An ^{18}O-Labeling Study of the β-(Nitroxy)alkyl and β-(Trifluoroacetoxy)alkyl Radical Migrations: Further Examples of a 1,2-Shift Mechanism

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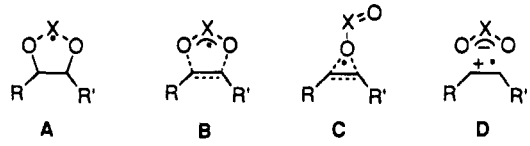
Received April 4, 1995[⊗]

The results of an ^{18}O labeling study of the β-(nitroxy)alkyl and β-(trifluoroacetoxy)alkyl radical migrations are presented. Phenacyl bromide dimethyl acetal was hydrolyzed with $H_2{}^{18}O$ water to give labeled phenacyl bromide and, following borohydride reduction, ^{18}O labeled styrene bromohydrin. Nitration and trifluoroacetylation gave the radical precursors which were allowed to react with tributyltin hydride and AIBN in benzene at reflux. After cleavage to 2-phenylethanol, the rearrangement products were examined by GC-MS. The β-(nitroxy)alkyl migration is found to occur, in benzene to the extent of 64% through a 1,2-, as opposed to a 2,3-shift, mechanism. The β-(trifluoroacetoxy)alkyl migration occurs 7% by the 1,2-pathway. It is suggested that, in general, faster ester migrations occur to a greater extent through the 1,2-shift pathway.

Introduction

Since its discovery in 1967[1] there has been much interest and even controversy surrounding the mechanism of the β-(acyloxy)alkyl radical migration (Scheme 1), a number of which have been considered (**A**–**D**, X = CR″).

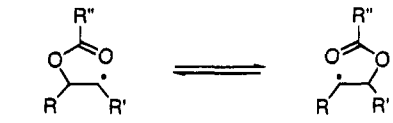


1: R = R′ = Me, R″ = Ph
2: R = R′ = R″ = Me
3: R = Me, R′ = Ph, R″ = Me
4: R = R′ = Me, R″ = CF_3

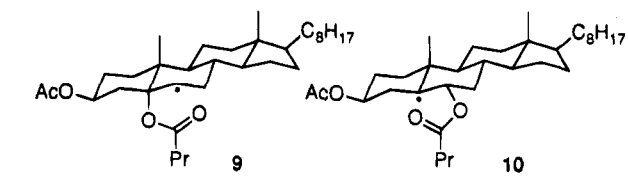
5: R = R′ = Me, R″ = Ph
6: R = R′ = R″ = Me
7: R = Me, R′ = Ph, R″ = Me
8: R = R′ = Me, R″ = CF_3

Early experiments by Beckwith ruled out the possibility of a stepwise mechanism via **A** (X = CR″) when it was revealed that this species, generated by an independant route, did not undergo ring opening on the time scale of the rearrangement.[2] ^{18}O-Labeling studies, with **1**,[3] indicated its rearrangement to **5** to proceed with inversion of the two carboxy oxygens, i.e. via a 2,3-shift, and led to the notion of a five-electron five-center pericyclic mechanism (**B**, X = CR″) or a fragmentation/recombination pathway involving an ion pair within a solvent cage (**D**, X = CR″). Kinetic studies revealed the rate constant to be dependant on the substituent in the acyloxy group, with a trifluoroacetate undergoing migration approximately 10^2 times faster than a corresponding

Scheme 1



acetate (Table 1, entries 2 and 3), and also on solvent polarity, with significant rate increases in more polar solvents (Table 1, entries 2 and 4).[3,4] These observations provided support for the ion pair mechanism (**D**, X = CR″) or at least for a mechanism with significant separation of charge at the transition state. Ab initio calculations for the degenerate migration of the β-(formyloxy)-ethyl radical provided support for a five-membered cyclic transition state (**B**, X = CH) differing in geometry from a 1,3-dioxolanyl radical.[5] Stereospecific migrations were reported in the steroid and carbohydrate series by Julia[6] and Giese,[7] respectively, with the latter providing an excellent source of 2-deoxypyranose esters.[8] *o*-(Acyloxy)-aryl radicals were shown not to undergo an analogous rearrangement by Shevlin.[9]



In 1986 Kocovsky reported on an ^{18}O-labeling study which showed that steroidal 5α-(acyloxy)-5β-bromo derivatives suffered migration of the carboxylate, on treatment with tributyltin hydride and AIBN, with 77% retention of configuration of the two carboxy oxygens, i.e.

