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Does Activation of the Anti Proton, Rather than Concertedness, Determine the Stereochemistry of Base-Catalyzed 1,2-Elimination Reactions? Anti Stereospecificity in E1cB Eliminations of β-3-Trifluoromethylphenoxy Esters, Thioesters, and Ketones

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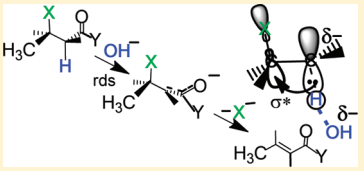
Supporting Information

ABSTRACT: As part of a comprehensive investigation on the stereochemical aspects of base-catalyzed 1,2-elimination reactions, we have studied a set of acyclic carbonyl substrates that react by an irreversible E1cB mechanism with largely anti stereospecificity. ^{2}H NMR data show that these reactions using KOH in EtOH/H_2O under non-ion-pairing conditions produce a minimum of 85−89% anti elimination on stereospecifically labeled *tert*-butyl (2*R**,3*R**)- and (2*R**,3*S**)-3-(3-trifluoromethylphenoxy)-2,3-$^2H_2$-butanoate, *S*-*tert*-butyl (2*R**,3*R**)- and (2*R**,3*S**)-3-(3-trifluoromethylphenoxy)-2,3-$^2H_2$-butanethioate, and the related ketones, (4*R**,5*R**)- and (4*R**,5*S**)-5-(3-trifluoromethylphenoxy)-4,5-$^2H_2$-3-hexanone. With both diastereomers of each substrate available, the KIEs can be calculated and the innate stereoselectivities determined. The elimination reactions of the β-3-trifluoromethylphenoxy substrates occur by E1cB mechanisms with diffusionally equilibrated enolate-anion intermediates. Thus, it is clear that anti elimination does not depend solely upon concerted E2 mechanisms. Negative hyperconjugation provides a satisfactory explanation for the anti stereospecificity exhibited by our carbonyl substrates, where the leaving group activates the anti proton, leading to the enolate intermediate. The activation of the anti proton by negative hyperconjugation may also play a role in the concerted pathways of E2 mechanisms. We have also measured the rates of the hydroxide-catalyzed elimination reactions of butanoate, thiobutanoate, and ketone substrates in EtOH/H_2O, with β-tosyloxy, acetoxy, and 3-trifluoromethylphenoxy nucleofuges.



INTRODUCTION

Some years ago we set out to understand the stereochemical features of base-catalyzed 1,2-elimination reactions of β-substituted acyclic carbonyl compounds. When we began our research, virtually nothing was known about the stereochemistry of elimination reactions that produce conjugated carbonyl compounds, despite their great importance in organic and biochemistry. Many 1,2-elimination reactions of carbonyl compounds having β-nucleofuges are thought to follow a two-step pathway with a carbanion intermediate, called the E1cB mechanism (elimination, unimolecular, conjugate base).[1] When formation of the carbanion is slow and loss of the nucleofuge is fast, formation of the carbanion is essentially irreversible, and the reaction is called E1cB$_I$ or E1cB$_{irreversible}$. When the carbanion intermediate is formed reversibly, the mechanism is called E1cB$_R$. We already have insights into the stereoselectivity of the elimination reactions of stereospecifically deuterated *tert*-butyl β-trimethylacetoxy- and β-tosyloxybutanoate and thiobutanoate esters for which 94−95% anti elimination occurs.[2,3] Liquid-phase density functional theory (DFT) calculations support a stepwise E1cB$_I$ pathway for these reactions, except for the elimination of TsOH from the tosyloxyester, which follows a concerted but asynchronous E2 pathway with an E1cB-like transition state.[4]

It is generally recognized that anti elimination will dominate over syn elimination under normal conditions, where ion pairing or complex conformational factors of cyclic compounds do not play a major role.[5,6] In anti E2 eliminations orbital overlap can be maximized, and torsional strain is minimized. However, it has been suggested that E1cB-transition states may favor syn elimination.[5,7−9] Our experiments with the β-trimethylacetoxy and β-tosyloxy nucleofuges are not consistent with this suggestion.

Over sixty years ago Cristol observed facile anti elimination from stereoisomeric 1,2,3,4,5,6-hexachlorocyclohexanes and suggested that the concerted E2 mechanism proposed by Ingold provided a smooth path for anti elimination that was not as readily available to syn elimination.[10−13] Early quantum mechanical calculations confirmed the anti preference, which could be relaxed when there is little or no π-overlap between the α- and β-carbons in the transition state.[6] In other words, E1cB pathways were expected to lead to a diminished amount of anti elimination. There has been a good deal of study of E1cB and E1cB-like concerted E2 pathways. Although many

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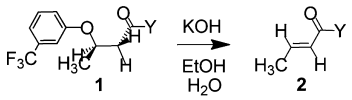
complexities, especially conformational effects and aggregation phenomena, have arisen in studying these mechanisms, Bartsch and Závada noted that the tendency for activated syn eliminations will, in general, be low for acyclic substrates.[14] What is needed to discover whether E1cB reactions proceed mainly with anti or with syn stereospecificity is a careful stereochemical study of elimination reactions that are unambiguously E1cB and which avoid large conformational effects and ion-pair phenomena. To provide the necessary evidence on the stereospecificity of E1cB eliminations, we chose to study stereospecifically deuterated *tert*-butyl 3-(3-trifluoromethylphenoxy)butanoate (**1a**), its analogous thioester, *S*-*tert*-butyl 3-(3-trifluoromethylphenoxy)butanethioate (**1b**), and a related ketone, 5-(3-trifluoromethylphenoxy)-3-hexanone (**1c**), (eq 1).



a Y = $OC(CH_3)_3$
b Y = $SC(CH_3)_3$
c Y = CH_2CH_3

The 3-trifluoromethylphenoxy nucleofuge is the poorest leaving group we have studied that did not also produce competing H/D exchange by an $E1cB_R$ pathway. In addition to using this nucleofuge to tilt the pathway toward the E1cB end of the mechanistic spectrum, the pK_a of the substrate can be important. The range of acidities of the α-protons in **1a**–**c** is approximately 10^6. Our data provide unambiguous evidence that the pathway for the base-catalyzed loss of 3-trifluoromethylphenol from **1a**–**c** is a stepwise $E1cB_I$ mechanism with an enolate anion intermediate, confirming that E1cB pathways do not reduce the importance of anti elimination.

RESULTS

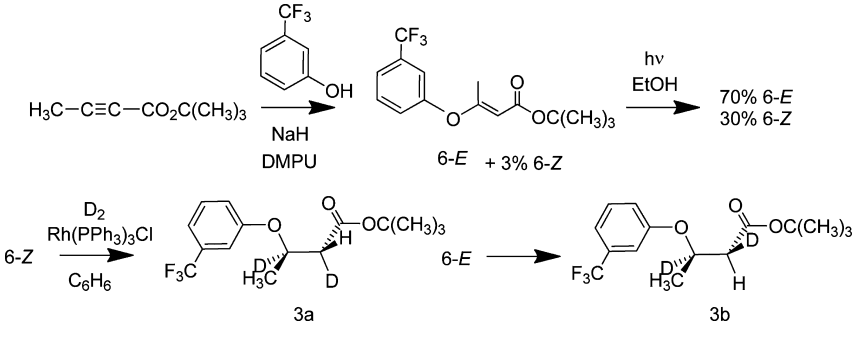
The six substrates that form our data set are stereospecifically labeled *tert*-butyl (2*R**,3*R**)-3-(3-trifluoromethylphenoxy)-2,3-$^2H_2$-butanoate (**3a**) and its (2*R**,3*S**) diastereomer (**3b**), *S*-*tert*-butyl (2*R**,3*R**)-3-(3-trifluoromethylphenoxy)-2,3-$^2H_2$-butanethioate (**4a**) and its (2*R**,3*S**) diastereomer (**4b**), and (4*R**,5*R**)-5-(3-trifluoromethylphenoxy)-4,5-$^2H_2$-3-hexanone (**5a**) and its (4*R**,5*S**) diastereomer (**5b**). In order to determine the innate elimination stereospecificity (% anti vs % syn) of compounds **1a**–**c**, both stereospecifically deuterated, diastereomeric (*R**,*R**) and (*R**,*S**) analogues of each substrate must be available so that the kinetic isotope effects (KIEs) can be factored out.

