of the MOM protecting group by Lipshutz procedure.[4e,14] The stereochemistries of these three diastereomers were determined by X-ray crystallographic analysis. The observed endo preference (**17a**,**d**/**17b**,**c** = 1:2.4), which is essentially independent of E/Z ratio of the precursor **16** and the reaction conditions, can be explained by secondary orbital interactions as observed in intermolecular version and/or less predictable conformational factors.

Finally, reaction of **17a** with $LiBF_4$ in aqueous MeCN at reflux for 10 h afforded diol **18a** in 73% yield. The diol was transformed into (±)-24-*O*-methylchlorothricolide (**19**) by sequential oxidation with active MnO_2 and $NaClO_2$. The stereostructure was confirmed by X-ray crystallographic analysis of the methyl ester **20** (CH_2N_2).

In conclusion, the first synthesis of (±)-24-*O*-methylchlorothricolide has been achieved. Although the key internal cycloaddition (**16** to **17a**) is not efficient in terms of diastereofacial selectivity, we believe that simplicity of the overall scheme compensates for the drawback.

Supplementary Material Available: Complete experimental procedure including copies of ^1H NMR spectra, X-ray crystallographic data, and ORTEP drawings for compounds **17b**, **17d**, **18c**, and **20** (37 pages). Ordering information is given on any current masthead page.

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Nucleophilic Cleavages of One-Electron σ Bonds Are Predicted To Proceed with Stereoinversion

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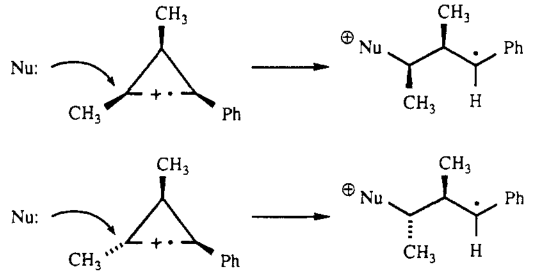
Summary: The valence-bond curve crossing model is used to analyze the stereochemistry of nucleophilic displacements on one-electron σ bonds. The model predicts that the stereochemistry of cleavage of one-electron σ bond by nucleophiles will be governed by the σ* orbital of the one-electron bonds. As a result such nucleophilic cleavages are predicted to proceed with inversion of stereochemistry at the center of attack. This prediction is in accord with recent experimental findings.

The cation radicals of several arylcyclopropanes have recently been generated by photooxidation and found to undergo cyclopropane ring cleavage in the presence of a variety of nucleophiles.[1] As previously suggested, these reactions can be rationalized as nucleophilic displacements on one-electron σ bonds. A stereochemical analysis of these reactions has shown that they occur with essentially complete inversion of configuration at the carbon atom undergoing nucleophilic substitution.



These stereochemical results are surprising because according to *perturbational* MO reasoning, both the SOMO σ orbital and the LUMO σ* orbital of the one-electron bond are capable of undergoing orbital interactions with the nucleophile, and with no obvious a priori preference for either one of these orbitals. At the simplest qualitative level, the number of electrons in the interaction (two vs three) will prefer the HOMO(Nu)-LUMO(σ*) interaction while the orbital energy gap factor will prefer the HOMO(Nu)-SOMO(σ) interaction. Therefore, no clear cut general prediction can be made about the stereospecificity of these nucleophilic reactions. Understanding the origins of this stereospecificity is thus required along with an analysis of the expected stereochemistry in the broader area of nucleophilic displacements on one-electron σ bonds.[2]

A theoretical model for nucleophilic attacks on cation radicals has recently been proposed by Pross based upon valence-bond curve crossing diagrams.[3] This model has subsequently been criticized,[4] and, despite a rebuttal of the main critical points,[5] there still exist doubts about the usefulness of the model.[6] The secondary purpose of this paper is to reclaim the usefulness of the curve crossing model by projecting the insight it provides onto the problem of stereospecificity in nucleophilic cleavages of one-electron σ bonds. As will be shown, the model predicts that the course of a nucleophilic cleavage of a one-electron σ bond is governed by the σ* orbital of the one-electron bond. As a result such nucleophilic cleavages *are predicted*

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[1] Dinnocenzo, J. P.; Todd, W. P.; Simpson, T. R.; Gould, I. R. *J. Am. Chem. Soc.* **1990**, *112*, 2462.

