Studies in the Regioselectivity of the Vinylogous Reformatsky Reaction with Ambident Electrophiles: Reversibility, Mechanism, and Synthetic Utility

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The additions of the organozinc reagent derived from ethyl 4-bromocrotonate to several unsaturated carbonyl substrates were investigated. The regiochemical outcome is reported for each reaction and some suggestions are advanced regarding the mechanism and possible control of experimental parameters influencing the regioselectivity of these additions. The reversibility of the Reformatsky reaction of ethyl 4-bromocrotonates with ketones and enones has been established by equilibration studies. Spectral data, especially ^{13}C NMR parameters, are provided for all compounds.

The Reformatsky reaction constitutes one of the most powerful methods of carbon–carbon bond formation under mild conditions.[2] To this date, it is also one of only two methods available for the carbon–carbon bond formation with hindered cyclopentanones, the other being the Conia–Dauben modification of the Wittig reaction performed under equilibrating conditions.[3] The organozinc reagent derived from α-halo esters has successfully been condensed with a wide variety of functional groups,[4] and the synthetic utility of the Reformatsky reaction has been thoroughly reviewed.[2,4,5] Although the Reformatsky reaction of vinylogous halo esters has also been investigated to a limited extent,[6] precise mechanistic studies are absent in the chemical literature, save for a few diffuse attempts at the investigation of regiochemical behavior of ambident organozinc reagents derived from vinylogous halo esters[7] or related reagents. We recently completed the first systematic study of the many experimental parameters which influence particularly the regiochemical course of the vinylogous Reformatsky reaction with simple carbonyl substrates, and we have succeeded in developing precise experimental conditions necessary for complete α- vs. γ-regioselection.[8] In this paper, we address the problems associated with the *hitherto unreported additions of ambident organozinc nucleophiles derived from γ-bromocrotonates* to unsaturated carbonyl compounds.[9]

The synthetic potential of such additions is depicted in Scheme I. In principle, the interaction of reagent **1** with an unsaturated carbonyl system could give rise to four possible adducts, **2–5**. It is not surprising that a detailed study of this type has not been undertaken, especially in view of the fact that of the two major problems associated with such regioselection, namely, the ambidently electrophilic behavior of enones and the nucleophilic behavior of dienolates, none has adequately been solved to date.[9,10,11] In addition to the usual steric, electronic, and energetic considerations, the reactivity of enones is believed to be governed by charge control (1,2-addition) or orbital control (1,4-addition) arguments,[10] whereas the behavior of ambident nucleophiles depends on the degree of charge localization as a function of the counterion and the possibility of either complexation or aggregation of the reagents.[11] The combination of these factors therefore poses a difficult problem. Although we recognized the potential difficulties associated with controlling the fourfold regioselection, we also anticipated the conversion of 1,2-adducts **2** and **3** to compounds **4** and **5**, respectively, by the application of some variant of the Cope rearrangement performed either in situ or with substrates **2** and **3** protected by O-alkylation, thereby reducing the experimental problem to a twofold regioselection. Since the Reformatsky reaction is amenable to asymetric induction,[12] we envisioned wide applicability of such sequences to the

(1) Fellow of the A. P. Sloan Foundation, 1981–85; Research Career Development Award recipient, 1984–89 (National Institutes of Health, AI-00564).

(2) For recent reviews and compilation of references, see: (a) Rathke, M. W. *Org. React. (N.Y.)* **1975**, *22*, 423. (b) Gaudemar, M. *Organomet. Chem. Rev. A* **1972**, *8*, 183; see also ref 8.

(3) The standard problem of enolization of cyclopentanones during their encounter with nucleophiles has been solved in this way. See: Conia, J. M.; Limassett, J. C. *Bull. Soc. Chim. Fr.* **1967**, *6*, 1936. Dauben, W. G.; Walker, D. M. *J. Org. Chem.* **1981**, *46*, 1103. The organozinc reagents derived from halo esters also add, even to hindered cyclopentanones, without enolization of the ketone and the necessary quench of the reagent.

(4) The Reformatsky reagents of simple halo esters have been condensed with alkyl halides: Orsini, F.; Pelizzoni, F. *Synth. Commun.* **1983**, *13*, 523. Nitrones: Stamm, H.; Stevolle, H. *Tetrahedron* **1979**, *35*, 647. Azirines: Kryczka, B.; Laurent, A.; Marquet, B. *Tetrahedron* **1978**, *34*, 3291. Imines: Furukawa, M.; Okawara, T.; Noguchi, Y.; Terawaki, Y. *Chem. Pharm. Bull. Jpn.* **1978**, *26*, 260. Bellassoued, M.; Arous-Chtara, R.; Gaudemar, M. *J. Organomet. Chem.* **1982**, *231*, 185. Arylations and vinylations: Faurarque, J. F.; Jutand, A. *Ibid.* **1977**, *132*, C17; **1979**, *177*, 273; **1981**, *209*, 109. For other uses see ref 2 and 8.

(5) (a) Collard, J. N.; Beriezra, C. *Tetrahedron Lett.* **1982**, *23*, 3725. (b) Gedye, R. N.; Arora, P.; Khalil, A. H. *Can. J. Chem.* **1975**, *53*, 1943. (c) Satoh, S.; Suginome, H.; Tolanda, M. *Tetrahedron Lett.* **1981**, *22*, 1895. (d) Orsini, F.; Pelizzoni, F.; Ricca, G. *Synth. Commun.* **1982**, *12*, 1147; *Tetrahedron Lett.* **1982**, *23*, 3948.

(6) See, for example: (a) Dreiding, A. S.; Pratt, R. J. *J. Am. Chem. Soc.* **1953**, *75*, 3717. (b) Bellasoued, M.; Dardoize, F.; Frangin, Y.; Gaudemar, M. *J. Organomet. Chem.* **1981**, *219*, C1. (c) Short, R. P.; Ranu, B. C.; Revol, J. M.; Hudlicky, T. *J. Org. Chem.* **1983**, *48*, 4453. (d) Short, R. P.; Hudlicky, T. *J. Org. Chem.* **1982**, *47*, 1522. (e) Ohler, E.; Reininger, K.; Schmidt, U. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 457; ref 8.

(7) See ref 6a, 6b, and 8. For a description of reactivity of related allylic species, see: (a) Negishi, E.; Miller, J. A. *J. Am. Chem. Soc.* **1983**, *105*, 6761. (b) Bernadou, F.; Miginiac, L. *Tetrahedron Lett.* **1976**, 3083. (c) Zweifel, G.; Hahn, G. *J. Org. Chem.* **1984**, *49*, 4565 (allenic zinc reagents).

(8) Rice, L. E.; Boston, M. C.; Finklea, H. O.; Suder, B. J.; Frazier, J. O.; Hudlicky, T. *J. Org. Chem.* **1984**, *49*, 1845.

