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1,2-Asymmetric Induction in Radical Reactions. Deuteration and Allylation Reactions of β-Oxy-α-Bromo Esters

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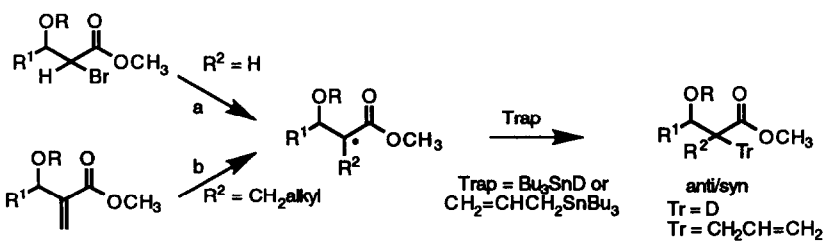
Summary: Chiral radicals were generated by halogen abstraction reactions of β-oxy-α-bromo esters and their asymmetric deuteration and allylation reactions were studied.

Introduction: The use of radical reactions to control acyclic stereochemistry is rapidly emerging as a vibrant subdiscipline in radical chemistry, and advances in both substrate-directed and chiral auxiliary-directed stereocontrol have recently appeared.[2] As summarized in the previous paper,[3] our interest in 1,2-induction reactions of β-oxycarbonyl radicals was driven by the promise of new synthetic methods that could use radical reactions to control relative stereochemistry of aldol adducts. Early in our study of β-oxyanilide radicals, we uncovered some unusual substituent effects[4] that were not consistent with an A-strain model.[5] These discoveries spawned a related study on the reactions of β-oxy ester-substituted radicals that this paper describes (eq 1). Our goals were to learn if the substituent effects discovered in the anilide series could be generalized to related ester-substituted radicals and to study other substituents (R, R^1, R^2) to help fill in the picture for 1,2-asymmetric induction in carbonyl-substituted radicals.

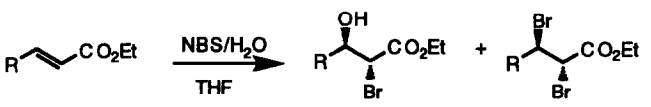
eq 1



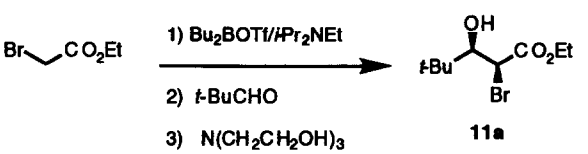
Early in this project, we learned that the Giese group was studying reactions of related radicals formed by addition reactions.[6] This is a natural route to 3°-radicals (eq 1, route b). Work underway in our group had started with reductions of halides (eq 1, route a), and we focused on 2°-radicals so that our work and Giese's would be complementary. We have studied a variety of oxygen substituents, though we deliberately neglected alkoxy groups to avoid duplication of ongoing work in Guindon's laboratory.[7] Very recently, we also learned about more closely related work by Hart and Krishnamurthy.[8] Four of our substrates (**2a**, **2f**, **8a**, **11a**) are identical or very similar to those studied by Hart,[8] and our results and his are comparable.[8b] More generally, related trends emerge from the two studies and this reinforces the notion that these trends are general. Taken together, this work on carbonyl-substituted radicals[3-8] provides by far the largest body of data for 1,2-induction in any class of radical reactions. Virtually all existing models to

interpret these reactions reflect the importance of $A^{1,3}$-strain in controlling ground state conformations of the intermediate radical. However, providing comprehensive rationales of the results taxes the existing models, indicating that there may still be fundamental aspects controlling acyclic stereochemistry that we do not yet understand.

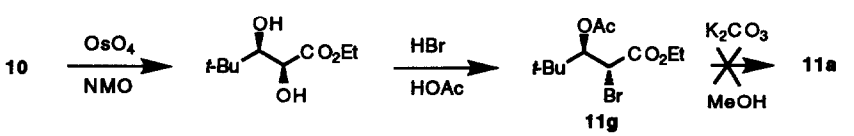
Results: The syntheses of the precursors and authentic products are summarized in eq 2a-e. Precursors bearing methyl (**2a**), *iso*-propyl (**5a**), and phenyl (**8a**) groups were prepared by reactions of β-substituted-α,β-unsaturated esters **1**, **4**, and **7** with NBS/H_2O/THF (eq 2a).[9] Yields in these reactions varied, and a common side product was the dibromide (**3**, **6**, or **9**). This reaction failed entirely for the *tert*-butyl substrate **10**, which was instead made by an aldol reaction[10] (eq 2b). Though this reaction was rather clean, the isolated yield was low due to difficulties in removal of the boron products. Most derivatives were prepared by standard silylation, acetylation, or sulfonation reactions of the alcohols. The exception was acetate derivative **11g**, which we prepared by an osmylation procedure of Sharpless (eq 2c).[11] Authentic samples of most unlabeled products were prepared either by reduction of the appropriate bromides with tributyltin hydride or by an aldol reaction. Allylated product **15a** was prepared by a Seebach-Fráter dianion alkylation (highly anti-selective, eq 2d),[12] and allylated product **13a** was deliberately prepared as an anti/syn mixture by reduction of the acetoacetate (eq 2e).



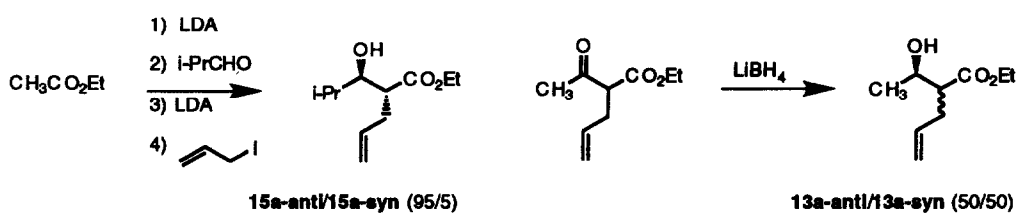
eq 2a



eq 2b



eq 2c



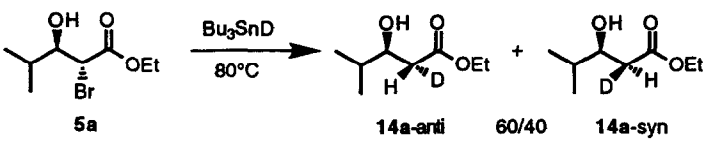
eqs 2d,e

For the deuterium labeling studies, resonances of syn and anti protons were first assigned in the unlabeled products by the standard coupling constant method.[13] We then reduced each substrate with Bu_3SnD at several temperatures. Reactions at 80°C were initiated with AIBN; reactions at all other

temperatures were initiated with triethylborane.[14] Product ratios were then determined by integration of resonances in both the ^1H NMR (300 MHz) and ^2H NMR (76 MHz, ^1H decoupled and unlocked) spectra. In general, these reactions were clean, high yielding, and gave exclusively mono-deuterated products. Ratios reported in Table 1 are those determined by ^1H NMR integration, which we deemed to be more accurate than ^2H NMR integration. In each series, all alcohol derivatives were correlated with free alcohols either by conversion of the alcohol to the derivative (for acetates and sulfonates) or by conversion of the derivative to the alcohol (for silyl ethers).

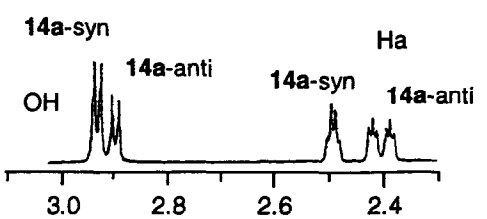
For the α-deuterated hydroxy esters, we discovered a significant isotope shift on the hydroxy proton that we used to confirm the isomer ratios obtained by integration of the syn and anti protons adjacent to the ester. Figure 1 provides an example of this effect. Reduction of *iso*-propyl-substituted alcohol **5a** at 80°C provides a 60/40 ratio of **14a-anti/14a-syn** as indicated by integration of the anti/syn protons. The hydroxy protons of these two isomers appear as two well resolved doublets, which are not concentration dependent. The hydroxy resonance of the syn-deuterated isomer (**14a-syn**) was consistently upfield from the anti-isomer (**14a-anti**), which in turn was usually slightly upfield from the non-deuterated product. Thus, a simple integration of the OH region of the ^1H NMR spectrum provided a ratio of non-deuterated/anti-deuterated/syn-deuterated products. Hydroxy resonances of the non-deuterated products were never observed, thereby confirming that deuterium transfer was uniformly efficient.

Figure 1. Representative Analysis of Reduction Products.