[2] Nucleophilic cleavages of one-electron σ bonds in several silane cation radicals have recently been observed: Dinnocenzo, J. P.; Farid, S.; Goodman, J. L.; Gould, I. R.; Todd, W. P.; Mattes, S. *J. Am. Chem. Soc.* **1989**, *111*, 8973. The stereochemistries of these cleavages are not yet known.

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[4] (a) Parker, V.; Tilset, M. *J. Am. Chem. Soc.* **1987**, *109*, 2521. (b) Drewello, T.; Heinrich, N.; Maas, W. P. M.; Nibbering, N. M. M.; Weiske, T.; Schwarz, H. *J. Am. Chem. Soc.* **1987**, *109*, 4810. (c) Parker, V. D.; Tilset, M. *J. Am. Chem. Soc.* **1988**, *110*, 1649. (d) Reitstöen, B.; Norrsell, F.; Parker, V. D. *J. Am. Chem. Soc.* **1989**, *111*, 8463.

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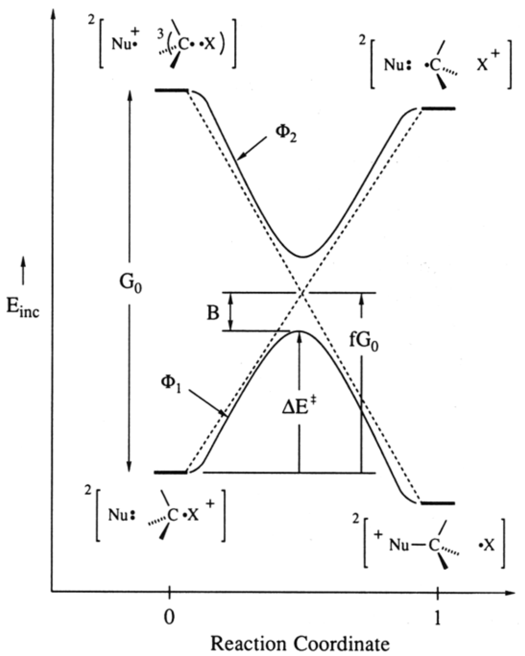


Figure 1. A curve crossing diagram describing the barrier formation for a nucleophilic substitution reaction between a nucleophile and a one-electron σ bond. The extremes of the reaction coordinate (0, 1) refer to the geometries of the encounter complexes. The three electrons are coupled to a total of a doublet spin in the two curves.

to proceed with inversion of stereochemistry at the center of attack.

Consider the reaction between a nucleophile (Nu:) and a one-electron σ bond ($R^\bullet X^+$) as shown in eq 1. Here R is an alkyl group while X can be a substituted carbon, as in the cyclopropane systems described above,[1] or any group capable of sustaining a σ one-electron bond with alkyl group (without converting to the distonic form[4b]).

$$\text{Nu:} + R^\bullet X^+ \rightarrow {}^+\text{Nu-R} + {}^\bullet X \qquad (1)$$

Following ref 3 and 5, the reaction profile can be generated by the avoided crossing of *mainly* two configurations, as shown in Figure 1. The first configuration, Φ_1, describes the electron distribution and bond pairing of the reactants: the nucleophile and the one-electron σ bond. The second configuration, Φ_2, describes the electron distribution and bond pairing of the substitution products: $^+$Nu-R and $X^\bullet$.[7] At the reactant extreme of the reaction coordinate, the Φ_2 configuration is high in energy due to the triplet relationship between the two σ electrons of the RX moiety. Moving along the reaction coordinate, the energy of this configuration descends and eventually becomes the product configuration as the odd electrons on $\text{Nu}^{\bullet+}$ and $R^\bullet$ are gradually coupled to form the Nu-R bond.[3,5]

The reaction barrier ($\Delta E^{\ddagger}$), relative to the energy of the reactants' encounter complex, is given by eq 2 as the difference between the height of the crossing point and the avoided crossing resonance interaction, B. The height of the crossing point is further expressed as a fraction, f, of the diagram gap at the reactants' extreme (G_0).

