alpha]^{24}_D$ −9.33° (c = 1.65, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 3.91 (d, 1 H, J = 5.5 Hz), 2.95 (d, 1 H, J = 5.5 Hz, OH), 1.22 (s, 9 H); IR (neat) 3500, 2990–2930 cm^{-1}; CIMS (triethylsilyl ether) 336 $(M + NH_4)^+$; HRMS (triethylsilyl ether) calcd for $(C_{12}H_{24}Cl_3OSi + NH_4)^+$ 336.1084, found 336.1057. **B. (*S*)-2-Azido-3,3-dimethylbutanoic acid**: To (*R*)-3,3-dimethyl-1,1,1-trichloro-2-butanol (6.49 g, 31.6 mmol) in 55 mL of dimethoxyethane at 10 °C was added a 10 °C solution of NaOH (5.1 g, 126 mmol) and NaN_3 (4.1 g, 63.2 mmol) in 235 mL of H_2O over 30 s with vigorous stirring. After 5 min, the cloudy mixture was warmed to 23 °C and stirred for 24 h. The mixture was washed with ether, and the ether was extracted with 25 mL of 5% aqueous NaOH. The aqueous extracts were acidified with solid KH_2PO_4 at 0 °C, extracted with ethyl acetate (3 × 40 mL), and dried ($MgSO_4$). The volume was brought to 200 mL by the addition of ethyl acetate, and 160 mL of this solution was hydrogenated directly to afford (*S*)-*tert*-butylglycine (vide infra). A smaller scale synthesis (124.7 mg, 83% yield) of (*S*)-2-azido-3,3-dimethylbutanoic acid afforded the following data after chromatography on silica gel (toluene, 3% AcOH): mp 65–7 °C; $[\alpha]^{24}_D$ −71.6° (c = 4.06, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 3.75 (s, 1 H), 1.08 (s, 9 H); FTIR (neat) 3400–2500, 2108, 1715 cm^{-1}; FABMS 180 $(M + Na)^+$; HRMS calcd for $(C_6H_{11}N_3O_2 + Na)^+$ 180.0749, found 180.0747. **C. (*S*)-*tert*-Butylglycine**: To the above ethyl acetate solution of (*S*)-2-azido-3,3-dimethylbutanoic acid (160 mL) in a 2-L flask was added 10% palladium on carbon (160 mg, ca. 20 wt %), and the mixture was vigorously stirred under H_2 at 1 atm. After 1 h, a white precipitate formed, more 10% palladium on carbon (40 mg, ca. 5 wt %) and 40 mL of ethyl acetate were added, and hydrogenation was continued for 12 h. The ethyl acetate was decanted, and the product was dissolved by boiling with 200 mL of water and 10 mL of ethanol with stirring. Filtration and concentration in vacuo afforded (*S*)-*tert*-butylglycine (2.58 g, 78% over two steps) as a colorless solid: mp 252–60 °C (sublimes); $[\alpha]^{24}_D$ −10.5° (c = 1.02, H_2O, absolute stereochem *S*); ^1H NMR (270 MHz, D_2O) δ 3.32 (s, 1 H), 0.928 (s, 9 H); FTIR (neat, (*S*)-*tert*-butylglycine·HCl) 3200–2700, 1733 cm^{-1}; FABMS 132 $(M + H)^+$; HRMS calcd for $C_8H_{14}NO_2^+$ 132.1024, found 132.1033. Recrystallization from ethanol–water afforded an 81% recovery (three crops) of pure (*S*)-*tert*-butylglycine: $[\alpha]^{24}_D$ −10.8° (c = 2.0, H_2O) (lit. $[\alpha]^{21}_D$ −10.9° (c = 1.0, H_2O)).

In summary, we have developed a novel enantioselective synthesis of α-amino acids in either (*S*) or (*R*) (unnatural) form (depending on the use of catalyst **1** or its enantiomer), which is broad in scope, simple in application, and advantageous for many α-amino acids of interest in chemistry, biology, and medicine.[9]

Supplementary Material Available: Experimental procedures, spectral data, and ^{1}H NMR spectra for trichloromethyl alcohols, α-azido acids, and α-amino acids (25 pages). Ordering information is given on any current masthead page.

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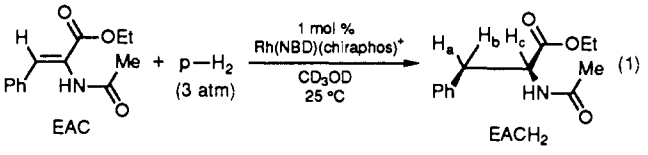
Rates of Catalytic Hydrogenation Estimated Spectroscopically through Enhanced Resonances

Mitchell S. Chinn and Richard Eisenberg*

Department of Chemistry
University of Rochester
Rochester, New York 14627
Received August 8, 1991

Parahydrogen-induced polarization (PHIP) can arise when H_2 enriched in the para state is added to substrate while maintaining spin correlation between the added protons, leading to unusual intensities in product NMR spectra.[1-7] Qualitative understanding of PHIP has led to its use as a mechanistic probe of whether hydrogenation proceeds by pairwise transfer of the component atoms of H_2. In this report, we describe a quantitative analysis of polarization behavior and its utility in determining *r*ates *o*f *c*atalytic *h*ydrogenation *e*stimated *s*pectroscopically *t*hrough *e*nhanced *r*esonances (ROCHESTER).