(9) To our knowledge, the addition of the vinylogous Reformatsky reagent to enones has not been performed to date. However, the lithio dienolate of crotonates has been condensed with enones to give a 1,4-α product. Oppolzer, W.; Pitteloud, R. *J. Am. Chem. Soc.* **1982**, *104*, 6478. Studies of limited scope have been performed regarding the ambident behavior of enones (ref 10), crotonate dienolates (ref 11), and vinylogous Reformatsky reagents (ref 6, 8).

(10) See, for example: (a) Sauretre, R.; Roux-Schmitt, M. C.; Seyden-Penne, J. *Tetrahedron* **1978**, *34*, 2135. (b) Goasdoue, N.; Gaudemar, M. *J. Organomet. Chem.* **1982**, *226*, 209.

(11) For the regiochemical outcome of alkylations of crotonate-type anions with electrophiles, see: (a) Kajikawa, A.; Morisake, M.; Ikekawa, N. *Tetrahedron Lett.* **1975**, 4135. (b) Evans, D. A.; Andrews, G. C.; Buckwalter, B. *J. Am. Chem. Soc.* **1974**, *96*, 5560. (c) Johnson, P. R.; White, J. D. *J. Org. Chem.* **1984**, *49*, 4425 and references within. (d) Pfeffer, P.; Silbert, L.; Kensel, E. *Tetrahedron Lett.* **1973**, 1163. (e) Suga, K.; Watanabe, S.; Fujita, T. *Aust. J. Chem.* **1972**, *25*, 2393. (f) Cainelli, G.; Cardillo, G.; Contento, M.; Trapani, G.; Vinani-Ronchi, A. *J. Chem. Soc., Perkin Trans. I* **1973**, 400. (g) Vedejs, E.; Gapinski, D. *Tetrahedron Lett.* **1981**, *22*, 4913.

(12) See, for example: (a) Lucas, M.; Quette, J. P. *Tetrahedron* **1978**, *34*, 1685.

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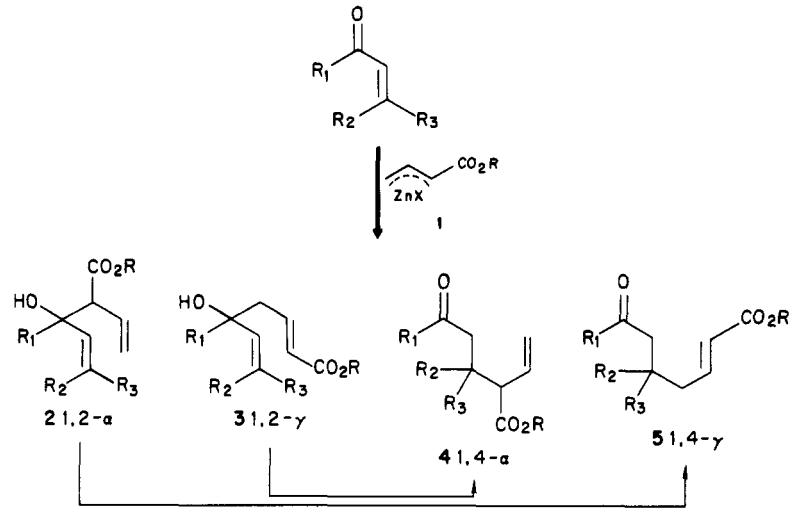
Scheme I. Cope Rearrangements[a]



[a] R = ethyl; R_1, R_2, R_3 = H, CH_3, alkyl; X = Br.

Table I

unsaturated carbonyl compound	reaction conditions[a]	product distribution (%)[b] 2	3	4	5
a	Zn/Cu (HOAc)/Et_2O, 3 min	>95			
	Zn/Cu (HOAc)/Et_2O, 1 h	28	26		46
	Zn, benzene	6	28		66
	Zn, THF, 4 h	10			90
b	Zn/Cu (HOAc)/Et_2O, <1 min	>90			<10
	Zn/Cu (HOAc)/Et_2O, 45 min	53	17		30
	Zn, benzene	30	40		30
	Zn, THF, 6 h				>90
	LDA, −78 °C, THF, $CH_3CHCHCO_2Et$			75	25
c	Zn/Cu (HOAc)/Et_2O, 1 min	100[c]			
	Zn/Cu (HOAc)/Et_2O, 1 h	16	26		58
	Zn, benzene	15	60		25
	Zn, THF, 4 h				>90
d	Zn/Cu (HOAc)/Et_2O, 3 min	>96			
	Zn, THF, 2 h	15			85
e	Zn/Cu (HOAc)/Et_2O, 30 s	100			
	Zn/Cu (HOAc)/Et_2O, 1 h	41	59		
	Zn, benzene	30	70		
	Zn, THF, 2 h		100		
f	Zn/Cu (HOAc)/Et_2O	35	55		<10
	Zn, benzene	<10	<10		>80

[a] Performed at reflux. [b] Determined by ^1H NMR integration (see ref 16). [c] Separable mixture of threo/erythro (hexane:EtOAc/75:25; R_f threo = 0.7, R_f erythro = 0.6).

regiocontrolled synthesis of chiral carbonyl compounds once the absolute control of regioselection had been solved.

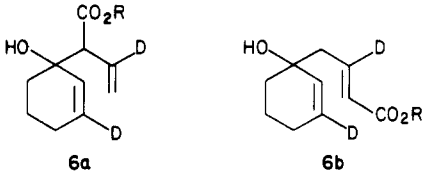
Results and Discussion

We chose a random sample of available α,β-unsaturated compounds for a preliminary study of regioselectivity of these additions and restricted our experiments to the application of only the previously optimized conditions of α- vs. γ-regioselection, the results of which we reported earlier.[8] Contrary to our earlier studies of additions of the Reformatsky reagent to simple carbonyl compounds, we have not investigated in any detail the effect of secondary metals in the catalyst, solvent profiles of the reactions for each catalyst, or additions of protic or Lewis acids to the reaction media. These restrictions, along with the postponment of any analyses regarding the ratios of threo/erythro diastereomers of the α-adducts, were necessary in order to establish preliminary trends and comparisons in the regioselectivities of this reaction for both simple and ambidently electrophilic carbonyl substrates.

The results of the initial set of experiments are summarized in Table I. In each case, the well-tested "polar" conditions (Zn/Cu (HOAc) in Et_2O) were used to produce the α-adducts and the "nonpolar" conditions (Zn/benzene) were utilized for the production of γ-adducts.[8] Each reaction was performed under conditions identical with those reported for simple aldehydes and ketones.[8] The product distribution was determined by integration of ^1H NMR spectra of crude reaction mixtures which showed in most cases nearly quantitative reaction. In some cases it proved possible to determine the ratios of products by gas chromatography.

