

Unexpected Selectivity in Sodium Borohydride Reductions of α -Substituted Esters: Experimental and Theoretical Studies

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The propensity of sodium borohydride to reduce the carbonyl group in eleven α -substituted and two aromatic esters has been investigated by experiments and at the B3LYP/6-31++G(d,p)//HF/6-31G(d,p) level of theory. The chemoselectivities in nine of these reductions have been examined by experiments. Experimental results agree well with the calcu-

lated order of activation energies for hydride transfer to the ester carbonyl group. Methyl α -bromoacetate reduces faster than methyl α -fluoroacetate.

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Introduction

Sodium borohydride reductions have been well studied,^[1–5] and reductions of esters or keto esters have been studied by Brown and others.^[6–8] Semi-empirical theoretical studies of aldehyde reductions with sodium borohydride have been reported,^[9] and HF theoretical studies of sodium borohydride itself have also appeared.^[10–12] Almost all of the selective reductions with sodium borohydride have been conducted on compounds containing two very different functional groups, e.g. $>C=C<$ vs. $>C=NH$,^[13] $>C=C<$ vs. $-CHO$,^[14] or $-CO_2Me$ vs. $-CO_2H$,^[1,6a,15] whose reduction activities are widely different. However, experimental and quantum (e.g. HF or DFT method) studies of chemoselective α -substituted ester reductions have never been reported (or compared) where the carbonyl groups may have similar reduction reactivities towards sodium borohydride.

The experimental and computational studies of different reactivities would be a valuable contribution because α -substituted alcohols derived from their corresponding esters are important intermediates in organic syntheses and as medicinal intermediates. The dramatic increase of new drug targets arising from genomics and proteomics has generated a need for efficient methods to assemble small molecules that exhibit an ever-increasing level of structural complex-

ity. Successful chemoselective reductions of various α -substituted esters could provide a useful tool for the syntheses of many poly-functional chiral compounds. Structurally complex natural products often have two or more carbonyl groups with similar, but different, reactivities, and the selective reduction of one carbonyl function would be especially valuable. Herein, we report some chemoselective α -substituted ester reductions with sodium borohydride where some unexpected chemoselectivities are observed.

It has been traditionally accepted that higher electronegativity values, χ , of the substituent at the α -carbon in esters, in the absence of steric effects and conjugation, increase the rate of $NaBH_4$ reduction. We now report that this is not correct for the α -halogenated esters based both on experimental and computational findings. Furthermore, a wide range of reactivities are demonstrated based on the nature of the α -substituent or the nature of the α -carbon.

Results and Discussion

Nine esters were reduced by sodium borohydride in diglyme solution. The conversions of esters **1**, **7** and **12–14** were determined by HPLC after 3 h. For esters **1** and **7**, toluene was used as the internal standard, for esters **12–14**, $PhCO_2Me$ was used. The temperature required for the first appearance of alcohol (on-set temperature) was employed for compounds **1**, **7**, and **12–14**. The other on-set temperatures were determined by the initial appearance of the products on a TLC plate where the products were sensitive to detection when exposed to I_2 or H_2SO_4 . These results are summarized in Table 1. The differences of on-set temperatures among these α -substituted esters are substantial and some of the observed selectivities are unexpected. For example, the on-set temperature for methyl α -hydroxyacetate

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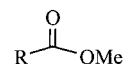
reduction is 5 °C while the on-set temperature is 64 °C for methyl α -amino acetate reduction when the molar ratio of NaBH₄ and methyl α -aminoacetate is 2. This on-set temperature rises to 68 °C if the molar ratio is decreased to 1. This difference may occur because the electronegativity of oxygen (3.5) is higher than that for nitrogen (3.0). The larger the electronegativity of the α -substituent, the lower the hydride-transfer barrier becomes according to traditional organic theory. If this conclusion can be generally applied, the predicted on-set temperature for the NaBH₄ reduction of methyl α -fluoroacetate should be lower than the on-set temperature for methyl α -bromoacetate, since fluorine has a larger electronegativity (4.0) than bromine (2.5). However, we now demonstrate experimentally that this prediction is not correct. In fact, the on-set temperatures for reductions of methyl α -fluoroacetate, methyl α -chloroacetate, and methyl α -bromoacetate exhibit the opposite order. Methyl α -fluoroacetate has the highest on-set temperature (-15 °C) and methyl α -bromoacetate has the lowest on-set temperature (-27 °C). Furthermore, the half-lives of these three α -haloester reductions with sodium borohydride were determined at -23, -20, and 10 °C, respectively; these values showed the same reactivity order shown by the on-set temperatures.

Table 1. Experimental reduction on-set temperatures for eight α -substituted esters.^[a]

Compound	On-set temp. [°C]	Compound	On-set temp. [°C]
1	5	11	104
3	64 (2:1), 68 (1:1) ^[b]	12	-15
7	-17	13	-23
10	154	14	-27

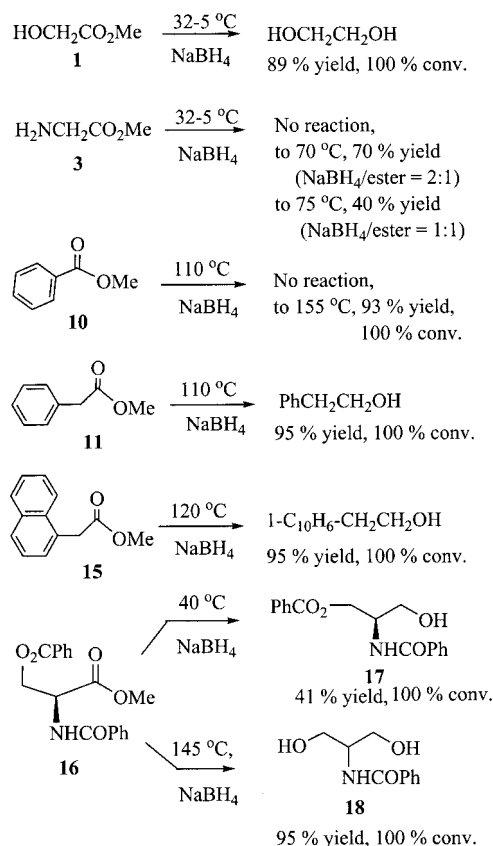
[a] Reactions to determine the initial appearance ($\leq 1\%$ yield) were run for 3 h in diglyme. Conversions were determined by HPLC using toluene as the internal standard for esters **1**, **7** and PhCO₂Me for **12–14**, respectively. The temperature required for the first appearance of alcohol (on-set temperature) was employed for compounds **1**, **7**, and **12–14**. The other on-set temperatures were determined by the initial appearance of the products on a TLC plate where the products were sensitive to detection when exposed to I₂ or H₂SO₄. [b] The NaBH₄/3 molar ratio was 2:1 and 1:1, respectively.