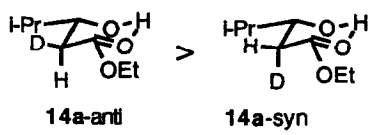


5a **14a-anti** 60/40 **14a-syn**

^1H NMR spectrum of **14a** (300 MHz)



Proposed Strength of Hydrogen Bonds



14a-anti **14a-syn**

This chemical shift effect is remarkable considering that substitution of deuterium for hydrogen normally has a negligible effect on the neighboring protons.[15] Even more remarkable is that the hydroxy proton that is shifted is separated by four bonds from the deuterium, and that the isotope shift is sensitive to configuration at the carbon bearing D. We interpret this shift as originating from isotope effects on intramolecular hydrogen bonds. In non-polar solvents like $CDCl_3$, β-hydroxy esters like **14a** are widely thought to exist in conformations with intramolecular hydrogen bonds. The chemical shifts of hydroxy protons are exquisitely sensitive to the strength of hydrogen bonds, and hydrogen bonding shifts hydroxy protons downfield. A deuterium is inferior to a proton in stabilizing a positive charge at an adjacent carbonyl. For example, acetophenone-d_3 is a much weaker base than acetophenone.[16] Thus, the α-deuterio-esters form slightly weaker intramolecular H-bonds and their OH protons resonate upfield from the

all-protio analogs. Within the deuterated isomers, we postulate that a stereoelectronic effect is operating;[17] the syn isomer has the C–D bond approximately aligned with the π-orbital of the ester carbonyl, and this forms the weakest H-bond. The anti isomer has the (better positive charge stabilizing) proton aligned with the carbonyl, and it forms the stronger hydrogen bond of the pair.

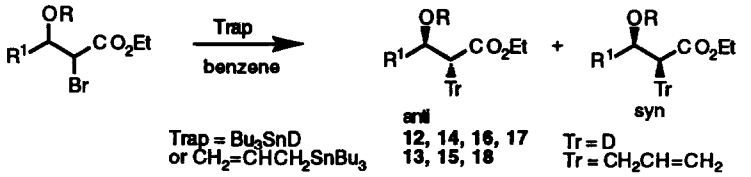
Allylations were conducted with allyltributyl stannane under standard conditions.[18] Irradiation with $Bu_3SnSnBu_3$ or AIBN was used to initiate reactions at 80° C and Et_3B[14] was used to initiate reactions at 25°C or below. Products were compared directly with the authentic samples, and stereoisomer ratios were determined by integration of appropriate resonances in the ^1H NMR spectra of the crude mixtures.

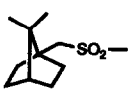
The results of all the deuteration and allylation studies are summarized in Table 1. Within the R^1 = methyl series, reductions of the free alcohol (entry 1), the methyl ether (entry 6), and the acetate (entry 7) with Bu_3SnD were unselective at all temperatures investigated. In contrast, the silyl ethers showed good selectivity that steadily increased both with decreasing temperature and increasing size of the substituents on silicon (entries 2-4). The camphor sulfonate (**2e**) also showed good anti selectivity (entry 5). Allylation of the free alcohol **2a** was unselective (entry 1). Most disappointingly (from the preparative viewpoint), allylations of the silyl ethers and the sulfonate do not progress at low temperatures and exhibit little or no selectivity at 80°C (entries 2-5). The alcohol **5a** (R^1 = *iso*-propyl) gives modest anti-selectivity in both deuteration and allylation (entry 8). Deuteration of the alcohol **11a** (R^1 = *tert*-butyl) exhibits good anti selectivity (entry 9) while the acetate **11g** gives good syn selectivity (entry 10). In the R^1 = phenyl series, deuteration of the free alcohol **8a** is unselective (entry 11) while that of the large silyl ether **8d** is anti selective (entry 12). Once again, the anti-selective deuteration of this silyl ether translates to an unselective allylation (entry 12).

In a previous series of experiments with oxygen-substituted radicals,[19] we had always observed slightly higher selectivities in allylations than in deuterations. This result seems logical based on the reactivity-selectivity principle. In the silyl ether series (entries 2-4 and 12), we were therefore initially surprised by the low selectivity of the allylations in the face of highly selective deuterations. However, this reversal is common for carbonyl-substituted radicals,[8b] and the trend in decreasing allylation selectivity is clearly connected with increasing difficulties in maintaining chains. That the ester substituted radicals gave poor allylation selectivities concerned us, and we conducted a detailed series of experiments whose goal was to prove that both the deuteration and allylation reactions were occurring by the expected radical mechanisms.

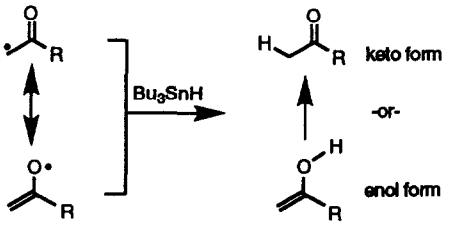
The literature on carbonyl-substituted radicals reveals occasional discussions of the regioselectivity.[20] In principle, such radicals can react with traps like Bu_3SnH on carbon or oxygen (eq 3). Both radical density and product stability arguments suggest that reactions should occur on carbon, and we and Snider provided hard evidence that cyclizations of such radicals did occur kinetically on carbon.[21] However, given that radical reactions have early transition states and are highly sensitive to polar effects, we did not feel it safe to assume that the reactions of such radicals with tin hydride occurred kinetically on carbon. Hydrogen transfer to oxygen would give an enol (eq 3). Subsequent tautomerization would then provide the expected product; however, the stereochemistry would be determined not in the (radical) hydrogen transfer step but in the (ionic) tautomerization step. This possibility also concerned Hart,[8] but his experiments and ours both suggest that such concerns are unfounded.

Table 1. Reductions and Allylations of α-Bromoesters



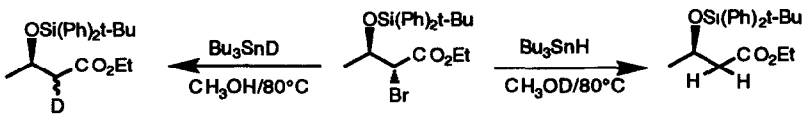
Entry	Bromide	R^1	R	Temp	anti/syn (deuteration)	anti/syn (allylation)
1	**2a**	CH_3	H	80°C	50/50 (**12a**)	
				25°C	50/50	55/45 (**13a**)
				0°C	50/50	
				45°C	50/50	
				−78°C	55/45	
2	**2b**	CH_3	$Si(Me)_3$	0°C	75/25 (**12b**)	
				−78°C	71/29	
3	**2c**	CH_3	Si(*t*-Bu)Me_2	80°C	77/23 (**12c**)	60/40 (**13c**)
				0°C	75/25	NR
				−78°C	82/18	
4	**2d**	CH_3	Si(*t*-Bu)Ph_2	80°C	76/24 (**12d**)	50/50 (**13d**)
				25°C	89/11	NR
				0°C	94/6	NR
				−78°C	97/3	NR
5	**2e**	CH_3		80°C		50/50 (**13e**)
				25°C	74/26 (**12e**)	
				−78°C	86/14	
6	**2f**	CH_3	CH_3	25°C	50/50 (**12f**)	
				−78°C	45/55	
7	**2g**	CH_3	Ac	25°C	42/58 (**12g**)	
				−78°C	36/64	
8	**5a**	*i*-Pr	H	80°C	60/40 (**14a**)	70/30 (**15a**)
				0°C	67/33	76/24
				−78°C	76/24	
9	**11a**	*t*-Bu	H	80°C	72/28 (**16a**)	
				−78°C	85/15	
10	**11g**	*t*-Bu	Ac	−78°C	12/88 (**16g**)	
11	**8a**	Ph	H	80°C	50/50 (**17a**)	
				−78°C	50/50	
12	**8d**	Ph	Si(*t*-Bu)Ph_2	80°C	85/15 (**17d**)	60/40 (**18d**)

eq 3



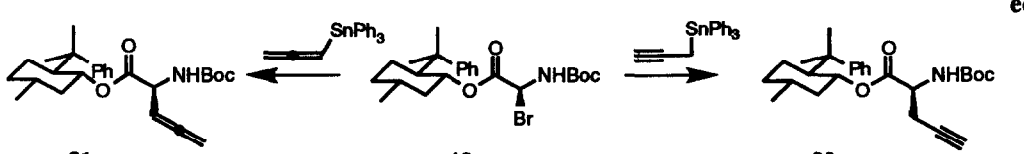
Reduction of **2d** with tributyltin hydride in CH_3OD provided the fully protiated product **12d-H** devoid of deuterium (eq 4) while reduction of **2d** with tributyltin deuteride in CH_3OH provided the fully mono-deuterated product **12d** as a 76/24 mixture of anti and syn isomers (eq 4). Since it is inconceivable that intramolecular enol/ester tautomerization without solvent exchange could occur in pure methanol, these results suggest that hydrogen abstraction from tin hydride occurs directly on carbon. Therefore, the high stereoselectivities observed in entries 2-5 are indeed due to 1,2-induction in the radical hydrogen transfer reaction. Hart conducted related experiments and drew similar conclusions.[8b]