All of the products were isolated by column chromatography and fully characterized by IR, ^1H and ^{13}C NMR, and mass spectral means. The *isolated yields* of any of the 1,2-adducts were low (5–31%) due to the inherent

Scheme II



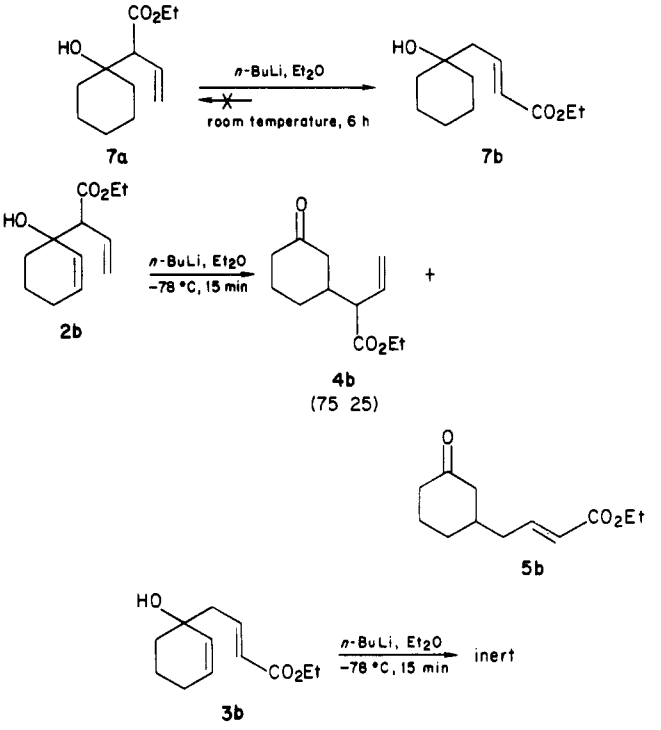
instability of these substances. Since we required the compounds **2** and **3** in high states of purity for further study, we purified them without derivatization; in practical applications however, the free hydroxyls were protected by O-alkylation [acetylation, silylation] which rendered their manipulations, as well as their synthetic transformations, facile (the acetates are stable indefinitely).[6c,d,8,17]

Under identical conditions, each of the substrates listed in Table I produced a mixture of isomers of varying proportions. This was somewhat surprising since the regioselection of simple aldehydes and ketones proved quite consistent with respect to the ambidence of the organozinc reagent. Closer monitoring of the reactions revealed product compositions which differed significantly as a function of *time* from the proportions obtained after the usual 1-h reaction times. In all instances, the 1,4-γ adduct, which was unexpectedly present in all crude reaction mixtures, proved to be completely absent during the *first few minutes*. As shown in Table I, the "polar" conditions yielded exclusively, within minutes, the 1,2-α adduct which was later transformed under the reaction conditions into the 1,4-γ adduct. Similarly, the "nonpolar" parameters gave mixtures of 1,2-γ and 1,4-γ adducts, with the latter originating in the initially formed 1,2-α adduct. No experimental conditions of the Reformatsky reaction yielded the 1,4-α adduct **4**, although this compound can be obtained (as illustrated for the case of cyclohexenone) either by the addition of the *lithium* dienolate of ethyl crotonate to the enone, in accord with the literature precedent,[9] or by the oxyanion Cope rearrangement of the 1,2-γ adduct, as well as by the low temperature dissociation/reassociation of the lithium alkoxide of **2a**. Finally, the 1,4-γ adduct **5** could be produced exclusively by using the "softest" conditions (Zn/THF, reflux).[13] Thus, *all four regioisomers* became accessible through careful control of the reaction conditions.

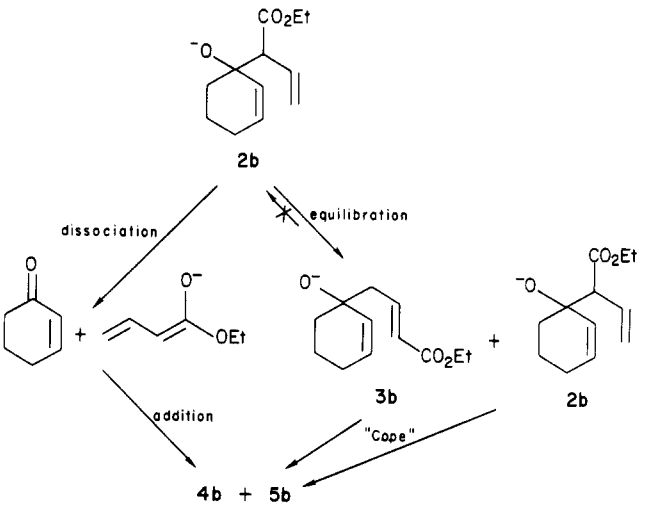
These observations suggested at least two possibilities for the origin of 1,4-γ adducts: an oxyanion Cope rearrangement of 1,2-α product via its zinc alkoxide *or* a dissociation of such alkoxide to a zinc dienolate and an equilibrium-governed competition of this dienolate for all reaction sites. To distinguish unambiguously between a Cope process and a *complete* dissociation will be possible through the use of deuterated substrates **6a** and **6b** in a crossover experiment with unlabeled materials (Scheme II); however, we decided to postpone the labeling experiments and to investigate instead the reversibility of the reaction.

It has been shown by Pfeffer,[11d] Watanabe,[11e] Cardillo,[11f] Vedejs,[11g] and most recently by White[11c] that lithium alkoxides of crotonate adducts of ketones indeed dissociate to give mostly the γ (or normal) addition product at equilibrium. We have confirmed these observations and found that cyclohexanone adduct **7a** was fully converted to **7b** by treatment with *n*-BuLi in Et_2O (unchanged for 1 h at −78 °C, 100% conversion after 6 h at room temperature) (Scheme III). By contrast, the reaction of cyclohexenone adduct **2b** under identical conditions was complete in 15 min and yielded a mixture of 1,4-α and 1,4-γ compounds, while the 1,2-γ adduct **3b** remained inert under the same conditions. This observation would support a dissociation/readdition fate for the lithium alkoxide although it does *not* exclude the Cope mechanism as shown in Scheme IV. It is, however, unlikely that **3b**, which contains a stable chromophore, would rearrange to **4b** at a rate comparable to the energetically more feasible conversion of **2b** → **5b**.

Scheme III



Scheme IV



We next turned to the investigation of reversibility of the vinylogous Reformatsky reaction. No quantitative data exist in the chemical literature although the reaction has always been "assumed" reversible by those investigators who reported cases of α- vs. γ-regioselectivity.[2,6a,b,8] We had assumed that the major reason for the quantitative regioselectivity observed in the additions of the zinc reagent to simple carbonyl substrates had been the combined polarity of the medium rather than a selection between kinetic vs. thermodynamic control.[14] As it turned

(13) These conditions were used previously in the few cases described in the literature concerning 1,4-addition of simple Reformatsky reagents to enones. Quette, J. P.; Lucas, M. *Bull. Soc. Chim. Fr.* **1975**, 2091; see also ref 2.