[⊗] Abstract published in *Advance ACS Abstracts,* July 15, 1995.

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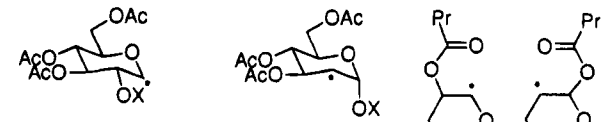
Table 1. Some Literature Rate Constants

entry	rearrangement	solvent	temp (°C)	rate constant (s^{-1})	ref
1	**1** → **5**	benzene	75	3.9×10^3	3
2	**1** → **5**	*tert*-butylbenzene	75	4.5×10^2	4
3	**4** → **8**	Freon 113	75	7.0×10^4	4
4	**1** → **5**	water	75	2.1×10^4	4
5	**2** → **6**	benzene	75	6.2×10^3	3
6	**2** → **6**	benzene	75	5.1×10^2	4
7	**3** → **7**	benzene	70	4.1×10^4	3
8	**9** → **10**	benzene	80	2.4×10^6	11
9	**17** → **18**	benzene	80	1.2×10^4	13
10	**11** → **14**	benzene	80	5.2×10^2	12
11	**13** → **16**	benzene	27	8×10^6	15

mainly by a 1,2- rather than a 2,3-shift.[10] This observation was rapidly confirmed by Beckwith who also measured the rate constant for this particular rearrangement (**9** → **10**) and found it to be abnormally high (Table 1, entry 8).[11] The same study prompted Giese to reinvestigate his carbohydrate based migration by ^{18}O-labeling, with the result that the rearrangement of **12** to **15** was shown to be "normal" and proceed through a 2,3-shift.[12] Subsequent work from Beckwith's laboratories using a combination of ^{17}O-labeling and ^{17}O-NMR analysis has identified a further example of an acyloxy migration (**17** → **18**) proceeding to a measureable extent (33%) through a 1,2-shift (Table 1, entry 9).[13] In the light of the work of Kocovsky and Beckwith with **9** and **17** the three-electron three-center pericyclic mechanism (**C**), initially dismissed on the grounds of the early labeling experiments, was revived.



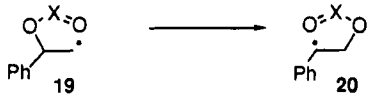
11: X = Ac
12: X = PhCO
13: X = P(O)(OPh)$_2$

14: X = Ac
15: X = PhCO
16: X = P(O)(OPh)$_2$

17 **18**

We, and Giese, demonstrated that phosphate esters migrate in a grossly analogous fashion to carboxylate esters [Scheme 2, X = P(OPh)$_2$],[14,15] and an analogous suite of mechanisms [**A**–**D**, X = P(OR)$_2$] have to be considered.

Scheme 2



19 **20**

A stereochemically labeled substrate was used to probe the nature of this rearrangement, with the result that the 1,2-shift was found to predominate over 2,3-shift typically to the extent of 65–75% depending on substrate.[16] Crude competition experiments[17] indicated the diphenylphosphatoxy migration to proceed at least 10^2 times faster than the analogous acetoxy migration. More accurate measurements by Giese demonstrated that this was indeed the case (Table 1, entries 10 and 11). No evidence was found for any dissociative pathway using a labeled substrate.[18] We also provided the first examples of the β-(nitroxy)alkyl and the β-(sulfatoxy)alkyl migrations (Scheme 2, X = NO, SOPh).[19] Although we did not conduct any accurate kinetic experiments, the β-(nitroxy)alkyl migration appeared to be more rapid than the β-(phosphatoxy)alkyl migration as we were unable to detect any reduction of the unrearranged radical **19** (X = NO) under conditions where that of the phosphate **19** [X = P(OPh)$_2$] was readily quantified.

Results and Discussion

Consideration of the above body of data led us to the hypothesis that the 1,2-shift mechanism predominates for the more rapid migrations and the 2,3-type mechanism for the slower examples studied initially. This in turn led us to suggest that the relatively rapid nitroxy migration would be predominantly a 1,2-shift and also that the trifluoroacetoxy migration would take place to a measureable extent through the 1,2-shift mechanism.