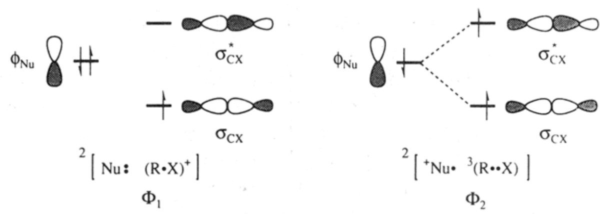
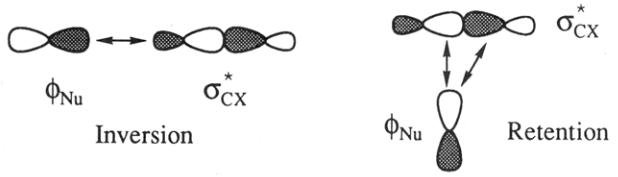


Figure 2. MO representations of the main configurations which describe the avoided crossing in Figure 1. The group R is an alkyl moiety. The resonance interaction (B) between Φ_1 and Φ_2 at the crossing point is proportional to the ϕ_{Nu}–σ^*_{CX} overlap. The dashed lines in Φ_2 indicate the spin pairing of the respective spins. For sake of simplicity, the C and X contributions to the σ_{CX} and σ^*_{CX} MO's are drawn as being equal.

$$\Delta E^{\ddagger} = fG_0 - B \qquad (2)$$

The stereochemistry of the substitution–inversion vs retention—will depend on the relative magnitudes of these two factors in the two stereochemical pathways. To assess these factors it is best to inspect the two configurations Φ_1 and Φ_2 in their MO representations as shown in Figure 2. Φ_1 describes two electrons on the nucleophile and a single electron in the σ_{CX} orbital, accounting for the one-electron bond of the reactants. Φ_2, on the other hand, involves a single electron on $\text{Nu}^{\bullet+}$ and a $^3(\sigma\sigma^*)$ configuration for the RX moiety, with a net doublet spin.

The avoided crossing interaction of Figure 1, B, is the resonance interaction due *mainly* to the mixing of configurations Φ_1 and Φ_2 at the crossing point. Following the rules of configuration mixing,[8] Φ_1 and Φ_2 will mix in proportion to the overlap of ϕ_{Nu} and σ^*_{CX}, *the two orbitals which participate in the switch of one electron between the two configurations.* Thus using the ϕ_{Nu}–σ^*_{CX} overlap as a guide,[9] it is easy to see that owing to the node which reduces the overlap of the frontside trajectory, a backside displacement will have a significantly larger avoided crossing interaction than a frontside displacement and thus $B_{inv} > B_{ret}$.



The height of the crossing point will also depend crucially upon the extent of self-stabilization of Φ_2 at the crossing point. The self-stabilization of Φ_2 arises from the bond coupling due to the pairing of the odd electrons on Nu and RX in Φ_2.[8] In the frontside displacement, the ϕ_{Nu}–σ^*_{CX} interaction is small and mainly the ϕ_{Nu}–σ_{CX} interaction contributes to the bond coupling. In contrast, both the ϕ_{Nu}–σ_{CX} and the ϕ_{Nu}–σ^*_{CX} interactions will contribute to the bond coupling in the backside displacement. Therefore, the height of the crossing point in eq 2, i.e. the fG_0 term, will normally be lower for a backside displacement.

It is apparent from the above discussion that both barrier factors in eq 2 favor backside nucleophilic displacement (inversion stereochemistry). The analysis

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[7] Another configuration, Φ_3, may be considered in which Nu possesses one electron like in Φ_2 but the two electrons in the C–X σ bond are singlet coupled. This configuration represents a simple electron transfer from Nu: to ($R^\bullet X^+$). Accordingly, there exist two distinct avoided crossings, Φ_1–Φ_2, shown in Figure 1, and Φ_1–Φ_3, which is not discussed here. These two avoided crossings will occur along two distinct reaction coordinates and give rise to two distinct transition states. The former will be for the nucleophilic cleavage reactions discussed here and the latter will be for electron transfer reactions, not discussed here. For each of these cases, the configuration which is not primarily involved in the avoided crossing will provide an orbital interaction of *secondary* importance. For more details, see refs 3 and 5, and Eberson, L.; Shaik, S. S. *J. Am. Chem. Soc.*, in press.

[8] Shaik, S. S. In *New Concepts for Understanding Organic Reactions*; NATO ASI Series, Vol. C267; Bertram, J., Csizmadia, I. G., Eds.; Kluwer Publications: Dordrecht, 1989.