eq 4

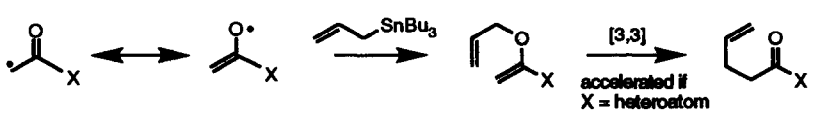


During the course of our work, some unusual observations by Hamon and coworkers[22] led us to consider another option to explain the absence of a parallel between deuteration and allylation: that the stereochemistry in the allylation reaction may not arise in a radical step. These workers reported that propargylation of **19** provided the propargyl product **20**, while allenylation provided the allenyl product **21** (eq 5a). Standard radical addition mechanisms[23] dictate that the propargylation should give the allenyl product and that allenylation should give the propargyl product. It occurred to us that both Hamon's results and ours might be explained by initial radical allylation (or propargylation or allenylation) on oxygen, followed by a Claisen rearrangement (eq 5b). Substituent effects on the Claisen rearrangement[24] could reduce the reaction temperatures in these substrates to 80°C or even below. In our case, low induction in the Claisen rearrangement might explain the low allylation selectivity. Further, the low reactivity of the silyl ether substrates enhanced our concern that a change in mechanism might have occurred. Despite this suggestive analysis, control experiments now indicate that radicals derived from **2d** undergo direct C-allylation.

eq 5a

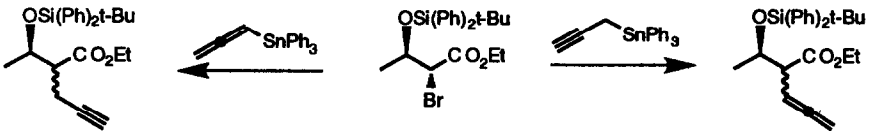


eq 5b



We first conducted several allylations with **2d** at room temperature in an NMR tube (as in Table 2, entry 4), but we observed only slow conversion to **13d-anti/13-syn** (50/50). There was no build up of a ketene acetal; however, this negative result does not permit a firm conclusion. After initial difficulties in preparing a selectively deuterated allylstannane, we simply decided to repeat Hamon's pair of experiments. Our observations did not mirror his, and instead we obtained the expected result based on direct reaction of the radical at carbon. Reaction of **2d** with propargyltrimethyl stannane gave the allenylated product **22** and reaction with allenyl triphenyl stannane gave the propargylated product **23** (eq 6). Both reactions were sluggish (especially the allenylation), and we did not push them to completion (hence the low yields). Both reactions also gave low selectivities. We conclude that our allylations are radical reactions that occur directly at carbon. Though it now seems unlikely, the possibly still exists that Hamon's substrates do undergo O-allylation/Claisen rearrangement.

eq 6

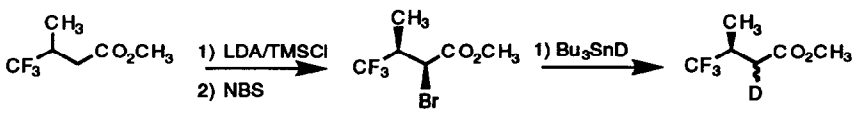


23, (6%) **2d** **22**, 65/35 (17%)

In the end, all the control experiments to detect reactions of ester enol radicals on oxygen were negative, and the implicit assumption that such radicals prefer kinetic reaction on carbon appears to be a good one. From the stereochemical perspective, it is now clear that different classes of radicals can respond differently to changes in the nature of the trap.

We also included in this study one example that was not a β-hydroxy carbonyl. This substrate, shown in eq 7, was chosen in an effort to help separate steric from electronic (or stereoelectronic) effects. Ionic bromination of the enolate derived from **24** provided **25** as a single isomer.[25] In contrast, radical reduction of **25** was unselective at 80°C (50/50) and only marginally selective at –78°C (60/40). We have not yet assigned the configuration of the deuterated products **26**.

eq 7



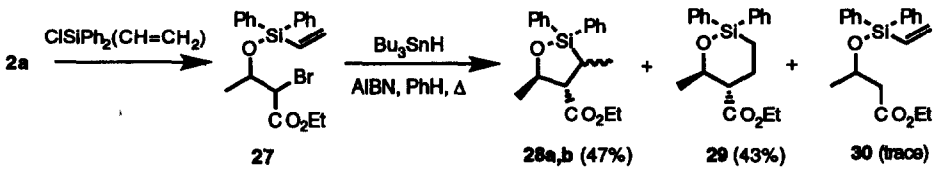
24 **25** **26** 80°C, 50/50
-78°C, 60/40

In view of the disappointing allylation results, we considered that good selectivities and high yields might be attained by replacing the radical addition with a cyclization. We envision that a new variant of the "silicon connection"[26] strategy might provide a general solution, and the single example that we have so far does indeed show promise. We have recently learned that conceptually related experiments are being successfully conducted by Guindon and coworkers.[27]

Silylation of **2a** with vinyldiphenylchlorosilane provided **27** in high yield (eq 8). Cyclization of **27** (0.01M) with tributyltin hydride provided a mixture of a single 6-endo isomer **29** (43% yield) and a 1/1 mixture of 5-exo isomers **28a,b** (47% yield) along with recovered **27** (7%). There was also a trace (<3%) of the directly reduced product **30**. That the 6-exo product is trans is evident from the coupling constants in the ^{1}H NMR spectrum. We assign both the 5-exo products as anti (epimeric at the silyl-bearing carbon)

based on strong experimental[28] and theoretical[29] precedents. Thus, this preliminary experiment indicates that the "silicon connection" strategy has good promise for the synthesis of anti aldols.

eq 8



Discussion: Inspection of the large number of examples of reactions of chiral radicals **32** (Figure 2) identifies two very broad trends in asymmetric deuteration reactions:[3-8] 1) large silyloxy groups are powerful "anti-directors", and 2) medium and large alkyl groups and (especially) phenyl groups[7] (X) are good "syn directors" when combined with small oxygen substituents (R^1) like acetoxy and (especially) methoxy. When pitted against each other, the first trend seems to override the second.

Within each trend are several common themes. The "anti" effect of the silyloxy groups appears to originate from size; larger silyl groups give higher selectivities and the large camphor sulfonyloxy group (which is electronically quite different from silyloxy) appears to mimic the effect of a medium-sized silyloxy group (Table 1, entry 5). Further, this "anti" directing effect is unique to hydrogen or deuterium transfer reactions; allylations give low selectivity. The syn directing effect of medium/large alkyl and phenyl groups is significantly enhanced for 3°-radicals over 2°-radicals,[5b] and allylations in this series often (though not always) give selectivities comparable to or higher than hydrogen transfer reactions. Free hydroxy groups upset the "syn" directing effect and typically give low selectivity, except with very large alkyl groups where anti selectivity is actually observed.

Models for asymmetric induction in chiral radicals have followed from Hart's suggestion[5] that stereoselectivity might be expected when A-strain dominates the conformation of a chiral radical adjacent a π-conjugating group. This simple yet powerful notion is useful, at least qualitatively, for rationalizing stereochemistry of radicals adjacent to carbonyls,[3-8] phenyl groups,[30a] and nitrogen atoms.[30b] Models of these asymmetric radical reactions often begin with ground state considerations, and then project these considerations into proposed transition states. A clear shortcoming of current models[2,6-8] is that they do not attempt to evaluate interactions of the radical with the incoming reagent. Considering the present body of results, it is not clear to us how to remedy this shortcoming; however, that such a shortcoming exists is clearly suggested by a number of our results. We will briefly discuss the ground state conformations of these radicals, and then summarize both the transition state models and the trends that they rationalize. We will then discuss results that do not appear to integrate well with existing models.

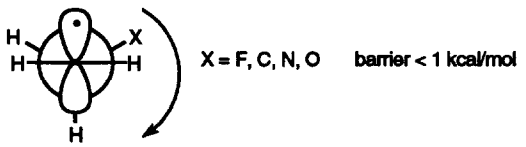
Because most radical reactions are relatively rapid and have early transition states, ground state considerations are important in thinking about transition state models. Stable molecules like Z-alkenes,[31] Z-enol ethers,[32] and enolates[33] should provide relatively good models for ground state conformations of transient radicals. Radicals adjacent to esters have a significant barrier to rotation (~12 kcal/mol) and best evidence indicates that both E and Z isomers are energetically accessible (Figure 2, **31Z/31E**).[34] A-strain considerations suggest that the C–H bond on the stereocenter should roughly eclipse the C–CO bond.[35] This dihedral angle is not expected to be exactly zero, and it is usually thought that for stable molecules subject to A-strain, there is a broad, shallow potential between 0° and ±20-30°.