The unexpected chemoselectivities of the haloesters cannot be satisfactorily explained only by electron-withdrawing effects. Coordination, conformational effects, conjugation, and solvation could also play major roles that are not easy to predict in advance. Transition state energies are needed to analyze the orders of the barriers, and, importantly, to construct the relationship between the activation barriers and the on-set temperatures. If such a correlation could be demonstrated, and if the activation barriers could be successfully predicted computationally by an efficient method, then the chemoselectivities of compounds containing two or more carbonyl groups could be predicted and more understanding of structure vs. reactivity obtained. Also, demonstrating an agreement between computed ΔE^\ddagger values and experimental reactivity results would generate more confidence in the ability to predict reactivities of reactions with significant charge separation in polar solvents.



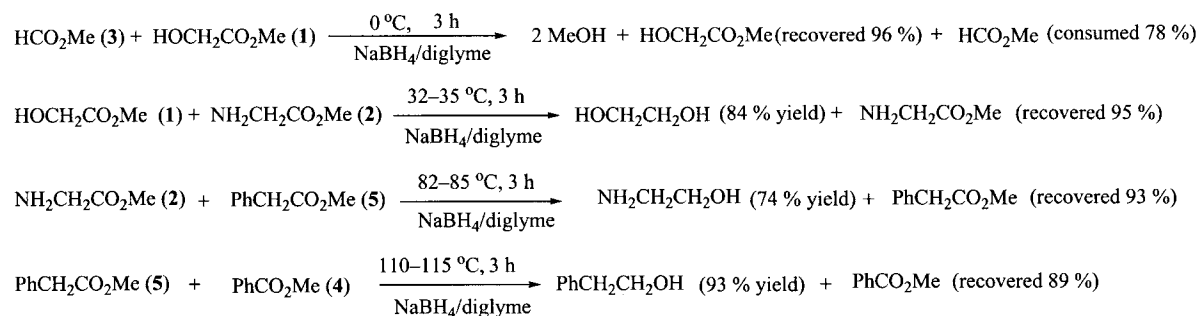
- | | |
|---|--|
| 1: R = -CH ₂ OH | 8: R = -CH=CH ₂ |
| 2: R = -CH(Me)OH | 9: R = -CH ₂ CH=CH ₂ |
| 3: R = -CH ₂ NH ₂ | 10: R = -Ph |
| 4: R = -CH(Me)NH ₂ | 11: R = -CH ₂ Ph |
| 5: R = -CH ₂ NHMe | 12: R = -CH ₂ F |
| 6: R = -CH ₂ Me ₂ | 13: R = -CH ₂ Cl |
| 7: R = -H | 14: R = -CH ₂ Br |

Several reductions were also carried out in higher yields, and these results are compared in Scheme 1. The reactivity orders **1** > **3** and **11** > **10** were confirmed under these conditions. Diester **16** contains both a benzoate ester and an α -amido-substituted ester along with a secondary aryl amide function. At 40 °C, reduction of the α -amidoester function occurs selectively to give **17**. At 145 °C, the benzoate ester group is also reduced to give diol **18**, but the amide carbonyl remains unchanged. *N*-Methylacetamide has a very high predicted ΔE^\ddagger barrier^[16] (42.2 kcal mol⁻¹ in THF). Thus, the barrier to *N*-methylbenzamide reduction may be even higher than 42.2 kcal mol⁻¹ in THF, hence the benzamide group's resistance to hydride reduction in **16** at 145 °C is not surprising.



Scheme 1. Comparative experimental reactivities in ester reductions with NaBH₄ in diglyme (isolated yield).

Competitive reduction experiments were conducted on equimolar mixtures of four pairs of esters: (1) methyl formate vs. methyl α -hydroxyacetate, (2) methyl α -hydroxyace-



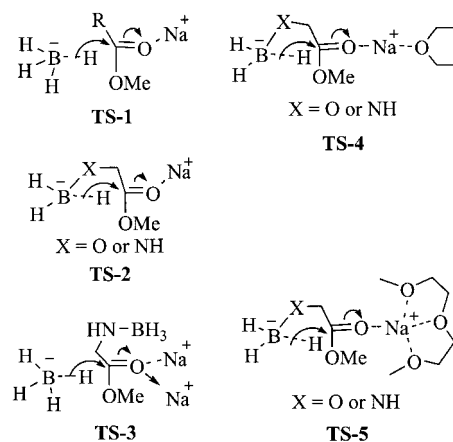
Scheme 2. The selectivities in four competitive methyl ester reductions with sodium borohydride in diglyme (isolated yields).

tate vs. methyl α -aminoacetate, (3) methyl α -aminoacetate vs. methyl 2-phenylacetate, and (4) methyl 2-phenylacetate vs. methyl benzoate. These results are summarized in Scheme 2.

Since α -substituted alcohols derived from esters are important intermediates, chemoselective reductions of various α -substituted esters functions could provide a useful tool for the synthesis of many poly-functional chiral compounds. Structurally complex natural products often have two or more chemically nonequivalent carbonyl groups where the selective reduction of one carbonyl function would be valuable. The experiments described above show that it is not always possible to predict the relative energies of ester group reduction based on simple organic precepts. Could quantum mechanical calculations be used to predict the activation barriers and transition state structures and provide useful insights into these reductions? If the computed barriers match the experimental results, then predictions could be made of reduction selectivities for other systems.

Twenty seven optimized transition states (TS) were obtained at the HF/6-31G(d,p) and B3LYP/6-31++G(d,p) levels of theory and these were used to analyze the selectivities computationally for comparison with the observed selectivities.^[17] The calculations focused on rate-determining hydride attack on the carbonyl carbon of esters **1**–**13**.^[18] Two types of transition state (TS) structures were found. These are illustrated by **TS-1** and **TS-2**. **TS-1** was used for computations of the reduction activation barriers for compounds **3** and **5**–**14** because it has a lower energy than **TS-2**. **TS-2** was used for compounds **1**–**5**, where it was more stable. Prior to the formation of **TS-2**, one mol of hydrogen gas had previously been formed by initial fast hydride attack on the acidic proton. This is followed by subsequent hydride attack on the carbonyl carbon through **TS-2**. The structures of both **TS-1** and **TS-2** were used for comparative computations of the activation barriers for reduction of methyl α -aminoacetate (**3**) and methyl α -*N*-methylacetate (**5**). If two equivalents of NaBH₄ are present during the rate-determining step for the reduction of **3**, then **TS-3** will apply. Two sodium ions in **TS-3** enhance the polarity of the carbonyl carbon. This might lead to rate enhancement relative to a pathway through either **TS-1** or **TS-2**. The structure of **TS-3** is similar to, but more complex than, that of **TS-1**. Thus, the reduction barrier of **3** was computed

with **TS-1**, **TS-2**, and **TS-3**, where two equivalents of NaBH₄ are present.



Only **TS-2** was employed for the reduction of **1** and **2** since the hydroxy proton is acidic and rapid hydrogen evolution is observed experimentally. The hydroxy proton reacts easily and irreversibly with a hydride from NaBH₄ long before carbonyl reduction begins. Furthermore, additional calculations were performed where a single molecule of THF or diglyme was added to both the starting material and the TSs of **1** and **3**. Since NaBH₄ is an ionic species and charge separation exists in the transition states, the use of computations dealing with solvent was thought to be necessary to be able to make comparisons with gas-phase computational results. The general geometries for these NaBH₄ reductions containing a single added THF or diglyme molecule (supramolecular solvent method) are labeled as **TS-4** and **TS-5**, respectively. The PCM method^[19] was also applied to predict the effects of THF or diglyme (solvent) on the ΔE^\ddagger values for reduction.