Substrate Synthesis. Our synthesis of pure **3a** and **3b** depends on the rigorous syn deuteration of *tert*-butyl (*Z*)-3-(3-trifluoromethylphenoxy)-2-butenoate (**6-*Z***) and *tert*-butyl (*E*)-3-(3-trifluoromethylphenoxy)-2-butenoate (**6-*E***) using homogeneous catalysis.[2] Thus, pure **6-*Z*** and **6-*E*** were required. The base-catalyzed conjugate addition of phenols to 2-butynoate esters in DMPU has produced a preponderance (>90%) of the (*E*)-3-phenoxy-2-butenoate in every case we have studied, including the addition of phenol and 3-nitrophenol.[15] Configurational assignments of the (*Z*)- and (*E*)-isomers have been established by the X-ray crystallographic structure of *tert*-butyl (*E*)-3-phenoxy-2-butenoate (**7**), as well as by NMR chemical shift correlations of the C-2 proton of the alkenes and of stereospecifically deuterated (*R**,*R**) and (*R**,*S**) diastereomers.[15] We obtained a 97:3 **6-*E*/6-*Z*** mixture from the conjugate addition of 3-trifluoromethylphenol to *tert*-butyl 2-butynoate, too small an amount of the (*Z*)-isomer for our mechanistic studies. This problem was resolved by a partial photochemical isomerization of **6-*E***.[16] Subsequent flash chromatography on SiO_2 led to the recovery of pure **6-*Z*** and **6-*E*** (Scheme 1). Thioesters **4a** and **4b** were synthesized by deblocking **3a** and **3b** with TFA, activation of the carboxylic acids by TFAA, and esterification with 2-methyl-2 propanethiol. There was no indication of significant H/D exchange in any of the stereospecifically deuterated substrates **3a**–**4b**.

We had expected to model the synthesis of stereospecifically deuterated ketones on that of *tert*-butyl (2*R**,3*R**)-3-acetoxy-2,3-$^2H_2$-butanoate and its (2*R**,3*S**) diastereomer, which involved syn deuterogenation of the (*E*)- and (*Z*)-isomers of *tert*-butyl 3-acetoxy-2-butenoate by Wilkinson's catalyst.[2] Although the (*E*)- and (*Z*)-isomers of 4-acetoxy-3-penten-2-one could be prepared easily by acetylation of 2,4-pentanedione, deuterogenation consistently gave a 1:1 mixture of the (3*R**,4*R**) and (3*R**,4*S**) diastereomers of 4-acetoxy-3,4-$^2H_2$-2-pentanone, even after ensuring substrate and product stability under the reaction conditions and investigating several experimental variants. This lack of stereospecificity suggests that the greater proclivity of ketones for enolization promotes a reversible n–π rearrangement of the alkylrhodium intermediate in the deuterogenation reaction.

Our second attempt was to produce the ketone from stereospecifically deuterated 3-acetoxy-2,3-$^2H_2$-butanoic acid and MeLi/THF, with the expectation that any 4-hydroxy-3,4-$^2H_2$-2-pentanone that might be produced could be reacetylated. Although initial trials were promising, the complex reaction mixtures that resulted could not be purified by chromatography. Use of BuLi and dimethoxyethane (DME) was more effective, but despite using a workup involving Me_3SiCl, some tertiary alcohol always resulted. We then turned to using the

Scheme 1



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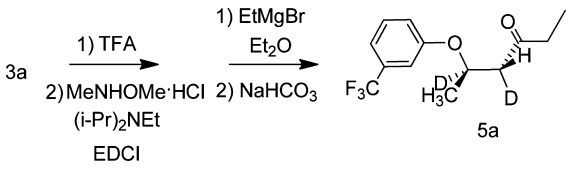
3-trifluoromethylphenoxy leaving group. Attempts to add BuLi to 3-(3-trifluoromethylphenoxy)butanoic acid produced only starting material, 2-octen-4-one, and 3-trifluoromethylphenol. However, use of Weinreb amide methodology proved to be far more successful.[17,18]

Reaction of *N*-methoxy-*N*-methylamides with organometallic species provided a clean method for the synthesis of **5a** and **5b**. The only significant question was if this methodology would lead to our ketone substrates without H/D exchange or loss of stereospecificity. Fortunately, there was little or no H/D exchange (<3%), and any loss of stereospecificity was undetectable by ^{2}H NMR analysis. Scheme 2 shows the synthesis of ketone **5a** from **3a**; ketone **5b** was produced from **3b** in like manner.

Scheme 2



Use of hexanones **5a** and **5b** was determined by practical constraints. Solubility of the analogous octanones in EtOH/H_2O was too limited for our studies, and the volatility of the pentanones produced unacceptable reaction yields. The overall yield of **5a** from ester **3a** was 65%, and the yield of **5b** from **3b** was 61%. It is likely that the yields could have been greater with more experimentation. Use of alkyllithiums, rather than the Grignard reagent, use of THF as the solvent, and use of DCC rather than EDCI as the coupling agent lowered the yields considerably. A small amount of elimination of 3-trifluoromethylphenol decreased the yields of **5a** and **5b**, and use of too great an excess of EtMgBr led to 10% or more of the tertiary alcohol side product.

Conformational Analysis. Two staggered rotational isomers of each *R***R** diastereomer (**3a**−**5a**) and two for each *R***S** diastereomer (**3b**−**5b**) will have the periplanar arrangement conducive to anti elimination, as shown in Figure 1.

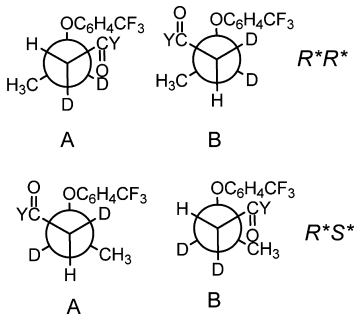


Figure 1. Staggered rotational isomers leading to antiperiplanar elimination.

If the elimination reactions were E2, only the A conformers in Figure 1 could give a concerted anti elimination reaction that would lead to (*E*)-alkenes. In the *R***R** diastereomer a deuteron will be lost by an anti process, whereas in the *R***S** diastereomer a proton will be lost.

However, if the elimination reactions are E1cB and the lifetimes of the enolate-anion intermediates are long enough for rotation to occur about the C2−C3 bond of the enolate anions in the reactions of **3a**−**4b** (and C4−C5 of **5a** and **5b**), rotamer B of the *R***R** diastereomer could lose a proton by anti elimination and still produce the (*E*)-alkene. Thus, two staggered conformers of the *R***R** substrates could undergo anti elimination and produce the (*E*)-alkene product. An anti elimination from conformer B is indistinguishable from a syn elimination from conformer A in our experiments.

To ascertain if any substantial changes in the populations of the three staggered rotational isomers could influence the percentage of anti elimination from **1a**−**c**, we used 1D NMR to measure the vicinal coupling constants in the eight-line ABX pattern of the C-2 protons of **1a** and **1b** and the C-4 protons of **1c** in 3:1 and 5:1 EtOH/H_2O.[19] J_{AX} and J_{BX} were used to calculate the populations of the three rotational isomers by means of an extended Karplus equation.[20] This NMR study will be published separately; however, it showed that neither differing substituents nor different solvents have any significant effect on the conformational populations. The NMR study showed that the population of conformer B is about one-half the population of A in **1a**−**c**. The possibility that both rotational isomers A and B produce anti elimination from the *R***R** diastereomers may play a role in the lesser amount of apparent "*anti*" elimination in the reactions of **1a**−**c** than we saw in our earlier study of *β*-trimethylacetoxy and *β*-tosyloxy substrates.