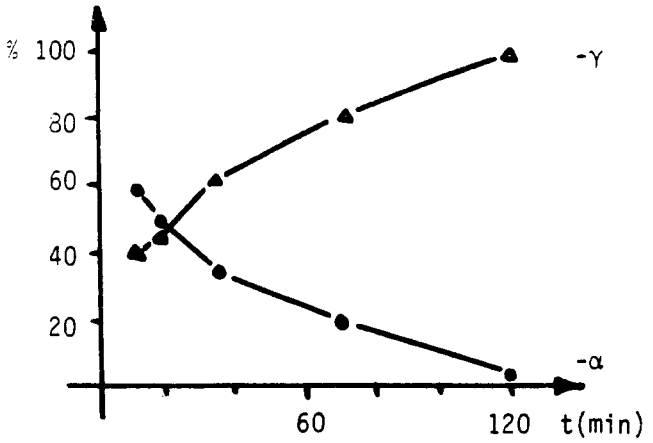


Figure 1. Reaction profile for cyclohexanone (Zn, Benzene, reflux).

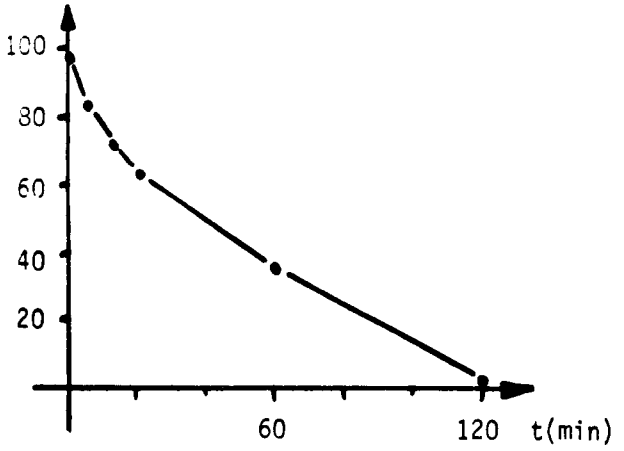


Figure 2. Decomposition of zinc alkoxide of **7a** in refluxing benzene.

out, this initial observation was only partially correct. The literature contains one report on kinetic vs. thermodynamic product control (although no equilibration studies are mentioned) using *pre-made* zinc reagent (kinetic) vs. simultaneous addition of the mixture of bromo ester and ketone to a suspension of the catalyst (thermodynamic).[6b] We have not been able to reproduce these results and have succeeded in producing only the dimer of ethyl crotonate during any attempts to stoichiometrically generate the zinc dienolate from 4-bromocrotonate. The confirmation of reversibility came from repeating some of the experiments of our recent study but using longer reaction times. For example, cyclohexanone yielded a 60:40 mixture of γ:α adducts after 45 min (Zn, benzene).[8] When this reaction was carefully monitored by ^{1}H NMR of aliquots, it revealed a *competition* of α vs. γ rates immediately after initiation (5 min at reflux; 60:40 (α:γ)) and then a slow equilibration to produce *exclusively the* γ*-isomer* after 2 h (Figure 1). When the α-isomer was generated in Et_2O under "polar" conditions, solvent was removed in vacuo, replaced with benzene, and the mixture was refluxed, the alkoxide of **7a** produced **7b** quantitatively in 2 h also (Figure 2)! It is interesting to note that the equilibration of zinc alkoxide is much *slower* than that of *lithium* as borne out by a comparative experiment in refluxing benzene (2 h vs. 20 min, respectively).

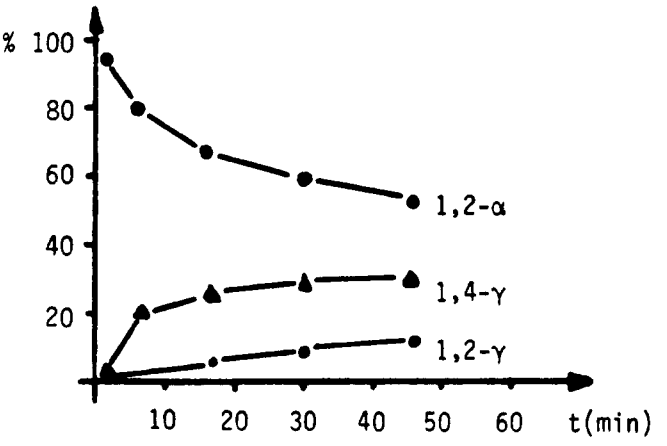


Figure 3. Reaction profile for cyclohexenone (Zn/Cu (HOAc), Et_2O, reflux).

Careful monitoring of the reaction between cyclohexenone, ethyl bromocrotonate, and zinc revealed the almost quantitative content of **2b** shortly after initiation. This compound was then transformed to the 1,4-γ product as well as to the 1,2-γ product during the course of 1 h.[15] The presence of the 1,2-γ adduct **3b** would favor a dissociative mechanism and equilibration in this reaction, whereas the 1,2-α → 1.4-γ conversion may be indicative of either a similar dissociation/readdition *or* an energetically feasible Cope rearrangement accelerated by the zinc alkoxide (Figure 3). Precise mechanistic distinction will have to await further experiments.

Finally, the oxyanion Cope Rearrangement of **2b** and **3b** (DME, 18-C-6, KH, reflux) gave low yields (~20%) of the 1,4-adducts **5b** and **4b**, respectively, due to fragmentation of the potassium alkoxide at elevated temperatures. It is clear that any true Cope rearrangements will have to be performed on either the relatively stable zinc alkoxides or the O-alkylated adducts. Further experimentation is necessary in the mechanistic as well as the synthetic aspects of these processes.

Conclusions

We have succeeded in providing the conditions for excellent 1,2-α and 1,4-γ regioselectivity and for moderate 1,2-γ and regioselectivity in the additions of the vinylogous Reformatsky reagent to enones. It is, however, apparent that the experimental parameters controlling the regioselection of the vinylogous Reformatsky reaction with enones are far more subtle than those responsible for the regiochemical outcome of additions to simple carbonyls. In addition to the now resolved issue of reversibility of the Reformatsky reaction of 4-halocrotonates, future study must address such parameters as the effect of secondary metals, donor properties of solvents, hardness/softness of counterions, Lewis or protic acid additives, and the modes of generation of the Reformatsky reagent and its subsequent interaction with enones.

From the analysis of the results, a trend emerges which merits detailed investigation. The 1,2-α adducts can be obtained through early workups of the Reformatsky reactions performed under "polar" conditions. It appears that a delocalized, relatively "hard" dienolate (M = Li) furnishes a 1,4-α adduct at low temperatures. Conversely, a delocalized, "soft" dienolate (M = Zn) in a coordinating

(14) The question of reversibility of the Reformatsky reaction has not been previously answered, although it appears to have been adequately addressed for lithium dienolate additions. For a discussion of these results, see ref 6b and 11c, respectively.