Frequency calculations were performed for all TSs. One negative imaginary frequency was found for each TS and the direction of hydride vibration in the TS is from atom B towards the carbonyl carbon. IRC calculations for each TS structure were done and one optimized point was found in each of the TSs, which is located at the highest energy point in the IRC plot.

Four different computation methods (A, B, C, and D) are discussed here. In Method A, two different situations were examined (the gas phase and solution phase). In the

first case ΔE^\ddagger was computed in the gas phase. The TS and complex geometries were both first optimized at the HF/6-31G(d,p) level. Then, single-point (SP) energy computations for these geometries were then performed at the B3LYP/6-31++G(d,p) level and the resulting energies were used to define $\Delta E^\ddagger_{\text{gas}}$. In the second case ΔE^\ddagger was computed in THF. The PCM method was selected for SP computations in THF at the B3LYP/6-31++G(d,p) level, employing HF/6-31G(d,p)-optimized geometries. These energies were used to define $\Delta E^\ddagger_{\text{THF}}$. The effect of diglyme, which was also used as the solvent in higher temperature experimental reductions, was considered to resemble that of THF with respect to its effect on TS barriers based on its similar dielectric constant.

Method B was also applied to gas-phase and solution-phase situations. To calculate ΔE^\ddagger in the gas phase, the geometries of the TS and the NaBH_4 /ester complex were both optimized at the B3LYP/6-31++G(d,p) level and the energies of these calculations were then used to determine $\Delta E^\ddagger_{\text{gas}}$. ΔE^\ddagger was also calculated in THF (PCM method). The SP energy corrections in THF for these geometries were then carried out at the same level using the PCM model for $\Delta E^\ddagger_{\text{THF}}$ computations.

In method C, ΔE^\ddagger was computed in THF. The TS and NaBH_4 /ester complex geometries were both optimized at the HF/6-31G(d,p) level in THF using the PCM model. Then, SP energy corrections for these geometries were completed at the B3LYP/6-31++G(d,p) level to give $\Delta E^\ddagger_{\text{THF}}$.

In method D, ΔE^\ddagger was calculated with THF (diglyme) using the supramolecular approach. One THF (diglyme) molecule was added to both the TS and NaBH_4 /ester complex geometry optimizations for compounds **1** and **3**. These geometries were optimized at the HF/6-31G(d,p) level (**TS-4** and **TS-5**). SP energy calculations were then completed at the B3LYP/6-31++G(d,p) level for these geometries and used to give $\Delta E^\ddagger_{\text{THF}}$ or $\Delta E^\ddagger_{\text{diglyme}}$ values. All these calculated results for **1** and **3** are summarized in Table 2.

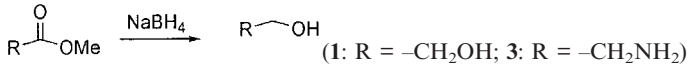
Experimental reductions of methyl α -aminoacetate in THF were then carried out. Unfortunately, the solubility of NaBH_4 in THF is very low, therefore a sharp on-set temperature for the reductions could not be determined because the rate is very low in this solid-liquid, two-phase reaction system. The solubility of NaBH_4 is much higher

in diglyme than in THF. Thus, diglyme was employed in experiments where reduction occurred in a single phase. The $\Delta(\Delta E^\ddagger)$ values between the reductions of methyl α -aminoacetate and methyl α -hydroxyacetate are slightly lower in diglyme (3.4 kcal mol⁻¹) than in THF (6.1 kcal mol⁻¹) using method D. However, the order of the barriers obtained in diglyme should be the same as that in THF. THF has a dielectric constant of 7.58 while that of glyme is 7.20. Diglyme's dielectric constant is somewhere between 7.58 and 7.20, although an experimental value could not be obtained. The solvent effect of diglyme on the TS barriers was therefore assumed to be similar to that of THF (for use in the PCM method). Therefore, THF was the solvent applied in the computations where the PCM method was used. These computations were compared to experimental on-set temperatures which were readily obtained in diglyme.

The on-set temperatures (Table 1) for reductions of **1** and **3** with sodium borohydride are 5 and 68 °C, respectively, with a NaBH_4 /ester ratio of 1:1. The on-set temperature decreased to 64 °C for the reduction of **3** when the ratio of NaBH_4 to **3** was increased to 2:1. The barriers computed by method B for the reduction of **3** gave much higher activation energies in THF (40.4 kcal mol⁻¹ via **TS-2**). This energy increased to 48.6 kcal mol⁻¹ if **TS-1** was used. In contrast, method A predicted a 32.1 kcal mol⁻¹ barrier in THF at a 1:1 molar ratio of NaBH_4 and **3** (**TS-2**). This barrier decreased to 30.7 kcal mol⁻¹ when this ratio was increased to 2:1 (**TS-3**). These predicted barriers agreed with the on-set temperature changes (68 °C vs. 64 °C for 1:1 vs. 2:1 NaBH_4 /**3**). Method B overestimated the barriers in the methyl α -aminoacetate reactions. Methods C and D provided good predictions for the reductions of **1** and **3**, but they are costly.

Overall, the barriers predicted by method A in THF provided more accurate model predictions and also used less computational time. Therefore, method A was selected to predict the ΔE^\ddagger values of the other eleven α -substituted ester reductions via **TS-1** and/or **TS-2**. The order of the resulting $\Delta(\Delta E^\ddagger)$ values from computations was used to predict the reaction activity sequence for this series of NaBH_4 ester reductions. The computed results are summarized in Table 3 and they agree with several experimental comparisons. Three-dimensional structural figures for the TS struc-

Table 2. The effects of different computational methods on the predicted activation barriers in methyl α -hydroxy- and α -aminoacetate reductions with NaBH_4 .



Compd.	Method A, ^[a] ΔE^\ddagger ^[b]			Method B, ΔE^\ddagger			Method C, ΔE^\ddagger			Method D, ΔE^\ddagger		
	Gas	$\Delta(\Delta E^\ddagger)$	THF	$\Delta(\Delta E^\ddagger)$	Gas	$\Delta(\Delta E^\ddagger)$	THF	$\Delta(\Delta E^\ddagger)$	THF	$\Delta(\Delta E^\ddagger)$	THF/diglyme	$\Delta(\Delta E^\ddagger)$
3 ^[c]	31.7	6.8	33.0	9.8	37.8	12.6	48.6	25.2	32.9	7.3	– ^[f]	–
3 ^[d]	32.3	7.4	32.1	8.9	31.8	7.2	40.4	17.0	32.1	6.5	29.8/23.1	6.3/3.4
3 ^[e]	37.7	12.8	30.7	7.5	–	–	–	–	–	–	–	–
1 ^[d]	24.9	0.0	23.2	0.0	25.2	0.0	23.4	0.0	25.6	0.0	23.7/19.7	0.0/0.0

[a] A detailed description of methods A–D is given in the text. [b] In kcal mol⁻¹. [c] **TS-1** was selected for the TS barrier computations. [d] **TS-2** was selected. [e] **TS-3** was used. [f] Attempts to obtain the TS geometry via **TS-4** failed.