Elimination Results. Our elimination reactions of **3a**−**4b** were carried out with KOH in v/v 3:1 EtOH/H_2O (1:1 mol/mol). The elimination reactions of ketones **5a** and **5b** were carried out in 5:1 EtOH/H_2O due to the limited solubility of the ketone in 3:1 EtOH/H_2O, and the thioesters **4a** and **4b** were also reacted in 6:1 EtOH/H_2O in order to evaluate the effect of solvent change on the reaction stereospecificity. The elimination reactions led almost entirely to (*E*)-alkene products, with <1.5% of the (*Z*)-alkenes, except in the case of esters **1a**, **3a**, and **3b**, where a small amount of conjugate addition occurred. *tert*-Butyl (*E*)-2-butenoate **8a**, *S*-*tert*-butyl (*E*)-2-butenethioate **8b**, and (*E*)-4-hexen-3-one **8c** from the base-catalyzed elimination of 3-trifluoromethylphenol from the isotopically labeled substrates **3a**−**5b** were purified by preparative GC before NMR analysis. Multiple ^{2}H NMR integrations were used to determine the amount of deuterium lost at C-2 of **8a** and **8b** and C-4 of **8c**, compared to the deuterium content at C-3 and C-5, respectively. This deuterium loss is shown in Table 1 as % "*anti*"$_{R^*R^*}$ and % *syn*$_{R^*S^*}$. These column headings assume that anti elimination, which leads to the (*E*)-alkene, removes a deuteron from the *α*-carbon of the *R***R** diastereomer and a proton from the *α*-carbon of the *R***S** diastereomer. The small amounts of *R***S** diastereomers in *R***R** substrates (∼0.9%) and vice versa (∼0.3%) were taken into account in the data presented. The percentages of anti and syn elimination are the averages from duplicate or triplicate reactions. The *R***S** diastereomers produce much more anti elimination than the *R***R** diastereomers due to the adverse primary KIE for anti elimination from conformer A of the *R***R** compounds.

Control Experiments. In order to ensure the validity of the results shown in Table 1, we have carried out three sets of control experiments on **1a**−**c** and **5a**−**5b**, as well as on the (*Z*)-isomers of the alkenes produced in the elimination reactions. These experiments show that there is no significant isotopic rearrangement nor any significant H/D exchange on the stereospecifically deuterated substrates **3a**−**5b**.

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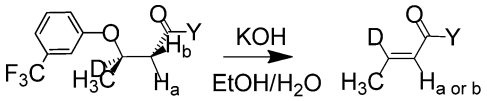
Table 1. Stereospecificity Data and KIEs



	Y	
3a and **3b**	$OC(CH_3)_3$	**8a**
4a and **4b**	$SC(CH_3)_3$	**8b**
5a and **5b**	CH_2CH_3	**8c**

(*R*R**) **3a**, **4a**, **5a**, H_a=D, H_b=H
(*R*S**) **3b**, **4b**, **5b**, H_a=H, H_b=D

	$\%\text{“anti”}_{R^*R^*}$	$\%syn_{R^*S^*}$	$k_{R^*S^*}/k_{R^*R^*}$[a]
3[b]	74.5	3.91	2.14
4[b]	59.7	1.65	3.21
4[c]	55.8	2.41	2.96
5[d]	48.6	1.86	3.03

	$(k_H/k_D)_{anti}$[e]	$(k_H/k_D)_{syn}$[f]
3a and **3b**	2.8	2.9
4a and **4b**	5.3	7.6
4a and **4b**	5.2	6.2
5a and **5b**	6.1	9.1

[a] $k_{R^*S^*}/k_{R^*R^*} = \dfrac{\log([R^*S^*]_i/[R^*S^*]_f)}{\log([R^*R^*]_i/[R^*R^*]_f)}$

[b] 3:1 v/v $EtOH/H_2O$; [c] 6:1 v/v $EtOH/H_2O$; [d] 5:1 v/v $EtOH/H_2O$

[e] $(k_H/k_D)_{anti}$ = % $anti_{R^*S^*}$/% $\text{“anti”}_{R^*R^*}$ × $k_{R^*S^*}/k_{R^*R^*}$

[f] $(k_H/k_D)_{syn}$ = % $\text{“syn”}_{R^*R^*}$/% $syn_{R^*S^*}$ × $k_{R^*R^*}/k_{R^*S^*}$

When the elimination reaction was carried out on **1a** and **1b** with KOD in 3:1 EtOD/D_2O and with **1c** in 5:1 EtOD/D_2O, NMR analysis on the recovered alkenes **2a**–**c** showed no significant H/D exchange. After preparatory GC purification of **2a** from the reaction of **1a**, using 75–103% of the KOD needed for complete reaction, < 0.2% D was observed at C-2 of **2a**. In a similar manner, using 75% of the KOD needed for complete reaction of **1b**, **2b** showed 0.1% D. These elimination products did not contain any H/D exchange that would add complexity to the percentages of anti and syn elimination that we have observed.

Given its two α-carbons, where H/D exchange could occur separately, the ketone **1c** presented a more complex situation. In 5:1 EtOD/D_2O with 50% of the KOD necessary for complete elimination, ^{2}H NMR analysis of **2c** showed no observable deuterium signal at C-4; however, there was a small amount of H/D exchange at C-2. In addition, using ^{2}H NMR analysis of six pooled H/D exchange reactions, the unreacted **1c**, while showing no evidence of H/D exchange at C-4, did show evidence of 2.9 ± 0.5% H/D exchange at C-2. A ^{13}C-DEPT experiment showed that the deuterium was attached to C-2, which had a small ^{2}H-induced ^{13}C upfield triplet; when a DEPT 90° pulse was used to eliminate the original C-2 peak, the deuterium splitting was easily visible.

To test for any isotopic rearrangement at C-4 of **5a**, an elimination reaction was carried out in 5:1 EtOD/D_2O with 50% of the KOD necessary for complete reaction. ^{2}H NMR analysis of the reaction mixture showed that the recovered **5a** showed no loss of stereochemical integrity; by ^{2}H NMR analysis, the initial substrate **5a** contained 0.8% of **5b**, which was within experimental error of the amount of **5b** at 50% reaction.

The third set of control experiments involved determining the extent of *Z* to *E* isomerization of the alkene products. This was important since loss of the isotopic label at the α-carbon leading to the (*Z*)-alkene from conformer A of the (*R*R**) diastereomers is the reverse of that leading to the (*E*)-alkene. The (*E*)-alkenes were formed almost exclusively.[2,3] GC analysis of the elimination mixtures showed only 1.3% of *tert*-butyl (*Z*)-2-butenoate (**9a**) from **1a** during the entire course of the reaction and no discernible amount of *S*-*tert*-butyl (*Z*)-2-butenethioate (**9b**) from **1b**. Under the reaction conditions for **1a**, 29 ± 2% of **9a** was shown to isomerize to **2a**; thus, no more than 0.5% rearrangement could have taken place in the elimination reactions of **3a** and **3b**. Less than 1% of **9b** rearranged to **2b** under the reaction conditions for **1b**. Hence, virtually no isomerization of **9a** to **8a** and **9b** to **8b** took place under reaction conditions. GC analysis of the elimination product mixture from **1c** showed less than 1.5% (*Z*)-4-hexen-3-one (**9c**). Under our reaction conditions, 5% ± 2.5% of **9c** was shown to isomerize to **2c**; thus, only 0.1% of **9c** would have rearranged to **8c** in the reactions of **5a** and **5b**, a minuscule amount that would not affect our interpretation of the stereochemical data.

KIEs and Innate Stereospecificity. The largest errors in the data of Table 1 are in the values for $(k_H/k_D)_{syn}$, which depend on very small amounts of syn elimination from the (*R*S**) diastereomers. Because anti elimination from (*R*S**) compounds results from loss of a proton, the small amount of syn elimination had to be determined by subtraction of two large ^{2}H NMR integrals. We calculated the innate percentages of anti and syn elimination using the far more reliable values of $(k_H/k_D)_{anti}$, which are ±0.23–0.33 (7–11%) at the 90% confidence level. Although $(k_H/k_D)_{syn}$ is subject to a substantial error, this error is not propagated to the innate stereospecificities. Any error in $(k_H/k_D)_{syn}$ is offset by a compensating error in the percentage of syn elimination from the (*R*S**) diastereomer by which it is multiplied to obtain the innate stereospecificity. Calculation of the innate percentages of anti and syn elimination using either $(k_H/k_D)_{anti}$ or $(k_H/k_D)_{syn}$ gave the same values.