Phenacyl bromide dimethyl acetal (**21**) was hydrolyzed with 70% ^{18}O water[20] in THF with catalysis by concd H_2SO_4 giving labeled phenacyl bromide (**22**). Inspection of the molecular ion of this sample by GC-MS revealed an ^{18}O/^{16}O isotope ratio of 2.06/1 (Table 2, entry 1). Beside the mass spectrometric method for determining isotope ratios, we also employed the ^{13}C-NMR isotope shift method[21] whenever resolution permitted integration to be performed accurately on spectra acquired under conditions that ensured full relaxation between pulses. Reduction of **22** with methanolic sodium borohydride gave ^{18}O-labeled styrene bromohydrin (**23**). The GC-MS of this substance gave a reduced isotope ratio of 1.77/1 (Table 2, entry 2), suggesting possible depletion of the ^{18}O content in the course of the reduction or isolation. However the ^{13}C-NMR method, applied to the same sample, showed little or no depletion of the ^{18}O content. Subsequent mass spectrometric measurements, *vide infra*, with 1-phenylethanol (Table 2, entries 5 and 6) all gave ^{18}O/^{16}O ratios close to 2.0/1. Clearly the mass spectrometric ratio of 1.77/1 for **23** is an, as yet unexplained, artifact.

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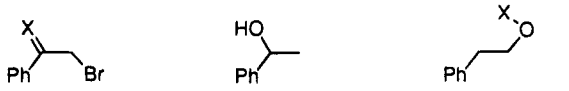

21: X = $(OMe)_2$
22: X = O
23: X = OH, H
24: X = ONO_2, H
25: X = $OCOCF_3$, H

26

27: X = NO_2
28: X = $COCF_3$
29: X = H

Nitration of **23** with fuming nitric acid in acetic anhydride[22] gave analytically pure **24** with an isotope ratio of 2.19/1 as determined by GC/MS (Table 2, entry 3). Trifluoroacetylation of **23** gave **25** with an isotope ratio of 2.17/1 (Table 2, entry 4). Blank experiments established the stability of both **24** and **25** in benzene at reflux for prolonged periods of time. Reduction of **24** with excess tributyltin hydride according to the method of Fraser-Reid,[23] and of **25** with $LiAlH_4$ in ether, gave 1-phenylethanol **26**, which was shown by GC/MS to have an isotope ratio of 2.01/1 and 1.96/1, for the two runs, respectively (Table 2, entries 5 and 6).

Dropwise addition of tributyltin hydride, and catalytic AIBN, in benzene, to **24** at reflux in benzene resulted in its clean rearrangement to **27** in high yield. Reduction of **27** with more concentrated tributyltin hydride, again according to Fraser-Reid, gave 2-phenylethanol **29**, which on examination by GC/MS was found to have an $^{18}O/^{16}O$ ratio of 1.29/1 (Table 2, entry 9) from which it is immediately obvious that **24** underwent the β-(nitroxy)-alkyl migration to **27** predominantly via the 1,2-shift. Taking a value of 2.01/1, the measured value for **26** obtained by tributyltin hydride reduction of **24** (Table 2, entry 5), for the maximum possible $^{18}O/^{16}O$ ratio in **29**, corresponding to a pure 1,2-shift, and zero incorpoartion of ^{18}O for a pure 2,3-shift, we calculate the rearrangement of **24** to **27** to have occurred by $1.29 \div 2.01 \times 100 = 64\%$ by the 1,2-shift pathway.

A similar experiment was conducted with **25**, giving rise to **28** and, after reduction with $LiAlH_4$, **29** with a measured $^{18}O/^{16}O$ ratio of 0.14/1 (Table 2, entry 10). If the maximum $^{18}O/^{16}O$ ratio for **29** in this experiment is 1.96/1, as determined by the $LiAlH_4$ reduction of **25** (Table 2, entry 6), then this rearrangement has occurred $0.14 \div 1.96 \times 100 = 7\%$ by the 1,2-shift pathway.

Table 2. Isotope Ratios

entry	compound	GC-MS ratio $^{18}O/^{16}O$	^{13}C-NMR ratio $^{18}O/^{16}O$
1	**22**	2.06/1	2.12/1
2	**23**	1.77/1	2.01/1
3	**24**	2.19/1	2.03/1
4	**25**	2.17/1[a]	*b*
5	**26** (ex-**24**)	2.01/1	*b*
6	**26** (ex-**25**)	1.96/1	*b*
7	**27**	2.12/1	*b*
8	**28**	*c*	*b*
9	**29**[d]	1.29/1	*b*
10	**29**[e]	0.14/1	*b*

[a] Isotope ratio for $[M - CH_2Br]^+$. [b] This ratio could not be measured owing to insufficient resolution. [c] No reliable molecular ion, or useful fragment was obtained, hence the ratio was not measured. [d] From Bu_3SnH reduction of **27**. [e] From $LiAlH_4$ reduction of **28**.