Table 3. Calculated TS barriers (by method A) using single point B3LYP/6-31++G(d,p) energy values for methyl esters **1**–**13**. The effect of the different transition state structures (**I**, **II**, and **III**) on the activation barriers are shown here for the methyl α -haloesters after optimization of the TS geometries at the HF/6-31G(d,p) level.

Entry	Cpd.: -R	χ of R ^[a]	ΔE^\ddagger ^[b] (in gas)	ΔE^\ddagger ^[b] (in THF)	$\Delta(\Delta E^\ddagger)$ ^[c] (in gas)	$\Delta(\Delta E^\ddagger)$ ^[c] (in THF)			Charge on C=O in TS ^[d]
1	1 : -CH ₂ OH	2.59	24.9 ^[e]	23.2 ^[e]	6.5	2.4	1.314	2.134	0.553
2	2 : -CH(Me)OH	2.59	23.4 ^[e]	21.4 ^[e]	5.0	0.6	1.308	2.138	0.563
3	3 : -CH ₂ NH ₂	2.54	31.7, 32.3 ^[e]	33.0, 32.1 ^[e]	13.3, 13.9 ^[e]	12.2, 11.3 ^[e]	1.155, 1.404 ^[e]	2.076, 2.131 ^[e]	0.456, 0.588 ^[e]
4	4 : -CH(Me)NH ₂	2.54	–, ^[f] 31.2 ^[e]	–, 30.8 ^[e]	–, 12.8 ^[e]	–, 10.0 ^[e]	–, 1.416 ^[e]	–, 2.132 ^[e]	–, 0.615 ^[e]
5	5 : -CH ₂ NHMe	2.54	31.6, 32.3 ^[e]	32.7, 33.4 ^[e]	13.2, 13.9 ^[e]	11.9, 12.6 ^[e]	1.159, 1.444 ^[e]	2.075, 2.126 ^[e]	0.464, 0.616 ^[e]
6	6 : -CH ₂ NMe ₂	2.54	34.3	36.7	15.9	15.9	1.164	2.082	0.452
7	7 : -H	2.1	18.4	20.8	0.0	0.0	1.275	2.141	0.419
8	8 : -CH=CH ₂	2.78	33.6	34.3	15.2	13.5	1.219	2.145	0.496
9	9 : -CH ₂ CH=CH ₂	2.51	30.2	27.8	11.8	7.0	1.235	2.149	0.542
10	10 : -Ph	2.78	44.8	42.1	26.4	21.3	1.129	2.012	0.427
11	11 : -CH ₂ -Ph	2.51	31.8	36.4	13.4	15.6	1.217	2.117	0.547
12	12 : -CH ₂ F	2.64	21.8 (I)	24.5 (I)	3.4(I)	3.7 (I)	1.184 (I)	2.105 (I)	0.465 (I)
			25.1 (II)	26.1 (II)	6.7(II)	5.3 (II)	1.307 (II)	2.142 (II)	0.566 (II)
			26.1 (III)	26.2 (III)	7.7(III)	5.4 (III)	1.298 (III)	2.134 (III)	0.553 (III)
13	13 : -CH ₂ Cl	2.54	20.0 (I)	21.8 (I)	1.6 (I)	1.0 (I)	1.230 (I)	2.103 (I)	0.693 (I)
			23.2 (II)	23.8 (II)	4.8(II)	3.0 (II)	1.322 (II)	2.144 (II)	0.601 (II)
			24.7 (III)	24.5 (III)	6.3(III)	3.7 (III)	1.303 (III)	2.137 (III)	0.582 (III)
14	14 : -CH ₂ Br	2.50	19.2 (I)	22.1 (I)	0.8 (I)	1.3 (I)	1.260 (I)	2.118 (I)	0.573 (I)
			23.6 (II)	24.2 (II)	5.2 (II)	3.4 (II)	1.330 (II)	2.144 (II)	0.604 (II)
			26.4 (III)	27.0 (III)	8.0 (III)	6.2(III)	1.291 (III)	2.130 (III)	0.572 (III)

[a] For group electronegativity, see ref.^[20] [b] In kcal mol⁻¹. Using **TS-1** unless otherwise stated. All the ΔE^\ddagger values are based on the most stable conformational energy of the complex between NaBH₄ and the ester. [c] In kcal mol⁻¹. For entries 1 to 12 the lowest TS energy barrier (19.3 kcal mol⁻¹) was used as the standard for computations of $\Delta(\Delta E^\ddagger)$ in the gas phase and the lowest energy barrier (22.0 kcal mol⁻¹) was used as the standard for computations of $\Delta(\Delta E^\ddagger)$ in THF. [d] The charges were obtained at the B3LYP/6-31++G(d,p) level using NPA from single-point energy computations. [e] Using the **TS-2** model. [f] The TS via **TS-1** was not obtained.

tures obtained by method A for all substrates **1**–**14** for all five TS models (**TS-1**, **TS-2**, **TS-3**, **TS-4**, and/or **TS-5**) are provided in the Supporting Information.

Reduction of **1** to ethylene glycol (predicted $\Delta E^\ddagger = 23$ – 25 kcal mol⁻¹) requires a temperature of 30 °C to proceed readily (initial on-set reaction temperature is 5 °C but the reaction rate is very slow). However, **3**, must be heated to about 65 °C or above to achieve reduction to 2-aminoethanol. The on-set temperature for reduction of methyl formate (**7**) with sodium borohydride was measured by determining the consumption rate of methyl formate at different temperatures over a period of 3 h by HPLC with toluene as the internal standard. Methyl formate's measured on-set temperature is -17 °C. This temperature is 22 °C lower than that of methyl α -hydroxyacetate. Methyl benzoate (**10**) was recovered unchanged after treatment with NaBH₄ at 110 °C for 3 h. In contrast, methyl phenylacetate (**11**) gave a 95% isolated yield (100% conversion) of 2-phenylethanol at 110 °C in 2 h. The on-set temperature for the reduction of **11** was observed at 104 °C. Methyl benzoate (**10**) was finally reduced to benzyl alcohol (100% conversion, 93% isolated yield) at 162 °C in 3 h, with an on-set temperature of 154 °C. These experimental results all agree well with the theoretically predicted order of $\Delta(\Delta E^\ddagger)$ values in the gas phase. Furthermore, methyl α (1-naphthyl)acetate (**15**), which has a structure very similar to **11**, was reduced (100% conversion, 95% isolated yield) to the corresponding alcohol at 120 °C in 2 h, with an on-set temperature of

104 °C, indistinguishable from that of **11**. The reduction of multifunctional diester amide **16** with NaBH₄ exhibits the high selectivity discussed earlier (Scheme 1).