The $(k_H/k_D)_{anti}$ value of 2.8 for esters **3a** and **3b** is similar to those seen for the elimination reactions of β-acetoxy- and β-tosyloxyesters and thioesters.[2,3] However, the substantially greater $(k_H/k_D)_{anti}$ values for the β-3-trifluoromethylphenoxy thioester and ketone substrates may bear further consideration. Given the reactions' E1cB pathways, with the rate-determining step being the formation of the carbanion, it is possible that earlier transition states are involved in the formation of more stable enolate anions from the thioester and ketone substrates, as the Hammond postulate would predict. If the transition state position is one where the C–H bond is approximately half broken, $(k_H/k_D)_{anti}$ values in the 5–6 range can be explained by classical KIE theory. Tunneling may also be involved, which calls for DFT calculations to sort out. It appears that a carbanionic transition state is especially conducive to tunneling.[21,22]

Using the data in Table 1, the innate percentages of anti and syn elimination, those that can be expected in the absence of isotopic labels, can be calculated in a straightforward manner. The results are shown in Table 2. Secondary deuterium KIEs are unlikely to be greater than 1.03 and would have a negligible

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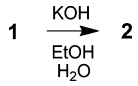
effect on the results.[23] The percentages of anti elimination are the minimum amounts that occur, since it is not unlikely that a component of the "syn" elimination of the *R**R* diastereomers is due to anti elimination of the B rotamers with loss of a proton (see Figure 1). However, it is unlikely that conformer B of the *R**S* diastereomers plays any significant role, since in anti elimination a deuteron would be lost from a higher-energy conformer; our data show that there is only a small amount of deuterium loss (1.6−3.9%) from the *R**S* diastereomers.

Although it appears that there is a smaller amount of anti elimination as the acidity of the substrate increases, our analyses indicate that all of the stereopecificities in Table 2 are probably within experimental error, which we estimate to be ±1.4%. An additional factor is that the change to a more ethanol-rich solvent may tilt the reactions to slightly less anti stereochemistry, as demonstrated by the thioester results. All of the β-3-trifluoromethylphenoxy substrates exhibit largely anti elimination, even though they have E1cB mechanisms with enolate-anion intermediates.

Table 2. Innate Stereospecificity of Base-Catalyzed Eliminations

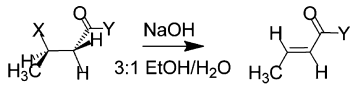


	% *anti* elimination[a]
1a[b]	89.0
1b[b]	88.7
1b[c]	86.7
1c[d]	85.3

[a]% *anti* elimination = (% "*anti*"$_{R^*R^*}$ × $(k_H/k_D)_{anti}$)/(% "*syn*"$_{R^*R^*}$ + (% "*anti*"$_{R^*R^*}$ × $(k_H/k_D)_{anti}$)). [b]3:1 v/v EtOH/H_2O. [c]6:1 v/v EtOH/H_2O. [d]5:1 v/v EtOH/H_2O.

Rate Studies. In order to gain further insight into the mechanisms of these elimination reactions, we also determined the second-order rate constants for each of the substrates for which we have measured the elimination stereospecificity. The results are shown in Table 3.

Table 3. Rate Constants for NaOH-Catalyzed 1,2-Elimination Reactions in 3:1 EtOH/H_2O



Rate Constants ($M^{-1}s^{-1}$)

X \ Y	$OCMe_3$	$SCMe_3$	CH_2Me
H_3C–C_6H_4–SO_3	1.41	25.3	—
CH_3CO_2	0.022	1.4	—
F_3C–C_6H_4–O	0.0115	0.814	3.2

Rate constants for the β-acetoxy substrates were measured using only 100 mM $NaClO_4$ to provide constant ionic strength, rather than the 120 mM $NaClO_4$ used with the tosyloxy and 3-trifluoromethylphenoxy substrates. However, a control experiment in which the rate of **1b** was measured using 100 mM $NaClO_4$ gave a rate constant of 0.82 ± 0.03 M^{-1} s^{-1}; this was within our experimental error of 0.814 ± 0.009 M^{-1} s^{-1} for the rate constant at 120 mM $NaClO_4$. It seems appropriate to compare directly the rate constants of the β-acetoxy and other substrates.

In addition to measuring reaction kinetics in 3:1 EtOH/H_2O, we examined the effect of the proportion of EtOH and H_2O on the reaction rates. Using 5:1 EtOH/H_2O with **1b** and **1c** produced rate constants of 0.989 ± 0.008 and 3.3 ± 0.2 M^{-1} s^{-1}, respectively. The rate constant for **1b** is 21% greater in 5:1 than in 3:1 EtOH/H_2O, whereas the rate constants for **1c** are within experimental error. In addition, the rate constant for **1b** in 1.67:1 EtOH/H_2O was 0.621 ± 0.012 M^{-1} s^{-1}, 24% smaller than the rate constant in 3:1 EtOH/H_2O. This rate pattern is not uncommon in base-catalyzed elimination reactions; hydroxide ion is a stronger base in a less polar solvent, and the enolate anion produced in the rate-determining step has the negative charge spread out over a larger volume than in the hydroxide reactant. However, the rate differences are small enough that we seem safe in comparing the stereospecificity results in 3:1 and 5:1 EtOH/H_2O.

The expected reactivity pattern is immediately apparent in the data of Table 3. Increasing the acidity of the protons α to the carbonyl group and having a better β-leaving group that can provide greater activation of the anti proton produce a larger rate constant. The innate reactivity of the β-acetoxy and 3-trifluoromethylphenoxy thioesters is 70−71-fold greater than that of the analogous esters, reflecting the greater acidity of the thioesters. However, the rate differential of the β-tosyloxy ester and thioester is only 18-fold. DFT calculations support a stepwise $E1cB_I$ pathway for the β-tosyloxythioester but an asynchronous E2 pathway for the β-tosyloxyester.[4] This change of mechanism is probably responsible for the smaller rate differential in the tosyloxy substrates. It is interesting to note that the ratio of rate constants ($k_{ketone\,1c}/k_{thioester\,1b}$ = 3.9) is comparable to the ratio of rate constants for hydroxide-catalyzed proton exchange at the α-carbon atoms of acetone and ethyl thioacetate in water, where $k_{ketone}/k_{thioester}$ = 4.25.[24] This is consistent with the rate-determining formation of enolate anions in an E1cB mechanism for **1b** and **1c**.

DISCUSSION

All of the acyclic β-oxycarbonyl compounds in Table 2 show a distinct preference for anti elimination. Ranging from an ester activating group (pK_a ~25),[25] through a thioester (pK_a ~21),[26] to a ketone (pK_a ~19),[27] 85−89% anti stereoselectivity was observed. The stereochemical results from our three β-3-trifluoromethylphenoxy substrates in Table 2 show somewhat less anti elimination than we found earlier with the analogous β-tosyloxy and β-trimethylacetoxy substrates (~94% anti). However, the observed anti stereospecificity of the β-3-trifluoromethylphenoxy substrates is a minimum amount, since the percentage of "syn" elimination from the *R**R* diastereomers may include the loss of a proton by anti elimination from B rotamers (Figure 1).

These are E1cB reactions, yet they have the same anti stereospecificity shown in E2 reactions. This calls into question the commonly accepted rationale for anti elimination, which is the concerted nature of E2 reactions. While there is little doubt that simple acyclic substrates with good leaving groups show a strong preference for anti elimination and have E2 mechanisms, this may be a matter of correlation rather than causality. Now

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that we have clear evidence that E1cB reactions, which proceed through enolate-anion intermediates, show the same preference for anti elimination, it seems that a more general cause for this anti preference must be identified.

Over 45 years ago Fukui made a frontier electron-density calculation, which showed that the β-proton anti to the vicinal chlorine atom in the lowest-energy conformational isomer of chloroethane has the least bonding character.[28] However, other calculations indicated that the preference for antiperiplanar elimination can be relaxed when there is little or no π-overlap between the α- and β-carbon atoms in the transition state for E2 elimination. It was suggested that if a molecule that would normally prefer anti elimination is substituted by a strong activating group, syn elimination would often be faster.[6] The situation was made more complex by the difficulty of distinguishing between an E1cB mechanism and an E2 mechanism in which the transition state is carbanion-like.[29] Another sticking point was the absence of synthetic routes to stereospecifically labeled acyclic substrates that followed unambiguous E1cB pathways.