Evidently, there is a correlation between the rate of rearrangement and mechanism, with the faster migrations showing a higher proportion of the 1,2-shift. As initially pointed out by Ingold for the acyloxy migration, there is a correlation between the ability of the migrating group to accommodate negative charge and reaction rate. This was originally interpreted in terms of a five-center transition state with significant charge separation (**E**, X = CR). We suggest that there is a more extensive correlation between reaction rate, ability of the migrating group to support negative charge, and propensity toward 1,2-shift. This indicates that a faster rearrangement should be interpreted in terms of a greater proportion of the reaction proceeding through a three-center mechanism with significant charge separation (**F**). Nevertheless, it is wise to recall that the ability of the migrating group to support negative charge cannot be the whole raison d'être of the 1,2-shift and therefore that a linear correlation of percentage 1,2-shift with pK_A of the migrating group should not be expected. Other factors also have a role to play, as indicated by the abnormally high rate of the rearrangement of **9** to **10** (Table 1, entry 8)[24] as compared to that of **1** to **5** (Table 1, entries 1 and 2) under similar conditions, and by the differing ratios of 1,2- and 2,3-shifts for diastereoisomeric phosphate ester migrations.[16]

E F

Experimental Section

General. ^1H-NMR spectra were recorded in $CDCl_3$ at 300 MHz with a Bruker AC 300 instrument. ^{13}C-NMR spectra were recorded at 75 MHz with the same instrument operating in the ^{13}C mode. Chemical shifts (δ) are in ppm downfield from tetramethylsilane as internal standard, J-values are given in hertz. EI mass spectra were recorded at 70 eV. Unless otherwise stated, $^{18}O/^{16}O$ ratios were determined on the molecular ion. FTIR spectra were recorded with a Perkin Elmer 1605 spectrophotometer. All solvents were dried and distilled by standard techniques. Tetrahydrofuran (THF) was distilled under nitrogen from sodium benzophenone ketyl before use. Ether refers to diethyl ether. Microanalyses were performed by Midwest Microanalytical, Indianapolis.

Preparation of ^{18}O-Labeled Phenacyl Bromide (22). A solution of the dimethyl ketal (**21**)[25] (2.58 g, 10.53 mmol), 70% ^{18}O labeled water (1 mL, 52.6 mmol), and concd H_2SO_4 (6 μL) in THF (50 mL) was heated under N_2 at 45–55 °C on a water bath for 18 h. After cooling, the reaction mixture was diluted with dry Et_2O (100 mL) and solid Na_2CO_3 (50 mg) added. The organic layer was then filtered and concentrated *in vacuo* to give ^{18}O-labeled **22** (2.01 g, 96%) as a pale yellow solid whose spectra data corresponded to that of an authentic unlabeled sample and which required no additional purification for subsequent use. Examination of this product by GC/MS revealed a 2.06:1 $^{18}O/^{16}O$ ratio. A ^{13}C-NMR spectrum recorded with a relaxation delay of 2 s showed two fully resolved carbonyl carbon signals at δ 191.13 and 191.09 in the ratio 2.12/1.

Preparation of ^{18}O-Labeled Styrene Bromohydrin (23). The above sample of **22** (2.01 g, 10.1 mmol) was dissolved in MeOH (100 mL) at 0 °C and $NaBH_4$ (83 mg, 2.21 mmol) added portionwise over 30 min. After stirring for 4 h at that temperature the reaction mixture was allowed to come to room temperature, quenched with saturated NH_4Cl solution (20 mL), and extracted with Et_2O (2 × 100 mL). The combined extracts were dried over Na_2SO_4 and concentrated *in vacuo*

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to give ^{18}O-labeled **23** (1.61 g, 82%) as a pale yellow syrup, whose spectral data matched those of authentic styrene bromohydrin and which required no additional purification for subsequent use. Examination of the product by GC/MS showed a 1.77:1 ^{18}O/^{16}O ratio for the molecular ion. A ^{13}C-NMR spectrum recorded with a relaxation delay of 2 s showed two fully resolved benzylic carbon signals at δ 73.73 and 73.71 in the ratio 2.01/1.