Reductions of Methyl α -Haloacetates

The α -substituted haloesters (F, Cl, Br) represent a series of substantial interest. Traditionally, a larger value of the α -substituent's electronegativity, χ , suggests a faster rate of hydride attack on the carbonyl carbon. Thus, methyl α -fluoroacetate (**12**) would be expected to have the lowest ΔE^\ddagger , while methyl α -bromoacetate (**14**) would have the highest ΔE^\ddagger of these three α -halo-substituted esters. Experimentally, this expectation did not occur. Instead, the opposite order was found. Furthermore, the computed ΔE^\ddagger barriers in the gas phase and in THF (method A) for these three substrates exhibit the same opposite order, where the methyl α -fluoroacetate is predicted to reduce the slowest.

The dependence of ΔE^\ddagger on the exact location of the halogen (X = F, Cl and Br) and the coordination geometry of Na⁺ in the transition state were examined, as illustrated in the TS structures **I**, **II**, and **III** for each α -halogenated ester (Figure 1). For all three α -halogenated esters, the lowest energy TS occurs where the Na⁺ ion is coordinated to both the α -halogen and the carbonyl oxygen, i.e. **I**. This was found both in solvent and in the gas phase. The predicted gas-phase barriers are 21.8 (F), 20.0 (Cl), and

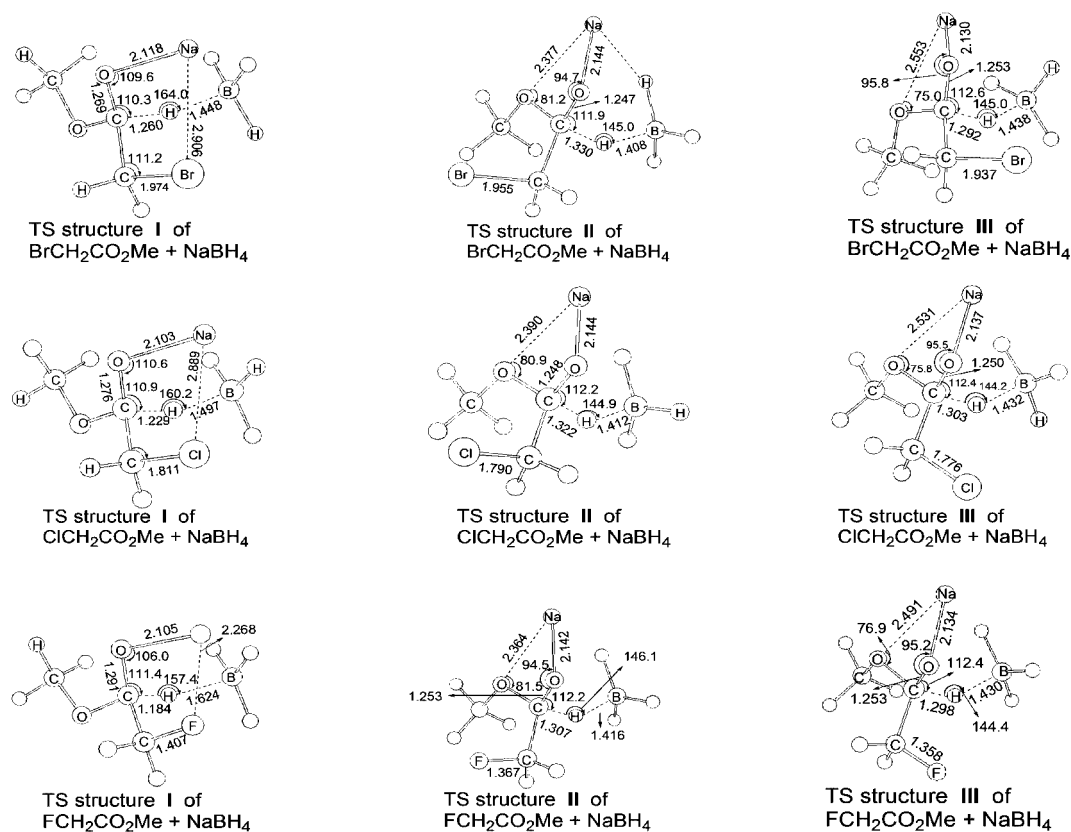
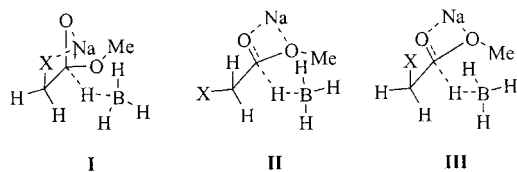


Figure 1. The 3D structures for reductions of α -haloesters with NaBH_4 for the TS conformations I, II, and III listed above. Bond lengths are given in angstroms.

19.2 kcal mol⁻¹ (Br; Table 3). In THF, the predicted ΔE^\ddagger values were 24.5 (F), 21.8 (Cl), and 22.1 kcal mol⁻¹ (Br). Methyl α -fluoroacetate (**12**) exhibits the highest calculated ΔE^\ddagger value in both cases. An analysis of the charge on the carbonyl carbon, performed at the B3LYP/6-31++G(d,p)//HF/6-31G(d,p) levels, did not give a linear relationship of the ΔE^\ddagger values (Table 3). The hydride-to-carbonyl carbon bond lengths in the optimized transition states (Table 3) become longer on going from **12** (1.184 Å) to **13** (1.230 Å) to **14** (1.260 Å) and the boron-to-hydride distances progressively shorten in this series. This is in agreement with the Hammond postulate (e.g. the transition state is reached earlier going from F to Cl to Br as the ΔE^\ddagger values decrease in this same direction).^[21] The shorter the hydride-to-carbonyl carbon bond length in the TS is, the higher the TS barrier becomes (Hammond postulate).



The THF solvent effect on the magnitude of the activation barriers was studied. As in the gas-phase calculations, methyl α -fluoroacetate has the largest

(25.5 kcal mol⁻¹) predicted activation barrier of the α -halo series in THF (Table 3, entry 12). The α -Cl- and α -Br-substituted methyl acetates have lower and almost equal predicted activation barriers (21.8 and 22.1 kcal mol⁻¹, respectively; Table 3, entries 13 and 14).

Experimental reductions of these three halogenated esters in diglyme were conducted and compared. The rates were followed by determining the amount of methyl α -haloacetate remaining vs. time by HPLC at a series of temperatures. The 2-haloethanols formed were also followed but they were more difficult to accurately determine. The temperatures at which these reductions can just begin to be detected were -15, -23, and -27 °C, for methyl α -F, α -Cl-, and α -Br-substituted acetate reductions, respectively. These results, summarized in Table 4, are in agreement with the calculated order of ΔE^\ddagger values using method A (both gas phase and in THF). Due to the small (4 °C) difference between the on-set temperatures of reduction for **13** (α -Cl) and **14** (α -Br), the half lives ($t_{1/2}$) of these α -halo ester reductions by sodium borohydride were determined in order to absolutely confirm their reactivity order. These half-lives verify the same reactivity order indicated by the on-set temperatures (Table 4). Figure 2 shows plots of α -haloester consumption vs. time at specific temperatures. These plots are in agreement with the on-set temperatures and show that the α -fluoro ester reduces more slowly.

Table 4. The effects of temperature on methyl α -halogenated acetate reductions with NaBH₄ in diglyme.