E1cB$_I$ Mechanism. A large body of research points to the E1cB mechanism being operative in elimination reactions where strongly activating electron-withdrawing groups (EWGs) are present.[30] In a study of β-cyanothioethers, which proceed through a stepwise E1cB mechanism, Fishbein and Jencks suggested that since the E1cB mechanism operates with a cyano EWG, it is unlikely that β-carbonyl or nitro-activated compounds with reasonable leaving groups will undergo elimination by a concerted mechanism.[31] Consistent with this suggestion, Fedor and Glave observed saturation kinetics at high buffer concentrations in the general-base catalysis of *para*-substituted phenol elimination from 4-phenoxy-2-butanones by tertiary amines in water.[32] This provides convincing kinetic evidence for an E1cB mechanism where partitioning of the enolate anion is kinetically important.

The results of Crosby and Stirling on the elimination of phenol from ethyl 3-phenoxypropanoate (**10**) and 4-phenoxy-2-butanone (**11**) also validate E1cB pathways for the elimination reactions of **1a**−**c**. Rate constants obtained in EtOH, where the EWGs ranged from NO_2 to S(O)Me, correlated well with pK_a and log $k_{ionization}$ and with σ^-_R, which measures resonance effects.[33] In addition, rate constants obtained in water using $PhOCH_2CH_2S(O)CH_3$, as well as the dideuterated substrate $PhOCH_2CD_2S(O)CH_3$, showed a primary k_H/k_D of unity, which is consistent with an E1cB$_R$ mechanism.[34] The authors pointed out that it is highly likely that all of their substrates that have greater rates, including **10** and **11**, also follow E1cB$_R$ pathways. In NaOH/H_2O with 2% added EtOH at 25.4 °C the second-order rate constants were 0.015 M^{-1} s^{-1} for **10** and 3.1 M^{-1} s^{-1} for **11**, a ratio of k_{11}/k_{10} = 207. Our rate constants in 3:1 EtOH/H_2O at 30 °C (Table 3) for ester **1a** and ketone **1c** were 0.0115 and 3.2 M^{-1} s^{-1}, respectively, for a ratio of k_{1c}/k_{1a} = 278.

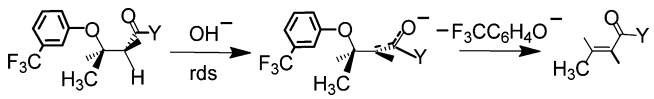
Three compelling lines of evidence from our research support the E1cB$_I$ pathway for our substrates. First of all, DFT calculations offer good support for a stepwise E1cB$_I$ pathway for the elimination of acetic acid from *tert*-butyl 3-acetoxybutanoate and the analogous thioester in 3:1 EtOH/H_2O.[4] The enolate intermediates should be even more likely in the elimination pathways for **1a**−**c**, which contain a poorer nucleofuge as well as a more potent activating group in the case of **1c**. Consistent with this evidence and with the experimental results of Crosby and Stirling on **11**,[34] the rate evidence of Cavestri and Fedor provides strong support for an E1cB$_I$ mechanism for the elimination of *para*-substituted benzoic acids in water using a range of *para*-substituted 4-benzoyloxy-2-butanones and amine bases.[35] The rates were almost independent of the nature of the leaving group (ρ = +0.18) and demonstrated saturation kinetics, and their rates correlated well with the rates of H/D exchange of 4-methoxy-2-butanone using hydroxide as the base.

Second, with 50% of the KOD necessary for complete elimination of ketone **1c**, the recovered (*E*)-alkene **8c** showed no observable deuterium signal at C-4. However **8c**, as well as unreacted **1c**, did show evidence for a small amount of H/D exchange at C-2. Thus, H/D exchange was occurring concurrently at the C-2 α-carbon while the elimination was proceeding at C-4 and C-5. Our earlier H/D exchange reactions on 3-substituted butanoate esters had shown that a 3-phenoxy substituent increased the rate of exchange at the α-carbon by over 10-fold compared to an alkyl substituent.[15] It is unlikely that enolate-anion intermediates are produced at C-2 but not at C-4 of **1c**.

Lastly, our strategy was to use the poorest leaving group that would not lead to concurrent H/D exchange. Whereas *tert*-butyl 3-phenoxybutanoate gave approximately 8:1 elimination/exchange in 3:1 EtOH/H_2O, **1a** gave 0.1−0.2% H/D exchange. The correlation between leaving-group ability and pK_a is known to be good if variation in the leaving group is small.[36,37] The pK_a of phenol in water is 9.95,[38] whereas the pK_a of 3-trifluoromethylphenol is 8.95.[39] Thus, 3-trifluoromethylphenoxide is expected to be only a slightly better leaving group than phenoxide. The pathway for elimination of 3-trifluoromethylphenol from **1a** is close to the E1cB$_R$ mechanistic interface, where protonation and extrusion of the nucleofuge are competing reactions of an enolate intermediate.

Although there is unambiguous evidence that our β-3-trifluoromethylphenoxy substrates have E1cB$_I$ mechanisms as shown in Scheme 3, it is important to know if the intermediate enolate anions are diffusionally equilibrated in the reaction solution.

Scheme 3



Our determination of the elimination stereospecificity depended upon the fact that protonation of the intermediate carbanions is slow, which is thought to result from nonperfect synchronization, where electronic delocalization stabilizes the enolate anion more than the transition state in which the C−H bond is only beginning to form, thereby producing a higher activation energy.[40] There is good evidence that the large activation barriers observed for thermodynamically favorable protonation of enolate anions are caused by the requirement that movement of electron density from the enolate oxygen to carbon be coupled to C−H bond formation.[41] Chiang and Kresge have reported that in water the first-order rate constant for protonation at carbon of the enolate anion of acetone by H_2O is 5×10^4 s^{-1}.[27] In the case of ethyl acetate $k_{DOD} < k_{HOH} = 5 \times 10^8$ s^{-1}.[25] The rate constant for diffusional equilibration to produce a hydrated "free" enolate anion for ethyl thioacetate has been estimated to be 1.6×10^{10} s^{-1}.[26] The lifetimes of simple enolates in aqueous solution are ~10^{-9} s for esters

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and ~10^{-5} s for thioesters and ketones, which represent the approximate maximum lifetimes for the enolate intermediates in our elimination reactions of **1a**–**c**.[25,27]

It is difficult to estimate the enolate lifetime before the nucleofuge is lost. Kinetic studies suggest that the first-order rate constant for loss of phenoxide from the hydroxide-generated enolate of 4-phenoxy-2-butanone is 9×10^5 s^{-1},[32] and the 3-trifluoromethylphenoxy substituent is only a slightly better leaving group than the phenoxy group. It seems likely that all of the enolate anions in the mechanisms we have studied are free, diffusionally equilibrated carbanions. The only case where there may be doubt is ester **1a**. However, the research of Amyes and Richard on H/D exchange of ethyl acetate in water shows that diffusion of the ester enolate is faster than its reaction with solvent by a factor of ~300.[25] One could expect that the rate of protonation of an enolate anion by HOH might be marginally less in an EtOH/H_2O mixture, where water is a somewhat weaker acid. Thus, it is likely that the elimination of 3-trifluoromethylphenol from **1a** also involves a diffusionally equilibrated enolate intermediate.

Negative Hyperconjugation. All of this evidence shows that the base-catalyzed elimination of 3-trifluoromethylphenol from **1a**–**c** proceeds in EtOH/H_2O by an E1cB mechanism through fully formed, diffusionally equilibrated enolate anion intermediates. Yet the innate stereospecificity of these elimination reactions is overwhelmingly anti. The anti stereospecificity must arise from factors other than a concerted E2 process. A likely cause of the anti stereochemistry is negative hyperconjugation, the interaction of the lone pair of electrons developing in the transition state for deprotonation of **1a**–**c** with the vacant σ^* orbital of the bond to the antiperiplanar β-leaving group as shown in Figure 2.

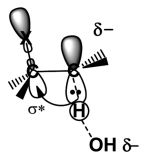

Figure 2. Activation of the anti proton by negative hyperconjugation.

Negative hyperconjugation is an intramolecular analogue of the common orbital explanation of inversion in S_N2 reactions, where the electron-rich HOMO of the nucleophile maximizes its interaction with the LUMO of the electrophile at the relatively low-energy C-X σ^* antibonding orbital, which is polarized toward carbon. Negative hyperconjugation was first used to account for the barriers to internal rotation for $FCH_2CH_2^-$.[42] Subsequent calculations have suggested that negative hyperconjugation is a major factor in the stereochemical outcomes of nucleophilic vinylic substitution.[43,44] King and Payne have provided experimental evidence for negative hyperconjugation as a component of the polar effect in the rates of H/D exchange of the α-hydrogens in a series of cyclic sulfones having electronegative β-substituents with known or strongly preferred torsion angles.[45,46] Their data are consistent with a substituent effect of a torsion-angle dependent donation of the partial negative charge of the incipient carbanion into the σ^*_{C-X} orbital, in addition to a smaller inductive effect.