Prepartion ^{18}O-Labeled 2-Bromo-1-phenylethyl Nitrate (24). A solution of the above sample of **23** (0.23 g, 1.15 mmol) in $CHCl_3$ (25 mL) at 0 °C was treated with a solution of fuming nitric acid (1 mL) in acetic anhydride (20 mL). After stirring for 2 h at 0 °C, the reaction mixture was diluted with $CHCl_3$, washed with saturated $NaHCO_3$ (1 × 50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash column chromotography (5:1 hexane/Et_2O) yielded **24** (0.262 g, 93%) as a colorless liquid. ^{1}H-NMR, δ: 7.45−7.38 (m, 5H), 6.02 (dd, J = 5.00, 8.57, 1H), 3.70 (dd, J = 8.57, 11.38, 1H), 3.59 (dd, J = 5.00, 11.38, 1H); ^{13}C-NMR, δ: 135.0, 129.9, 129.1, 126.6, 83.9, 30.5; IR (CH_2Cl_2): 1644 cm^{-1}. Anal. Calcd for $C_8H_8O_3BrN$: C, 39.05; H, 3.28. Found: C, 39.20; H, 3.34. Examination of the product by GC/MS showed a 2.19:1 ^{18}O/^{16}O ratio for the molecular ion. A ^{13}C-NMR spectrum recorded with a relaxation delay of 2 s showed two fully resolved benzylic carbon signals at δ 83.94 and 83.90 in the ratio 2.03/1.

Prepartion ^{18}O-Labeled 2-Bromo-1-phenylethyl Trifluoroacetate (25). A solution of the above sample of **23** (0.422 g, 2.1 mmol) in dry pyridine (2 mL) and dry CH_2Cl_2 (10 mL) was treated with excess trifluoroacetic anhydride (1.48 g, 7.1 mmol) and stirred overnight at room temperature. The reaction mixture was then diluted with Et_2O (50 mL), washed with water (1 × 50 mL), and dried (Na_2SO_4). The solvent was then evaporated *in vacuo* to give crude **25**. Purification by flash column chromotography (3:1 hexane/Et_2O) yielded 0.480 g (77%) of **29** as a colorless oil. ^{1}H NMR, δ: 7.42 (m, 5H), 6.14 (dd, J = 4.20, 8.91, 1H), 3.74 (dd, J = 8.91, 11.31, 1H), 3.63 (dd, J = 4.20, 11.31, 1H); ^{13}C-NMR, δ: 156.3 (q, $^2J_{CF}$ = 32.0 Hz), 135.3, 129.7, 129.1, 126.4, 114.4 (q, $^1J_{CF}$ = 212.8 Hz), 79.1, 32.5; IR, (CH_2Cl_2): 1789 cm^{-1}. Anal. Calcd for $C_{10}H_8O_2BrF_3$: C, 40.43; H, 2.71. Found: C, 40.42; H, 2.84. Examination of the product by GC/MS showed a 2.17:1 ^{18}O/^{16}O ratio for [M − CH_2Br]$^+$.

Reduction of 24 to 1-Phenylethanol (26). A solution of **24** (49 mg, 0.199 mmol), tri-*n*-butyltin hydride (266 μL, 0.987 mmol), and catalytic AIBN were refluxed in benzene (30 mL) under nitrogen for 18 h. The solvent was evaporated *in vacuo* and the remaining crude reaction mixture was diluted in CH_3CN (50 mL) and washed with hexane (3 × 50 mL) to yield crude **26** (29 mg) containing <5% of 2-phenylethanol by ^{1}H-NMR. Examination of this product by GC/MS showed a 2.01:1 ^{18}O/^{16}O ratio.

Reduction of 25 to 1-Phenylethanol (26). A solution of **25** (60 mg, 0.201 mmol) in THF (25 mL) at 0 °C was treated with $LiAlH_4$ (16 mg, 0.422 mmol) over 10 min. The reaction mixture was stirred for 3 h and then diluted with Et_2O (25 mL). The organic layer was then washed with a 1:1 mixture of brine/2 M HCl solution (1 × 50 mL) and dried (Na_2SO_4), and the solvent was evaporated *in vacuo* to yield crude **26** (36 mg). Examination of this product by GC/MS showed a 1.96:1 ^{18}O/^{16}O ratio.