(15) The small amount of 1,2-γ product could be interpreted as having arisen from either independent competition or equilibration since we have demonstrated that *zinc* alkoxides, contrary to *lithium* alkoxides, are subject to slow equilibration.

solvent like THF gives the 1,4-γ adduct, whereas it adds 1,2 in Et_2O or benzene. Without invoking any arguments of kinetic vs. reversible additions dominating the Reformatsky pathway, it is conceivable that localized organometallic reagents will add 1,2-α in polar solvents and 1,2-γ in nonpolar ones without undergoing further transformations, provided the time element is carefully controlled (i.e., an early quench as described for the cases of cyclohexanone and cyclohexenone). It may also prove possible to influence 1,2-γ regioselection through the use of bulky ligands associated with metal counterions in nonpolar medium. Finally, a detailed study of the influence of substituents on both bromocrotonate and enone units is necessary to establish complete regiochemical trends.

Although the volume of literature dealing with the Reformatsky reaction seems tremendous, there exists no detailed investigation of this type. It is only through precise definition of the above-mentioned parameters that a multifold regioselection capacity can be delivered for the vinylogous or doubly vinylogous Reformatsky reaction with enones, dienones, etc. We will report on further developments in due course.

Experimental Section

All nonhydrolytic reactions were carried out in a nitrogen or argon atmosphere, using standard techniques for the exclusion of air and moisture. Glassware used for moisture sensitive reactions was flame-dried with an internal inert gas sweep.

All solvents were distilled prior to use. THF, toluene, and benzene were distilled from sodium benzophenone ketyl, ether from LAH, and CH_2Cl_2 from CaH_2.

Infrared spectra were recorded using neat samples, unless otherwise specified, on a Perkin-Elmer 257 spectrometer; ν_{max} is expressed in cm^{-1}. ^1H NMR spectra were obtained on varian EM390, JEOL-FX-200, or IBM-200 and IBM-WP-270 instruments, using $CDCl_3$ as solvent and Me_4Si as internal reference. Chemical shifts are expressed in δ units, and the coupling constants are indicated in parentheses and expressed in hertz; multiplicities of the signals are indicated as follows: d for doublet, t for triplet, q for quartet, p for pentet, m for multiplet, and any combinations as appropriate. Unspecified signals are singlets. The abbreviation "br" next to signal multiplicity connotes broad. ^{13}C spectra were recorded on JEOL-FX-200, IBM-200, IBM-WP-270, or NR-80 instruments using $CDCl_3$ as solvent and Me_4Si as internal reference. Chemical shifts are in δ units and multiplicities are as d for doublet, etc.

Flash chromatography was performed by the procedure of Still and co-workers,[6] using Kiesel gel 60 (230–400 mesh) from EM reagents. Column chromatography was performed on Macherey Nagle Co. silica gel 60.

Mass spectra were recorded on a DuPont 20-491 or a Varian MAT-112 instrument (low resolution) or on a double focusing DuPont 21-110C instrument (exact mass).

General Experimental Procedure. The appropriate catalyst was prepared from vacuum-dried Zn and a solution of metal acetate in HOAc as described previously.[8] The catalyst (2–4-fold excess) was covered with 5 mL of the solvent of choice, and a crystal of iodine was added. To this mixture were added a solution of ethyl 4-bromocrotonate (0.0011 mol) and a carbonyl substrate (0.001 mol) until the reaction initiated, whereupon the rest of the solution was added to maintain reflux. After the indicated amount of time, the reaction was quenched with a saturated solution of NH_4Cl and extracted with ether. Evaporation yielded an oil which was analyzed by ^1H NMR within minutes of workup. In most cases ^1H NMR analysis indicated the complete absence of starting materials and showed the presence of particular sets of product(s).

The crude reaction mixtures were either filtered through a short plug of silica (in cases of >95% regioselection) or chromatographed (flash chromatography; silica, hexane/EtOAc, 75:25) to provide pure samples for spectral characterization. The 1,2-adducts decomposed almost completely during chromatography or on storage and were isolated only to provide pure standards for NMR so that precise monitoring of reaction mixtures became possible. All attempts to analyze these compounds by combustion means failed. In most cases the material balance and the NMR evidence prior to purification supported nearly quantitative yields, while isolated yields were in the range of 5–31%.

In practical application acetates can be obtained directly and in good yields by subjecting the crude products to acetylation (dissolve 1 mmol of substrate in 10 mL of acetic anhydride containing 1 equiv of triethylamine and 0.1 equiv of (dimethylamino)pyridine, room temperature, overnight).[17]

Dissociation Experiments. The α-adduct of cyclohexanone (**7a**) (106 mg, 0.0005 mol) was dissolved in anhydrous ether (5 mL) and cooled to −78 °C under nitrogen. A solution of *n*-BuLi in hexane (0.35 mL of 1.5 M solution) was added, and the mixture was slowly warmed to room temperature. Analysis of aliquots taken at 1-h intervals showed quantitative equilibration to **7b** after 6 h. Similarly, **2b** and **3b** were treated with *n*-BuLi at −78 °C. The conversion of **2b** to a mixture of 1,4-adducts **4b** and **5b** (75:25) was complete in 15 min, whereas **3b** remained inert to the reaction conditions.

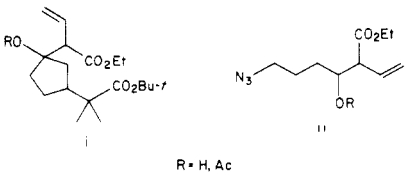
Time Profile Experiments. The reactions were initiated as described above. Aliquots were withdrawn at appropriate time intervals, quenched with NH_4Cl/Et_2O, evaporated, and analyzed by ^1H NMR for the content and distribution of regioisomers.

Spectral Data.[20] **2a**: IR (neat) 3500, 1720, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (s, 3 H), 1.16 (s, 3 H), 1.28 (t, 3 H, J = 7 Hz), 1.9 (d, 2 H, J = 3 Hz), 3.2 (d, 1 H, J = 8 Hz), 4.2 (q, 2 H, J = 7 Hz), 5.1 (m, 2 H), 5.75 (AB q, 2 H, J = 3 Hz), 6.0 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 28.7 (CH_3), 30.2 (CH_3), 43.0 (C), 51.7 (CH_2), 59.9 (CH), 60.8 (CH_2), 79.2 (C), 119.6 (CH_2), 129.9 (CH), 133.0 (CH), 146.0 (CH), 173.8 (C); mass spectrum (70 eV), m/e (relative intensity) 225 (M^+ + 1) (17), 207 (8), 179 (59), 133 (9), 114 (B), 86 (67), 69 (46), 55 (40).