Both E2 and E1cB transition states could be stabilized by hyperconjugative interactions with the leaving group.[47−49] This kind of donor–acceptor interaction has been cited as a possible factor in the anti stereospecificity of E2 elimination reactions.[50] It is likely that a continuum links negative hyperconjugation to both E2 and E1cB reaction pathways. In each case orbital overlap between the activated C–H bond and the low-lying C–X σ^* antibonding orbital leads to anti elimination. In the concerted E2 case the bond breaking and making steps are nearly simultaneous, whereas in the E1cB case the leaving group is expelled only after a carbanion intermediate has formed.

One facet of negative hyperconjugation is its influence on the barrier to internal rotation of the C–C bond, which was calculated to be 9.2 kcal/mol for $FCH_2CH_2^-$.[42] Calculations have also shown that EWGs can reduce the rotation barriers significantly. For the $ClOCH_2CHNO_2^-$ anion a barrier of 6.6 kcal/mol has been calculated.[51] If one assumes an activation barrier of 8 kcal/mol for bond rotation, the rate constant at 25 °C would be 8.5×10^6 s^{-1}, which is approximately 10-times larger than the estimated rate constant for the extrusion of phenoxide from the enolate of **11**.[32] The relevance of these estimates to our reactions can only be an approximation, but it is not unreasonable to assume that bond rotation is faster than loss of the 3-trifluoromethylphenoxy nucleofuge. Thus, 85–89% of anti elimination from **1a**–**c** represents a lower limit, with anti elimination from the less favored B conformer of the *R***R** diastereomer appearing as "syn" elimination.

The importance of negative hyperconjugation in the activation of the anti proton in E1cB reactions depends on the electronegativity of the β-leaving group. These electronegativity differences may also play a role in understanding the greater amount of anti elimination with the β-tosyloxy substrates, which gave 94% anti stereospecificity, than with the β-3-trifluoromethylphenoxy substrates, which gave approximately 87%. Better leaving groups are inherently more electronegative. Hammett σ_m and Taft σ_I values, which have been used to measure inductive effects, are more positive for OTs (0.36 and 0.59, respectively) than for OPh (0.25 and 0.40).[52]

It would be interesting to discover if negative hyperconjugation also has a substantial role in the stereospecificity of 1,2-elimination reactions of nitro-activated acyclic substrates that follow $E1cB_I$ mechanisms under non-ion-pairing conditions.

EXPERIMENTAL SECTION

tert*-Butyl (*Z*)- and (*E*)-3-(3-Trifluoromethylphenoxy)-2-butenoate 6-*Z* and 6-*E*.** Under N_2, 50 mL of DMPU (distilled over CaH_2) and 4.18 g (0.174 mol) of NaH were stirred at 0 °C while a solution of 3-trifluoromethylphenol (51.3 g, 0.316 mol) in 90 mL of DMPU was slowly added. *tert*-Butyl 2-butynoate (31.4 g, 0.224 mol) was then added over 15 min. After 24 h at rt 4.8 mL of AcOH was added. After another 24 h 100 mL of 5% $NaHCO_3$ was added to the viscous reaction mixture, and it was extracted with hexanes. The combined hexane solution was washed with 0.1 M NaOH and dried ($MgSO_4$), and the solvent was removed by evaporation. A 97:3 mixture of **6-*E and **6-*Z*** (63.5 g, 94%) was recovered as a yellow-brown oil.

Photoisomerization of the crude alkene mixture (57.8 g) in 350 mL of degassed 95% ethanol was carried out using a high-pressure quartz Hg-vapor lamp in three separate reactions. After irradiation for 3.3–5 h the stirred reaction was stopped when GC showed that degradation of product had begun to compete with formation of **6-*Z***. The 70:30 *E*:*Z* mixture was evaporated to remove EtOH, and **6-*Z*** and **6-*E*** were separated by flash chromatography (25:1 SiO_2/alkene) by applying less than 20 g of a 1:1 alkene/SiO_2 mixture to each column. Good separation was achieved using a gradient of 1–10% cold Et_2O/hexane. Fractions of the individual **6-*Z*** and **6-*E*** isomers were combined and dried ($MgSO_4$), and the solvent removed by evaporation. **6-*Z***: mp 41–42.5 °C; ^1H NMR ($CDCl_3$, δ) 7.44 (t, 1H), 7.34 (d, 1H), 7.24 (s, 1H), 7.18 (d, 1H), 5.43 (s, 1H), 1.92 (s, 3H), 1.37 (s, 9H). **6-*E***: mp

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76.5−77.5 °C; ^{1}H NMR ($CDCl_3$, δ) 7.54−7.47 (m, 2H), 7.29 (s, 1H), 7.22 (d, 1H), 4.78 (s, 1H), 2.45 (s, 3H), 1.43 (s, 9H); ESIMS m/z 325.1041 (M^+, 325.1022 calcd for $C_{15}H_{17}O_3F_3Na$).

tert*-Butyl 3-(3-Trifluoromethylphenoxy)butanoate 1a.** The crude **6-*Z*/6-*E mixture (13.98 g, 46.2 mmol) was hydrogenated for 24 h in 170 mL of 2-propanol using 2.5 g of 5% Pd/C under 75 psi H_2. Filtration through Celite and evaporation produced 13.85 g (45.5 mmol) of product (99%) as a thick yellow oil. Purification by flash chromatography (25:1 SiO_2/ester) with Et_2O/hexane gave **1a**: ^{1}H NMR ($CDCl_3$, δ) 7.37 (t, 1H), 7.19 (d, 1H), 7.15 (s, 1H), 7.08 (d, 1H), 4.85 (sextet, 1H), 2.69 (dd, J = 7.2, 15.3 Hz, 1H), 2.5 (dd, J = 5.7, 15.3 Hz, 1H), 1.42 (s, 9H), 1.36 (d, 3H); ESIMS m/z 327.1192 (M^+, 327.1179 calcd for $C_{15}H_{19}O_3F_3Na$).

tert*-Butyl (2*R**3*R**)- and (2*R**3*S**)-3-(3-Trifluoromethylphenoxy)-2,3-$^2H_2$-butanoate 3a and 3b.** ***6-Z (15.4 g, 50.9 mmol) or ***6-E*** (19.9 g, 65.8 mmol) was dissolved in 100 mL of degassed anhydrous benzene in a high-pressure Parr flask. Wilkinson's catalyst ($Rh(PPh_3)_3Cl$) was added so that the molar ratio was 25:1 alkene/catalyst. The Parr flask was flushed with ∼100 psi of D_2 (99.8%) and then allowed to stir at 50 °C for 24−96 h at 460 psi. The solvent was evaporated, and $Rh(PPh_3)_3Cl$ was removed by precipitation with pentane. Remaining catalyst was removed by filtration through a short SiO_2 column. Flash chromatography (SiO_2, 10−30% chilled Et_2O/hexane), drying, and evaporation produced 15.3 g (50.0 mmol) of **3a** (98%) or 19.79 g (64.6 mmol) of **3b** (98%). **3a**: ^{2}H NMR (C_6H_6, δ) 4.53, 2.10; ^{1}H NMR ($CDCl_3$, δ) 7.37 (t, 1H), 7.19 (d, 1H), 7.15 (s, 1H), 7.08 (d, 1H), 2.68 (s, 1H), 1.42 (s, 9H), 1.36 (s, 3H); ESIMS m/z 329.1322 (M^+, 329.1304 calcd for $C_{15}H_{17}D_2O_3F_3Na$). **3b**: ^{2}H NMR (C_6H_6, δ) 4.53, 2.45; ^{1}H NMR ($CDCl_3$, δ) 7.37 (t, 1H), 7.19 (d, 1H), 7.15 (s, 1H), 7.08 (dd, 1H), 2.45 (s, 1H), 1.42 (s, 9H), 1.36 (s, 3H); ESIMS m/z 329.1317 (M^+, 329.1304 calcd for $C_{15}H_{17}D_2O_3F_3Na$).