[9] For a treatment of MO overlaps in retention vs inversion S_N2 (C and Si), see: Anh, N. T.; Minot, C. *J. Am. Chem. Soc.* **1980**, *102*, 103.

therefore provides a rationale for the nucleophilic ring opening reactions of the arylcyclopropane cation radicals described earlier.[1] The model makes a further general prediction that *the stereochemical course of nucleophilic displacements on σ one-electron bonds will be governed by the σ* (LUMO) orbital of the one-electron bond and will therefore proceed with inversion of configuration at the site of attack.*[10,11] We should caution, however, that when overlap binding ceases to be the dominant factor, as in metallic or higher row elements, the stereoselection rule will accordingly be weakened and stereoretention may become competitive with stereoinversion.

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(10) It is worth pointing out an isoelectronic analogy of the nucleophilic cleavages of one-electron σ bonds, namely, the cleavages of two-electron σ bonds by radicals. This isoelectronic analogy implies isostereospecificity. Indeed, although the analysis is less straightforward,[8,12] it is still possible to identify the σ*(LUMO) orbital of the two-electron bond as the main stereoelectronic component which controls the reaction stereochemistry. Thus, much the same as in the nucleophilic cleavages of one-electron σ bonds, the radical cleavages of two-electron σ bonds are also predicted to proceed with stereoinversion. In fact, they do.[13]

(11) In principle, the valence-bond model can also be used to analyze the *regiochemistry* of nucleophilic additions to cation radicals. In practice, this problem is more complicated, however, because it requires consideration of both the thermochemistries of the various regiochemical pathways and the orbital interaction terms. This problem is discussed in detail in a forthcoming paper on the isoelectronic reaction of radical additions to olefins. See: Shaik, S. S.; Canadell, E. *J. Am. Chem. Soc.* **1990**, *112*, 1446.

(12) See discussion on p 197 of ref 8 using a classical valence bond treatment. By analyzing the problem in fragment MO's, as done in the present paper, and by using the mixing rules in ref 8, it is possible to show that the resonance interaction in the radical cleavage of two-electron σ bonds will be proportional to the *product* of overlaps between the orbital of the radical and both the σ and σ* orbitals of the R–X bond, $(\phi_{rad}-\sigma_{CX})(\phi_{rad}-\sigma^*_{CX})$, and that this product virtually vanishes for frontside attack, prefering the backside cleavage.

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The Synthesis of Substituted Lactones by Intramolecular Chirality Transfer with Stereodifferentiating Chiral α-Ester Radical Intermediates

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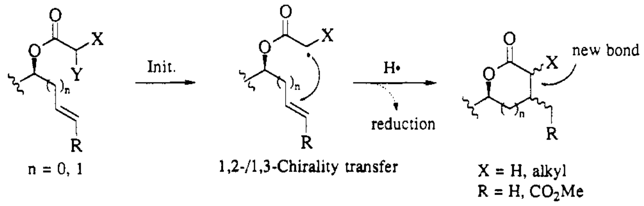
Summary: Carbon radicals generated from α-halo acetate, propionate, and related allylic and homoallylic esters can cyclize onto activated and unactivated olefins to give α,β-substituted lactones with good to excellent stereochemical control in yields ranging from 52 to 90%.

The many attributes of carbon–carbon bond formation through free-radical processes have been lauded in recent years,[1] primarily as a result of a number of elegant studies on the mechanism and preparative aspects of these reactions. Because of their stabilized nature, ester α-radical species have been considered unsuitable[2,3] for C–C bond formation in the presence of tin hydrides, as exemplified by the synthesis of lactones[4] from such radicals and olefins (Scheme I). This prompted Ueno[5] and Stork[6] to develop the α-bromo acetal method as an indirect yet efficient route to γ- and δ-lactones. Another practical solution to this problem has been devised by Curran and Chang[2] based on the halogen atom transfer method. The prospects of a direct formation of lactones by intramolecular capture of an ester radical as shown in Scheme I has a number of redeeming features. Moreover, the potential for stereochemical control at the newly formed sterogenic centers presents additional amenities and obvious challenges in free-radical processes.[2,6,7]

Scheme I



We report herein that primary and secondary radicals generated from α-halo esters with triphenyltin (or tributyltin) hydride at low concentrations (0.02–0.012 M

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(3) Surzur, J.-M.; Bertrand, M. P. *Pure Appl. Chem.* **1988**, *60*, 1659.

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(7) For some recent examples, see: Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500. Koreeda, M.; George, I. A. *J. Am. Chem. Soc.* **1986**, *108*, 8098. Rajanbabu, T. V.; Fukunaga, T.; Reddy, G. S. *J. Am. Chem. Soc.* **1988**, *111*, 1759.

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