3a: IR (neat) 3500, 1720, 1640, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (s, 3 H), 1.15 (s, 3 H), 1.28 (t, 3 H, J = 7 Hz), 1.78 (s, 2 H), 2.5 (d, 2 H, J = 8 Hz), 4.22 (q, 2 H, J = 7 Hz), 5.52 (AB q, 2 H, J = 8 Hz), 5.75 (d, 1 H, J = 14 Hz), 6.9 (dt, 1 H, J = 14, 8 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3), 28.9 (CH_3), 30.4 (CH_3), 44.6 (CH_2), 44.6 (C), 52.8 (CH_2), 60.1 (CH_2), 85.3 (C), 124.3 (CH), 132.4 (CH), 144.6 (CH), 145.2 (CH), 166.3 (C); mass spectrum (70 eV), m/e (relative intensity) 225 (M^+ + 1) (5), 206 (24), 177 (27), 161 (21), 160 (18), 145 (23), 133 (53), 131 (22), 117 (39), 114 (64), 112 (50), 111 (B), 105 (30), 95 (37), 93 (43), 91 (60), 86 (62), 77 (44), 69 (32), 68 (35), 55 (63).

(16) The relative composition of reaction mixtures was determined by the inspection of ^1H NMR spectra of crude mixtures which were rapidly filtered through a 1 × 2 cm plug of silica. The NMR spectra and TLC analysis showed the absence of starting materials. The analysis was confirmed by the comparison of spectral parameters of crude products with those of pure components. The relevant functionalities had the following chemical shifts. 1,2-α: α-methine, d, 3.1; vinyl group, m, 5.2 and 5.8; ring protons, m, 5.3 ppm. 1,2-γ: γ-methylene, d, 2.36; ring protons, m, 5.6; α-proton, d, 5.7; β-proton, dt, 6.9 ppm. 1,4-α: α-methine, t, 2.8; vinyl group, m, 5.2 and 5.8 ppm. 1,4-γ: γ-methylene, t, 2.35; α-proton, d, 5.75; β-proton, dt, 6.95 ppm.

(17) During many synthetic applications the zinc alkoxide is conveniently trapped in situ as a lactone (see ref 6c,d and 8). In some cases the acetate protection is essential during a synthesis and proceeds with the overall yields of >80%, as in cases of i[18] and ii.[19]



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(20) Combustion analytical data were not obtained due to instability (1,2-adducts) or hygroscopic properties (1,4-adducts) of samples. Purity of compounds was judged solely on the basis of their proton and carbon spectra (270 MHz).

5a: IR (neat) 1730, 1710, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (s, 3 H), 1.18 (s, 3 H), 1.3 (t, 3 H, J = 7 Hz), 2.0 (br s, 4 H), 2.1 (d, 2 H, J = 8 Hz), 2.4 (m, 1 H), 4.2 (q, 2 H, J = 7 Hz), 5.75 (d, 1 H, J = 14 Hz), 7.85 (dt, 1 H, J = 14, 8 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 21.6 (CH_3), 27.5 (CH_3), 32.5 (CH_2), 38.5 (C), 42.5 (CH_2), 42.5 (CH_2), 45.3 (CH), 54.9 (CH_2), 60.1 (CH_2), 122.7 (CH), 147.1 (CH), 166.2 (C), 216.7 (C); mass spectrum (70 eV), m/e (relative intensity) 225 ($M^+ - 1$) (3), 179 (57), 114 (B), 95 (27), 86 (57), 69 (32), 68 (30), 55 (30).

2b: IR (neat) 3550, 1720, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3 H, J = 7 Hz), 1.4–1.8 (m, 6 H), 2.9 (d, 1 H, J = 8 Hz), 4.1 (q, 2 H, J = 7 Hz), 5.0 (m, 2 H), 5.6 (br s, 2 H), 5.85 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.8 (CH_3), 18.2 (CH_2), 24.8 (CH_2), 34.6 (CH_2), 59.7 (CH), 60.5 (CH_2), 69.9 (C), 119.6 (CH_2), 128.8 (CH), 131.1 (CH), 132.4 (CH), 172.8 (C); mass spectrum (70 eV), m/e (relative intensity) 192 ($M^+ - H_2O$) (0.2), 164 (0.4), 114 (22), 97 (B), 86 (27), 79 (13), 68 (30), 54 (16).

3b: IR (neat) 3500, 1710, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3 H, J = 7 Hz), 1.4–1.8 (m, 6 H), 2.4 (d, 2 H, J = 8 Hz), 4.1 (q, 2 H, J = 7 Hz), 5.6 (m, 2 H), 5.7 (d, 1 H, J = 14 Hz), 7.9 (dt, 1 H, J = 14, 8 Hz); ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3), 18.9 (CH_2), 25.1 (CH_2), 35.9 (CH_2), 45.0 (CH_2), 60.5 (CH_2), 69.5 (C), 124.6 (CH), 131.1 (CH), 131.9 (CH), 144.4 (CH), 166.4 (C); mass spectrum (70 eV), m/e (relative intensity) 211 ($M^+ + 1$) (6), 192 (16), 147 (17), 119 (39), 118 (16), 177 (30), 114 (23), 97 (B), 92 (13), 91 (43), 86 (25), 79 (40), 68 (18), 55 (20).

4b: IR (neat 1720, 1710, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (t, 3 H, J = 7 Hz), 1.4–2.6 (m, 10 H), 2.9 (br t, 1 H), 4.2 (q, 2 H, J = 7 Hz), 5.2 (m, 2 H), 5.8 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 24.5 (CH_2), 27.9 (CH_2), 40.4 (CH), 41.0 (CH_2), 45.7 (CH_2), 56.1 (CH), 60.6 (CH_2), 119.1 (CH_2), 133.6 (CH), 172.0 (C), 210.3 (C).

5b: IR (neat) 1700, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (t, 3 H, J = 7 Hz), 1.5–2.4 (m, 9 H), 2.2 (d, 2 H, J = 8 Hz), 4.1 (q, 2 H, J = 7 Hz), 5.7 (d, 1 H, J = 14 Hz), 6.8 (dt, 1 H, J = 14, 8 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 24.8 (CH_2), 30.8 (CH_2), 38.1 (CH), 38.8 (CH_2), 41.2 (CH_2), 47.6 (CH_2), 60.2 (CH_2), 123.5 (CH), 145.6 (CH), 166.2 (C), 210.6 (C); mass spectrum (70 eV), m/e (relative intensity) 211 ($M^+ + 1$), 193 (20), 165 (30), 147 (25), 137 (17), 119 (37), 117 (19), 114 (46), 97 (B), 91 (30), 86 (34), 79 (32), 68 (21), 55 (24).