The system chosen for analysis is the asymmetric hydrogenation of ethyl (*Z*)-α-acetamidocinnamate (EAC) using [Rh(NBD)(chiraphos)]BF_4 (**1**) as the catalyst. The choice of this system was based on the following facts: (a) it is well understood mechanistically, and (b) in hydrogenations utilizing RhP_2^+ catalysts (P_2 = diphos or dipamp), no para to ortho H_2 conversion occurs while substrate is present.[8] The latter fact precludes simple H_2 oxidative addition and reductive elimination for converting para-enriched H_2 to normal H_2 when excess EAC is present. In a typical experiment, a 210 mM solution of EAC was hydrogenated under ca. 3 atm of para-enriched H_2 (eq 1).[9] Prior to reaction the sample was stored at 77 K. Rapid thawing in a 25 °C water bath and shaking of the sample followed by insertion into the probe led to data acquisition within 60 s of initiating the reaction.



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(9) Parahydrogen was enriched to ca. 50 mol % by immersing a 1-L flask containing iron(III) oxide on silica in liquid N_2 up to its neck. H_2 was added while 730 mm ambient hydrogen pressure was maintained. In this manner, 3-4 atm of para-enriched hydrogen could be produced.

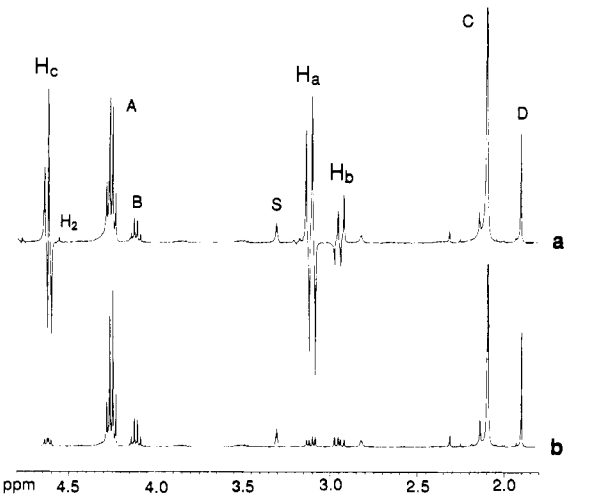

Figure 1. PHIP in the hydrogenation of EAC with Rh(chiraphos)$^+$ 60 s after shaking and insertion into the probe (a). Resonances H_a, H_b, and H_c are assigned in the text. Resonances A and B are ethyl resonances of EAC and $EACH_2$, C and D are methyl acyl resonances of EAC and $EACH_2$, and S is from CHD_2OD in CD_3OD solvent. (b) Same sample ca. 450 s later.

Table I. Kinetic Data for the Hydrogenation of EAC by [Rh(NBD)(chiraphos)]BF_4[a,b]

$[Rh]_T$ (× 10^3 M)	k_{obsd}(PHIP) (× 10^3 s^{-1})	k_2'(PROD) (× 10^3 s^{-1})
2.1	1.23 (1)	4.3 (2)
8.8	6.6 (2)	6.1 (4)
17	15 (1)	15 (2)

[a] k_{obsd} values were determined from PHIP runs; corresponding k_2' values were obtained from product integrals vs time (PROD). Reported values are the average of two or more runs. [b] Uncertainties are averaged standard deviations from curve fitting analysis.

The ^{1}H NMR spectrum upon initial exposure of the sample to para-enriched H_2 displayed large net effect polarization[2,10] in the vinyl and aliphatic regions of 1-norbornene.[6] This polarization decayed within ca. 60-90 s, consistent with rapid hydrogenation of chelated norbornadiene producing catalytically active Rh(chiraphos)(EAC)$^+$ (**2**). Little polarization was realized during this run in the hydrogenated EAC substrate. Depletion of H_2 from NBD hydrogenation was evident as little NMR-active ortho H_2 was observed in solution. The ^{1}H NMR spectrum, after the sample was removed from the probe, reshaken to reestablish dissolved H_2, and reinserted into the probe, revealed multiplet effect polarization[1] in the methine and diastereotopic benzyl protons of the hydrogenation product, *N*-acetyl-(*R*)-phenylalanine ethyl ester ($EACH_2$) (Figure 1). The resonances at δ 4.61 and 3.10 ppm correspond respectively to the methine proton H_c and a benzyl proton H_a, which exhibit absorption/emission/absorption/emission (a/e/a/e) patterns of similar intensity. Benzyl proton H_b at δ 2.94 ppm shows a weaker pattern of opposite phase (e/a/e/a). The similar polarization of the first two resonances indicates that these protons originate from the same para H_2 molecule, while the weaker polarization and opposite phase of the third resonance arise via cross-relaxation from H_a to H_b as seen previously.[1] The specific occurrence of polarization in Figure 1 thus allows a definitive assignment of diastereotopic proton resonances consistent with the established cis addition of H_2 to the EAC substrate.[11]

The decay of polarization intensity in protons H_a and H_b was followed by ^{1}H NMR spectroscopy at 400 MHz; resonance H_c at δ 4.61 ppm was often obscured by a large solvent resonance,[12]

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