***S*-*tert*-Butyl (2*R**3*R**)- and (2*R**3*S**)-3-(3-Trifluoromethylphenoxy)-2,3-$^2H_2$-butanethioate 4a and 4b.** To **3a** or **3b** at 0 °C (N_2, stirring) was added 3.0 molar equiv of TFA, and the mixture was reacted for 23−26 h. The ice bath was replaced, and 1.2 molar equiv of TFAA was added. After 1 h 1.2 molar equiv of Me_3CSH was added, and the reaction continued for 18−22 h. Aqueous workup (Et_2O, $NaHCO_3$, drying, evaporation), followed by flash chromatography (25:1 SiO_2/product, 0.5−4% chilled Et_2O/hexane) produced **4a** or **4b** (∼88% yield). **1b**: ^{1}H NMR (C_6D_6, δ) 7.23 (s, 1H), 6.98 (d, 1H), 6.83 (t, 1H), 6.77 (dd, 1H), 4.59 (ddq, 1H), 2.68 (dd, 1H), 2.27 (dd, 1H), 1.33 (s, 9H), 0.94 (d, 3H). **4a**: ^{2}H NMR (C_6H_6, δ) 4.58, 2.23; ^{1}H NMR (C_6D_6, δ) 7.22 (s, 1H), 6.98 (d, 1H), 6.83 (t, 1H), 6.77 (dd, 1H), 2.65 (s, 1H), 1.32 (s, 9H), 0.94 (s, 3H); ESIMS m/z 345.1091 (M^+, 345.1076 calcd for $C_{15}H_{17}D_2O_2F_3SNa$). **4b**: ^{2}H NMR (C_6H_6, δ) 4.58, 2.62; ^{1}H NMR (C_6D_6, δ) 7.22 (s, 1H), 6.98 (d 1H), 6.83 (t, 1H), 6.77 (dd, 1H), 2.22 (s, 1H), 1.32 (s, 9H), 0.94 (s, 3H); ESIMS m/z 345.1087 (M^+, 345.1076 calcd for $C_{15}H_{17}D_2O_2F_3SNa$).

(4*R5*R**)- and (4*R**5*S**)-5-(3-Trifluoromethylphenoxy)-4,5-$^2H_2$-3-hexanone 5a and 5b.** **3a** (6.0 g, 19.6 mmol) or **3b** (5.12 g, 16.7 mmol) were deblocked using 4.5−6.0 equiv of TFA at rt for 19−25 h, when TLC showed the reaction to be complete. TFA was evaporated and (2*R**3*R**)-3-(3-trifluoromethylphenoxy)-2,3-$^2H_2$-butanoic acid (4.75 g. 97%) or (2*R**3*S**)-3-(3-trifluoromethylphenoxy)-2,3-$^2H_2$-butanoic acid (3.63 g, 87%) were obtained. Nondeuterated acid: ^{1}H NMR ($CDCl_3$, δ) 8.77 (s, 1H), 7.38 (t, 1H), 7.21 (d, 1H), 7.15 (s, 1H), 7.09 (d, 1H), 4.87 (sextet, 1H), 2.86 (dd, J = 7.3, 15.9 Hz, 1H), 2.64 (dd, J = 5.5, 15.9 Hz, 1H), 1.40 (d, 3H). 2*R**3*R**: ^{1}H NMR ($CDCl_3$, δ) 7.75 (s, 1H), 7.39 (t, 1H), 7.22 (d, 1H), 7.15 (s, 1H), 7.09 (dd, 1H), 2.82 (s, 1H), 1.39 (s, 3H). 2*R**3*S**: ^{1}H NMR ($CDCl_3$, δ) 10.22 (s, 1H), 7.38 (t, 1H), 7.23 (d, 1H), 7.15 (s, 1H), 7.08 (dd, 1H), 2.62 (s, 1H), 1.39 (s, 3H).

(2*R**3*R**)-3-(3-Trifluoromethylphenoxy)-2,3-$^2H_2$-butanoic acid (4.8 g, 19.2 mmol) or the (2*R**3*S**) diastereomer (3.63 g, 14.5 mmol) and diisopropylethylamine (DIEA, 1.2 equiv) were dissolved in 55 mL of CH_2Cl_2 (0 °C, N_2). *N*-Methoxymethylamine hydrochloride (1.03 equiv) was then added to the stirred solution. Finally, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide·HCl (EDCI, 1.2 equiv) was added. The flask was removed from the ice bath and allowed to stir (N_2) for 37−39 h at rt. Extraction with 0.1 M HCl, followed by extraction of the combined aqueous solutions with CH_2Cl_2, drying ($MgSO_4$), filtration, and evaporation produced the product amides, which were purified by flash chromatography (20:1 SiO_2/product using 5−20% chilled Et_2O/hexane). The product-containing fractions were dried ($MgSO_4$) and evaporated. *N*-Methyl-*N*-methoxy-(2*R**3*R**)-3-(3-trifluoromethylphenoxy)-2,3-$^2H_2$-butanamide (4.19 g, 79%) or the (2*R**3*S**) diastereomer (3.39 g, 84%) were isolated as light-yellow oils. Nondeuterated amide: ^{1}H NMR ($CDCl_3$, δ) 7.36 (t, 1H), 7.18−7.15 (m, 2H), 7.10 (dd, 1H), 4.98 (sextet, 1H), 3.71 (s, 3H), 3.19 (s, 3H), 3.03 (dd, J = 6.7, 15.6 Hz, 1H), 2.59 (dd, J = 5.9, 15.6 Hz, 1H), 1.38 (d, 3H). 2*R**3*R**: ^{1}H NMR ($CDCl_3$, δ) 7.37 (t, 1H), 7.18−7.15 (m, 2H), 7.10 (dd, 1H), 3.72 (s, 3H), 3.19 (s, 3H), 3.00 (s, 1H), 1.38 (s, 3H). 2*R**3*S**: ^{1}H NMR ($CDCl_3$, δ) 7.37 (t, 1H), 7.19−7.15 (m, 2H), 7.11 (dd, 1H), 3.72 (s, 3H), 3.19 (s, 3H), 2.56 (s, 1H), 1.38 (s, 3H).

Using syringe techniques *N*-methyl-*N*-methoxy-(2*R**3*R**)-3-(3-trifluoromethylphenoxy)-2,3-$^2H_2$-butanamide (3.00 g, 10.8 mmol) or the (2*R**3*S**) diastereomer (3.13 g, 11.3 mmol) in 130 mL of anhydrous Et_2O (0 °C, N_2) were stirred for 10 min before 4.5 equiv of 3.0 M EtMgBr in Et_2O was added dropwise over 7−8 min. After 4 h at 0 °C the reactions were quenched with 250 mL of 5% $NaHCO_3$ (0 °C). Insoluble salts were filtered off, the reaction mixtures were extracted with Et_2O until GC showed no product remaining in the aqueous layer and dried ($MgSO_4$), and the solvent was evaporated. Flash chromatography on SiO_2 (0.25%−10% Et_2O/hexane) gave **5a** (2.07 g, 73%) or **5b** (2.09 g, 71%). **1c**: ^{1}H NMR (C_6D_6, δ) 7.24 (s, 1H), 7.00 (d, 1H), 6.85 (t, 1H), 6.77 (d, 1H), 4.66 (m, 1H), 2.38 (dd, J = 6.8, 16.8 Hz, 1H), 1.93 (dd, J = 5.6, 16.8 Hz, 1H), 1.84 (m, 2H), 0.95 (d, 3H), 0.84 (t, 3H); ^{13}C NMR (C_6D_6, δ) 207.2 (C-3), 113.8−158.7 (Ar), 132.7 (q, J = 31 Hz, CF_3), 71.1 (C-5), 48.8 (C-4), 37.1 (C-2), 20.0 (C-6), 8.0 (C-1); ESIMS m/z 283.0910 (M^+, 283.0916 calcd for $C_{13}H_{15}O_2F_3Na$). **5a**: ^{2}H NMR (C_6H_6, δ) 4.61, 1.94; ^{1}H NMR ($CDCl_3$, δ) 7.37 (t, 1H), 7.19 (d, 1H), 7.12 (s, 1H), 7.07 (d, 1H), 2.92 (s, 1H), 2.49 (q, 2H), 1.33 (s, 3H), 1.06 (t, 3H); ^{13}C NMR (C_6D_6, δ) 207.3, 113.8−158.7, 132.7 (q), 70.7 (t), 48.4 (t), 37.0, 19.9, 8.0. **5b**: ^{2}H NMR (C_6H_6, δ) 4.62, 2.39; ^{1}H NMR ($CDCl_3$, δ) 7.36 (t, 1H), 7.18 (d, 1H), 7.12 (s, 1H), 7.06 (dd, 1H), 2.58 (s, 1H), 2.48 (q, 2H), 1.32 (s, 3H), 1.06 (t, 3H); ESIMS m/z 285.1032 (M^+, 285.1042 calcd for $C_{13}H_{13}D_2O_2F_3Na$).