Figure 2. Geometries of Ester- and Amide-Substituted Radicals

By analogy with amide enolates, amide-substituted radicals should favor a Z-orientation (Figure 2, **32Z**) because of highly unfavorable interactions in the E-isomer.[36] ESR evidence supports this conclusion.[33b] Very little is known about the E/Z ratio of complex ester-substituted radicals, and models for asymmetric induction ignore this issue by assuming that E and Z isomers will give similar selectivities. This assumption seems intuitively reasonable, and the stereochemical parallels that we see between ester-substituted radicals (probably E/Z mixtures) and amide-substituted radicals[4] (probably only Z) provide some reassurance that E/Z stereochemistry is not a dominant factor in controlling 1,2-asymmetric induction in ester-substituted radicals.

Some models also suggest the importance of electronic effects in dictating ground state conformations of these radicals. Are there any large electronic or stereoelectronic effects that might compete with A-strain? Hyperconjugative effects are very important in cation chemistry[37] and they have also been considered in enolate chemistry.[38] However, in radical intermediates, such effects may be vanishingly small.[39] Both experiments and high level calculations indicate that barriers to rotation in ethyl radicals substituted with first row elements are nearly non-existent (Figure 3).[40] The tiny barriers that do exist probably arise from destabilizing eclipsing interactions of substituents rather than from any stabilizing orientation of the substituent X relative to the singly-occupied orbital. Thus, standard steric and electrostatic effects between substituents probably mask any small stereoelectronic effects between the C–X or C–R^1 bonds and the radicals **31** and **32**. Said another way, if certain pairs of substituents R^1 and X favor conformations other than those anticipated by A-strain, this is more likely due to the interactions of R^1 and X with the other substituents than to the interactions of R^1 and X with the radical.

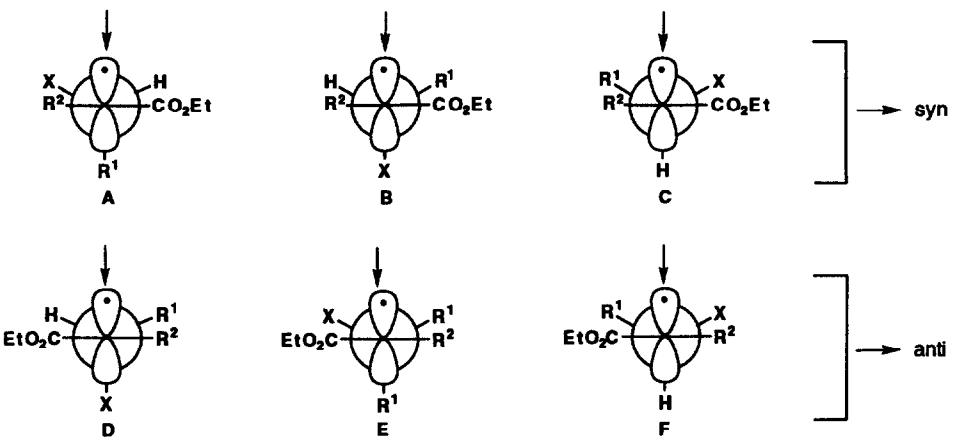
Figure 3. Rotational Profile of Substituted Ethyl Radicals



To move from the ground state to the transition state, one must evaluate the energy changes that occur as the reagent approaches the radical. Models for early transition states can do this in a qualitative way by estimating the increase in cost in ground state energy to attain an appropriate transition state geometry and adding this to an estimate of the cost in steric energy required for approach of a reagent. Superimposed on this cost in steric energy for reagent approach must be any important electronic accelerating (or decelerating) effects that are unique to certain geometries of substituents (stereoelectronic effects).[41] For such radical reactions, the most important change in ground state geometry will probably be rotation of the bond from the radical to the adjacent stereocenter to permit an approximately staggered approach of the reagent.[42,43]

This analysis leads to the six staggered transition state models shown in Figure 4.[2,6-8] For the substrates in this paper (R^1 = alkyl, phenyl; X = OR), models A-C lead to syn products and models D-F lead to anti products. Consideration of *only* ground state geometry suggests that models A and D should be favored over B, C, E, and F.[5] Our results clearly show that steric energy costs in approach of reagents could equal or outweigh ground state considerations. A simple steric approach analysis suggests that models C and F are higher in energy than the other four because reagents must approach between the two largest groups R^1 and X. Thus, we believe that a discussion need only evaluate models A, B, D, and E.

Figure 4. Transition State Models



Are reactions of these radicals accelerated by electronic effects in certain rotameric orientations? The question of transition state stereoelectronic effects is a crucial issue about which little information is available. "Polar effects" as interpreted by FMO theory form the basis by which we understand substituent effects on rates of additions of radicals to alkenes.[44] These effects can be very large. There is no information about polar effects on hydrogen transfer reactions from tin hydride; however halogen abstraction reactions of tin radicals (an admittedly stretched model for the reverse reaction of hydrogen transfer) are susceptible to small polar effects.[45] It is not clear if any of these polar effects have a stereoelectronic component, or if this stereoelectronic component could be large enough in energy to be manifested in one of the above transition states. Radicals adjacent to esters are now considered to be ambiphilic,[46] and both allyl stannanes[47] and tin hydride are probably nucleophilic in character. Thus, accelerating stereoelectronic effects, such as they are, should be manifested in conformations that make the radical more electrophilic (X anti).

Results from several groups[3-8] now combine to suggest that good syn selectivities can be obtained by choosing substituents to disfavor transition states D and E relative to A. Modest selectivity is observed based only on size differences between X (smaller group) and R^1 (larger group). As the size of R^1 increases, TS B quickly rises in energy since it is disfavored both by A-strain and because the reagent must approach between H and R. Reagents approach both TSs A and E between H and X, but E is disfavored relative to A by $A^{1,3}$-strain. TSs A and D are roughly comparable based on $A^{1,3}$-strain but D is now disfavored because attack between H and R^1 is less favored than attack between H and X. Changing the

R^1 group from H to methyl probably increases the selectivity by favoring TS A over D. This is essentially a ground state effect caused by increased repulsion between R^2 and R^1 ($A^{1,2}$-strain) in TS D relative to repulsion between X and R^2 in TS A. Several groups have recently shown that huge R^2 groups can upset the selectivities as $A^{1,2}$-strain (interactions of R^2 with R^1 and X) begins to dominate over $A^{1,3}$-strain (interactions of the ester with R^1 or X).[7c,8]

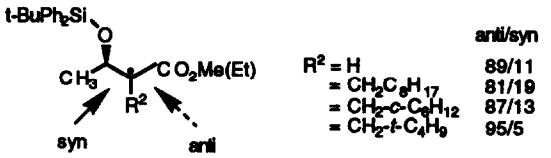
However, outstanding selectivities are not usually obtained based on size alone, probably because altering the relative sizes of R^1 and X increases the energy of TS D relative to A, but does not greatly effect the energy of E relative to A.[7c] (Ground state calculations estimate that it costs only 1-2 kcal/mol to place a methyl group (X = Me in TS E) inside.)[7c,34] Combining medium-to-large R^1 groups with X groups having some dipolar component (X = F, OMe, OAc, CO_2R) can now lead to very high selectivities. This is probably because reagent approach effects still disfavor D relative to A and dipolar effects now disfavor E relative to A.[7] These dipolar effects arise in the ground state and translate to the transition state.

This analysis, which combines our insights with those of others,[5-8] is intended to interpret only the broad trends in syn-selective reactions. Given the large number of examples now available, it is not difficult to find puzzling selectivities by looking with this view of simple models that do not consider either the structure of the attacking reagent or the structure or conformations of the R and X groups. However, the results do support a reasonably general model by which large alkyl or phenyl groups and smaller dipolar substituents can be combined to give excellent syn selectivities.

The problems with this model arise in considering systems that exhibit anti selectivity. The model clearly predicts[6] that anti selectivity should increase as a dipolar X substituent becomes larger than R^1. A glance at the results of R^1 = Me versus X = $OSiR_3$ seems to confirm this prediction: these reactions are indeed anti selective and the selectivity parallels the size of the silyl group (Table 1). Within the model, this selectivity is explained by suggesting that approach to TS A is now more hindered than TS D because approach between H and X is now more hindered than that between H and R^1. There are three problems with this interpretation: 1) The anti selectivities are too high. If TS E erodes selectivity when R^1 is large and X is methyl, then TS B should do likewise when X is large and R^1 is methyl. This is clearly not the case since combinations of R^1 = methyl with large silyl groups give spectacular anti selectivities in hydrogen (deuterium) transfer reactions. 2) If the selectivity arises because reagent approach to TS D is less hindered than TS A, then the use of larger, less reactive reagents should give increased anti-selectivity. This is contrary to the observations; changing from tin hydride to allyl stannane consistently erases anti-selectivity. 3) If the selectivity arises because reagent approach to TS D is less hindered than TS A, then increasing the size of R^2 relative to $OSiR_3$ should erode and eventually reverse the anti selectivity. This is not observed either. Large *O*-silyl groups give good anti selectivity even when pitted against Ph and *t*-Bu, the best syn-directing groups. Being reluctant to propose that $OSiR_3$ is larger than *t*-Bu, we submit instead that there are important features of these reactions that are not yet understood.