		$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{OMe} \xrightarrow{\text{NaBH}_4} \text{R}-\text{OH}$						
Entry	R	-18 to -20 °C	-8 to -10 °C	0 to 2 °C	$t_{1/2}$	$t_{1/2}$	$t_{1/2}$	On-set reaction temp. [°C]
		Conv. [%] ^[a]	Conv. [%] ^[a]	Conv. [%] ^[a]	at -10 °C [min]	at -20 °C [min]	at -23 °C [min]	
1	F (12)	0	56	76	80	–	–	-15
2	Cl (13)	26	–	84	< 0.5	265	–	-23
3	Br (14)	41	88	98	< 0.5	80	175	-27

[a] The conversions of the ester reductions were determined by HPLC using PhCO₂Me as the internal standard.

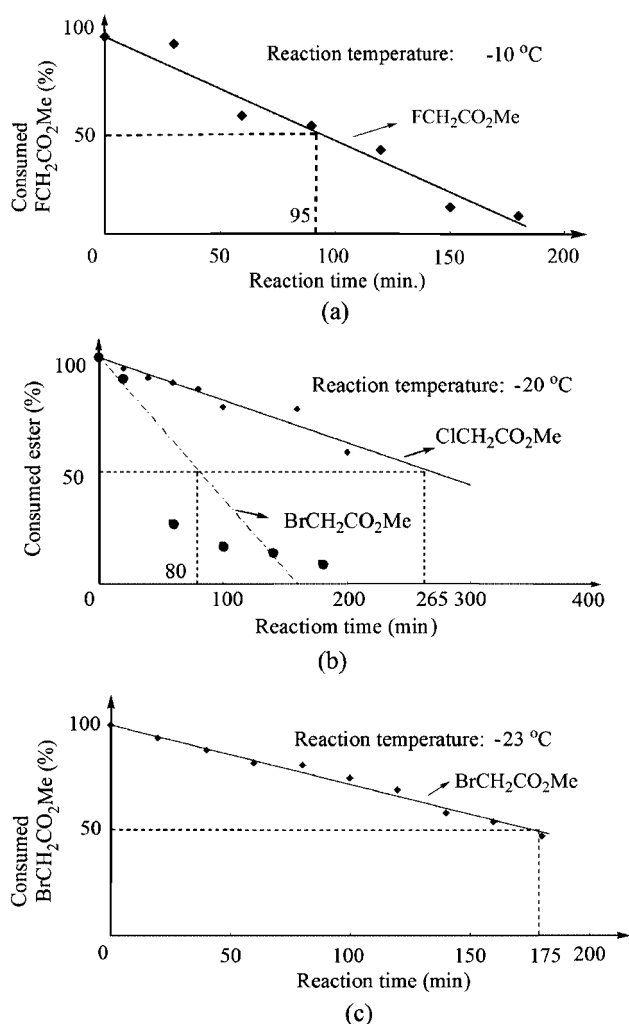


Figure 2. The consumption vs. time plots for α -haloesters during NaBH₄ reductions in diglyme. (a) Reduction of FCH₂COOCH₃ at -10 °C; (b) BrCH₂COOCH₃ and ClCH₂COOCH₃ at -20 °C; (c) BrCH₂COOCH₃ at -23 °C.

Linear relationships between these experimentally determined on-set reaction temperatures, T , in diglyme and the calculated activation barriers in both THF ($\Delta E_{\text{THF}}^\ddagger$) and in the gas phase ($\Delta E_{\text{gas}}^\ddagger$) are illustrated in Figure 3. The correspondence is excellent. These plots can be fitted by:

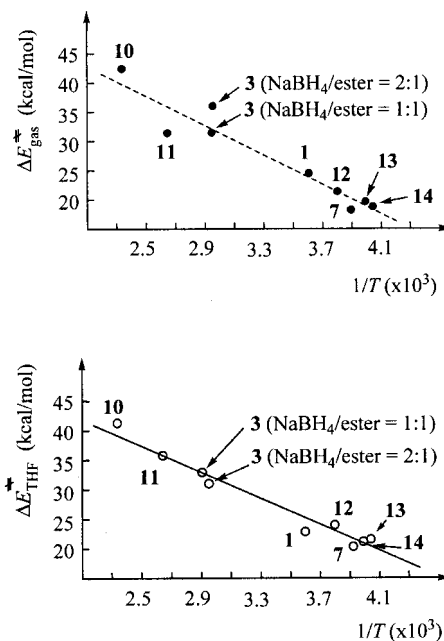


Figure 3. The relationship between computed ΔE^\ddagger magnitudes and the reciprocal of the experimental on-set temperature in diglyme ($1/T$, K) in NaBH₄ reductions of methyl α -substituted acetates.

$$\Delta E_{\text{THF}}^\ddagger = -11383.0/T + 66.6 \text{ (correlation coefficient is } -0.975)$$

$$\Delta E_{\text{gas}}^\ddagger = -13468.6/T + 73.2 \text{ (correlation coefficient is } -0.946)$$

The activation barriers estimated from these equations in THF and in the gas phase (in parentheses) in kcal mol⁻¹ are: PhCO₂Me 39.1 (40.8), PhCH₂CO₂Me 35.6 (36.6), NH₂CH₂CO₂Me 32.0 (32.3) for 2:1 NaBH₄/ester, HOCH₂CO₂Me 27.4 (26.8), FCH₂CO₂Me 21.6 (19.8), ClCH₂CO₂Me 20.2 (18.1), and BrCH₂CO₂Me 19.6 (17.5). The barriers estimated for α -naphthCH₂CO₂Me (**15**) from its on-set temperature are 36.4 (37.6) kcal mol⁻¹.

In summary, nine chemoselective reductions of α -substituted and aromatic esters with sodium borohydride have been investigated using both theoretical computations at the B3LYP/6-31++G(d,p)//HF/6-31G(d,p) levels of theory and experiments. Four others were studied theoretically. The experimental results agree well with the theoretically predicted order of activation energies in these reductions. The notion that higher electronegativities in α -halogenated

esters reductions necessarily enhance the rate of hydride transfer to the carbonyl carbon has been corrected. Linear relationships between the computed ΔE^\ddagger values and the reciprocal of the on-set reaction temperature were obtained in THF and in the gas phase. The use of these linear relationships could provide a useful tool to predict reduction behavior in similar NaBH_4 ester reductions when using B3LYP/6-31++G(d,p)//HF/6-31G(d,p) level computations.

Experimental Section

A Bruker-AV-400 instrument was used for NMR determinations using CDCl_3 as the solvent unless another solvent is specifically stated. Chemicals were bought from Aldrich Co. and were used as received. A Waters model 2695 high-pressure liquid chromatography instrument was used for HPLC analyses. Thermometers used in the reaction temperature determinations were not corrected. Silica gel (200–400 mesh) was produced by Qingdao Makall Group Co. Ltd. A Bruck Tensor 27 was used for IR analyses and an Autospec 3000 model was used for MS or HRMS determinations.