***tert*-Butyl (*E*)-3-Phenoxy-2-butenoate 7.** *tert*-Butyl 2-butynoate (2.51 g, 17.8 mmol) was stirred at rt with a solution of phenol (3.51 g, 37.3 mmol) in 20 mL of (0.81 M *t*-BuOK/*t*-BuOH)/25 mL DMPU/7 mL THF. After 2 h the reaction mixture was extracted (H_2O/Et_2O) and dried (Na_2SO_4), and the solvent was removed by evaporation. Flash chromatography (SiO_2, 5−10% Et_2O/hexane) produced 3.6 g of **7** (86%, mp 85−87 °C). NMR analysis indicated that only the (*E*)-isomer of the conjugate addition product was present. Recrystallization from acetone produced **7** suitable for an X-ray crystallographic structure determination. **7**: ^{1}H NMR ($CDCl_3$, δ) 7.42−7.35 (m, 2H), 7.24 (d, 1H), 7.02 (d, 2H), 4.80 (s, 1H), 2.45 (s, 3H), 1.43 (s, 9H).

(*Z*)-4-Hexen-3-one 9c.[53] **9c** was produced by oxidation of 4-hexyn-3-ol with the Dess−Martin periodinane reagent, followed by hydrogenation of 4-hexyn-3-one with Pd/$BaSO_4$/quinoline in Et_2O. The hydrogenation was stopped at 50% reaction to avoid extensive isomerization of **9c** to **2c**; **9c** was purified by preparatory GC (8 ft × 3/8 in. 15% methylsilicone column) at 105 °C. **9c**: ^{1}H NMR (C_6D_6, δ) 5.70 (m, 2H), 2.024 (dd, 3H), 2.00 (q, 2H), 0.94 (t, 3H).

(*E*)-4-Hexen-3-one 2c. ^{1}H NMR (C_6D_6, δ) 6.45 (dq, 1H), 5.86 (dq, 1H), 2.10 (q, 2H), 1.33 (dd, 3H), 1.00 (t, 3H); ^{13}C NMR (C_6H_6, δ) 199.2 (C-3), 141.2 (C-5), 132.5 (C-4), 33.6 (C-2), 18.2 (C-6), 8.7 (C-1). **8c**: ^{2}H NMR (C_6H_6, δ) 6.45, 5.86.

General Method for Elimination Reactions of Deuterated Substrates. Stereospecifically deuterated ester and thioester substrates (300−400 mg) were stirred in 3:1 v/v EtOH/H_2O in a 22−25 °C water bath. Concentrations of **3a** and **3b** were 1.7−2.3 M, which were reacted with 70% of the KOH necessary for complete reaction, and 2.22 M for **4a** and **4b**, which were reacted with a 3% molar excess of KOH. Thioester eliminations were quenched with AcOH after 15 s. After quenching all reactions with AcOH and addition of a saturated NaCl solution, the reaction mixtures were extracted 3−4 times with

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pentane. Combined pentane extracts were dried ($MgSO_4$), and the solvent was evaporated at 35 °C. After capillary GC analysis of the reaction mixtures and before NMR analysis, **8a** and **8b** were collected by preparatory GC (8 ft × 3/8 in. 5% Carbowax 20 M or 15% methylsilicone). There was 70−85% product recovery of **8a** and **8b**, which were analyzed by multiple 61 MHz ^{2}H NMR integrations (C_6H_6) of samples from three separate experiments. In calculating the amounts of syn and anti elimination, the integrations were corrected for the presence of small amounts of diastereomeric impurities, which were determined by ^{2}H NMR integrations of the reaction substrates.

Elimination reactions of ketones **5a** and **5b** to give **8c** were carried out in 5:1 v/v EtOH/H_2O, and **4a** and **4b** were also studied in 6:1 v/v EtOH/H_2O. Elimination reactions of the ketones and the thioesters involved reacting 250−300 mg of substrate with 88−98% of the KOH necessary for complete reaction. Concentrations were 2.38 M for **5a** and **5b** and 2.22 M for **4a** and **4b**. After 15 s for the ketones and 50 s for the thioesters the reactions were quenched with AcOH. All other procedures remained the same as those used for the 3:1 EtOH/H_2O elimination reactions.

k_H/k_D Kinetic Isotope Effects. KIEs were determined from the percentages of syn and anti elimination from substrates **3a**−**5b** and the relative rates of the diastereomeric pairs by a series of competition reactions using an ∼1:1 ratio of the (*R**,*R**) and (*R**,*S**) diastereomers with 60−80% of the KOH necessary for complete elimination. All other procedures remained the same as used for the elimination reactions. For each pair of substrates 3−4 competition reactions were run, which reached 35−85% completion; product recoveries were >80%. The relative rates were corrected for the percentages of (*Z*)-alkenes from the two diastereomers in the calculation of $k_{R^*S^*}/k_{R^*R^*}$. In general, the extent and diastereomeric composition in the reactions of **3a**/**3b** and **4a**/**4b** were determined directly by multiple 61 MHz ^{2}H integrations (C_6H_6) of the C-3 alkene and substrate signals and of the C-2 signals of (2*R**,3*R**) and (2*R**,3*S**) substrates, respectively, although for the thioesters the % completion was determined by capillary GC. The diastereomeric composition in reactions of **5a**/**5b** was determined using ^{2}H integrations of the C-5 alkene and substrate signals and of the C-4 signals of **5a** and **5b**. The values of $(k_H/k_D)_{anti}$, which were ±0.23−0.33 (7−11%) at the 90% confidence level, were used to calculate the innate stereospecificities for the elimination reactions. Errors in $(k_H/k_D)_{syn}$ values were estimated to be ±0.7 for **3a**−**3b** and ±1.4 for **4a**−**5b**.

Elimination Kinetics. All experiments using the 3-trifluoromethylphenoxy and tosyloxy substrates (0.3−3 mM) were run in triplicate or quadruplicate in 3:1 v/v EtOH/H_2O at constant ionic strength (120 mM $NaClO_4$) at 30.0 ± 0.1 °C. Timing began upon addition of 1.5−7.5 equiv of NaOH in boiled, distilled water. Aliquots were removed by syringe every 4−10 s and immediately added through 0.22 μm filters into preprepared HPLC vials containing 2−8 equiv of filtered AcOH. The quenched reaction mixtures had a pH of 5−7. Reverse-phase HPLC was used to separate a minimum of 10 reaction samples for each run using 70:30 MeOH/H_2O or 55:45 MeOH/H_2O and a diode-array UV detector at 225 nm. No byproducts were observed. There was demonstrable systematic nonstochastic distribution about the predicted fit of a first-order rate law, but a better correlation with a more random distribution of residuals for a second-order rate law. The linearity of second-order rate laws was followed to 46−92% reaction. Kinetics on **1b** and **1c** were also measured in 5:1 EtOH/H_2O using the same techniques. The linearity of second-order rate laws was followed to 76−77% reaction.

For acetoxy substrates the thioester concentrations were 0.2−0.3 mM, and the ester concentration was 0.012 M in 3:1 v/v EtOH/H_2O at constant ionic strength (100 mM $NaClO_4$) using a 5-fold excess of NaOH at 30.0 ± 0.1 °C. Three consistent kinetic runs were carried out in quartz cells at 260.7 nm for the thioester and 255.4 nm for the ester. Beer's Law linear fits were excellent (<1% error). Kinetic runs were followed for at least three second-order half-lives.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures not reported in the Experimental Section, copies of ^{1}H and ^{2}H NMR spectra for all new compounds plus representative ^{2}H NMR spectra for elimination products, and X-ray structural data for **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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