Comparisons of our silyl ether selectivities with radical results of Giese[6d] (Figures 5 and 6) and the ionic results of Kita[47] (Figure 6) are interesting. Though the methyl-substituted example is lacking, increasing the size of R^2 from hydrogen to neopentyl results first in a decrease in selectivity in radical hydrogen transfer reactions, then in an increase. This is exactly the reverse of most "syn-selective" substituent pairs, where changing R^2 from H to Me gives increased selectivity, followed ultimately by a selectivity reversal with very large R^2 groups.[8]

Figure 5. Comparison of Selectivities with Changing R^2



"anti" and "syn" refer to indicated direction of hydrogen transfer from Bu_3SnH at 20-25°C.

Kita's amine catalyzed additions of thiol[48] to acrylates (eq 9) presumably involve ionic protonation of an ester enolate, and they observe very similar trends to those of the radical reactions (Figure 6). Stereochemical parallels between radical and ionic reactions are surprisingly common,[6] and sustained parallels must reflect similarities in transition states of radical and ionic reactions. Similar transition states are likely to occur when structures of the intermediates (in this case, an enolate and a radical adjacent to a carbonyl) and the approach of reagents are similar. While steric interactions in radical and ionic reactions may be similar, strong electronic or stereoelectronic interactions need not be reflected in this parallel. This analysis suggests that the anti-directing effect of the OTBS in radical hydrogen transfer and protonation is steric, not electronic or stereoelectronic in nature.

eq 9

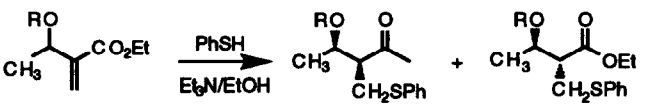
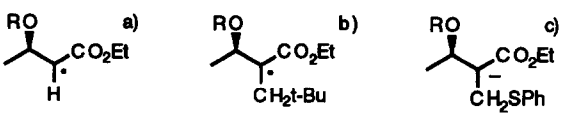


Figure 6. Comparison of Ionic and Radical Selectivities (at 25°C)



R	anti/syn	anti/syn	anti/syn
H	50/50	—	50/50[d]
$SiMe_3$	75/25	83/17	—
$SiMe_2t$-Bu	79/21	91/9	75/25
$SiPh_2t$-Bu	89/11	95/5	94/6

Footnotes: a) this work; b) reference 6a; c) reference 46; d) 5°C

The high selectivities in the enolate reaction of **24** compared to the unselective radical reactions of **25** provide a striking exception to the ionic/radical parallel (eq 7). A stereoelectronic effect for the enolate selectivities has been advanced,[36b] and we suggest that the radical reaction is unselective because it does not mirror this effect and because simple size differences between CH_3 and CF_3 are not sufficient to effect selectivity.

The origin of the unusual effects of the OH substituent in combination with phenyl or alkyl groups is open to question. Intramolecular hydrogen bonding is an obvious possibility to consider.[8b] However, a carbonyl-substituted radical must be a significantly poorer hydrogen bond acceptor than a carbonyl group.

Therefore, that the precursor and product exhibit an intramolecular H-bond does not alone warrant the conclusion that the radical will also. Intramolecular hydrogen bonding would favor ground states with the OH group inside. This translates to TSs C and E. Of the two, approach of a reagent to TS E is clearly favored. This predicts that OH groups should exhibit increased anti selective relative to OMe groups. This is not always what is observed.[8b] Though results with alcohols are more variable, one generally observes that when low selectivities are observed with OMe, low selectivities are also observed with OH. In contrast, when syn selectivities are observed with OMe, anti selectivities are observed with OH. H-bond acceptor solvents might disrupt intramolecular H-bonds and restore syn selectivity for alcohols, but the jury is still out on solvent effects. Hart has observed increased anti selectivities in changing from benzene to THF[8b] while we have observed very little selectivity shift in going from benzene to DMSO (a very powerful H-bond acceptor).

EXPERIMENTAL

Ethyl 2-Bromo-3-hydroxybutanoate (2a). Ethyl crotonate (24.86 mL, 200 mmol) was dissolved in THF (75 mL) and recrystallised NBS (40.04 g, 225 mmol) and water (75 mL) were added to the reaction. A yellow slurry formed and this was stirred vigorously at 25°C until it became colorless. The reaction was extracted into methylene chloride, dried and concentrated. Purification by flash column chromatography (pentane/ether = 70/30) gave **2a** (29 g, 68%): ^{1}H NMR ($CDCl_3$) δ 4.25 (q, J = 7.1 Hz, 2 H), 4.18 (m, 1 H), 4.08 (d, J = 7.7 Hz, 1 H), 2.5 (br. s, 1 H), 1.39 (d, J = 6.4 Hz, 3 H), 1.30 (t, J = 7.1, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.3 (s), 68.9 (d), 62.3 (t), 49.5 (d), 20.0 (q), 14.0 (q); IR (neat) 3447, 2984, 1736, 1458, 1375, 1304, 1192, 1151, 1091, 1026 cm^{-1}; MS, *m/z* 211, 197, 195, 168, 166, 140, 138, 45; HRMS, m/z calcd. for $C_5H_8O_3Br$ [M – CH_3], 194.9657, found, 194.9657.

Ethyl 2-Bromo-3-trimethylsilyloxybutanoate (2b). Compound **2b** was prepared by the procedure described for **2c** with **2a** (0.211 g, 1 mmol), trimethylsilyl chloride (140 μL, 1.1 mmol) and triethylamine (181 μL, 1.3 mmol) in THF (5 mL). Purification by flash column chromatography (pentane:ether = 90:10 with 1% triethylamine) gave **2c** (0.216 g, 76%): ^{1}H NMR ($CDCl_3$) δ 4.21 (m, 3 H), 3.94 (d, J = 9.0 Hz, 1 H), 1.36 (d, J = 6.0 Hz, 3 H), 1.29 (t, J = 7.1 Hz, 3 H), 0.10 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 169.0, 70.0, 61.7, 50.1, 21.1, 14.0, 0.1; IR (in $CDCl_3$) 1747, 1375, 1304, 1252, 1199, 1149, 1103, 1032, 997, 843 cm^{-1}; MS, *m/z* 269, 267, 241, 239, 195, 145, 119, 103, 75.

Ethyl 2-Bromo-3-(t-butyldimethyl)silyloxybutanoate (2c). In a dry flask, compound **2a** (0.415 g, 1.96 mmol) was dissolved in CH_2Cl_2 (15 mL) and t-butyldimethylsilyl chloride (0.904 g, 6.0 mmol) and imidazole (0.650 g, 10.0 mmol) were added. The reaction was stirred at 25°C for 24 h, diluted with CH_2Cl_2, washed with water, dried and concentrated. Purification by flash column chromatography (pentane:ether = 98:2) gave pure **2c** (0.445 g, 72%): ^{1}H NMR ($CDCl_3$) δ 4.20 (m, 3 H), 3.94 (d, J = 9.0 Hz, 1 H), 1.36 (d, J = 6.0 Hz, 3 H), 1.29 (t, J = 7.1 Hz, 3 H), 0.83 (s, 9 H), 0.07 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.2, 70.0, 61.9, 50.4, 25.7, 21.3, 17.9, 14.0, –4.2, –5.1; IR (in $CDCl_3$) 2932, 1745, 1255, 1147, 1103, 995, 829, 777 cm^{-1}; MS, *m/z* 325, 311, 309, 281, 269, 239, 159, 119, 75; HRMS *m/z* calcd. for $C_{11}H_{22}O_3SiBr$ [M – CH_3], 309.0522; found, 309.0522.

Ethyl 2-Bromo-3-(t-butyldiphenyl)silyloxybutanoate (2d). Compound **2d** was prepared by the procedure described for **2c** with **2a** (0.640 g, 3.03 mmol), t-butyldiphenylsilyl chloride (1.56 mL, 6.0 mmol) and imidazole (0.680 g, 10.0 mmol) in CH_2Cl_2 (15 mL). Purification by flash column chromatography (pentane:ether = 96:4) gave **2d** (1.1 g, 81%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.68 (m, 4 H), 7.43 (m, 6 H), 4.25 (m, 1 H), 4.13 (m, 3 H), 1.24 (t, J = 7.2 Hz, 3 H), 1.20 (d, J = 6.0 Hz, 3 H), 1.00 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.7 (s), 135.9 (d), 133.7 (s), 133.0 (s), 129.9 (d), 129.8 (d), 127.7 (d), 127.6 (d), 70.6 (d), 61.9 (t), 51.4 (d), 26.8 (q), 20.8 (q), 19.3 (s), 13.9 (q); IR (in $CDCl_3$) 2934, 1745, 1427, 1140, 1111 cm^{-1}; MS, *m/z* 393, 391, 227, 199, 183, 139; FAB in MNBA/MeOH, 449, 393, 391, 373, 371, 227, 199, 197, 183, 154, 139, 121, 105, 91.