A Typical Reduction Procedure: NaBH_4 was added all at once to a diglyme (or THF) solution of the α -substituted methyl ester at room temperature. The solution was then heated to the specified reaction temperature. After the reaction ended, most of the diglyme (or THF) was removed under reduced pressure (about 1–3 Torr) since the product formed will exist in the form of a $\text{Na}^+[\text{BH}_2(\text{OR})]^-$ salt and it cannot be removed under vacuum. A modified method was used when esters **1** and **3** were employed in the reductions (see below). The residue was then cooled with ice-water, and a saturated aqueous NH_4Cl solution was added to decompose the unreacted borohydrides. The mixture was extracted with ethyl acetate three or more times, and the combined organic layers were dried with anhydrous Na_2SO_4 . After the solvents had been removed, the residues were purified by column chromatography.

NaBH_4 Reductions of Methyl α -Hydroxyacetate (1**):** The procedure for this reduction was modified from the typical reduction procedure. A solution of NaBH_4 (209 mg, 5.5 mmol) in 10 mL of diglyme was added at about 0–3 °C to a diglyme solution of **1** (500 mg, 5.5 mmol). Hydrogen gas was immediately evolved. The solution was then heated to a temperature at which the reaction occurred (24–26 °C). Then the solution was warmed to 32–35 °C and held for 2 h. The reaction contents were then cooled to –20 °C and held for 10 min. The cold mixture was filtered to remove the diglyme. The solid residue was washed with dry diethyl ether (2 × 10 mL) to remove the remaining diglyme. The solid was then treated with several drops of concentrated aqueous HCl solution in diethyl ether (20 mL) at –20 to –10 °C. Anhydrous Na_2CO_3 and Na_2SO_4 were then added to absorb the water and excess HCl. This mixture was extracted with diethyl ether/methanol (1:1, v/v, 15 mL) a minimum of five times. The combined organic layers were dried with anhydrous Na_2SO_4 . The solvents were then removed and the residue was purified by column chromatography to give pure, liquid ethylene glycol (305 mg, 89% yield). ^1H NMR (400 MHz, D_2O): δ = 2.0 (t, J = 6.0 Hz, 4 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 62.2 ppm. IR (KBr): $\tilde{\nu}$ = 3384 cm^{-1} . HRMS (FAB⁺) calcd. for $\text{C}_2\text{H}_7\text{O}_2$: 63.0446; found 63.0427.

NaBH_4 Reductions of Methyl α -Aminoacetate (3**) ($\text{NaBH}_4/3 = 1$):** A solution of NaBH_4 (150 mg, 4.0 mmol) in diglyme (10 mL) was added to a solution of methyl α -aminoacetate (350 mg, 4.0 mmol) in 10 mL of diglyme at room temperature. The solution was incrementally heated until the on-set of reaction could just be detected

at a temperature of 68–70 °C. The temperature was increased to 79–82 °C and held for 3 h. Then, the mixture was cooled to about –20 °C, held for 10 min, and filtered to remove diglyme. The solid mixture was washed with dry diethyl ether to remove the residual diglyme. The solid was then treated with concentrated aqueous HCl solution dropwise in diethyl ether (20 mL) at –10 °C. Next, anhydrous Na_2CO_3 and Na_2SO_4 were added to absorb the water and excess HCl. This mixture was extracted with diethyl ether/methanol (1:1, v/v, 15 mL) five or more times. The combined organic layers were dried with anhydrous Na_2SO_4 , the solvents removed, and the residue purified by column chromatography to give the pure, liquid, water-soluble 2-aminoethanol (74 mg, 40% yield based on methyl α -aminoacetate). Unreacted starting material (78 mg) was also recovered (conversion 78%). ^1H NMR (400 MHz, CHCl_3): δ = 3.58 (t, J = 4.9 Hz, 2 H), 2.78 (t, J = 4.9 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, CHCl_3): δ = 62.8, 43.6 ppm. IR (KBr): $\tilde{\nu}$ = 3356 cm^{-1} . HRMS (FAB⁺): calcd. for $\text{C}_2\text{H}_8\text{NO}$, 62.0605; found 62.0608.

NaBH_4 Reductions of Methyl α -Aminoacetate (3**) ($\text{NaBH}_4/3 = 2$):** A solution of NaBH_4 (300 mg, 8.0 mmol) in 10 mL of diglyme was added to a solution of methyl α -aminoacetate (350 mg, 3.9 mmol) in 10 mL of diglyme at room temperature. The solution's temperature was increased until the reduction began to occur (detected by TLC). The temperature required was about 64–66 °C. Heating was continued until the temperature reached 76–78 °C and this temperature was maintained for 3 h. The reaction mixture was then cooled to –20 °C and held for 10 min. The cold mixture was filtered at –20 °C to remove the diglyme. The solid obtained was washed with anhydrous diethyl ether to remove the residual diglyme. The solid was treated with concentrated aqueous HCl solution in 20 mL of diethyl ether at –10 °C. Anhydrous Na_2CO_3 and Na_2SO_4 were added to remove the water and excess HCl. The mixture was then extracted with diethyl ether/methanol (1:1, v/v, 15 mL). The combined organic layers were dried with anhydrous Na_2SO_4 , and the solvents were removed in vacuo. The residue was purified by column chromatography to give the pure, liquid 2-aminoethanol (147 mg, yield 70%). Unreacted starting material (43 mg) was also recovered (conversion 88%). ^1H NMR (400 MHz, CHCl_3): δ = 3.58 (t, J = 4.9 Hz, 2 H), 2.78 (t, J = 4.9 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, CHCl_3): δ = 62.8, 43.6 ppm.

NaBH_4 Reductions of Methyl Formate (7**):** NaBH_4 (300 mg, 8.0 mmol) in 10 mL of diglyme was added to a solution of methyl formate (8.0 mmol) in 10 mL of diglyme at –25 °C. After 3 h, the mixture was filtered and the solid was washed with dry diethyl ether. A drop of concentrated aqueous HCl solution was added to the combined organic solution. This solution was then dried for 30 min over anhydrous Na_2SO_4 . The dried solution was analyzed by HPLC and the percent of the unreacted starting material was obtained by HPLC using toluene as the internal standard. The on-set temperature was –17 °C.

NaBH_4 Reductions of Methyl Benzoate (10**):** The reduction was carried out using the general procedure mentioned above. On-set reaction temperature was 154 °C in diglyme. Yield: 93%. ^1H NMR (400 MHz, CHCl_3): δ = 7.38–7.30 (m, 5 H), 4.58 (s, 2 H) ppm. ^{13}C NMR (100 MHz, CHCl_3): δ = 140.7, 128.3, 127.4, 126.8, 64.8 ppm. IR (KBr): $\tilde{\nu}$ = 3331, 3031, 1038, 1021, 735, 698 cm^{-1} . HRMS (AP-PIA, M-1): calcd. for $\text{C}_7\text{H}_7\text{O}$ 107.0496; found 107.0496.

NaBH_4 Reductions with $\text{PhCH}_2\text{CO}_2\text{Me}$ (11**):** The reduction was carried out using the general procedure mentioned above. The on-set reaction temperature was 104 °C. Yield: 95%. ^1H NMR (400 MHz, CHCl_3): δ = 7.30 (m, 5 H), 3.86 (t, J = 6.6 Hz, 2 H), 2.87 (t, J = 6.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, CHCl_3): δ = 138.7, 129.0, 128.5, 126.3, 63.4, 39.1 ppm. IR (KBr): $\tilde{\nu}$ = 3339,

3004, 1046, 748, 699 cm^{-1} . HRMS (APPIA, M-1): calcd. for $\text{C}_8\text{H}_9\text{O}$ 121.0653; found 121.0631.