2c (obtained as a separable mixture of threo/erythro isomer), R_f 0.7: IR (neat) 3600, 1725, 1650, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (t, 3 H, J = 7 Hz), 1.28 (s, 3 H), 3.1 (d, 1 H, J = 8 Hz), 4.02 (q, 2 H, J = 7 Hz), 5.2 (m, 2 H), 6.0 (m, 1 H), 6.3 (d, 1 H, J = 14 Hz), 6.7 (d, 1 H, J = 14 Hz), 7.2 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3), 25.5 (CH_3), 59.4 (CH), 60.7 (CH_2), 73.4 (C), 120.4 (CH_2), 126.4 (CH) (double intensity), 127.4 (CH), 128.2 (CH), 128.4 (CH) (double intensity), 131.9 (CH), 134.8 (CH), 136.7 (C), 173.2 (C); mass spectrum (70 eV), m/e (relative intensity) 260 (M^+) (0.6), 225 (10), 181 (20), 180 (30), 147 (B), 129 (16), 103 (9), 79 (10).

2c, R_f 0.6: IR (neat) 3600, 1730, 1660, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (t, 3 H, J = 7 Hz), 1.42 (s, 3 H), 3.2 (d, 1 H, J = 8 Hz), 4.2 (q, 2 H, J = 7 Hz), 5.2 (m, 2 H), 5.9 (m, 1 H), 6.2 (d, 1 H, J = 14 Hz), 6.7 (d, 1 H, J = 14 Hz), 7.25 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3), 27.1 (CH_3), 59.9 (CH), 60.9 (CH_2), 73.5 (C), 119.7 (CH_2), 126.4 (CH) (double intensity), 127.4 (CH), 128.4 (CH) (double intensity), 128.8 (CH), 132.2 (CH), 132.9 (CH), 136.8 (C), 173.2 (C); mass spectrum (70 eV), m/e (relative intensity) 260 (M^+) (0.3), 148 (11), 147 (B), 131 (11), 129 (23), 103 (12), 86 (10), 77 (10), 69 (5).

3c: IR (neat) 3500, 1720, 1660, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (t, 3 H, J = 7 Hz), 1.4 (s, 3 H), 2.5 (d, 2 H, J = 8 Hz), 4.2 (q, 2 H, J = 7 Hz), 5.9 (d, 1 H, J = 14 Hz), 6.45 (AB q, 2 H, J = 16 Hz), 6.9 (m, 1 H), 6.9–7.3 (br s, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3), 28.2 (CH_3), 45.6 (CH_2), 60.3 (CH_2), 72.7 (C), 125.0 (CH), 125.8 (CH), 126.6 (CH), 127.5 (CH), 127.8 (CH), 128.0 (CH), 128.7 (CH), 135.7 (CH), 143.8 (CH), 144.4 (C), 166.0 (C); mass spectrum (70 eV), m/e (relative intensity) 261 ($M^+ + 1$) (12), 243 (7), 215 (16), 169 (21), 157 (B), 147 (40), 129 (46), 128 (16), 115 (35), 114 (39), 111 (21), 91 (21), 86 (32), 68 (21).

5c: IR (neat) 1705, 1640, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, 3 H, J = 7 Hz), 2.0 (s, 3 H), 2.5 (t, 2 H, J = 8 Hz), 2.75 (d, 2 H, J = 7 Hz), 3.32 (p, 1 H, J = 7 Hz), 4.15 (q, 2 H, J = 7 Hz), 5.76 (d, 1 H, J = 14 Hz), 6.8 (dt, 1 H, J = 14, 8 Hz), 7.25 (br s, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 30.5 (CH_3), 38.8 (CH_2), 40.1 (CH), 49.4 (CH_2), 60.1 (CH_2), 123.4 (CH), 126.8 (CH), 127.4 (CH), 128.7 (CH), 143.2 (C), 145.9 (CH), 178.7 (C), 206.8 (C); mass spectrum (70 eV), m/e (relative intensity) 203 (42) ($M^+ - 57$ (CH_2COCH_3)), 171 (25), 169 (16), 157 (59), 147 (B), 143 (15), 131 (21), 130 (17), 129 (96), 128 (51), 115 (29), 114 (71), 105 (17), 104 (27), 103 (28), 91 (51), 86 (54), 78 (18), 77 (28), 68 (35).

2d: IR (neat) 3500, 1730, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (t, 3 H, J = 7 Hz), 1.8–2.4 (m, 4 H), 3.1 (d, 1 H, J = 8 Hz), 4.15 (q, 2 H, J = 7 Hz), 5.2 (m, 2 H), 5.7 (m, 1 H), 5.8 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3), 31.2 (CH_2), 36.6 (CH_2), 59.2 (CH), 60.8 (CH_2), 86.0 (C), 119.6 (CH_2), 132.7 (CH), 133.5 (CH), 135.1 (CH), 173.2 (C).

5d: IR (neat) 1735, 1710, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (t, 3 H, J = 7 Hz), 1.2–2.2 (m, 7 H), 2.4 (d, 2 H, J = 8 Hz), 4.2 (q, 2 H, J = 7 Hz), 5.85 (dd, 1 H, J = 14, 8 Hz), 7.0 (dt, 1 H, J = 14, 8 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3), 30.9 (CH_2), 37.7 (CH_2), 40.1 (CH_2), 44.6 (CH_2), 45.7 (CH), 124.7 (CH), 144.2 (CH), 173.2 (C).

2e: IR (neat) 3500, 1715, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (t, 3 H, J = 7 Hz), 3.0 (t, 1 H, J = 8 Hz), 4.05 (q, 2 H, J = 7 Hz), 4.2 (m, 1 H), 5.1 (m, 4 H), 5.7 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3), 56.4 (CH), 61.0 (CH_2), 73.0 and 73.4 (CH), 116.5 and 116.8 (CH_2), 119.6 and 120.3 (CH_2), 132.0 and 132.5 (CH), 137.3 and 137.9 (CH), 172.7 (C) [duplicate signals correspond to erythro/threo isomers]; mass spectrum (70 eV), m/e (relative intensity) 171 ($M^+ + 1$) (10), 153 ($M^+ + 1 - H_2O$) (40), 114 (B), 86 (B), 69 (35), 68 (75), 56 (42).

3e: IR (neat) 3500, 1715, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3 H, J = 7 Hz), 2.32 (t, 2 H, J = 7 Hz), 4.1 (q, 2 H, J = 7 Hz), 4.2 (m, 1 H), 5.1 (m, 4 H), 5.7 (m, 1 H), 5.7 (d, 1 H, J = 14 Hz), 6.8 (dt, 1 H, J = 14, 8 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 39.6 (CH_2), 61.0 (CH_2), 71.3 (CH), 115.2 (CH_2), 123.8 (CH), 139.5 (CH), 144.5 (CH), 166.3 (C); mass spectrum (70 eV), m/e (reltive intensity) 171 ($M^+ + 1$) (40), 153 ($M^+ + 1 - H_2O$) (B), 135 (30), 125 (35), 114 (40), 107 (52), 95 (45), 86 (60), 81 (65), 79 (80), 69 (50), 68 (B), 41 (62).