Ethyl 2-Bromo-3-(camphorsulfonyl)oxybutanoate (2e). Compound **2a** (0.808 g, 3.8 mmol) was dissolved in CH_2Cl_2 (10 mL) and racemic camphorsulfonyl chloride (0.902 g, 3.6 mmol) and triethylamine (0.557 mL, 4.0 mmol) were added. The reaction was stirred at 25°C for 20 h and then subjected to workup. The crude product was passed through a small column of alumina and concentrated under vacuum to give pure **2e** as a 50:50 mixture of diastereomers (1.03 g, 65%): ^{1}H NMR ($CDCl_3$) δ 5.17 (m, 1 H), 4.42 (d, J = 4.3 Hz, 0.5 H), 4.40 (d, J = 4.5 Hz, 0.5 H), 4.25 (q, J = 7.1 Hz, 2 H), 3.67 (d, J = 15.1 Hz, 0.5 H), 3.55 (d, J = 15.0 Hz, 0.5 H), 3.09 (d, J = 15.0 Hz,

0.5 H), 2.99 (d, J = 15.1 Hz, 0.5 H), 2.41 (m, 2 H), 1.99 (m, 3 H), 1.66 (m, 1 H), 1.64 (d, J = 2.17 Hz, 1.5 H), 1.63 (d, J = 2.1 Hz, 1.5 H), 1.43 (m, 1 H), 1.31 (t, J = 7.1 Hz, 3 H), 1.12 (s, 1.5 H), 1.11 (s, 1.5 H), 0.88 (s, 3 H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 213.9, 213.8, 167.0, 166.8, 76.8, 62.5, 57.8, 48.4, 48.30, 47.7, 47.5, 42.5, 42.2, 26.7, 24.8, 19.6, 19.4, 18.7, 18.6, 13.7; IR (in $CDCl_3$) 2984, 2350, 1743, 1377, 1304, 1261, 1217, 1149, 1045, 1024, 908 cm^{-1}; MS (EI), *m/z* 427, 425, 345, 318, 273, 233, 215, 195, 167, 151, 133, 123, 109, 93, 81, 69, 55; CI *m/z* 428, 427, 426, 425, 367, 345, 318, 316, 233, 215.

Ethyl 2-Bromo-3-methoxybutanoate (2f). Ethyl crotonate (6.2 mL, 50 mmol) was dissolved in THF (20 mL) and NBS (10 g, 51.6 mmol) and methanol (20 mL) were added. The reaction was stirred at 25°C for 6 h, subjected to workup, dried and concentrated. Successive Kugelrohr distillation and flash column chromatography (pentane:ether = 95:5) gave pure **2f** (1.11 g, 10%): ^{1}H NMR ($CDCl_3$) δ 4.23 (m, 2 H), 4.09 (d, J = 8.31 Hz, 1 H), 3.74 (m, 1 H), 3.36 (s, 3 H), 1.34 (d, J = 6.12 Hz, 3 H), 1.30 (t, J = 7.17 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.87, 77.61, 62.05, 57.52, 48.65, 16.49, 14.04; IR (neat) 2984, 1743, 1377, 1304, 1261, 1217, 1149, 1101, 1045, 1024 cm^{-1}; MS (EI), *m/z* 225, 223, 181, 179, 142, 115, 59; HRMS *m/z* calcd. for $C_5H_8O_2Br$, 178.9708; found, 178.9708.

Ethyl 3-Acetoxy-2-bromobutanoate (2g). Compound **2a** (0.259 g, 1.22 mmol) was dissolved in triethylamine (6 mL) and acetic anhydride (1 mL, 10.6 mmol) and 4-dimethylaminopyridine (0.175 g, 1.4 mmol) were added. After stirring at 25°C for 24 h, the reaction was diluted with ether and washed with 1.0 N HCl and satd. aqueous $NaHCO_3$ solutions successively. It was then dried and concentrated. Purification by flash column chromatography (pentane:ether = 92:8) gave **2g** (0.130 g, 42%): ^{1}H NMR ($CDCl_3$) δ 5.28 (m, 1 H), 4.33 (d, 1 H), 4.25 (m, 2 H), 2.09 (s, 3 H), 2.05 (s, 3 H), 1.40 (m, 3 H), 1.30 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.6, 167.5, 70.1, 62.3, 48.2, 21.0, 17.3, 14.0; MS, *m/z* 255, 253, 210, 208, 168, 166, 120, 87; CI, *m/z* 255, 253, 195, 193, 168, 166, 149, 131, 121, 115, 101, 87, 85, 73, 69.

Ethyl 2-Bromo-3-hydroxy-4-methylpentanoate (5a). The procedure used for the preparation of compound **2a** was followed with **4** (3.5 g, 24.6 mmol), NBS (6.2 g, 35 mmol), THF (16 mL) and water (16 mL) to give **5a** (0.72 g, 12%): ^{1}H NMR ($CDCl_3$) δ 4.26 (q, J = 7.1 Hz, 2 H), 4.19 (d, J = 8.2 Hz, 1 H), 3.85 (m, 1 H), 2.56 (d, J = 6.3 Hz, 1 H), 2.12 (m, 1 H), 1.31 (t, J = 7.1 Hz, 3 H), 1.02 (d, J = 6.8 Hz, 3 H), 0.91 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.8, 76.4, 62.3, 45.6, 29.5, 19.9, 15.1, 14.0; IR (neat) 3505, 2966, 2878, 1730, 1468, 1375, 1323, 1284, 1184, 1149 cm^{-1}; MS, *m/z* 241, 239, 223, 221, 197, 195, 168, 166, 140, 138, 73, 53; HRMS *m/z* calcd. for $C_5H_8O_3Br$ [M – C_3H_7], 194.9657, found, 194.9657.

Ethyl 2-Bromo-3-hydroxy-3-phenylpropanoate (8a). Ethyl cinnamate (1.67 mL, 10 mmol) was dissolved in DMSO (10 mL) and water (0.5 mL) was added. To the reaction, NBS (3.5 g, 20 mmol) was added, resulting in a dark red solution. The reaction turned colorless after 30 min and was stirred at 25°C for 24 h. Purification by flash column chromatography (pentane:ether = 80:20) gave pure **8a** (0.550 g, 20%): ^{1}H NMR ($CDCl_3$) δ 7.38 (m, 5 H), (5.08, dd, J = 8.1 Hz, 5.5 Hz, 1 H), 4.36 (d, J = 8.2 Hz, 1 H), 4.25 (q, J = 7.1 Hz, 2 H), 3.19 (d, J = 5.5 Hz, 1 H), 1.28 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.5, 139.1, 128.8, 128.6, 127.0, 75.2, 62.4, 47.8, 13.9; IR (in $CDCl_3$) 3443, 1722, 1699, 1456, 1373, 1284, 1151, 1061 cm^{-1}; MS, *m/z* 274, 272, 229, 227, 193, 168, 166, 140, 138, 107, 79; HRMS *m/z* calcd. for $C_{11}H_{13}O_3Br$, 272.0048; found, 272.0048.

Ethyl 2-Bromo-3-phenyl-3-(t-butyldiphenyl)silyloxypropanoate (8d). Compound **8d** was prepared by the procedure described for **2c** with **8a** (0.10 g, 0.36 mmol), *t*-butyldiphenylchlorosilane (0.142 mL, 0.54 mmol), imidazole (0.049 g, 0.72 mmol) and CH_2Cl_2 (5 mL). Purification by flash column chromatography (pentane:ether = 96:4) gave **8d** (0.130 g, 70%): ^{1}H NMR ($CDCl_3$) δ 7.55 (d, 2 H), 7.37 (m, 6 H), 7.14 (m, 7 H), 5.03 (d, J = 9.3 Hz, 1 H), 4.43 (d, J = 9.3 Hz, 1 H), 4.13 (m, 2 H), 1.22 (t, J = 7.2 Hz, 3 H), 0.91 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 168.8, 139.2, 136.1, 135.9, 133.2, 132.5, 129.7, 128.5, 128.0, 127.9, 127.5, 127.4, 62.1, 49.8, 26.8, 19.4, 13.8; IR (in $CDCl_3$) 1743, 1101, 1024, 1045, 1261, 2936, 1149, 1304, 1458, 2984 cm^{-1}; MS *m/z* 455, 435, 427, 375, 337, 301, 261, 227, 199, 183, 167, 131; CI *m/z* 513, 511, 455, 453, 435, 433, 257, 255, 199, 177, 135.