NaBH_4 Reductions of 1- $\text{C}_{10}\text{H}_7\text{CH}_2\text{CO}_2\text{Me}$ (15): The reduction was carried out using the general procedure mentioned above. The on-set reaction temperature was 114 $^\circ\text{C}$. Yield: 95%. ^1H NMR (400 MHz, CHCl_3): δ = 8.05 (d, J = 7.9 Hz, 1 H), 7.86 (d, J = 7.6 Hz, 1 H), 7.75 (d, J = 8.1 Hz, 1 H), 7.52 (m, 2 H), 7.41 (m, 2 H), 3.92 (t, J = 6.7 Hz, 2 H), 3.31 (t, J = 6.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, CHCl_3): δ = 134.3, 133.9, 132.0, 128.8, 127.2, 127.1, 125.9, 125.6, 125.4, 123.6, 62.9, 36.1 ppm. IR (KBr): $\tilde{\nu}$ = 3363, 3289, 3048, 1042, 1015, 800, 776 cm^{-1} . HRMS (FAB⁺): calcd. for $\text{C}_{12}\text{H}_{12}\text{ONa}$ 195.0785; found 195.0779.

NaBH_4 Reductions of 2-Benzoylamino-2-(methoxycarbonyl)ethyl Benzoate (16): The reduction was carried out using the general procedure mentioned above at 40 $^\circ\text{C}$.

17: Liquid. Yield: 41%. ^1H NMR (400 MHz, CHCl_3): δ = 8.02 (d, J = 1.4 Hz, 2 H), 7.76 (d, J = 1.6 Hz, 2 H), 7.44 (m, 6 H), 6.90 (d, J = 7.3 Hz, 1 H), 4.55 (m, 3 H), 3.83 (m, 2 H) ppm. ^{13}C NMR (100 MHz, CHCl_3): δ = 167.8, 167.5, 133.8, 133.5, 131.8, 129.8, 129.3, 128.6, 128.5, 127.0, 63.1, 61.8, 51.2 ppm. IR (KBr): $\tilde{\nu}$ = 3407, 3318, 3064, 1725, 1637, 711, 694 cm^{-1} . HRMS (FAB⁺): calcd. for $\text{C}_{17}\text{H}_{18}\text{NO}_4$ 300.1235; found 300.1245.

18: Liquid. Yield: 95%. ^1H NMR (400 MHz, CH_3OH): δ = 7.83 (d, J = 7.7 Hz, 2 H), 7.52 (m, 1 H), 7.43 (m, 2 H), 4.17 (m, 1 H), 3.73 (t, J = 5.8 Hz, 4 H) ppm. ^{13}C NMR (100 MHz, CH_3OH): δ = 170.5, 135.7, 132.6, 129.5, 128.4, 62.2, 55.2 ppm. IR (KBr): $\tilde{\nu}$ = 3379, 3290, 3085, 1637, 1552, 1341, 1075, 1036, 694, 672 cm^{-1} . HRMS (FAB⁺): calcd. for $\text{C}_{10}\text{H}_{14}\text{NO}_3$ 196.0973; found 196.0981.

NaBH_4 Competitive Reductions: An equimolar mixture of **1** and **3** (180 and 178 mg, respectively; 1:1 mol/mol, 2.0 mmol of each) was dissolved in diglyme (15 mL). NaBH_4 (2 equiv., 2.0 mmol) was then added (in 15 mL diglyme) at 0–4 $^\circ\text{C}$ (ice bath cooled). The reaction temperature was then raised to 33–35 $^\circ\text{C}$. After 3 h, the reaction mixture was filtered to remove diglyme. The residue was then washed three times with dry diethyl ether, followed by the addition of drops of concentrated aqueous HCl solution to decompose unreacted borohydride. The resulting mixture was then extracted a minimum of five times with methanol/diethyl ether (50:50, v/v, 15 mL). The combined organic layers were dried with anhydrous Na_2SO_4 . The solvents were then removed in vacuo. This residue was purified by column chromatography to give ethylene glycol (105 mg, 84% yield). Unreacted **3** (169 mg) was recovered in 93% yield.

Competitive reductions of **3** with **11** (178 and 300 mg, respectively) and **11** with **10** (86 and 78 mg, respectively) were carried out in the same manner as described above for the competitive reduction of equimolar amounts of **1** with **3**, except different temperatures were employed and the diglyme was removed at about 40 $^\circ\text{C}$ under 1–3 Torr. The competitive reductions of **3/11** were performed at 82–85 $^\circ\text{C}$ for 3 h. 2-Aminoethanol was produced (90 mg, 74% yield) and **11** (278 mg) was recovered in 93% yield. The competitive reductions of **10** and **11** were performed at 110–5 $^\circ\text{C}$. Benzyl alcohol (65 mg) was obtained in 93% yield and 89% of **10** (70 mg) was recovered.

General Procedure for NaBH_4 Reductions of Methyl α -Haloacetates 12–14: NaBH_4 (300 mg, 8.0 mmol) in 10 mL of diglyme was added to a solution of methyl α -haloacetate (34.0 mmol) in 10 mL of diglyme at the previously determined on-set reaction temperature for each. After 3 h, the mixture was filtered and the solid was washed with dry diethyl ether. A drop of concentrated aqueous HCl solution was added to the combined organic solution. This solution was then dried for 30 min over anhydrous Na_2SO_4 . The dried solu-

tion was analyzed by HPLC and the percent of the unreacted starting material was obtained by HPLC using PhCO_2Me as the internal standard.

NaBH_4 Reductions with α -Halogenated Methyl Acetates: NaBH_4 (300 mg, 8.0 mmol) in 10 mL of diglyme was added to a solution of methyl α -halogenated ester (4.0 mmol) in 10 mL of diglyme at the on-set reaction temperature. After 3 h, the mixture was filtered and the solid was washed with dry diethyl ether. A drop of concentrated aqueous HCl solution was added to the combined organic solution. This solution was then dried with anhydrous Na_2SO_4 for 30 min. The dried solution was analyzed by HPLC and the percent of the unreacted starting material was obtained using PhCO_2Me as the internal standard.

The obtained NMR spectroscopic data for products from the two α -haloester reductions are listed below ($\text{FCH}_2\text{CH}_2\text{OH}$ is so soluble in water that it is difficult to purify because of its low boiling point and so we were unable to obtain it pure enough to record the NMR spectra, even though the reaction was repeated several times):

$\text{ClCH}_2\text{CH}_2\text{OH}$: ^1H NMR (400 MHz, CHCl_3): δ = 3.65 (t, J = 5.0 Hz, 2 H), 3.84 (t, J = 5.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, CHCl_3): δ = 62.8, 46.7 ppm.

$\text{BrCH}_2\text{CH}_2\text{OH}$: ^1H NMR (400 MHz, CHCl_3): δ = 3.51 (m, 2 H), 3.88 (t, J = 5.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, CHCl_3): δ = 62.6, 35.6 ppm.

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