2f: IR (neat) 3500, 1715, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3 H, J = 7 Hz), 1.1 (s, 3 H), 3.2 (m, 1 H), 4.2 (q, 2 H, J = 7 Hz), 5.0 (m, 4 H), 5.8 (m, 2 H). This compound proved extremely unstable in manipulations; protected as an acetate: IR (neat) 1720, 1715, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) acetate signal, δ 2.1 (s, 3 H).

3f: IR (neat) 3500, 1715, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3 H, J = 7 Hz), 1.1 (s, 3 H), 2.2 (d, 2 H, J = 8 Hz), 4.1 (q, 2 H, J = 7 Hz), 5.0 (m, 2 H), 5.8 (m, 1 H), 5.75 (d, 1 H, J = 14 Hz), 6.9 (dt, 1 H, J = 14, 8 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 26.8 (CH_3), 44.7 (CH_2), 60.0 (CH_2), 72.1 (C), 121.6 (CH_2), 124.4 (CH), 144.3 (CH), 148.5 (CH), 166.0 (C).

5f: IR (neat) 1720, 1710, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (t, 3 H, J = 7 Hz), 1.8–2.3 (m, 4 H), 2.1 (s, 3 H), 2.4 (m, 2 H), 4.2 (q, 2 H, J = 7 Hz), 5.8 (d, 1 H, J = 14 Hz), 6.8 (dt, 1 H, J = 14, 8 Hz); ^{13}C NMR ($CDCl_3$), δ 14.1 (CH_3), 22.7 (CH_2), 29.7 (CH_2), 31.1 (CH_2), 42.4 (CH_2), 60.0 (CH_2), 122.0 (CH), 147.8 (CH), 166.4 (C), 207.8 (C); mass spectrum (70 eV), m/e (relative intensity)) 184 (M^+) (5), 161 (40), 120 (40), 109 (B), 99 (80), 94 (75), 81 (60), 58 (70).

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Registry No. **2a**, 98269-33-1; **2b**, 98269-36-4; (*R**,*S**)-**2c**, 98269-40-0; (*R**,*R**)-**2c**, 98269-41-1; **2d**, 98269-44-4; **2e**, 98269-46-6;

2f, 98269-48-8; **3a**, 98269-34-2; **3b**, 98269-37-5; **3c**, 98269-42-2; **3e**, 98269-47-7; **3f**, 98269-49-9; **4b**, 98269-38-6; **5a**, 98269-35-3; **5b**, 98269-39-7; **5c**, 98269-43-3; **5d**, 98269-45-5; **5f**, 98269-50-2; **7a**, 50745-74-9; **7b**, 98269-51-3; (*E*)-PhCH=CHC(O)CH_3, 1896-62-4; CH_2=CHCHO, 107-02-8; CH_2=CHC(O)CH_3, 78-94-4; CH_3CH=CHC(O)OEt, 10544-63-5; ethyl 4-bromocrotonate, 6065-32-3; 4,4-dimethylcyclopent-2-en-1-one, 22748-16-9; cyclohex-2-en-1-one, 930-68-7; cyclopent-2-en-1-one, 930-30-3.

Oxidation of Hydrocarbons. 16. Mechanism of the Reaction between Alkynes and Permanganate Ion

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The kinetics and mechanism of the oxidation of alkynes by tetrabutylammonium permanganate in methylene chloride have been studied. Second-order rate constants have been determined for several different alkynes in an attempt to evaluate the extent of electronic and steric effects on the reaction. The rates are found to be very sensitive to electronic effects, but much less dependent on steric effects. A concave plot is obtained when the logarithms of the rate constants are plotted against Taft's σ^* substituent constants. This result is explained in terms of a reaction that can proceed via two pathways of almost equal activation energy. The transition state in one pathway has a positively charged carbon and is thus favored when the alkyne bears electron-donating substituents, while the other pathway has a carbanion-like transition state that is stabilized by substituents which are able to delocalize a negative charge. As a consequence the rate of reaction is greatly accelerated for α-oxoalkynes.

Permanganate is one of the most versatile oxidants available[1] with applications ranging from its use in the elegant stereospecific syntheses of substituted tetrahydrofuran derivatives[2] to its much less esoteric, but nevertheless very necessary, use in the fumigation of chicken coops.[3] In recent years the scope of its reactions has been increased by the discovery that it can be used, with the assistance of phase-transfer agents, in nonaqueous solvents[4] or as a heterogeneous oxidant under a variety of nonpolar organic solvents.[5]

Because of its wide use in organic synthesis the reactions of permanganate have been the subject of mechanistic speculations for almost a century.[6] Most recently, an improved understanding of the reactions between high valent transition metal oxidants, such as permanganate, and unsaturated compounds has come from several theoretical studies, the most important of which were made by Sharpless[7] (who first suggested that organometallic intermediates might be involved) and Goddard[8] (who drew attention to factors which would lead to stabilization of the intermediates). Although the results of these studies have been applied primarily to an understanding of the reactions of alkenes,[9,10] we wish, in this paper, to show that they can also be used, in conjunction with certain experimental results, to develop a reasonable mechanism for the oxidation of alkynes by permanganate.

Table I. Rate Constants for the Oxidation of Ethyl 2-Butynate by Tetrabutylammonium Permanganate[a]

[alkyne], M × 10^2	$[QMnO_4]_i$, M × 10^4	initial slope,[b] M s^{-1} × 10^7	k_1,[c] s^{-1} × 10^3	k_2, M^{-1} s^{-1} [d]
1.52	1.67	−5.27	3.16	0.208
1.52	1.92	−6.05	3.15	0.207
1.52	2.51	−7.63	3.04	0.200
1.52	3.63	−11.2	3.09	0.203
1.06	3.51	−8.20	2.34	0.221
0.608	3.42	−4.37	1.28	0.211

[a] Temperature 22.0 °C in methylene chloride. [b] Initial slope = $d[QMnO_4)_i/dt$. [c] k_1 = −initial slope/$[QMnO_4]_i$. [d] $k_2 = k_1/$[ethyl 2-butynate].

Table II. Rate Constants for the Oxidation of Substituted Alkynes by Tetrabutylammonium Permantanage[a]

alkyne	[alkyne], M × 10^3	k_1, s^{-1} × 10^3	k_2, M^{-1} s^{-1} × 10^3
4-phenyl-3-butyn-2-one	12.7	12.0 ± 0.1	945 ± 8
ethyl 2-butynate	15.2	3.10 ± 0.05	204 ± 3
ethyl 1-propynyl ether[b]	16.4	0.18 ± 0.03	11 ± 2
1-phenyl-1-butyne	12.4	0.037 ± 0.006	3.0 ± 0.5
2-heptyne	14.0	0.046 ± 0.001	3.3 ± 0.1

[a] In methylene chloride at 22.0 °C. Symbols defined in Table I. [b] Unstable compound. Kinetics were determined by using a freshly distilled sample.

Experimental Section

Materials. Tetrabutylammonium permanganate was prepared and handled as previously described.[11] The alkynes were obtained

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