Ethyl 2-Bromo-4,4-dimethyl-3-hydroxypentanoate (11a). Ethyl bromoacetate (1.108 mL, 10 mmol), was dissolved in CH_2Cl_2 (2 mL) and the solution was cooled to –78°C. Dibutylborontriflate (1.0 M in CH_2Cl_2, 11 mL, 11 mmol) and diisopropylethylamine (2.09 mL, 12 mmol) were added and the reaction was warmed to 25°C over 2 h. The reaction was cooled to –78°C and trimethylacetaldehyde (1.08 mL, 10 mmol) was added. After 3 h, the cold bath was removed and the reaction was allowed to warm for 15 min. It was then quenched with 5% $NaHCO_3$ solution and extracted into CH_2Cl_2. The organic layer was washed, dried and concentrated. The crude ^{1}H NMR indicated the desired product along with the α,β-epoxy ester. The crude yield was good. Triethanolamine (1.46 mL, 11 mmol) was added to the crude mixture and the reaction was stirred at 25°C for three days during which time a

white suspension formed. The reaction was diluted with ether, washed, dried, and concentrated. Purification by flash column chromatography (pentane:ether = 90:10) gave the α,β-epoxy ester (0.261 g, 15%) followed by **11a** (0.150 g, 6%): ^{1}H NMR ($CDCl_3$) δ 4.43 (d, J = 5.55 Hz, 1 H), 4.23 (d, J = 7.14 Hz, 2 H), 3.65 (dd, J = 5.49 Hz, 4.05 Hz, 1 H), 2.69 (d, J = 4.02 Hz, 1 H), 1.30 (t, J = 7.14 Hz, 3 H), 0.99 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 169.93, 76.58, 62.34, 50.53, 35.68, 26.55, 13.88.

Ethyl 3-Acetoxy-2-Bromo-4,4-dimethylpentanoate (11g). HBr in acetic acid (30 wt.% in acetic acid, 213 μL) was added to the ethyl 2,3-dihydroxy-4,4-dimethylpentanoate (40 mg, 0.21 mmol) and the reaction mixture was heated at 55°C for 1 h. The reaction was then cooled to 25°C over 1 h and methanol (10 mL) was added. The reaction was again heated at 55°C in an attempt to hydrolyze **11g** to the β-hydroxy compound **11a**. However, the acetate **11g** remained even after 24 h of heating and formation of the methyl ester of **11g** was observed. The reaction was cooled and purification by flash column chromatography (pentane:ether = 70:30) gave **11g** (18 mg, 30%): ^{1}H NMR ($CDCl_3$) δ 5.27 (d, J = 6.80 Hz, 1 H),δ 4.45 (d, J = 6.80 Hz, 1 H), 4.20 (q, J = 7.14 Hz, 2 H), 2.09 (s, 3 H), 1.30 (t, J = 7.14 Hz, 3 H), 1.00 (s, 9 H).

Ethyl 2-Deutero-3-hydroxybutanoate (12a): Typical Reduction Procedure at –78°C. Compound **2a** (0.105 g, 0.5 mmol) was dissolved in CH_2Cl_2 (2.5 mL) under argon and cooled to –78°C. Bu_3SnD (188 μL, 0.7 mmol) was added followed by triethylborane (50 μL, 0.05 mmol). The argon line was removed and a slow and steady flow of air was maintained throughout the reaction. After 3.5 h, the mixture was warmed to 25°C and concentrated. After I_2/DBU workup,[27] **12a** was isolated as a 50:50 mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 4.20 (q, J = 7.1 Hz, 2 H), 3.0 (two d, 1 H), 2.49 (q, J = 3.3, 2.5 Hz, 0.5 H), 2.40 (dt, J = 8.5, 2.5 Hz, 0.5 H), 1.27 (t, J = 7.1 Hz, 3 H), 1.22 (d, 3 H).

Ethyl 2-Deutero-3-trimethylsilyloxybutanoate (12b). ^{1}H NMR ($CDCl_3$) δ 4.26 (m, 1 H), 4.12 (m, 2 H), 2.46 (dt, major), 2.35 (m, minor), 1.28 (t, J = 7.1 Hz, 3 H), 1.21 (d, J = 6.0 Hz, 3 H), 0.10 (s, 9 H).

Ethyl 2-Deutero-3-(t-butyldimethylsilyl)oxybutanoate (12c): Typical Reduction Procedure at 80°C. In a dry flask, compound **2c** (50 mg, 0.15 mmol) was dissolved in benzene (1.5 mL) and AIBN (3 mg, 0.02 mmol) and Bu_3SnD (80.9 μL, 0.30 mmol) were added. The reaction was heated at 90°C for 2 h. Pure **12c** was obtained after an I_2/DBU workup (29 mg, 78%) as a 77:23 mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 4.26 (m, 1 H), 4.11 (m, 2 H), 2.44 (d, J = 7.6 Hz, major), 2.33 (t, minor), 1.25 (t, J = 7.1 Hz, 3 H), 1.19 (d, J = 6.1 Hz, 3 H), 0.86 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 3 H).

Ethyl 2-Deutero-3-(t-butyldiphenyl)silyloxybutanoate (12d). ^{1}H NMR ($CDCl_3$) δ 7.68 (m, 4 H), 7.38 (m, 6 H), 4.30 (m, 1 H), 4.05 (m, 2 H), 2.52 (d, major), 2.36 (m, minor), 1.20 (t, J = 7.1 Hz, 3 H), 1.11 (d, J = 6.1 Hz, 3 H), 1.03 (s, 9 H).

Ethyl 2-Deutero-3-(camphorsulfonyl)oxybutanoate (12e). Characteristic peaks are: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21 (m, 1 H), 4.18 (m, 2 H), 3.70 (d, 0.5 H), 3.57 (d, 0.5 H), 3.11 (d, 0.5 H), 3.00 (d, 0.5 H), 2.80 (dt, major 1 H), 2.59 (t, minor 1 H), 2.48 (m, 1 H), 2.39 (dt, 1 H).

Ethyl 2-Deutero-3-methoxybutanoate (12f). ^{1}H NMR ($CDCl_3$) δ 4.15 (q, J = 7.14 Hz, 2 H), 3.78 (m, 1 H), 3.33 (s, 3 H), 2.45 (dt, 0.5 H), 2.35 (m, 0.5 H), 1.21 (t, J = 7.14 Hz, 3 H), 1.20 (d, J = 6.20 Hz, 3 H).

Ethyl 3-Acetoxy-2-deuterobutanoate (12g). ^{1}H NMR ($CDCl_3$) δ 5.25 (m, 2 H), 4.14 (q, 2 H), 2.60 (dt, minor 1 H), 2.48 (m, major 1 H), 2.01 (s, 3 H), 1.29 (d, 3 H), 1.25 (t, 3 H).

4-Carbethoxy-5-hydroxy-1-hexene (13a). ^{1}H NMR ($CDCl_3$) δ 5.75 (m, 1 H), 5.05 (m, 2 H), 4.15 (m, 2 H), 3.96 (m, 1 H), 2.60 (d, 1 H), 2.45 (m, 3 H), 1.25 (m, 3 H), 1.21 (m, 3 H).

4-Carbethoxy-5-(t-butyldimethyl)silyloxy-1-hexene (13c-anti/syn). ^{1}H NMR ($CDCl_3$) δ 5.75 (m, 1 H), 5.00 (m, 2 H), 4.10 (m, 2 H), 3.98 (m, 1 H), 2.38 (m, 3 H), 1.24 (t, 3 H), 1.16 (d, 3 H), 0.89 (s, 5 H), 0.86 (s, 4 H), 0.05 (s, 4 H), 0.03 (s, 2 H).

4-Carbethoxy-5-(t-butyldiphenyl)silyloxy-1-hexene (13d-anti/syn). ^{1}H NMR ($CDCl_3$) δ 7.68 (m, 4 H), 7.38 (m, 6 H), 5.68 (m, 1 H), 4.97 (m, 2 H), 4.05 (m, 2 H), 2.55 (m, 1 H), 2.33 (m, 2 H), 1.21 (m, 3 H), 1.03 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 173.5, 136.0, 134.5, 134.5, 133.8, 133.7, 129.8, 129.7, 127.7, 127.5, 116.4, 116.4, 70.5, 70.4, 60.2, 53.7, 53.3, 32.9, 31.8, 27.0, 26.9, 20.8, 19.4, 19.3, 15.4, 14.3; MS *m/z* 365, 353, 227, 199, 183, 167, 139, 135, 123, 105, 77, 57; HRMS calcd. for $C_{22}H_{25}O_3Si$ [M – t-Bu], 353.1573, found, 353.1572.