Rearrangement of 24 to 2-Phenylethyl Nitrate (27). Tri-*n*-butyltin hydride (322 μL, 1.20 mmol) and catalytic AIBN in benzene (10 mL), were added over 12 h via motor driven syringe pump to a solution of **24** (226 mg, 0.92 mmol) at reflux under N_2 in benzene (20 mL). After the addition was complete, the reaction mixture was allowed to reflux an additional 6 h. The solvent was then evaporated *in vacuo*, and the remaining crude reaction mixture was diluted in CH_3CN (50 mL) and washed with hexane (3 × 50mL) to yield 173 mg of crude product. Examination of the crude reaction mixture by NMR showed 2-phenylethyl nitrate (**27**) and 1-phenylethyl nitrate in a 1.86:1 ratio respectively. 2-Phenylethyl nitrate (**27**)[26] was characterized by ^{1}H NMR, δ: 7.38−7.23 (m, 5H), 4.65 (t, J = 7.14, 2H), 3.03 (t, J = 7.14, 2H), and 1-phenylethyl nitrate[26] by ^{1}H NMR, δ: 7.40−7.34 (m, 5H), 5.98 (q, J = 6.72, 1H), 1.64 (d, J = 6.72, 3H). Examination of **27** by GC/MS revealed an ^{18}O/^{16}O ratio of 2.12/1.

Reduction of 27 to 2-Phenylethanol (29). A solution of the above crude nitrate (**27**) (80 mg, 434 mmol), tri-*n*-butyltin hydride (351 mL,1.3 mmol), and catalytic AIBN were refluxed in benzene (30 mL) under nitrogen overnight. The solvent was evaporated *in vacuo*, and the remaining crude reaction mixture was diluted in CH_3CN (50 mL) and washed with hexane (3 × 50mL) to yield crude **29** (53 mg). After separation from 1-phenylethanol by preparative TLC on silica gel (eluent: hexane/Et_2O 1/1), examination of **29** (8 mg) by GC/MS showed a 1.29:1 ^{18}O/^{16}O ratio.

Rearrangement of 25 to 2-Phenylethyl Trifluoroacetate (28). Tri-*n*-butyltin hydride (185 mL, 0.69 mmol) and catalytic AIBN in benzene (10 mL), were added over 12 h via motor driven syringe pump to **25** (158 mg, 0.53 mmol) in benzene (25 mL) at reflux under N_2. After the addition was complete, the reaction mixture was allowed to reflux an additional 6 h. The solvent was then evaporated *in vacuo*, and the remaining crude reaction mixture was diluted in CH_3CN (50 mL) and washed with hexane (3 × 50 mL) to yield 139 mg of crude product. Examination of the crude reaction mixture by ^{1}H-NMR showed 2-phenylethyl trifluoroacetate (**28**) and 1-phenylethyl trifluoroacetate in a 1.62:1 ratio, respectively. 2-Phenylethyl trifluoroacetate (**28**)[27] was characterized by ^{1}H NMR, δ: 7.40−7.10 (m, 5H), 4.50 (t, J = 9.4, 2H), 3.05 (t, J = 9.4, 2H) and 1-phenylethyl trifluoroacetate[28] by ^{1}H NMR, δ: 7.40−7.10 (m, 5H), 6.03 (q, J = 7.5, 1H), 1.65 (d, J = 7.5, 3H). Examination by GC/MS was not possible due to the absence of a reliable molecular ion or fragment ion.

Reduction of 28 to 2-Phenylethanol (29). A solution of the above crude trifluoroacetate (**28**) (46 mg, 0.212 mmol) in THF (25 mL) at 0 °C was treated with $LiAlH_4$ (13 mg, 0.339 mmol) over 10 min. The reaction was stirred for 3 h, diluted with Et_2O, washed with a 1/1 brine/2 M HCl solution (1 × 50 mL), and dried over (Na_2SO_4), and the solvent was evaporated *in vacuo* to yield crude **29** (28 mg). After separation from 1-phenylethanol by preparative TLC on silica gel (eluent: hexane/Et_2O 1/1), examination of **29** (7 mg) by GC/MS showed a 0.14:1 ^{18}O/^{16}O ratio.

Acknowledgment. We thank the National Science Foundation (CHE 9222697) for support of this work. D.C. is a Fellow of the AP Sloan Foundation. G.F.F. is the recipient of an Illinois Consortium for Educational Opportunity Program Award.

JO950646N

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