4-Carbethoxy-5-(camphorsulfonyl)oxy-1-hexene (13e-anti/syn): Typical Allylation Procedure. Compound **2a** (0.10 g, 0.23 mmol) was dissolved in benzene (1.15 mL) and allyltributyltin (142 μL, 0.46 mmol) and hexabutylditin (15 μL, 0.03 mmol) were added. The reaction was irradiated with a sunlamp for ~4 h. An I_2/DBU workup gave **13e** (0.114 g, 99%) as a 50:50 mixture of diastereomers. Characteristic peaks are: ^{1}H NMR

($CDCl_3$) δ 5.75 (m, 1 H), 5.05 (m, 3 H), 4.18 (q, 2 H), 3.59 (m, 1 H), 3.00 (m, 1 H), 2.75 (m, 1 H).

Ethyl 2-Deutero-3-hydroxy-4-methylpentanoate (14a). ^1H NMR ($CDCl_3$) δ 4.18 (q, 2 H), 3.76 (m, 1 H), 2.92 (d, major), 2.89 (d, minor), 2.47 (q, minor), 2.39 (dt, major), 1.7 (m, 1 H), 1.29 (t, 3 H), 0.95 (d, 3 H), 0.92 (d, 3 H).

Ethyl 2-Allyl-3-hydroxy-4-methylpentanoate (15a anti and syn). ^1H NMR ($CDCl_3$) δ 5.74 (m, 1 H), 5.07 (m, 2 H), 4.15 (m, 2 H), 3.55 (q, minor), 3.33 (m, major), 2.65 (m, 1 H), 2.63 (d, J = 13.8 Hz, major), 2.44 (m, 2 H), 2.35 (d, J = 4.3 Hz, minor), 1.68 (m, 1 H), 1.26 (t, J = 7.1 Hz, major), 1.25 (t, J = 7.1 Hz, minor), 0.95 (m, 6 H); MS, *m/z* 182, 157, 128, 111, 100, 95, 83, 69, 55, 43; HRMS *m/z* calcd. for $C_8H_{13}O_3$ [M – C_3H_7], 157.0865, found, 157.0865.

Ethyl 2-Deutero-4,4-dimethyl-3-hydroxypentanoate (16a). ^1H NMR (500 MHz, $CDCl_3$) δ 4.17 (q, 2 H), 3.69 (dd, J = 10.7 Hz, 2.1 Hz, 1 H), 2.89 (d, J = 3.6 Hz, major 1 H), 2.85 (d, J = 3.6 Hz, minor 1 H), 2.50 (q, J = 2.2 Hz, minor 1 H), 2.33 (dt, J = 10.8 Hz, 2.3 Hz, major 1 H), 1.27 (t, 3 H), 0.92 (s, 9 H).

Ethyl 2-Deutero-3-hydroxy-3-phenylpropanoate (17a). ^1H NMR ($CDCl_3$) δ 7.40 (m, 5 H), 5.13 (m, 1 H), 4.18 (q, J = 7.1 Hz, 2 H), 3.29 (two d, 1 H), 2.73 (dt, J = 9.7 Hz, 2.22 Hz, 0.5 H), 2.7 (q, J = 2.7 Hz, 0.5 H), 1.26 (t, J = 7.1 Hz, 3 H).

Ethyl 2-Deutero-3-phenyl-3-(t-butyldiphenyl)silyloxypropanoate (17d). ^1H NMR ($CDCl_3$) δ 7.64 (d, 3 H), 7.40 (m, 6 H), 7.20 (m, 7 H), 5.12 (d, 1 H), 3.92 (m, 2 H), 2.83 (d, J = 7.4 Hz, major 1 H), 2.56 (d, J = 5.9 Hz, minor 1 H), 1.10 (t, 3 H), 1.00 (s, 9 H).

Ethyl 2-Bromo-3-trifluoromethylbutanoate (25). Diisopropylamine (1.96 mL, 14 mmol) was dissolved in THF (20 mL) and cooled to –78°C. Then n-BuLi (8.75 mL, 14 mmol) was added and after 15 min at –78°C, **24** (2 g, 10.86 mmol) was added dropwise. After 30 min, chlorotrimethylsilane (1.77 mL, 14 mmol) was added. After a further 30 min, the reaction was poured into a cold water/ether mixture. The organic layer was washed, dried and concentrated. The crude silyl enol ether was redissolved in THF (20 mL) and cooled to –78°C. A solution of NBS (1.95 g, 11 mmol) in THF (25 mL) was added to the reaction and after 20 min at -78°C, the reaction was allowed to warm to 25°C and subject to a workup. Purification by flash column chromatography (pentane/ether = 96:4) gave **25** (1.4 g, 50%): ^1H NMR (C_6D_6) δ 4.18 (d, J = 6.8 Hz, 1 H), 3.80 (q, J = 7.1 Hz, 2 H), 2.68 (m, 1 H), 1.03 (d, J = 6.9 Hz, 3 H), 0.81 (t, J = 7.1 Hz, 3 H); ^1H NMR ($CDCl_3$) δ 4.43 (d, 1 H), 4.25 (q, 2 H), 2.98 (m, 1 H), 1.36 (d, 3 H), 1.30 (t, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.2, 126.1 (q, $J_{C,F}$ = 279.1 Hz), 62.7, 44.3, 40.9 (q, $J_{C,F}$ = 27.1 Hz), 13.9, 11.9.

Ethyl 2-Deutero-3-trifluoromethylbutanoate (26). In a dry flask, compound **25** (0.225 g, 0.85 mmol) was dissolved in benzene (4 mL) and AIBN (0.016 g, 0.1 mmol) and Bu_3SnD (0.234 mL, 0.87 mmol) were added. The reaction was heated at 80°C for 2 h. It was then cooled and a crude spectrum was obtained of **26** as a 50:50 mixture of diastereomers. Characteristic peaks of **93**; ^1H NMR (C_6D_6) δ 3.83 (q, 7.1 Hz, 4 H), 2.60 (m, 2 H), 2.36 (m, 1 H), 1.89 (dt, J = 9.2 Hz, 2.5 Hz, 1 H).

Ethyl 2-Bromo-3-(diphenylvinyl)silyloxybutanoate (27). Silylation of **2a** (0.210 g, 1 mmol), diphenylvinylchlorosilane (0.329 g, 1.34 mmol) was accomplished with imidazole (0.340 g, 5 mmol) and CH_2Cl_2 (11 mL). Purification by flash column chromatography (pentane:ether = 98:2) gave **27** (0.250 g, 60%): ^1H NMR ($CDCl_3$) δ 7.57 (m, 4 H), 7.39 (m, 6 H), 6.50 (dd, J = 20.3 Hz, 14.9 Hz, 1 H), 6.29 (dd, J = 14.9 Hz, 3.8 Hz, 1 H), 5.86 (dd, J = 20.3 Hz, 3.9 Hz, 1 H), 4.41 (m, 1 H), 4.12 (d, J = 8.6 Hz, 1 H), 4.03 (m, 2 H), 1.38 (d, J = 6.1 Hz, 3 H), 1.18 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.93, 137.84, 135.08, 134.06, 133.87, 133.34, 130.18, 127.91, 70.81, 61.95, 50.43, 21.09, 13.87; IR (neat) 2982, 1741, 1429, 1404, 1377, 1302, 1263, 1199, 1113, 1030, 995, 949 cm^{-1}; MS (EI) *m/z* 393, 391, 343, 199, 183, 149, 105; CI *m/z* 421, 419, 343, 341, 263, 209, 149.

Cyclization products of 27. Compound **27** (0.10 g, 0.24 mmol) was dissolved in benzene (4.8 mL) and AIBN (4 mg, 0.025 mmol) and Bu_3SnH (70.6 μL, 0.26 mmol) were added. The reaction was heated at 100°C for 20 h. The crude product was subjected to an I_2/DBU workup and then purified by flash column chromatography (pentane:ether = 98:2) to give three fractions. The least polar fraction was unreacted starting material **27** (30 mg, 30%). The intermediate fraction was a 10:1 mixture of the 6-endo product **29** and directly reduced starting material **30** (combined 16.5 mg, 20%). The most polar fraction was the 5-exo product **28** as a 2:1 mixture of diastereomers (29 mg, 36%). A related experiment at 0.01 M gave the results listed in eq 8. Characteristic peaks for **29**: ^1H NMR ($CDCl_3$) δ 7.7 (m, 2 H), 7.5 (m, 2 H), 7.4 (m, 6 H), 4.25 (m, 1 H), 4.1 (q, 2 H), 2.4 (m, 1 H), 2.3 (m, 1 H), 2.0 (m, 1 H), 1.3 (d, 3 H), 1.25 (t, 3 H). Characteristic peaks for **28**: ^1H NMR ($CDCl_3$) δ 7.5 (m, 10 H), 4.65 (m, 1H, minor), 4.4 (m, 1H, major), 4.2 (m, 2 H), 2.8 (dd, 1H, minor), 2.4 (dd, 1H, major), 2.1 (m, 1 H), 1.5 (d, 2 H), 1.4 (d, 1 H), 1.3 (m, 3 H), 1.05 (d, 2 H), 0.9 (d, 1 H).

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